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Protocol & Statistical Analysis Plan

Title: Ketamine Versus Midazolam for Recurrence of Suicidality in Adolescents

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Double-Blind Randomized Controlled Trial of Acute-Course of Ketamine Versus Midazolam for Recurrence of Suicidality in Adolescents

Extended Protocol: Confidential

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1.0 LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
AE	Adverse Event
ARI	Affective Reactivity Index Self Report
ASRM	Altman Self-Rated Mania Scale
BPFS-C	Borderline Personality Features Scale for Children
BPRS	Brief Psychiatric Rating Scale
CADSS	Clinician-Administered Dissociative States Scale
CAST-IRR_E	Concise Associated Symptom Tracker – Irritability Extended Version
CC	Concomitant Treatment
CD-RISC	Connor-Davidson Resilience Scale
CGI-I	Clinical Global Impressions - Improvement
CGI-S	Clinical Global Impressions - Severity
CHRT-C	Concise Health Risk Tracking Clinician-Rated Behavior Module
CHRT-SR_{16}	Concise Health Risk Tracking Self-Report
CRF	Case Report Form
DESS	Discontinuation-Emergent Signs and Symptoms
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DUSI	Drug Use Screening Inventory
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EEG	Electroencephalogram
EDC	Electronic Data Capture system
EHR	Electronic Health Record
GAD-7	Generalized Anxiety Disorder – 7 item scale
GCP	Good Clinical Practice
IAT	Implicit Association Task
ICF	Informed Consent Form
IDS	Inventory of Depressive Symptomology
IOP	Intensive Outpatient Program
IRB	Institutional Review Board
LAR	Legally Authorized Representative
MHHQ	Mental Health History Questionnaire
MINI-KID	Mini International Psychiatric Interview for Children and Adolescents
PD	Protocol Deviation
PG	Pregnancy
PI	Principal Investigator
SAE	Serious Adverse Event
SAPAS-AV	Standardized Assessment of Personality. Abbreviated Scale Adapted for Adolescents
SCQ	Self-Administered Comorbidity Questionnaire
SMURF	Safety Monitoring Uniform Report Form
SPARC	Suicide Prevention and Resilience at Children's
TESI-C	Traumatic Event Screening Inventory
TLFB	Timeline Follow Back
TRD	Treatment Resistant Depression
UPIRSO	Unanticipated Problems Involving Risks to Subjects or Others

2.0 LIST OF TERMS AND DEFINITIONS

TERM	Definition
Guardian	An individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care when general medical care includes participation in research
Legally Authorized Representative (LAR)	A person authorized either by statute or by court appointment to make health care decisions on behalf of another person who is Incapacitated, Incompetent, or has Impaired Decision-Making Capacity
Parent	A child's biological or adoptive mother or biological or adoptive father
Study Completer	A subject that completes screening, 4 infusions (V1-V4) and the 2 clinical follow-up visits (V5 and V15).
Study Physician	For the purposes of this study, this role may be filled by trained Doctors of Medicine (MD), Doctors of Osteopathic Medicine (DO), or Advance Practice Providers (APP).

3.0 SYNOPSIS

Title of Study:	**Double-Blind Randomized Controlled Trial of Acute-Course of Ketamine Versus Midazolam for Recurrence of Suicidality in Adolescents**
Objective:	This project aims to examine the signal for efficacy of ketamine, a rapidly acting medication shown to decrease suicidality in adults in as short as hours or days, as opposed to weeks.
Methodology:	The study design is a double-blind, randomized, active-control trial of adolescents (ages 13-18 years) with recent suicidal behaviors (suicide attempt or increased suicidal ideation). All participants must be receiving standard of care treatment which may range broadly from both outpatient and inpatient programs which include clinically indicated psychosocial and/or psychopharmacological treatments. Ketamine/midazolam treatment will occur twice weekly during the first two weeks of the study, followed by weekly assessments through week 12.
Number of Participants:	114 Participants
Criteria for Inclusion:	This study will enroll youth with depression and suicidal behaviors, and meet all of the following criteria: • Be adolescents (aged 13-18 years); • Have had a recent suicidal event (suicide attempt or significant suicidal ideation with a plan or intent warranting emergency evaluation or inpatient hospitalization within the past 90 days) • Receiving standard of care treatment that includes clinically indicated psychosocial and/or psychopharmacological treatment • Have a current primary diagnosis of a depressive disorder based on the MINI-KID (other psychiatric disorders are acceptable, but must not be primary) • Participants must be able to complete assessments in English. However, the parent(s) or legal guardians of minors may either speak English or Spanish. • Use effective method of contraception during and for 90 days following the end of treatment for female and male participants. Recommended methods of birth control are namely, consistent use of an approved hormonal birth control (pill/patches, rings), an intrauterine device (IUD), contraceptive injection, double barrier methods, sexual abstinence, or sterilization.
Visit Schedule:	Screening Visit, 4 Study Treatment Visits, 11 Follow-Up Visits (combination of in-person and remote visits). Duration of study is approximately 3 months; some visits may be conducted remotely.
Outcome Measures:	Multiple streams of outcome measures will be utilized for this protocol, including self-report measures, research assessor-completed measures, clinic level measures, and behavioral measures.
Safety and Tolerability Measures:	Adverse event (AE) recording, Concise Health Risk Tracking (CHRT-SR_{16}), Safety Monitoring Uniform Report Form (SMURF), Brief Psychiatric Rating Scale (BPRS) Psychosis items, Clinician-Administered Dissociative States Scale (CADSS), and Discontinuation Emergent Signs and Symptoms (DESS) scale.

4.0 BACKGROUND AND RATIONALE

4.1. Background

Rates of suicide have increased by 178% and 76% respectively in youths aged 10-14 years and 15-19 years over the past decade (1). Currently available pharmacological treatments are of modest benefit and may take weeks to months to become effective. While combination of pharmacological and psychotherapy care remains the standard of care for youths with a recent suicidal event, we have found that *one in four youths experience a repeat suicidal event* (defined as suicide attempt or worsening of suicide risk that necessitates higher-level of care such as inpatient hospitalization that occur after initiation of treatment in youths with a recent suicidal event) within one month of discharge from intensive outpatient care (IOP) (2). Hence, there is an urgent need to identify rapid-acting treatments that ameliorate symptoms associated with suicidality and prevent repeat suicidal events. Based on evidence for efficacy of ketamine in reducing symptoms of suicidality in adults (Wilkinson et al., 2018), **augmentation of standard care with ketamine** appears to be a promising treatment approach for youths with a recent suicidal event. However, critical gaps in our knowledge prevent widespread use of this approach. To date, no study has reported evidence for 1) reduction in repeat suicidal events with ketamine either in adults or in youths, 2) reductions either in implicit cognition or in symptoms associated with suicidality in youths, and 3) underlying mechanisms that mediate the effects of ketamine on suicidality. Given that a previous report in adults found that ketamine reduces implicit suicidal cognition, we propose an experimental-medicine approach that evaluates whether implicit suicidal cognition is a mechanistic target for reducing symptoms and preventing suicidal events with ketamine.

The overall goal of this research program is to identify and integrate rapid-acting treatments in current standard-of-care for youths with a recent suicidal event. The central hypothesis of our submission is that augmentation of standard care with ketamine will result in greater symptomatic improvement in the short-term and lower likelihood of repeat suicidal event in the long-term as compared to midazolam (placebo condition). In this proposed first-of-its-kind study, we plan to recruit 114 medically healthy male and female youths with recent suicide events who are either seeking care at an emergency room, admitted to an inpatient unit, enrolled in an IOP, or receiving adequate outpatient care with either psychopharmacological or psychosocial treatment following a suicide event. In addition to their standard care, youths will be randomized in 1:1 fashion to either intravenous ketamine (0.5 mg/kg) or midazolam (0.02 mg/kg) twice weekly for 2 weeks followed by weekly visits for 10 weeks (for a total of 12-week post-randomization observation period). The duration and level of standard clinical care will be determined by the youth's clinical provider. At each visit, study clinicians will interview subjects, collect collateral information from family and clinical providers when available, along with information from any emergency room visits or hospital stays to ascertain the occurrence of suicidal event. Subjects will complete implicit association task (IAT) before treatment and at Day 14 and Day 84 after completing the four ketamine infusions. Subjects will complete measures of overall depressive symptoms and suicidal ideation at each visit.

4.1.1. Youth suicide is an urgent public health issue.

Deaths due to suicide in youths aged 10-14 years and 15-19 years has increased by 178% and 76% respectively over the over the past decade in the United States (1). In fact, suicide is now the second leading causes of mortality amongst adolescents and young adults (3, 4). Adolescent suicidality is common, with 7.4% of adolescents making an attempt within the prior 12 months of the survey in 2017, and 13.6% having reported clinically significant suicidal ideation with a plan (5). Prevalence of suicidal ideation in youth has been reported to range between 19.8% and

24.0% (6), and over one-third of adolescents who experience suicidal ideation go on to attempt suicide (7). Repeated self-harm and suicidal behavior are associated with functional impairment and high health care costs (8-11). Thus, there is a critical need for suicide prevention and evidence-based treatments for youth with suicidal behaviors.

The term “suicidal events” has been coined to refer to suicide attempts (actual, interrupted, and aborted attempts) and emergency evaluation and/or treatment resulting from increased suicidal ideation even in the absence of a suicide attempt. “Suicidal events” are often used as a proxy outcome in suicide research due to the low base rate of deaths by suicide. Thus, for this proposal, we refer to “suicidal events” as any suicidal attempts or behaviors, as well as emergency intervention strategies (e.g. emergency department [ED] visit or inpatient hospitalization) to prevent suicidal behaviors.

4.1.2. Current standard of treatment for youth with a recent suicidal event.

There are no currently approved treatments for reducing suicide risk following a recent suicidal event, and there are no currently effective treatments specifically for the prevention of recurrent suicidal behavior in adolescents (12). Rather, the standard of treatment for youth with serious suicidal ideation or behaviors is often inpatient psychiatric hospitalization, and the goal of inpatient treatment is predominantly for immediate safety, rather than specific treatments to reduce subsequent suicidal behaviors. Due to high costs associated with inpatient hospitalization, many hospitals and treatment centers have developed IOP programs to treat youth with suicidality. The standard of care remains psychopharmacological and psychosocial treatments targeting the underlying psychiatric illness associated with the suicide attempt. There remains no approved treatment for suicidal ideation or behaviors.

One of the potential IOP programs that will be used for recruitment of subjects is the Suicide Prevention and Resilience at Children’s (SPARC). To be eligible for the program, youths (ages 12-18 years) must have a recent suicide attempt or severe worsening of suicidal ideation warranting emergency services. Patients can be referred from within the hospital or from community providers, and are typically evaluated for IOP within a few days after the suicidal event or within a few days of discharge if they were hospitalized. The IOP program includes 3 hours of group therapy twice weekly, and utilizes cognitive behavior therapy (CBT) and dialectical behavior therapy (DBT) components focusing on skills to reduce risk factors associated with suicidal behaviors (13, 14). Timing of discharge from this IOP is based on individual patient need and is determined by the clinician based on the patient’s readiness for standard outpatient care. Length of treatment was typically 6-8 weeks of IOP, although discharge is based on the individual patient (2). For this study, SPARC IOP will serve as *one* option for the standard treatment.

4.1.3. The need for rapid-acting interventions.

IOPs are very time-intensive, and often require several weeks or months of participation. Similarly, the standard of treatments for underlying psychiatric disorders for youth are typically psychopharmacological or psychosocial, and these interventions also often take several weeks before substantial reductions in symptoms are seen. Thus, rapid-acting treatments to reduce symptoms and prevent suicidal behaviors in youth are critically needed.

In addition to the standard of treatment, several interventions specific to suicidal youths have been studied. Lyengar and colleagues conducted a systematic review of randomized controlled trials for interventions for suicide attempts and self-harm in adolescents and found that only five out of 18 interventions had a significant effect for primary outcomes of suicide attempts and self-harm. Cognitive behavioral therapy (CBT), which included Dialectical Behavior Therapy for Adolescents (DBT-A) as a type of CBT, was the only intervention with more than one positive trial showing

reduction in self-harm (15). CBT, as well as the other interventions included, despite specifically targeting suicidal youth and demonstrating some evidence of efficacy, are not rapid-acting.

Furthermore, a high proportion of suicide attempts occur during the first few weeks following discharge from an inpatient setting. In the Treatment of Adolescent Suicide Attempters study of depressed adolescent suicide attempters recently discharged from inpatient units, 40% of all suicidal events occurred within the first 4 weeks of treatment, before many of the putative active ingredients of the treatment intervention could be implemented (14). This lack of protection against events by best practice treatment highlights the importance of the development of rapid-acting and novel treatments, rather than simply improving the linkage between inpatient and outpatient care.

4.1.4. Rigor of prior research supporting Aim 1.

Potential of Ketamine as a rapid-acting treatment for suicidality. Ketamine, or its s-enantiomer (esketamine), has been extensively studied in treatment resistant depression (TRD), and has demonstrated rapid improvement in symptoms (16). During early trials of ketamine in TRD, there was evidence of rapid reductions in suicidal ideation. In a meta-analysis of 167 adults with suicidal ideation enrolled in randomized trials comparing single dose ketamine to midazolam or saline, the ketamine group showed significant reductions in suicidal ideation within one day and lasting for one week (17). **However, no studies to date have evaluated the use of ketamine to prevent repeat suicidal events.**

To date, no randomized, controlled trials of ketamine have been conducted in adolescent populations. One open trial examined the benefits of six ketamine infusions (0.5mg/kg) over two weeks in 13 adolescents (ages 12-18 years) with TRD. Average percent improvement on the Children's Depression Rating Scale – Revised (CDRS-R) was 42.5%, and 38% (5/13) of participants met response criteria (>50% reduction on the CDRS-R). Three of the responders remained in remission at the 6-week follow-up assessment. Dissociative symptoms were transient (18).

Ketamine has been safely used in youth and has been approved for anesthesia in youth for many years. Ketamine has been safely used as an anesthetic agent in children and adolescents for decades. Doses for anesthesia range from 1-3mg/kg as a rapid bolus. Dosing for adult trials of ketamine for TRD have used doses between 0.1-1.0mg/kg (19), well within the range of safe administration for youth. Notably, the doses of ketamine that are safely used for inducing anesthesia are over 4 times higher and given as a short bolus injection as compared to the slow 40-minute infusion used for treatment of depression.

4.1.5. Rigor of prior research supporting Aim 2.

In order to address the limitations of self-report, researchers have adapted the use of behavioral tools, such as the implicit association test (IAT) to identify markers of suicide risk (20). Specifically, the IAT is a digital measure administered via computer that examines attitudes operating outside of conscious control (21). The IAT is easy to administer, takes minimal time, and is less susceptible to bias compared to self-report measures (22). A prior meta-analysis of studies utilizing the IAT found that it was more predictive than self-report measures, especially on socially sensitive topics (23). Studies suggest that the IAT is useful in measuring implicit thinking about self-harm, and as a result, may help improve our ability to predict and prevent this behavior. Initial studies suggest that the IAT is helpful in measuring the extent to which individuals associate death/suicide with the self, and that this metric is useful in distinguishing those engaging in self harm from controls. Moreover, this tool has demonstrated improved prediction of self-harm above and beyond other well-understood predictors (24-26). In a study of adolescents who were non-suicidal (n=38), suicidal ideators (n=37), or suicide attempters (n=14), the self-injury IAT suicidal

ideators showed small positive associations between themselves and self-injury, and suicide attempters showed large positive associations, while non-suicidal adolescents showed large negative associations. In addition, the self-injury IAT accurately predicted current suicidal ideation, attempt status, and predicted future suicidal ideation (27). Similarly, in a study of 71 adolescents admitted to an inpatient psychiatric unit, self-harm IATs demonstrated good reliability and sensitivity to psychiatric change, although they did not prospectively predict suicide attempts (28).

Price and colleagues examined implicit and explicit suicidal ideation in a randomized controlled study of ketamine (n=36) versus midazolam (n=21). At 24 hours, 53% of ketamine-treated participants compared to 24% of midazolam-treated participants scored 0 on all three explicit suicide measures (Beck Scale for Suicidal Ideation, and the suicide items from the Montgomery-Asberg Depression Rating Scale [MADRS] and the Quick Inventory of Depression Symptomatology Self Report [QIDS-SR]) (p=.03). Implicit associations were also reduced with ketamine, but not with midazolam (29). However, further research is needed to achieve a better understanding of ketamine's mechanism of action, and the potential use of ketamine for treatment of adolescents with suicidal behaviors.

4.1.6. Rigor of prior research supporting Aim 3.

As noted above, ketamine has been shown to rapidly reduce depression symptoms and suicidal ideation in adults (16, 17). Ketamine showed significantly greater reduction in suicidal ideation, self-reported depression severity, clinician-rated depression severity, hopelessness, and anxiety compared to midazolam in 57 adults with TRD (29). Studies in youth are limited to case reports and an open study of adolescents with TRD, with some evidence of improvement in depression symptoms and suicidal ideation with ketamine (18, 30, 31).

4.1.7. Rigor of prior research supporting Exploratory Aim.

In the ketamine trial conducting by Price and colleagues, the implicit suicide-related association of "Escape = Me" was reduced with ketamine treatment over midazolam. The greatest differential effects of ketamine over midazolam were seen in individuals with high implicit and explicit suicidal cognitions at baseline. The findings are consistent with an open label trial by the same authors, demonstrating that the Escape = Me associations were improved with ketamine treatment and were predictive of better outcomes with ketamine (29). It remains unclear, however, what the exact mechanism of action is with ketamine and how that relates to both explicit and implicit suicidal cognitions. This will be the first study to test whether treatment-related changes to IAT during ketamine treatment can predict reduction in suicidal events.

4.2. Study Rationale

Despite the fact that suicide is the 2nd leading cause of death in adolescents, ages 15-24 years of age, there are no validated treatments to decrease the risk of adolescent suicidal behavior, and currently available standard treatments are of modest benefit and often take weeks or months to become effective. The status quo as it pertains to treatment of youths with recent suicidal events has resulted in frequent repeat suicidal events, marked burden on youths and their caregivers by frequent visits, and prolonged suffering by the delay between initiation of currently available pharmacotherapy and psychotherapy interventions and when they finally become effective. This project aims to examine the signal for efficacy of ketamine, a rapidly acting medication shown to decrease suicidality in adults in as short as hours or days, as opposed to weeks.

4.3. Significance of the Project to the Field

To date, no study has reported evidence for 1) reduction in repeat suicidal events with ketamine either in adults or in youths (AIM 1); 2) reductions either in implicit cognition (AIM 2) or in symptoms associated with suicidality (AIM 3) in youths; and 3) underlying mechanisms that mediate (EXPLORATORY AIM) the effects of ketamine on suicidality. This research intervention has high impact potential because it: 1) targets a common and serious public health problem, adolescent suicidal behavior; 2) tests the feasibility and safety of a rapid-acting intervention with the potential to reduce severe suicidal risk; 3) offers an intervention that can be delivered at a time and place when there is greatest clinical need, but for which there are no currently developed interventions; 4) focuses on dimensions of suicidal risk in a high risk sample; and 5) is designed to complement standard care.

Successful completion of this grant will inform future studies of the short- and long-term signal for efficacy of ketamine in youths with recent suicidal event, which can be used for a larger-scale effectiveness trial. Understanding the mechanistic link with implicit suicidal cognition will also guide research into development of novel therapeutics. Findings of this proposed project will have immediate relevance to clinical care as they may inform the use of ketamine, or its s-enantiomer (esketamine) in youths with a recent suicidal event.

5.0 OBJECTIVES

The objective of this study is to examine the signal for efficacy and safety of ketamine to reduce suicidal behaviors in youth with suicidality.

5.1. Study Aims

Aim 1. Evaluate reduction in repeat suicidal events with ketamine. Experiment 1: Compare the number of subjects with a repeat suicidal event over the 12-week post-randomization observation period. Hypothesis 1: Treatment with ketamine will result in markedly lower rates of repeat suicidal events compared to midazolam.

Aim 2. Evaluate reduction in implicit suicidal cognition with ketamine. Experiment 2: Changes in IAT after two weeks of twice-weekly ketamine vs. midazolam infusions. Hypothesis 2: Treatment with ketamine will result in greater baseline-to-week-2 reduction in implicit suicidal cognition compared to midazolam.

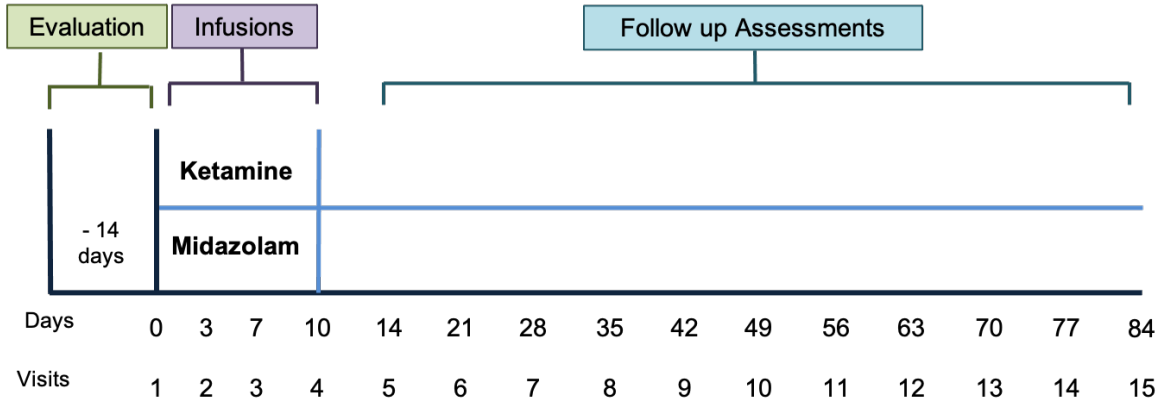
Aim 3. Evaluate reduction in depressive symptoms and suicidality with ketamine. Experiment 3: Changes in overall depression and suicidal ideation after two weeks of twice-weekly ketamine vs. midazolam infusions. Hypothesis 3: Treatment with ketamine will result in greater baseline-to-week-2 reduction in overall depressive symptoms and suicidal ideation compared to midazolam.

Exploratory Aim: Explore whether reduction in IAT mediates the improvement in suicidality with ketamine. In this exploratory analysis, we will use a mediation analysis to test whether changes in IAT from baseline-to-week-2 mediates the reduction in repeat suicidal events with ketamine, and whether youths with low levels of implicit suicidal cognition at Week 2 are less likely to experience recurrence of suicidal events over the remaining 10-week observation period.

6.0 DESIGN

6.1. Overview of Study Design

The study design is a double-blind, randomized, active-control trial of adolescents (ages 13-18 years) with recent suicidal events (suicide attempt or increased suicidal ideation warranting urgent evaluation). All participants must be receiving standard of care treatment that includes clinically indicated psychosocial and/or psychopharmacological treatments. Ketamine/midazolam treatment will occur twice weekly during the first two weeks of the study, followed by weekly follow-up assessments through day 84 (see figure below).



6.2. Design

Adolescent patients (ages 13-18) who have recent suicidality (defined as suicide attempt or urgent evaluation for a suicidal ideation or behavior), and who are receiving standard of care treatment (e.g., psychosocial and/or psychopharmacological treatment) will be recruited for participation in the study. Upon informed consent/assent, screening data will be collected regarding mood symptoms, suicidal ideation and behavior, associated comorbidities, and treatment history. Youth participants will be randomized to receive infusions of either ketamine or midazolam, which will be provided twice weekly for two weeks. Participants will then have follow-up assessments visits through week 12 to continue to monitoring outcome measures.

6.3. Participant Selection

6.3.1. Inclusion Criteria

Study participants ***must***:

1. Be adolescents (aged 13-18 years);
2. Have had a recent suicidal event (suicide attempt or significant suicidal ideation with a plan or intent warranting emergency evaluation or inpatient hospitalization within the past 90 days);
3. Receiving standard of care treatment that includes clinically indicated psychosocial and/or psychopharmacological treatment;
4. Have a current primary diagnosis of a depressive disorder based on the MINI-KID (other psychiatric disorders are acceptable, but must not be primary);

5. Participants must be able to complete assessments in English. However, the parent(s) or legal guardians of minors may either speak English or Spanish.

6. Use effective method of contraception during and for 90 days following the end of treatment for female and male participants. Recommended methods of birth control are namely, consistent use of an approved hormonal birth control (pill/patches, rings), an intrauterine device (IUD), contraceptive injection, double barrier methods, sexual abstinence, or sterilization;

6.3.2. Exclusion Criteria

Study participants ***must not***:

1. Have a psychotic disorder, such as lifetime schizophrenia, or a pervasive or intellectual developmental disorder requiring substantial or very substantial support.

2. Have current mania, hypomania, mixed episode, or obsessive-compulsive disorder;

3. Have a primary diagnosis other than a depressive disorder;

4. Have moderate to severe alcohol or substance use disorder within the past six months (based on MINI-KID); If there is a positive urine drug screen at screening, the urine drug screen will be repeated at each infusion visit. Positive urine drug screen will be reviewed by study physician and infusion will proceed as long as no safety risk was identified;

5. If female, be pregnant, lactating, or nursing; Women of childbearing potential must have a negative urine pregnancy test prior to all infusions;

6. Have unstable medical conditions (stable for less than 3 months) or with clinically significant laboratory values or an electrocardiogram (ECG) that would pose significant risk;

7. Be at serious suicidal risk that cannot be managed in the outpatient setting;

8. Have prior treatment for depression with or contraindications to ketamine, esketamine, or, midazolam;

9. Treatment with medications that may alter pharmacokinetics of ketamine, including moderate-to-strong inhibitors or inducers of CYP3A4 and CYP2B6, is exclusionary. Regarding pharmacodynamic interactions, medications that may increase heart rate or blood pressure such as the ADHD stimulant medications will be permitted with last dose at least 24 hours prior to infusion. All concomitant medications will be evaluated by the study physician to determine if the type and dose of concomitant medication requires discontinuation and will be excluded if the concomitant medication could substantially increase the risk of study infusion. A complete list of medications that are Not Allowed is available in Appendix D of the protocol. The study team will not ask the participant to discontinue any treatment (except for not taking ADHD medications for 24 hours before study treatment) just for the sake of taking part in this study;

10. Weigh >120 kilograms at baseline. If participants are enrolled but exceed 120 kilograms at any time during the treatment period, they will be removed from the treatment portion of the study.

6.4. Recruitment of Participants

Participants may be recruited directly from their standard care outpatient provider, SPARC Intensive Outpatient Program (IOP) located at Children's Health Medical Center, from the Children's Health Emergency Department or inpatient psychiatric unit located at the Dallas campus. Participants may also be recruited into the study even if they are seen in the emergency departments or inpatient hospitalization outside of UT Southwestern, Children's Health Medical Center, and other study sites. Recruitment and consent procedures may begin during ED or inpatient hospitalization; however, as the study is an outpatient study, study procedures will not begin until the participant is discharged from the ED or inpatient hospital.

All recruitment materials and language will be submitted for UT Southwestern IRB approval. Recruitment efforts will target medically healthy male and female youths with recent suicide events who are either seeking care at an emergency room, admitted to an inpatient unit, enrolled in an IOP, or receiving adequate outpatient care with either psychopharmacological or psychosocial treatment following a suicide event.

6.5. Duration of Participation and Visit Schedule

Enrollment of 114 subjects is expected to take place over a period of approximately 36 months. Enrolled participants will be involved in the study for approximately 14 weeks. Visits include a Screening Visit, 4 Study Intervention Visits, and 11 Follow-Up Visits (combination of in-person and remote visits).

6.6. Outcome Measures

Multiple streams of outcome measures will be utilized for this protocol, including self-report measures, research assessor-completed measures, clinic level measures, and behavioral measures. More detail on outcome measures is listed below Assessment section (7.0).

7.0 ASSESSMENT

7.1. Research Visit Assessment Schedule

The following table is an overview of the research visit assessment schedule.

Table 1. Schedule of assessments

Visit Number	Screening	V1	V2	V3	V4	V5	V6-14	V15**
Day(s)	(Day – 14)	0	3	7	10	14	21, 28, 35, 42, 49, 56, 63, 70, 77	84
Visit Window	(- 14 days)	(+/- 0)	(+/- 1)	(+/- 1)	(+/- 1)	(+/-7)	(+/-7)	(+/-7)
Induction								
Consent/Assent	X							
Demographics	X							
Medical History Review								
Adverse Events	X	X	X	X	X	X	X	X
Family Health Screen	X							
Mental Health History	X							
Concomitant Treatment Log	X	X	X	X	X	X	X	X
CIRCAS	X							
CIRCAS-Parent (if applicable)	X							
SCQ	X							
SCQ-Parent (if applicable)	X							
Interview Administered Assessments								
BPRS - Psychosis		X^^	X^^	X^^	X^^	X		X
CADSS		X^	X^	X^	X^			
CGI-I			X	X	X	X		X
CGI-S	X	X	X	X	X	X		X
CHRT-C	X	X*	X*	X*	X*	X	X	X
CHRT Behavior Module Supplement	X	X	X	X	X	X	X	X
MINI-KID	X							
MINI-KID-Parent (if applicable)	X							
SMURF		X^	X^	X^	X^	X	X	X
TESI-C	X							
TLFB	X	X	X	X	X	X	X	X
Self-Report Assessments								
ARI	X	X	X	X	X	X	X	X
ASRM	X	X	X	X	X	X	X	X
BPFS-C	X							
CAST-IRR$_E$	X	X	X	X	X	X	X	X
CD-RISC	X					X		X
CHRT-SR$_{16}$	X	X*	X*	X*	X*	X	X	X
DESS	X	X				X		X
DUSI	X	X						X
GAD-7	X	X	X	X	X	X	X	X
IAT		X				X		X
IDS-SR	X	X	X	X	X	X	X	X
SAPAS-AV	X							
Blinding evaluation – Participant						X		
Parent-Report Assessments								
IDS-SR (if applicable)	X	X	X	X	X	X	X	X
FHS (if applicable)	X							
CAST-IRR$_E$ (if applicable)	X	X	X	X	X	X	X	X
Clinical Laboratory Items								

Visit Number	Screening	V1	V2	V3	V4	V5	V6-14	V15**
Physical Exam	X	X	X	X	X	X		X
Vital Signs[§§]	X	X	X	X	X	X		X
Safety Labs	X[§§§]					X[§§§]		
Biobanking[O]	X					X		X
EEG[O]	X					X		X
Urinalysis	X	X	X	X	X	X		X
Urine Drug Screen	X	X[†]	X[†]	X[†]	X[†]			
Urine PG Test	X[§]	X[§]	X[§]	X[§]	X[§]			
ECG	X							
Randomization		X						
Study Drug Infusion		X	X	X	X			
Blinding evaluation - Investigator						X		

*CHRT-SR and CHRT-C also administered approximately -5 and 100-minutes post infusion start
** Early withdraw visits will replicate the completion of a final study visit
^ CADSS/SMURF administered at approximately -5, 40, and 100 minutes post infusion start
^^ BPRS Psychosis administered at approximately -5, 40, and 100 minutes post infusion start
[†] Urine drug screen will be repeated at infusion visits when screening urine drug test is failed
[§] Urine pregnancy will be collected on females of child-bearing age
[§§] Components of vital signs include weight (measured with calibrated equipment), heart rate, systolic and diastolic blood pressure (measured with age-appropriate and calibrated equipment).
[§§§] Lab tests will include completed blood count, hepatic and renal assessments (i.e., serum sodium, serum potassium, serum chloride, blood urea nitrogen, creatinine, serum bicarbonate, blood glucose, alanine aminotransferase, aspartic aminotransferase, and bilirubin).
[O] Optional study procedure

7.2. Outcome Measures

7.2.1. Aim 1 Outcome Measure.

The outcome measure for the study is “suicidal events”. Suicidal event is defined as a suicide attempt, or emergency department visit or inpatient hospitalization due to suicidality. Suicide attempt is defined as a non-fatal, self-directed, potentially injurious behavior with an intent to die as a result of the behavior, which may or may not result in injury. Thus, all suicide attempts are included in the “suicidal events” category.

7.2.2. Aim 2 Outcome Measure.

Death/Suicide Implicit Association Test (IAT). The IAT is a performance-based measure of cognition that has demonstrated good reliability and sensitivity to change (28). It has been shown to distinguish suicide attempters from non-suicidal adolescents and predict future suicidal behavior in adolescents (26), and has been shown to reduce suicidal cognitions following treatment with ketamine (29). The IAT measures associations based on response latency where the response time is compared across categorization tasks. Positive scores represent faster response time on association between death and self, while negative scores represent stronger associations between life and self. The IAT will be administered prior to infusion and at days 14 and 84.

7.2.3. Aim 3 Outcome Measure.

1. Concise Health Risk Tracking Self-Report (CHRT-SR_{16}). The CHRT-SR_{16} (32, 33) consists of 16 **self-reported** questions with responses ranging from 0 (strongly disagree) to 4 (strongly agree). Three subscale scores are calculated: 1) the Propensity subscale, which consists of 9 questions and 4 factors (pessimism, helplessness, social support, and despair) and a score

range of 0-36; and the Suicidal Thoughts subscale, which consists of 3 questions and a score range of 0-9 (which will serve as the primary suicidal behavior outcome in this study); and 3) Impulsivity, which consists of 2 questions and a score range of 0-6. A total score is also calculated, ranging from 0 to 56.

2. Concise Health Risk Tracking Clinician-Rated Behavior Module (CHRT-C). The CHRT-C (34) consists of 9 **clinician-rated** yes/no items about specific behaviors (i.e., suicidal ideation, suicidal attempt, preparatory acts, non-suicidal self-injury (NSSI), other injuries, etc.). At the initial administration, this instrument captures lifetime information and at subsequent administrations, it will capture information since the last visit.

3. Inventory of Depressive Symptomatology (IDS) Self-Report and Parent Report. The IDS is a depressive symptom severity measure that rates all nine criterion symptoms of MDD, and includes an irritability item for adolescents. Both the **self-report** (IDS-SR) and the **parent report** (IDS-SR Parent) will be completed at each visit. The IDS has strong psychometric properties (35, 36).

7.3. Additional Measures

7.3.1. Medical History Review

1. Family Health Screen (FHS). The FHS is a **self-report** completed by parents (18 years and older) or by participant (< 18 years old), assessing for family history of depression, anxiety, bipolar disorder, suicide, schizophrenia, alcohol abuse, and other psychiatric disorders.
2. Mental Health History Questionnaire (MHH). The MHH is a **self-report** measure that documents the participant's mental health history.
3. Concomitant Treatment Log. This log provides an accounting of current medications and treatments (e.g., types, dosages, start and end dates, etc.). This will be used to capture excluded medications at the screening visit, and to capture medication/treatment data as to characterize the sample and use as covariates when applicable.
4. Comprehensive Interview Regarding Child Assistive Services (CIRCAS). CIRCAS is an **interview** in which parents respond to questions about mental health services their child has received or is currently receiving (37).
5. Self-Administered Comorbidity Questionnaire (SCQ). The SCQ is a **self-report** that assesses the presence of medical problems, whether treatment is received for the condition, and whether or not the condition limits functioning. Each question is answered on a yes/no basis (38). For participants less than 18 years old, SCQ will be completed by the parent.

7.3.2. Clinician Administered Assessments

1. Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). The MINI-KID is a short, structured diagnostic **interview** for DSM-V psychiatric disorders in children and adolescents and also includes an accompanying parent version, in order to achieve a best estimate rating of diagnoses (39). Psychometrics among children and adolescents have been well-established. For this study, the MINI-KID will also be utilized for participants over the age of 18, though these participants will not have the accompanying parent version and the best estimate will be based on the participant version only.

2. Traumatic Events Screening Inventory (TESI-C). The TESI-C is a **clinician administered**

interview that assesses a child's experience of a variety of potential traumatic events including current and previous injuries, hospitalizations, domestic violence, community violence, disasters, accidents, physical, and sexual abuse (40).

3. Safety Monitoring Uniform Report Form (SMURF). The SMURF was adapted from the Systematic Assessment for Treatment of Emergent Events (SAFTEE) to develop an instrument to assess adverse events aimed specifically at pediatric populations in psychiatric clinical trials (41). The SMURF includes a general inquiry and review of 26 body systems. Positive responses lead to additional query by the assessor to determine onset, duration, severity, current status, actions taken to address the AE, and potential contributing factor for the AE. The SMURF has been used in several clinical trials (reviewed by Coates and colleagues) (42). AEs recorded will be any adverse change from initial treatment visit that occurs at any time during the course of the study.

4. Clinical Global Impressions Scale (CGI) – S and I. The CGI has two components—the CGI-Severity, which rates illness severity, and the CGI-Improvement, which rates change from the initiation of treatment (43). The CGI-S rating is based upon observed and reported symptoms, behavior, and function in the past seven days. Clearly, symptoms and behavior can fluctuate over a week; the score should reflect the average severity level across the seven days. The CGI-I is similarly simple in its format. Each time the patient is seen after medication has been initiated, the clinician compares the patient's overall clinical condition to the one-week period just prior to the initiation of medication use.

5. Brief Psychiatric Rating Scale (BPRS) Psychosis items. The BPRS, version 4.0 is a **clinician-rated** 24-item scale that assesses symptoms from a variety of psychiatric disorders, including mood disorders, anxiety, psychotic symptoms, etc. (44). We will use the 4-item psychosis module. Items are rated on a 1-7 Likert scale, with 1 referring to not present and 7 referring to extremely severe. The total score ranges from 7-28. The BPRS Psychosis module is used in this study to examine dissociative symptoms following infusions. Thus, it will be completed at three times during each infusion (immediately prior to infusion, post-infusion, and 1-hour post infusion), as well as at each in-person follow-up visit (approximately -5, 40, and 100 minutes).

6. Clinician-Administered Dissociative States Scale (CADSS). Due to potential for dissociative symptoms with ketamine treatment, we will use the CADSS to measure dissociative symptoms. The CADSS is a 27-item scale (19 subject-rated and 8 clinician-observed items), with responses on a 0–4-point scale (0=not at all to 4= extremely). The CADSS has demonstrated reliability and validity (45). The CADSS has been used in several clinical trials of ketamine, including the open label adolescent study (19). The CADSS is used in this study to assess for dissociative adverse events following infusions. Thus, it will be completed at three times during each infusion (approximately -5, 40, and 100 minutes).

7. CHRT Behavior Module Supplement. The CHRT supplement is a follow-up **interview** that will be used to collect further information regarding suicidal behaviors observed in the CHRT-C assessment.

8. Timeline Followback Method Assessment (TLFB). The TLFB is a questionnaire to assess recent cigarette, marijuana, and other drug use. It involves asking participants to retrospectively estimate their drug use which can include quantity and frequency of consumption (46).

7.3.3. Self-Report Assessments

1. Discontinuation-Emergent Signs and Symptoms (DESS) (47). The DESS is a 43-item checklist to assess for discontinuation syndrome symptoms. The scale is available as a self-report or clinician-rated measure. For this study, we will use the **self-report** version.

2. Drug Use Screening Inventory (DUSI). The DUSI is a **self-report** and among one of the most widely used substance use measures in research and clinical settings. It has demonstrated norms and sensitivity/specificity in adolescents (48).

3. Altman Self-Rated Mania Scale (ASRM). The ASRM is a 5-item **self-report** measure that assesses the presence and severity of manic symptoms. A cut-off score ≥6 indicates a high probability of mania/hypomania (49).

4. Generalized Anxiety Disorder – 7 item scale (GAD-7). The GAD-7 (49) is a 7-item **self-report** measure of anxiety symptoms, and has demonstrated reliability and validity in adolescents. Total scores ≥8 represent probable generalized anxiety disorder (50).

5. Concise Associated Symptom Tracker – Irritability Extended Version (CAST-IRR$_E$); **self-report** and parent report. 10 item scales that assesses irritability (51). Additional 5 items will measure irritability in a comprehensive fashion.

6. Affective Reactivity Index Self Report (ARI); self-report and parent report. The ARI is 7 item **self-report** measure that assesses irritability (52). It contains 6 irritability symptom items plus one impairment item that must be scored if present during the previous six months.

7. Borderline Personality Features Scale for Children (BPFS-C). The BPFS-C is 11-item **self-report** version, which has demonstrated good construct and criterion validity (53).

8. Standardized Assessment of Personality. Abbreviated Scale Adapted for Adolescents (SAPAS-AV). The SAPAS-AV is a **mini-interview** in which youth respond *yes* or *no* to a series of 8 questions and has been shown to be a reliable and valid measure of personality disorders (54).

9. Connor-Davidson Resilience Scale (CD-RISC). This scale is intended to measure resilience. The 10 is a shortened version of the original 25-item CD-RISC. Participants rate items on a 5-point Likert scale, ranging from 0 (not true at all) to 4 (true nearly all the time). Each item has a minimum score of 0 and a maximum score of 4. A higher score indicates higher resilience (55).

8.0 STUDY PROCEDURES

8.1 Screening Visit (Day -14)

The screening phase will start with informed consent procedures. All potential participants will undergo a screening visit once informed consent/assent is obtained, to include:

- Medical History Review
- Clinician/Assessor Rated Assessments
- Self-report Assessments
- Clinical Laboratory Items
  - Vital signs, physical examination (includes include cardiac, pulmonary, and neurologic exams), safety labs, drug testing, pregnancy testing (if applicable), EEG (optional) and ECG.

Once participants provide informed consent/assent, will be asked about basic demographic (e.g., age, date of birth, biological sex, gender identification, sexual orientation, race/ethnicity) and medical information (including disease history and all medications and/or other treatments) as outlined in Table 1. Participants and, if applicable, their parents/LAR/guardians will be interviewed using the Mini International Psychiatric Interview for Children and Adolescents (MINI-KID; 32) to assess the participant's psychiatric diagnoses. In addition, severity measures of suicidality, depression, mania, anxiety, and substance use will be obtained, as well as baseline measure of adverse events to monitor subsequent safety outcomes. Participants will also undergo a physical examination, safety labs, drug testing, pregnancy (if applicable), EEG (optional) and ECG.

Participants who have completed recent (within 4 weeks of screening) labs and ECG may use those medical records to satisfy eligibility criteria provided there are no clinically significant abnormalities warranting repeat testing, and a release of information is signed by the participant and/or their legal guardian if under the age of 18.

Blood samples will be collected from participants by trained phlebotomists, who will draw the sample using standard venipuncture procedures, through a single venipuncture using a small gauge needle. Universal precautions will be observed by the phlebotomists during all draws. Each tube will be labeled and packaged for processing and storage. About 25 ml (around 5 teaspoons) of venous blood will be collected at each visit for safety tests. If the parent/participant consented to it, about 52 ml (around 3.5 tablespoons) will be collected for biobanking. A tracking and specimen inventory system will be used to catalogue and track samples. A sample will be stored indefinitely until the sample runs out or it is destroyed. The sample collection tubes, priority and volume collected are indicated in Tables 2 and 3 below. Biobanking is an optional procedure, inability to collect blood for subjects who consented into biobanking is not considered a missed study procedure, and thus will not be filed as a Protocol Deviation.

Table 2. Details of Blood Samples Being Collected for safety labs

Collection tube, types and purpose	**Max volume (ml)**
SST (up to 2 tubes per draw)	17
EDTA (up to 2 tubes per draw)	8

Table 3. Details of Blood Samples Being Collected for biobanking

Collection tube, types and purpose	**Max volume (ml)**

SST (up to 2 tubes per draw)	17
EDTA (up to 3 tubes per draw)	30
PAXgene tube (up to 2 tubes per draw)	5

Urine samples will be collected from the participant for urinalysis and drug and pregnancy screening. A urinalysis will be completed at every in-person visit. Pregnancy tests will be repeated at each treatment visit prior to infusion. Drug testing will be repeated prior to each treatment visit if the screening results are positive. Positive urine drug screen will be reviewed by study physician and infusion will proceed as long as there is no safety risk.

An electrocardiogram (ECG) will be completed at screening as a safety measure. Sticky electrode patches will be placed on the participant's chest, which are connected to a machine that will record the electrical activity of the heart. Readings will be reviewed by a licensed physician to assess for any potential safety concerns or evidence of exclusionary conditions.

Resting electroencephalogram (EEG) will be acquired (10 minutes of resting EEG) from participants at screening, day 14 and day 84 to provide measures of functional network connectivity, so that we can determine the predictive utility of EEG-derived measures in treatment response. As it is an optional procedure, inability to collect EEG is not considered a missed study procedure, and thus will not be filed as a Protocol Deviation.

The EEG will be conducted by placing an elastic cap containing electrodes on the participant's scalp. These electrodes are previously soaked in a potassium chloride saline solution (similar to salt water) in order to better conduct electrical signals at the scalp. The technician ensures correct alignment of the cap and the quality of measured signals. This process takes approximately 10-15 minutes. The participant's brain activity is then recorded for 5 minutes as they sit quietly with their eyes open, generally fixating a marked point in front of them. This procedure is repeated for 5 minutes but with the participant's eyes closed as the rest quietly but awake. The cap is then removed, and the participant can pat dry their hair with a provided towel. The total time estimate for completion of the EEG collection at each visit is approximately 30 minutes. The EEG workgroup will ensure that adequate training, standardization of measures, and validation of equipment is maintained for data consistencies and quality control purposes.

Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly 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, and eligibility criteria.

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a modifiable factor (e.g., age and standard of care) may be rescreened. Screen failures resulting from participants taking exclusionary medications may be referred back to their primary treating clinician to determine if the exclusionary medication may be discontinued, halted, or replaced during the treatment phase of the study, and the participant may be rescreened upon subsequent eligibility.

8.2 Randomization

Participants will be randomized in a 1:1 fashion to either intravenous ketamine (0.5mg/kg) or midazolam (0.02 mg/kg) for 4 infusions during the first two weeks (days 0, 3, 7, 10) of study participation. The weight of the participant collected at baseline will be the value used when preparing drug infusion. A total dose of 60mg of ketamine or 2.4 mg of midazolam will not be exceeded, regardless of weight. If participants exceed 120 kilograms at any time during the treatment period, they will be removed from the treatment portion of the study. Randomization will use blocking with a variable block size and will be stratified by presence of a suicide attempt, as well as age group (13-14 years and 15-18 years). The randomization list will be created by the statistician using a random number generating program (SAS Proc Plan).

Each drug is dissolved in 0.9% sodium chloride in a total volume of 100 mL and administered with an infusion pump at a constant rate. Study medication will be prepared and blinded by the site's pharmacy. All participants must also be receiving standard of care treatment, which includes clinically indicated psychopharmacological and/or psychosocial interventions, for the duration of the study.

All study personnel and participants will be blinded, included those collecting, entering and analyzing all outcome data. Randomization codes are maintained by the pharmacy and the identity of study drug can be made available if needed in the rare event of an emergency. A copy of the codes will also be provided to the site's unblinded personnel who is available 24 hours per day in the event of an emergency after hours when the pharmacy is unavailable.

8.3 Treatment Visits (Days 0, 3, 7, and 10)

8.3.1 Pre-Infusion Assessment

Treatment visits will occur on days 0, 3, 7, 10 (±1 day to allow for holidays, weekends, and missed visits). Participants will be required to be fasting prior to administration of study drug. Fasting will be nil per orally (NPO) for 6 hours for light meals and 8 hours for regular meals; clear liquids will be permitted until 2 hours before the infusion to prevent dehydration. The light meals consist of meals such as coffee with milk, orange juice, other fruit juice with pulp, cereal, toast, or crackers. These visits will occur at each site's infusion center. Treatment visits will begin with pre–infusion procedures, including the following:

- Ongoing subject review
    - Urinalysis, urine pregnancy test, urine drug screen (if indicated), concomitant medication, adverse events
- Vital signs, physical examination (includes include cardiac, pulmonary, and neurologic exams)
- Assessor-, Self-, and Parent/LAR/Guardian Completed Measures
- Study Physician sign off

A urine pregnancy test will be completed prior to each treatment administration. Vitals (blood pressure, heart rate, pulse oximetry and temperature) will be assessed and must be within normal ranges prior to treatment administration. Participants will complete self-report measures, research assessor rated measures and the Implicit Association Tasks (IAT) prior to infusion (see Table 1 for assessment measures). If applicable, the parent/guardian of the participant will also complete self-report measures at this visit.

Implicit Association Test Procedures. In this study, we will utilize a version of the Implicit Association Test (IAT) that measures the association of death/suicide with self. Test users sit

individually in front of a computer screen and are prompted to respond to stimuli in the center of the screen as quickly as possible. Participants press “e” if they think the stimuli belongs in the category on the left of the screen and “I” if they think it belongs in the category on the right. Much like the Harvard Implicit Bias test, the IAT assumes that it should be easier to press the key when concepts are strongly associated verses when they are weakly associated. The IAT uses people’s reaction times when classifying stimuli to measure automatic mental associations they hold about topics such as death and suicide (26).

Specifically, the death/suicide IAT presents participants with a series of words related to death (i.e., die, dead, deceased, lifeless, and suicide) and life (i.e., *alive*, *survive*, *live*, *thrive*, and *breathing*) and asks them to classify each word between the two categories. The test also presents users with words that are self-relevant (e.g., *I*, *myself*, *my*, *mine*, and *self*) or others-focused (i.e., *they*, *them*, *their*, *theirs*, and *other*) and asks them to classify them as quickly as possible as falling into the category of “me” or “not me.” the attributes of “me” (i.e., *I*, *myself*, *my*, *mine*, and *self*) and “not me” (i.e., *they*, *them*, *their*, *theirs*, and *other*).

In the first round of the test, participants must press the same key when responding to “death” and “me.” They must press the other computer key in response to “life” and “not me.” Then, in the second round, the opposite sorting occurs, which pairs “death/not me” with the same key and “life/me” with the other key. The computer records response time for each trial and analyzes the data using the standard IAT scoring algorithm (22). Overall, higher association scores represent a faster response time when death/suicide and oneself are paired, revealing potential suicidal risk in test participants. We believe this tool will enable us to provide a behavioral marker of suicide risk based on automatic associations of self with death.

8.3.2 Study Drug Administration

Drug administration will take place in a setting capable of advanced resuscitation and to provide for life support. Each participant will be allowed to rest in a semi-recumbent position. A qualified study staff member or treating anesthesiologist will place an indwelling catheter in a peripheral vein of either arm of the participant. Heart rate, blood pressure and digital pulse-oximetry will be instituted. Oxygen by face mask or nasal cannula at 4 to 6 liters per minute will be administered as needed.

During the infusion treatment, the following will occur:

- Physiologic monitoring data will be recorded on a standard anesthesia record beginning five minutes prior to study drug administration.
- CADSS administered at approximately -5, 40, and 100 minutes to assess for dissociative symptoms.
- BPRS Psychosis administered at approximately -5, 40, and 100 minutes to assess psychosis.
- CHRT-C administered at approximately -5 and 100 minutes to assess for suicidality.

An anesthesiologist with privileges to administer ketamine to adolescents or a medical professional using ketamine and midazolam in their routine clinical practice, such as physicians who specialize in emergency medicine and critical care medicine will be present throughout the administration of study drug but will remain blinded to which treatment each participant is receiving. Each participant randomized to active treatment will receive a 40-minute slow infusion of 0.5 mg/kg of racemic ketamine hydrochloride dissolved in 0.9% saline in a total volume of 100 mL and administered with an infusion pump at a constant rate. Subjects randomized to placebo will receive 0.02 mg/kg of midazolam in 100 mL of 0.9% saline in a similar manner. The

supervising physician, study psychiatrist, study team, and participant will remain blind to treatment. The adolescent will receive standard of care continuous monitoring during infusion.

8.3.3 Post-Infusion Assessment

After the acute post-infusion period and attainment of sufficient recovery, the patient will be offered a snack and allowed to rest. At 2 hours post-infusion, the study physician will evaluate the youth for discharge readiness.

Discharge readiness will be ascertained by a licensed study physician or advanced practice provider (such as Nurse Practitioner) after at least 2 hours have elapsed since the end of the study drug infusion and will be based on clinical observations and evaluations that any study-drug related changes in mental status have resolved, and that balance is unimpaired and they are able to ambulate with steady gate, have unlabored respiration with ability to breathe deeply, and have stable heart rate and blood pressure on two occasions that are 15 minutes apart and are in the normal range). Participants will be monitored by the study team until they are ready for discharge with a responsible adult.

If stable, the participant is discharged in the care of a responsible adult. If a responsible adult is not available, transportation from the study site will be provided. Participants must agree to not drive or operate heavy machinery within 24 hours of treatment. Subsequent infusions will resemble the first infusion.

The post infusion period will include the following:

- Vital signs monitoring
- Clinician/Assessor and self-report measures to assess post treatment suicide ideation and discharge readiness

8.4 Observation (Through Day 77)

All participants will be assessed weekly (twice weekly during the first two weeks of treatments) for 12 weeks. This will allow for continued follow-up 11 weeks after the end of study drug (ketamine/midazolam treatment. Generally, assessments, as outlined in Table 1, from days 21-77 will be conducted remotely, unless the participant prefers to meet in person for the follow-up. If applicable, the parent/guardian of the participant will also complete self-report measures during this phase.

The weekly assessment will include:

- Ongoing subject review
    - Concomitant medication, adverse events
- Clinician/Assessor Rated Assessments
- Self-report Assessments

8.5 Visit 5 (Day 14) and Final Visit (Day 84)

The Day 14 and final study visit (Day 84) will be conducted in person. The following assessments, as outlined in Table 1, will be collected:

- Ongoing subject review
    - Concomitant medication, adverse events
- Clinician/Assessor Rated Assessments
- Self-report Assessments

- Clinical Laboratory Items
  - Vital signs, physical examination (includes include cardiac, pulmonary, and neurologic exams), biobanking labs (optional), EEG (optional)
- Subject completion/termination form (Day 84)

8.6 Early Withdraw/Termination Visit

An early withdrawal or termination visit will be conducted in person. The following assessments, as outlined in Table 1, will be collected:

- Ongoing subject review
  - Concomitant medication, adverse events
- Clinician/Assessor Rated Assessments
- Self-report Assessments
- Clinical Laboratory Items
  - Vital signs, urinalysis, biobanking labs (optional), EEG (optional)
- Subject termination

If a participant does not agree to an in-person visit, the following assessments will be collected remotely:

- Ongoing subject review
  - Concomitant medication, adverse events
- Clinician/Assessor Rated Assessments
- Self-report Assessments
- Subject termination

8.7 Subject Completion/Discontinuation of Study Treatment & Withdrawal from the Study

8.7.1 Completion

A subject will be considered to have completed the study if they have completed screening, 4 infusions (V1-V4) and the 2 clinical follow-up visits (V5 and V15).

Study staff does anticipate some participants will have a relapse of symptoms and will have a suicidal event. The study physician will work with the youth's clinical provider to ensure adequate treatment, which may include hospitalization, is provided. All participants will continue to receive assessments throughout the 12-week study period to obtain complete data for Aim 1 and the exploratory aim. For youths who are hospitalized or enter a residential treatment facility during the study, we will attempt to complete the research assessments remotely (via telephone for clinician rated and electronically for self-report) if feasible and will resume upon their discharge.

8.7.2 Discontinuation of Study Intervention

Discontinuation from infusion treatments (ketamine or midazolam) does not mean discontinuation from the study, and remaining study procedures will be completed as indicated by the study protocol. The study infusion will be discontinued in the event the treating anesthesiologist determines that the participant is not able to safely continue due to contraindications or side effects of the study drug. The anesthesiologist or medical professional overseeing the infusion will be prepared with peri-treatment anesthesia drugs for anticipated indications such as: dysphoria, agitation, anxiety, hallucinations, anaphylaxis, hyper/hypotension, nausea, vomiting or hypersalivation.

In addition, if during the period of infusion (Days 0 – 10) a participant has a suicidal event, and entered IOP care or in patient care, study intervention will be stopped. The participant can rejoin after being discharged but will only participate in follow-up assessments.

There may be instances where a participant has started a scheduled clinic visit in which an infusion treatment is planned, but due to treatment contraindication (e.g., blood pressure value), a decision is made to postpone/delay the infusion treatment session within the visit window permitted per protocol. In such cases, all treatment related procedures (including pre-dose) must be repeated on the rescheduled session day.

8.7.3 Participation Discontinuation/ Termination

If a clinically significant finding is identified (including, but not limited to changes from first infusion) 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 PI must apply clinical judgment to determine whether or not an adverse event is of sufficient severity to require that the participant is withdrawn from further study participation.

An investigator may discontinue or withdraw a participant from the study treatment 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

If a participant is withdrawn from the study treatment, every effort will be made to continue the participant in the study for follow-up assessments. Other reasons for terminating a participant from the study may include, but are not limited to, the participant becoming a threat to self or others, lack of funding, or early termination of the study for safety or effectiveness reasons.

8.7.4 Withdrawal of Consent

Participants are free to withdraw from the study at any time upon request. A participant may voluntarily withdraw from study participation due to what he/she perceives as an intolerable adverse event or for any other reason. Every effort will be made to ensure withdrawal of consent is not selected as a reason for discontinuation when in fact the participant withdrew for an identifiable reason.

Participants who wish to withdraw from the study will be asked if they are agreeable to be contacted for further follow-up (e.g., early withdrawal visit, adverse event follow-up). Subjects who are not agreeable to follow-up contact will be withdrawn from the study as “withdrawal of consent”.

Adolescents will be encouraged to continue with the follow-up assessments even if they have withdrawn from the treatment phase. However, if they choose to withdraw from all aspects of the study, they will be asked to return for a final assessment. If the participant would like to also

withdraw their data from being used, they are informed of their right to make this request during the consenting process.

The reason for participant discontinuation or withdrawal from the study will be recorded on the electronic Case Report Form (CRF). In addition, female participants who become pregnant during the study treatment period will be withdrawn from study treatments but will continue to be followed for the assessment period.

8.7.5 Lost to Follow Up

A participant will be considered lost to follow-up if they fail to return for visits and are unable to be contacted by the study site staff.

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

- The site will attempt to contact the participant and reschedule the missed visit within the permitted window per protocol 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. If unable to return within the window, the visit will be marked as missed and the next visit per protocol will be conducted.
- 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 attempts (telephone calls, email, and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8.8 Participant Compensation

Participants are compensated for a rate of $100 for the four infusion treatment visits, $75 for the longer assessment days (days 14 and 84), and $25 for all other follow-up visits. A total of $775.00 is not coercive in our view since it compensates individuals for their time (2-3 hours during infusions, and weekly visits).

9.0 STATISTICAL ANALYSES

Given the challenges of enrollment, the study will now plan to enroll N=114 individuals. Therefore, the statistical analysis has been updated to reflect this sample size.

Aim 1. Evaluate reduction in frequency of suicidal events associated with two-week twice-weekly course of ketamine treatment versus midazolam. We hypothesize that treatment with ketamine will result in markedly fewer participants experiencing repeat suicidal events as compared to midazolam over a 12-week observation period. With n = 57 in each arm (N = 114 total), the study provides 36% power to detect a 50% reduction in suicidal event rates in the ketamine arm relative to the midazolam arm (30% event rate in midazolam versus 15% event rate is ketamine arm) reduction in proportion of participants having suicidal events over a 12-week observation period assuming 10% attrition.

Aim 2. Evaluate reduction in implicit suicidal cognition with ketamine. Building on previous work (29) demonstrating significant reductions in IAT with ketamine in adults, we hypothesize that youths with recent suicidality will have significantly greater reduction in IAT with ketamine as compared to midazolam at the end of acute-course treatment (day 14). With n = 57 in each arm (N = 114 total), the study will have 75% power to detect a medium effect size (0.5) between the two study arms.

Aim 3. Evaluate reduction in depressive symptoms and suicidality with ketamine. We hypothesize that ketamine will be associated with greater reduction in depressive symptoms and suicidality than midazolam at the end of acute-course treatment (day 14). With n = 57 in each arm (N = 114 total), the study will have 65% power to detect a medium effect size (0.5) between the two study arms.

Sample Size and Power Analysis:

Power for Aim 1: Sample size was determined to adequately power the study to assess difference in rates of recurrent suicidal events between the two arms (ketamine versus midazolam) over the 12 weeks. In unpublished clinical data from SPARC IOP program, we observed a suicidal event rate of 31% (214 events in 691 participants) over an observation period 6-8 weeks. We hypothesized at least a 50% reduction in suicidal event rates in the ketamine arm relative to the control arm during this observation period (15% event rate in ketamine vs. 30% event rate in midazolam). Given a sample size of 114 (or 57 per group), alpha of 0.05, and 10% attrition, we will have 36% power to detect a 50% reduction in event rates.

Power for Aim 2: The hypothesis in aim 2 involves reduction in IAT from that at screening over the 2-weeks treatment period. We hypothesized that the subjects in the ketamine arm will have a greater reduction in IAT scores compared to those randomized to midazolam. With 57 subjects in each arm (N = 114 total), the study will have 75% power to detect a medium effect size (Cohen's d = 0.50) in change scores over the 2-weeks treatment period using a two-sample t-test. We do not expect any attrition during the first 2-weeks treatment period, as we will continue to conduct assessments during the first two weeks even if participants withdraw from the ketamine/midazolam treatment. Type 1 error rate was set at 0.05.

Power for Aim 3: The hypotheses in aim 3 involve reduction in depression severity (measured by IDS-SR) and suicidal thoughts (measured by CHRT-SR suicidal thoughts subscale) over the two weeks of treatment period. We hypothesized that the subjects in the ketamine arm will have a greater reduction in IDS-SR and CHRT suicidal thoughts scores compared to those randomized to midazolam. Using Bonferroni method, each of these hypotheses will be tested at 0.025 alpha-level. With 57 subjects in each arm (N = 114 total), the study will have 65% power to detect a medium effect size (Cohen's d = 0.5) in change scores over the 2-week treatment period using two-sample t-tests. As in aim 2, we do not expect any attrition during the 2-weeks treatment period.

Data Analyses and expected outcomes: Using a modified intention-to-treat principle, we will include all randomized subjects with at least one blinded treatment dose in the analyses. All models will be checked for validity of assumptions for continuous outcomes and appropriate transformations will be considered in case of gross violations were indicated. Aim 1 hypothesis will be tested using a survival analysis where Kaplan-Meier survival curves for each group will be compared by log-rank test. Time to first event will be measured from first day in study to day of first day on which one of the following occurs: completed suicide, suicide attempt, ED visit, or inpatient hospitalization. Time to event will be censored on the last day in study if no event has occurred. In addition, to assess the effect of varying standard of care treatments, a Cox proportional hazards regression analysis will be used. This analysis is comparable to the survival curve analysis but allows for the inclusion of covariates based on the type of care that the participant is receiving (e.g., cognitive therapy). Study hypotheses in aims 2 and 3 will be assessed using a mixed-effects linear model. The planned mixed model analysis will be a growth curve analysis (see for example, Singer (1998), page 348). Using SAS Proc Mixed, time will be specified as a continuous variable in the model statement and as a categorical variable in the repeated statement. Subjects are a random sample from a population, so a random intercept will be included in the random statement. All other effects will be fixed. There will be one between subjects effect (treatment arms: ketamine versus midazolam), one within subject effect (observation time: days 0, 3, 7, 10 and 14), and their interaction term in the model. An unstructured covariance matrix will be used. The hypotheses will be tested using t-tests for appropriate contrasts to compare the change scores of the relevant outcome measures between the two treatment arms. Use of mixed linear model above will allow more precise estimate of the variability of the corresponding outcome and thus provide greater power for the t-tests used to test the study hypotheses. Type 1 error rate for hypotheses in aims 1 and 2 will be set at 0.05 while that for each of the hypotheses in aim 3 will be set at 0.025. All analyses will be done using SAS version 9.4 (SAS Inc., Cary, NC).

Safety and Tolerability: The proportion experiencing a SAE at any point during the 12-week study period (the primary safety outcome), the maximum SMURF global assessment of side effects at any point during the 12-week study period, the maximal frequency, intensity, and burden of side effects at any visit will be compared between groups using Chi-square tests. A binary outcome (any side effect at any visit vs. none) will be created for each participant for each type of side effect reported and compared between groups using Chi-square. The mean number of worsening symptoms will be compared between groups using ANOVA or Kruskal-Wallace test, as appropriate. Similarly, the CADSS and DESS will be examined for safety during the two-week infusion period.

Exploratory Analyses: For the exploratory aim of whether reduction in IAT mediates the improvement in suicidality, we will compute the rate of IAT change over the first 2 weeks, a scalar value to summarize an individual's outcome using a mixed effects model with random subject's slope and intercept estimated separately for each treatment arm. As detailed by Petkova et al., the outcome was a sum of the main effect of time plus the estimated subject-specific random time slope (57). These slopes represent the change in severity over one week (i.e., rate of change in IAT points per week). As the goal of treatment is a reduction in IAT, *a negative slope indicates improvement*. We'll then evaluate these slope estimates as a mediator in two ways: a) a logistic regression analysis with presence of suicide events over 3-12 weeks as the outcome and the estimated rate of change in IAT, treatment arms, their interaction as independent variables; and b) a mixed linear model with $CHRT_{16}$ suicidal thoughts over 3-12 weeks as the outcome and treatment arms (ketamine versus midazolam), time (weeks: 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12), treatment arm by time interaction, main effect of rate of change in IAT, and the interaction of the IAT slope with time in the model and the intersection of IAT slope with treatment arm. $CHRT_{16}$ suicidal thoughts score at week 2 and IDS-SR scores at week 2 will be included as covariates.

The intercept will be random, and all other effects will be fixed. In both approaches, we'll test the mediation effect of early change in IAT measured by the slope-estimates by testing the interaction between the IAT slope with time.

Anticipated findings: We expect fewer participants in ketamine arm will experience a repeat suicidal event over the 12-week observation period as compared those randomized to midazolam. In particular, we expect a 50% lower rate in proportion of participants who experience a suicidal event among subjects in ketamine arm. We also expect to see a reduction in IAT scores as well as CHRT suicidal thoughts and depression severity measured by IDS-SR among all subjects in both treatment groups. However, we anticipate a greater reduction in all three outcomes (IAT, IDS-SR, and $CHRT_{16}$ suicidal thoughts) among subjects in the ketamine arm compared to those randomized to midazolam arm. Finally, we expect no significant difference between the treatment arms in terms of safety and tolerability measured by SMURF and CADSS.

Handling of missing data: To assess the degree to which missing data may be affecting the estimated treatment effects, we will compare screening clinical and demographic variables between participants who provide only initial treatment visit data and are not used in the mixed-effects models and participants with some initial treatment visit data who are used in the mixed-effects models. Standard multiple imputation procedures may be used to deal with missing data, as appropriate. Multiple datasets (e.g., 10 datasets) will be generated using SAS Proc MI, and the mixed-effects models will be fit using each dataset; then the results will be combined using standard formulas for combining results. If the missing data can be predicted from the variables included in the model then the data are missing at random [using the nomenclature of Little and Rubin (58) and the MMRM will provide unbiased estimates without resorting to multiple imputation (59). However, if the probability of dropout depends on variables which are not included in the model then the model estimates could be biased. Use of multiple imputation will include more variables (including reason for dropout) in the prediction of missing data and will increase the likelihood of the missing data being missing at random. We will perform diagnostics to determine the effectiveness of the multiple imputation (60). In case the missingness is still not missing at random even after multiple imputation, we will perform sensitivity analyses (e.g., pattern mixture models (61), local influence models (62) to determine how different types of missingness will affect the results (58, 59-61).

10.0 REGULATORY COMPLIANCE, REPORTING AND MONITORING

10.1 Statement of Compliance

This study will be conducted in compliance with the current version of the study protocol, in accordance with the ethical principles outlined in the Declaration of Helsinki, consistent with current International Conference on Harmonization Good Clinical Practice (GCP) Guidelines, and all other applicable regulatory requirements.

10.2 Institutional Review Board Approval

Before study initiation, the investigators must have written and dated approval from the UT Southwestern IRB for the protocol, consent form, patient recruitment materials/process (e.g., advertisements). Any amendments to the protocol or consent must be approved by the UT Southwestern Medical Center IRB before implementation. Progress reports, and any required post-approval reports will be submitted to the IRB at a frequency requested by the IRB so that continuous study approval is maintained without lapse.

10.3 Informed Consent

All potential participants for the study will be given a current IRB-approved consent and/or assent form in English to read. Parents/LAR/guardians will have the option to consent in English or Spanish. There are 3 separate consent/assent forms in this study: a consent document for participants who are 18 years of age, an assent document for participants ages 13-17, and a parent permission document to be completed by parent/LAR/guardian of minors. In accordance with IRB policies, appropriately trained and qualified study personnel will explain all aspects of the study in lay language and answer all the study potential participant's questions. The assenting process for minors will occur separately from their parent/guardian/LAR to ensure maximum comprehension of the research procedures, allow a comfortable place to ask questions, reduce undue influence from the parent and obtain affirmative agreement to participate in this research. Participants who remain interested after receiving an explanation of the study will be asked follow-up questions to assess their understanding of the project including the purpose, procedures involved, and the voluntary nature of participation. Those who cannot successfully answer all questions will have the study re-explained by research staff with a focus on aspects they did not understand. Anyone who cannot demonstrate appropriate understanding of the study will be ineligible to participate and will be assisted in finding other treatment resources. Potential participants who demonstrate understanding of the study and who voluntarily agree to participate will be asked to sign the IRB-approved ICF and/or assent that is appropriate for their age group. Upon confirming signed informed consent/assent study registration will occur. Participants will not be administered any assessments or participate in study procedures in any way prior to signing and dating the IRB-approved consent and/or assent forms.

The study team must maintain the original signed IRB-approved consent/assent forms for all study participants in a locked, secure location that is in compliance with IRB and institutional policies. Signed/dated IRB-approved consent/assent forms must be accessible for quality assurance review and regulatory compliance at all times. Every study participant will be provided with a copy of the signed/dated consent and/or assent form that can be used as continual reference for study information including procedures, possible risks and/or side effects, and contact information for questions and/or emergencies. Documentation of informed consent/assent will be described in the note section of the consent and/or assent form in the EDC.

All underage participants will be flagged in the Electronic Data Capture System (EDC) to ease the process of identifying those who are turning 18. The study team will be responsible for re-consenting all participants turning 18. Attempts at re-consent will include phone, email, and mail contact when needed. Re-consenting attempts and process will be documented in a Note to File and filed in the EDC and participant binder.

Subjects who decline future contact by the research teams must be logged and tracked by the Study Team.

For participants who may live outside of the region of the study site, screening procedures may be conducted remotely to confirm eligibility. In these cases, remote consenting and/or assenting will be utilized whereby participants will be sent the ICF via DocuSign. A virtual Telehealth appointment will be scheduled where appropriately trained staff will complete all of the Informed Consent and/or Assent procedures as detailed above remotely. Remote consenting/assenting procedures will be documented within the participant's chart.

10.3.1 Potential Risks and Benefits

Potential Risks of the Proposed Research to the Subject and Others

Risks from the research. The investigators have designed this study to learn how well the new treatment(s) compare to commonly accepted treatment(s). There is a risk that the effectiveness and/or safety of the treatment for both the ketamine or midazolam group may not be as good as the most commonly accepted treatments. Participants may get a treatment or drug that does not help treat their disease or that makes their condition or disease worse.

Risks from the specific study treatment. There are risks to taking part in this research study. One risk is that participants may have side effects while on the study. Side effects from this study will usually go away soon after participants stop taking the study interventions. In some cases, side effects can be long lasting or may never go away.

Everyone taking part in the study will be watched carefully for any side effects. However, the study doctors don't know all the side effects that may happen. Participants will be instructed to tell the study staff immediately, about any side effect that they have while taking part in the study.

Side effects can range from mild to serious. Serious side effects are those that may require hospitalization, are life threatening or fatal (could cause death). The frequency that people experience a certain side effect can range from many (likely), few (less likely) or only one or two (rarely). There may be unforeseeable side effects that could be life threatening or fatal (could cause death).

The research team will tell participants about any significant new findings which develop during the course of this research which may relate to their willingness to continue taking part.

Risks from Assessment/interview. While we have made every effort to reduce respondent burden, the initial assessment, which will include a research diagnostic interview, requires approximately 4 hours, and may bring up upsetting issues. Follow-up assessments are much shorter, requiring 30-60 minutes to complete. If child abuse is detected at any point during the study, the research team is obligated to follow mandatory state reporting laws.

Risks from Ketamine/Midazolam treatment. Ketamine is generally well tolerated. The most

common adverse events (AEs) associated with treatment are drowsiness, dizziness, blurred vision, poor coordination, and unusual feelings, headache, nausea, diarrhea, anxiety, dyspepsia, and abdominal pain. In addition, while less common, ketamine has been associated with transient neuropsychiatric AEs, including dissociative symptoms. Another possible side effect is ketamine-induced cystitis, which is inflammation of the bladder. High amounts of ketamine given to rats caused damage to different parts of the brain. It is not known whether this finding in rats will happen in humans. The amount of ketamine given to the rats was higher than what will be used in this study. In addition, the added effect of repeated ketamine infusions is unknown. Chronic ketamine users (mostly ketamine abusers) have structural and functional brain changes with associated cognitive problems. We are uncertain if this will occur at the frequency and duration proposed in this study. The most common AEs reported with midazolam infusions are hiccoughs, nausea, vomiting, coughing, headache, and drowsiness. Higher doses of midazolam may lead to more serious cardiorespiratory AEs, although the doses in the proposed study are much lower, and not expected to lead to serious AEs.

Use of ketamine and midazolam may be associated with the risk of misuse or dependence. Survey studies of youths in the United States estimate that less than 2% of youths misuse drugs that are similar to either ketamine or midazolam. If misused on a regular basis, suddenly stopping either ketamine or midazolam may be associated with symptoms of withdrawal such as excessive anxiety, shaking, and sweating. The use of ketamine or midazolam as planned in this study (twice a week for two weeks) has not been associated with symptoms of withdrawal.

Risks from Blood Draw and IV site tenderness. The risks involved in drawing blood from a vein may include, but are not limited to, momentary discomfort at the site of the blood draw, possible bruising, redness, and swelling around the site, bleeding at the site, feeling of lightheadedness when the blood is drawn, and rarely, an infection at the site of the blood draw. IV site tenderness may include pain during the injection, and tenderness, redness or swelling.

Risks from EEG. The risk of EEG includes discomfort from wearing a close-fitting elastic cap and the use of an electrolyte solution.

Risks from ECG: There is generally no risk with having an ECG. The sticky patches may pull on participant's skin or cause redness or itching.

Risks of Suicidal behavior. As all participants will have current suicidal ideation or have made a recent suicide attempt, ongoing suicidal ideation and behaviors is a risk throughout the study period.

Risks of Unimproved or worsening of psychiatric illness. Continued or worsening of the underlying psychiatric illness (e.g. depression, anxiety, etc.) is always a risk, even for those treated with medication and/or psychotherapy. Similarly, there are risks associated with specific treatments for these disorders, including risks of development of mania or behavioral activation, worsening of suicidal thoughts, etc. that are associated with antidepressant treatment. While these treatments are not specific to the proposed intervention, it is important for the study team, adolescents, and their families to be aware of the potential adverse events associated not only with the underlying illness, but with the treatments, as well.

Risks of Oxygen Use. Oxygen by face mask or nasal cannula at 4 to 6 liters per minute will be administered as needed. Some people may experience claustrophobia or discomfort wearing the oxygen mask or nasal cannula.

Risks of Loss of Confidentiality. The potential for a breach in confidentiality always exists,

specifically with the written research data and study databases. However, information that is obtained will be stored in locked file drawers in locked offices; data will have identifying information sheered from it to prevent loss of confidentiality.

Risks to Sperm, Embryo, Fetus or Breast-fed Infant. The effects of the study drug on fertility, the human embryo, the fetus, or the breast-fed infant are unknown.

Risk associated with genetic information. Releasing genetic information to participants could cause psychological distress, anxiety or family problems. Releasing this information to others, such as including it in your medical record, may pose a possible risk of discrimination, or increase difficulty in obtaining or maintaining disability, long-term care, or life insurance.

These risks would occur if your information is released by mistake. The measures being taken to protect your privacy are discussed below and make this possibility unlikely.

Even though the results of genetic testing may not be linked to a participant, it is possible that people of similar ethnic background may be found to be at more risk for certain diseases based on future genetic treatment and this information might harm a participant in the future as a member of the group. Also, there may be unknown risks of genetic testing in the future.

Potential Benefits of the Proposed Research to the Subjects and Others

Potential Benefits to Subjects. The benefits of participation include having a careful assessment of suicidal risk for twelve weeks. Such monitoring, which is above and beyond than would be ordinarily available in the community. The PI will be on call to help the interviewers and clinicians deal with any potential clinical emergencies that emerge either during the relatively brief intervention or during follow-up assessments. Participants may experience improvement in suicidality and/or their underlying psychiatric illness, regardless of treatment assignment. In addition, subjects may derive a sense of accomplishment from participation and research and contributing to the knowledge of treatment for youth with suicide attempts and suicidal ideation.

Potential Benefits to Others. Potential benefits to society may be considerable. This study will provide information about a high-intensity, brief psychopharmacological intervention to prevent future suicide attempts, which could help inform future acute treatment strategies for adolescents with suicidality. Given the careful assessment and monitoring for safety and tolerability, and the potential benefits to youth with suicidality, we believe that this study has a favorable risk to benefit ratio.

10.3.2 Planned Procedures for Protecting Against or Minimizing Risks

First and foremost, protection against risk will begin with careful clinical management and education of patients and families. As mentioned, informed consent will be obtained at the enrollment visit, and will include specific details of all risks, including consequences of psychiatric illnesses and suicidal behaviors.

Minimizing risk of research. The investigators will thoroughly explain to participants that this is a voluntary research trial and that there are other commonly accepted treatments for suicidal behaviors.

Minimizing risk of specific study treatment. A common risk of participating in a clinical trial is the rise of side effects. Study staff will follow-up with participants at each study visit about any

side effects they may be experiencing. Additionally, participants will be instructed to inform both the study staff and their medical provider of any side effects they experience during the study.

Minimizing risk due to assessment/interview. The risks due to interview are three-fold—discussion of potentially upsetting information, loss of confidentiality, and assessment burden. The interviewers will all be trained and skilled interviewers who can assess and monitor the reaction to questioning about sensitive topics; interviewees will be given the option to take a short break or end the interview at any time. The assessment has been streamlined to limit assessment burden. The initial screening interviews should take around 2-4 hours, and follow-up assessments of 30 minutes to 1 hour. Every effort will be made to schedule treatment visits and assessments at times that are suitable for participant and families (after school or after work) as needed in order to minimize negative impact on other important work, school, or social activities.

Another potential risk of assessment is the disclosure of abuse. We are very familiar with the assessment, management, and reporting of child maltreatment as this is considered part of standard clinical care in pediatric psychiatry. These incidents are common during clinical trials, and we have standards for both managing and reporting these incidents that are detailed below. In all cases, state law is followed.

Standard Procedures for Clinical Management of Child Maltreatment
Prior to any clinical interview confidentiality is discussed with the patient and family during the consent process. This includes state guidelines for reporting abuse. (1) Report of abuse by patient/family during diagnostic interview and evaluation assessment: The interviewer obtains additional information to determine whether abuse is in the past, or current and ongoing. This is reported to the PI within 48 hours. The child protective service agency is contacted, and a report is filed. In the event that it is not clear whether the incident is reportable, the service agency is contacted, and the event is discussed to ensure that our program is following the correct state guidelines. (2) Report of abuse by patient/family during the intervention. If abuse is disclosed, the clinician talks with the patient and family about the treatment team's legal responsibility to report the incident. Often the family is offered the opportunity to be present when the report is filed, to minimize the likelihood for miscommunication. The child protective service agency is contacted, and a report is filed. The PI is told of the report and the clinician's assessment of the subsequent impact of the disclosure on the patient and family. (3) All reports to the child protective service agency are documented in the patient's record. Any follow up correspondence received from the agency is also placed in the file.

Minimizing risk of Ketamine/Midazolam treatment. Medical staff will be monitoring vitals during the infusion and will be prepared to treat increases in blood pressure greater than 160/100 mm Hg or heart rate greater than 120 bpm. If these elevations resolve spontaneously within a short time period, they will generally not be treated. The anesthesiologist or medical staff overseeing the infusion will be prepared with peri-treatment anesthesia drugs for anticipated indications such as: dysphoria, agitation, anxiety, hallucinations, anaphylaxis, hyper/hypotension, nausea, vomiting or hypersalivation After the acute post-infusion period and attainment of sufficient recovery, the patient is given a snack and allowed to rest. At 2 hours post-infusion, the study physician will evaluate the teen for discharge readiness. If stable, the participant is discharged in the care of a responsible adult.

Minimizing risks of blood Draw/IV site tenderness. Staff at each site's infusion center will have extensive experience in a variety of medical procedures. To ensure patient safety, participants will be allowed to rest in a semi-recumbent position. A qualified study staff member or treating anesthesiologist will place an indwelling catheter in a peripheral vein of either arm of the participant, and a trained phlebotomist will perform all blood draws.

Minimizing risks from EEG and ECG. Participants will be informed of the test procedures prior to when study staff begins testing. Study staff that will be performing EEG and ECG testing have extensive experience and will adjust/arrange equipment to properly fit the participant and will provide cleansing materials to remove any residue left behind from the electrodes or elastic cap.

Minimizing risk of suicidal behaviors. By definition, since we are recruiting participants at high risk for suicidal behavior, the biggest risk for these participants is their risk for suicidal ideation, behavior, or even completed suicide. However, there is nothing that is being done in this study that would further increase risk. There is now clear evidence that asking about suicidal ideation and behavior will not increase the risk for such behavior (66). In addition, through repeated assessments of psychopathology, suicidal ideation, and behavior, we provide an additional safety net for the participants and their families beyond that which would occur in clinical care. There are several possible scenarios in which suicidal ideation/intent is detected. First, it could be detected in research visits during the course of treatment in IOP or other clinical setting. We will get permission to provide this information to the medical provider designated by the participant as part of informed consent, but prior to sharing this information with the provider, we will still review this information with the patient and family. This would also include clinically relevant information that might not have been obtained by the provider, namely alcohol/substance abuse, psychosis, or other clinical issues that would place the patient at risk for suicidal behavior.

The participant could disclose suicidal ideation/intent during the research study, but after discharge from an IOP, prior to initiation of outpatient treatment. Under those circumstances, our team would be clinically responsible to assist the family in getting the teen to the appropriate care. In this case, we would assess for suicidal risk, the ability to adhere to a safety plan, and confer with parents and the study physician as to whether or not the patient was safe to continue at the current level of care. The family will be encouraged to contact the adolescent's provider for additional treatment options.

If upon follow-up, participants are not in treatment and we identify serious psychopathology and/or suicidal risk, we will provide referral information to the participant and parents. If at any of these points, we perceive that the patient is in imminent suicidal risk and the parent or patient are not willing to address this issue, then we will contact emergency mental health services to initiate a commitment. In specific, adolescents will be evaluated to assess suicidal ideation and behaviors, as well as specific psychiatric illnesses, and may be given recommendations for additional treatment options should concerns arise during the evaluation. Finally, if there are concerns about continued suicidal behaviors, or other mental health concerns relevant to the participant's outpatient aftercare, the study team will obtain permission to contact the adolescent's community provider to inform him/her of concerns.

Subjects who are at risk of suicide attempts may need to be psychiatrically hospitalized, and this may occur at any time during the course of the study. We follow the procedures of the AACAP Practice Parameters on Suicidal Behavior. These parameters indicate that subjects should be referred for hospitalization if their condition is unstable—as manifested by, suicidal ideation with inability to contract for safety, psychosis, current intoxication, mania, rapid cycling, or mixed state. Social factors that may cause the clinician to consider hospitalization include lack of sufficient environmental support and structure to guarantee the child's safety. If the participant is still enrolled in an IOP program, we will refer them to their IOP providers; if the participant is under the care of an outpatient clinician, and it is the clinical opinion of the study team that an emergency evaluation or referral for hospitalization is indicated, then with permission, the study team will consult with the treating clinician(s) to discuss a plan of action. Again, if the study psychiatrist perceives imminent risk and the outpatient clinician cannot be reached, then the psychiatrist, in

consultation with the PI must act in the best interests of the participant and recommend an emergency evaluation and/or hospitalization.

Minimizing risk of unimproved or worsening of psychiatric illness. The risk of lack of improvement or worsening of suicidality or psychiatric illness will be addressed by monitoring subjects closely during follow-up visits. Some youth will encounter crises. Most crisis management involves a combination of case management and creative problem solving, which can be accomplished within the framework of the existing treatment with the community clinician. However, in some cases, participants may be non-adherent to treatment. In these cases, the study coordinator and/or evaluator will assist the family in re-entering treatment or locating alternative providers. Adverse effects of psychiatric treatments are also a risk. Participants will be encouraged to contact their community provider with any concerns reported to the study team during assessments or when paged. In cases of severe adverse effects, patients may be instructed to go to the nearest emergency department.

Minimizing risk of Oxygen Use: The site's staff are very familiar with providing oxygen to patients and will implement standard protocols related to oxygen use.

Minimizing risk of loss of confidentiality. Study procedures have been designed to protect the privacy and confidentiality of the research subjects. Throughout the study, all data will only be identified by a unique identification number and subject code using letters and numbers to protect against invasion of privacy. The data will be blinded correspondingly in all data analyses. Only authorized staff will have access to patient information. All study information containing identifying information will be stored separately from the study data and will be stored in a locked filing cabinet.
On the other hand, we notify the patient at the beginning of the study that if we detect information that could indicate that a participant's life or health is in danger, we will need to bring their parents into the discussion. We also tell parents, as well as patients, that if we learn of possible abusive behavior, that we must follow local and state reporting laws. Under Texas Privacy Laws, unless an exception applies (e.g., adolescent would be in danger), the study team is required to disclose results of pregnancy and drug screen testing to parent/LAR/guardian.

Minimizing risk to sperm, embryo, fetus or breast-fed Infant. The effects of the study drug on fertility, the human embryo, the fetus, or the breast-fed infant are unknown. Participants will be made aware of this information during the consenting processes. Female participants of childbearing age will be asked to agree to pregnancy testing at screening and prior to each treatment visit. Male participants will also be asked to disclose to study staff if they impregnate their partner during the study. In addition to this, a criterion for entry into the study is the use of an effective method of contraception during and for 90 days beyond the end of treatment. Recommended methods of birth control are namely, consistent use of an approved hormonal birth control (pill/patches, rings), an intrauterine device (IUD), contraceptive injection, double barrier methods, sexual abstinence, or sterilization.

Minimizing risk associated with genetic information. To protect your privacy, study samples will be labeled with study identifier and participant number. No personal identifiers are used (such as name, initials, social security number). Samples may also be shared with research partners for scientific research purposes. Samples will not be sold, loaned or given to any other independent groups for their own use. Research partners working with the investigators are not allowed to share samples with anyone who is not authorized by the sponsor, investigators, or UT Southwestern.

10.4 Unblinding

The investigator, patient, and majority of study staff will be blinded. Packaging and labeling of the study drugs will be performed by the pharmacy in a way to ensure blinding throughout the study. No members of the study team will have access to the randomization scheme during the conduct of the study. The pharmacists and the unblinded study personnel will have access to the treatment assignment for the purposes of preparing study drug (pharmacists only), data monitoring, and in the event of an emergency. The treatment code must not be broken except in medical emergencies when the appropriate management of the patient necessitates knowledge of the treatment randomization. The investigator retains the right to break the code for serious adverse events (SAEs) that are unexpected and are suspected to be causally related to a study drug and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

10.5 Health Insurance Portability Accountability Act (HIPAA)

Research personnel are required to obtain authorization from participants for use of protected health information. Releases of participant identifying information that are permitted by the HIPAA regulations, but which are prohibited by other applicable federal regulations and/or state/Commonwealth laws and regulations, are prohibited.

10.6 Financial Disclosure

All investigators will comply with the requirements of 42 CFR Part 50, Subpart F to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial interest. All study personnel with decision-making responsibilities regarding the protocol must comply with their institution's policy regarding conflict of interest.

10.7 Confidentiality

Confidentiality will be maintained in accordance with all applicable federal regulations and/or state law and regulations. Particular attention is drawn to the regulations promulgated by the Food and Drug Administration (FDA) under the Freedom of Information Act providing, in part, that proprietary information furnished to investigators and Institutional Review Boards will be kept confidential by the FDA only if maintained in confidence by the clinical investigator and Institutional Review Board (IRB). By signing the protocol signature page, the investigator affirms that information will be maintained in confidence and such information will be divulged to the IRB, Ethical Review Committee, or similar expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees.

Participant records will be kept confidential by using study codes for identifying participants on CRFs, secure separate storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data. All eCRFs, reports, and other data records will be identified by the participant identification number. Research records will be stored in a locked cabinet. Only authorized individuals will have access to the study records. Participant information will not be released without written permission, except as necessary for monitoring, IRB, or other compliance overseeing committee.

10.8 Regulatory Files

Essential documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the Research Team with the standards of Good Clinical Practice and with all applicable regulatory requirements. Regulatory files should be maintained throughout the lifecycle of the trial and should contain all required regulatory documents, study-specific documents, and all important study-related communications. Regulatory files will be checked for regulatory document compliance prior to study initiation, throughout the study, as well as at study closure.

10.9 Study Documentation

Study documentation includes, but is not limited to, all data-related forms, workbooks, source documents, monitoring logs, correspondence, signed protocols including amendments, Institutional Review Board correspondence, approved current and previous consent forms, and signed participant consent forms. Source documents include all recordings of observations or notations of research activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. All research information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification. The original recording of an observation should be retained as the source document.

10.10 Records Retention and Requirements

Research records for all study participants (e.g., case report forms, source documents, signed consent forms, and regulatory files) are to be maintained by the investigator in a secure location for a minimum of 3 years after the study is completed and closed. These records are also to be maintained in compliance with IRB, state and federal requirements, whichever is longest.

10.11 Safety Monitoring

The National Institute of Mental Health will oversee the protection of the rights and welfare of participants in funded research. For this study, it will be the responsibility of the study team to report the following occurrences to the NIMH:

- Adverse Events (AEs);
- Serious Adverse Events (SAEs);
- Unanticipated Problems Involving Risks to Subjects or Others;
- Protocol violations; non-compliance (serious or continuing); suspensions or terminations by monitoring entities (e.g., Institutional Review Board (IRB), Independent Safety Monitor (ISM);
- Suspensions or terminations by regulatory agencies (e.g., Office for Human Research Protections (OHRP) or the Food and Drug Administration (FDA))

See Appendix B for details of NIMH Reportable Events Policy.

10.11.1 Adverse Events (AEs)

Collection of AEs will begin at time of informed consent signatures and will continue throughout study participation. See Appendix A for more details.

10.11.2 Serious Adverse Events (SAEs)

For the purpose of this study, all SAEs will be collected and recorded in the EDC. See Appendix A for more details.

10.11.3 Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs)

All unanticipated problems will be assessed in the EDC for unexpectedness, relatedness, and risk of harm. All UPIRSOs meeting criteria will be reported to the IRB and NIMH as a reportable event.

10.12 Noncompliance

Noncompliance is any failure to follow:

- Applicable federal regulations, state and local laws, or institutional policies governing human subjects' protections, or
- The requirements or determinations of the IRB, including the requirements of the approved investigational plan (e.g., protocol, Smartform, ICD)
- Noncompliance can result from performing an act that violates these requirements or failing to act when required

Types of noncompliance:

Exceptions (also called single-subject exceptions or single-subject waivers) include any changes to the IRB-approved investigational plan that is not due to an emergency and is:

- intentional on part of the investigator;
- in the investigator's control;
- not intended as a systemic change (e.g., single-subject exceptions to eligibility [inclusion/exclusion] criteria);
- in rare instances, intended as a systemic change, but the change has not yet been IRB-approved
- Exceptions require prospective IRB approval before being implemented

Emergency deviations include any changes to the IRB-approved investigational plan that is necessary to:

- avoid immediate apparent harm, or
- protect the life or physical well-being of subjects or others
- Emergency deviations are reportable within 5 working days of occurrence

Serious noncompliance includes any noncompliance that:

- increases risk of harm to subjects; and/or
- adversely affects the rights, safety, or welfare of subjects (any of which may also be an unanticipated problem); and/or adversely affects the integrity of the data and research (i.e., substantially compromises the integrity, reliability, or validity of the research)
- reportable within 5 working days of occurrence

Continuing noncompliance includes:

- A pattern of repeated noncompliance (in one or more protocols simultaneously or over a period of time) which continues after initial discovery, including inadequate efforts to take or implement corrective or preventive actions within a reasonable timeframe, which may or may not also constitute Serious Noncompliance.

- Reportable within 5 working days of discovery

Noncompliance that is neither serious nor continuing includes:

- Events, incidents, outcomes, etc. that do not meet the definitions of either serious noncompliance or continuing noncompliance.
- Should be tracked and summarized in a progress report at next continuing review or notice of study closure, whichever comes first.

10.13 Protocol Deviations: Reporting and Management

All protocol deviations will be collected and assessed. Protocol deviations will be monitored for (1) significance, (2) frequency, and (3) impact on the study objectives, to ensure the integrity of the trial. The decision about whether a deviation from the protocol will be designated as minor or major will be made by local research staff and reviewed by the PI or designee.

All protocol deviations will be recorded in the Electronic Data Capture (EDC) system via the Protocol Deviation CRF.

All protocol deviations will be assessed for meeting UPIRSO criteria. All deviations meeting UPIRSO criteria (refer to Appendix A for criteria) will be entered into the EDC within 24 hours of discovery and reported to the IRB within 5 business days.

10.13.1 Protocol Deviation Reporting Guidelines

	Major Protocol Deviation	**Minor Protocol Deviation**
This list of examples is intended as a guide and is not all-inclusive.		
Definition	A deviation that **may:** • Impact subject safety, • Affect the integrity of study data, and/ or • Affect the subject's willingness to participate in the study.	A deviation that **does not:** • Impact subject safety, • Compromise the integrity of study data, and/ or • Affect the subject's willingness to participate in the study.
Examples *(not all-inclusive)*	• Failure to obtain informed consent • Informed consent obtained by an unauthorized individual • Enrollment of a subject who did not meet eligibility criteria for whom a protocol exception was not obtained • Performing a study procedure that is not approved by the IRB and/or is not in the protocol • Failure to perform or follow a study procedure that, in the opinion of the Investigator, may affect subject safety or data integrity • Failure to follow safety (AE) management plan	• Implementation of unapproved recruitment procedures • Only a photocopy of the signed/ dated consent form is available (the original is missing) • Pages are missing from the signed/ dated informed consent form • Use of invalid consent form (i.e., without IRB approval or outdated/expired form) • Failure to perform or follow an approved study procedure that, in the opinion of the Investigator, **does not** affect subject safety or data integrity • Study procedure conducted out of sequence

	• Failure to report a SAE/UPIRSO to the IRB	• Study Visit out of approved window • Missed Visit
Reporting Requirements	Record the date discovered, date occurred, description of event in the Protocol Deviation Log.	Record the date discovered, date occurred, description of event in the Protocol Deviation Log.

11.0 DATA MANAGEMENT AND PROCEDURES

A Data Safety Monitoring Plan will be developed by the study team. Research data management includes the:

- Definition of required study data
- Design of databases and case report forms
- Data entry process
- Development of a data dictionary
- Access and permissions to documents and data
- Collection and storage of participant details and study data
- Quality control and assurance of data
- Data access permissions for analysis ready data

Data will be collected through Research Electronic Data Capture (EDC) System – a self-managed, secure, web-based software solution designed to support data collection strategies for clinical research studies. The EDC system software helps researchers conveniently develop databases for collecting and managing research data. All authorized study personnel will have permission to submit validated data forms and receive feedback, alerts, or notifications from the EDC system as well as receiving reports and validation queries using secure transmission technology.

Data are collected in accordance with the study protocol and in compliance with applicable regulations including but not limited to the Health Insurance Portability and Accountability Act (HIPAA) Privacy and Security Policies and Procedures for “Protected Health Information” (PHI) and Family Educational Rights and Privacy Act (FERPA), as applicable. Each participant enrolled as a study participant is assigned a unique identifier by the EDC. No personal identifying information will be captured in the EDC, with the exception of both participant and parent/LAR/guardian’s email addresses which will be used to send out monthly assessments. Study personnel are responsible for keeping the identifying information secure and separate from the data used for analyses.

11.1 Design, Development, and Queries

The Center for Depression Research and Clinical Care (CDRC) Data Team will be responsible for the development of the Case Report Forms (CRFs) and Participant Reported Outcome (PRO) forms, development and validation of the clinical study database, ensuring data integrity, and training of staff on applicable data management procedures. A web-based distributed data entry model will be implemented. This electronic data capture system will be developed to ensure that guidelines and regulations surrounding the use of computerized systems used in research studies are upheld.

Queries will be built within the EDC. Data ranges, absolute minimum and maximum values and required fields will be defined. Reports (e.g., data quality, enrollment) will be generated by the system on a pre-defined schedule and as needed in the case of special requests based on need during the study. After the data has been captured, a validation process will ensure the data stored is within the correct value range, represents the correct data type, and is in a consistent and unambiguous form. If, or when, a data element is found to violate an accuracy or consistency rule the violation is recorded and acted upon for correction. All data accuracy and consistency violations will be communicated electronically via email to study personnel indicating the specific data element, violation, and recommended action to correct the data. The data validation process will also ensure corrections are completed in a timely manner. If data inaccuracies or

inconsistencies are not corrected within a specific timeframe, a built-in escalation procedure to communicate these violations will be triggered. Reports will be periodically delivered to the various data collection sites presenting accuracy and consistency violations in a detailed and summary format.

12.0 BLOOD BIOBANKING

Biological specimens will be collected at study sites and stored at the CDRC biorepository (IMPACT). As it is an optional procedure, inability to collect biological specimens for biobanking is not considered a missed study procedure, and thus will not be filed as a Protocol Deviation. A tracking and specimen inventory system will be used to generate subject ID numbers and to catalogue and track samples. A sample will be stored indefinitely until the sample runs out or it is destroyed. If a participant wishes to withdraw their sample from the biobank, written request must be sent to the P.I. as stated in the informed consent.

Upon study enrollment, all participants will be given a study identifier number (subject ID). Blood samples will be de-identified, processed, and stored using subject IDs. Coded Data (with subject IDs only) will be stored separately from information that could identify the participants. Linkage of the subject's PHI (identifying information) to their subject IDs will be stored separately (master log) and will be limited to clinic and data center staff. All information (including the link between identifiers and codes) will be stored in password-protected files.

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14.0 APPENDIX A - ADVERSE EVENT AND OTHER NON – AE UNANTICIPATED PROBLEMS REPORTING DEFINTIONS AND PROCEDURES

The Principal investigator is responsible for study oversight, including ensuring human research subject protection by designating appropriately qualified and trained study personnel to assess, report, and monitor adverse events. The Research Team will review each AE/SAE and unanticipated problem as needed. These reviews will include an assessment of the possible relatedness of the event to the study intervention or other study procedures. The Investigators will also provide advice for decisions to exclude, refer, or withdraw participants as required. The study staff will be trained to monitor for and report Adverse Events, Serious Adverse Events and UPIRSOs per the guidelines described below.

Definition of Adverse Events and Serious Adverse Events

Adverse Events (AEs)

An **adverse event** (AE) is any untoward medical occurrence in humans, whether or not considered study drug/intervention related, which occurs during the conduct of a clinical trial.

Adverse Events will be assessed from the time of informed consent until participant's exit from the study. All AEs will be collected and entered into the EDC for reporting.

Guidelines for Assessing Severity

The severity of an adverse event refers to the intensity of the event.

Grade 1	**Mild**	Transient or mild discomfort (< 48 hours), no or minimal medical intervention/therapy required, hospitalization not necessary (non-prescription or single-use prescription therapy may be employed to relieve symptoms, e.g., aspirin for simple headache, acetaminophen for post-surgical pain)
Grade 2	**Moderate**	Mild to moderate limitation in activity, some assistance may be needed; no or minimal intervention/therapy required, hospitalization possible.
Grade 3	**Severe**	Marked limitation in activity, some assistance usually required; medical intervention/ therapy required, hospitalization possible.

Serious Adverse Events

All SAEs, regardless of relatedness to study procedures will be captured and reported in the EDC within **24 hours of discovery.**

An **adverse event,** is considered "**serious**" if:

1. Results in death
2. Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
3. Requires inpatient hospitalization or prolongation of existing hospitalization
4. Results in persistent or significant disability/incapacity

5. Is a congenital abnormality or birth defect

6. Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the 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).

Relatedness to study intervention or procedure

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 study physician.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

The study physician will be responsible for determining whether an adverse event (AE) is expected or unexpected. An adverse event is considered unexpected if the nature or severity is not consistent with the applicable product reference safety information. For ketamine hydrochloride and midazolam hydrochloride, expectedness of an adverse event will be determined by whether or not it is listed in the safety information sections of the product's pharmaceutical insert.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs)

An event that meets ALL three (3) of the following criteria:

1. Unexpected (in nature, severity, or frequency), AND

2. Probably or definitely related to the research, AND
3. Suggests the research places subjects or others at a greater risk of harm than previously known or recognized

*UPIRSOs are reportable to IRB within 5 business days.

Unexpected

The incidence, experience, or outcome is unexpected given the research procedures described in protocol-related documents (e.g., the study protocol, the consent documents) and the characteristics of the subject population being studied. An event may be considered unexpected if it exceeds the nature, severity, or frequency described in the study-related documents.

Probably or definitely related

The incidence, experience, or outcome is related or probably related to participation in the research study. Probably related means the incidence, experience, or outcome is more likely than not to be caused by the research study procedures

Greater risk of harm

The occurrence of the incidence, experience, or outcome suggests that the research places subjects or others at a greater risk of harm (physical, psychological, economic, or social) than was previously known or recognized.

Study Staff's Role in Eliciting and Reporting Adverse Events

All adverse events (medical and/or psychiatric) occurring during the course of the study will be assessed. Documentation and reporting of such events will occur when the event meets reporting requirements specified above. Appropriately qualified and trained medical personnel will elicit participant reporting of AEs and SAEs at each study visit designated to collect AEs (i.e., the first visit following informed consent and at every visit thereafter). Study staff will follow-up on the status of any AEs that remain at follow-up visit assessment and at study termination/completion. Study personnel will obtain as much information as possible about the reported AE/SAE in order to complete AE/SAE documentation (i.e., log and CRFs) and will consult with study physicians as necessary.

Site staff is required to enter AEs and SAEs in the EDC as soon as they become aware of the event. The EDC AE log will be used to capture AEs (as defined in the protocol). Additional information may need to be gathered to evaluate serious adverse events and to complete the appropriate extended SAE forms in the EDC and in CRFs. This process may include obtaining hospital discharge reports, medical records, autopsy records or any other type of records or information necessary to provide a complete and clear picture of the serious event and events preceding and following the event. Because visits are scheduled weekly, we anticipate being informed of SAEs, including deaths, in close time proximity to the event. For participants who are lost to follow-up, we will conduct a search for death records at the time that the individual would have completed the study (Day 84). If the SAE is not resolved or stable at the time of the initial report or if new information becomes available after the initial report, follow-up information must be submitted as soon as possible.

Adverse events will be followed until resolution, stabilization or study end. Any serious adverse reactions will be followed until resolution or stabilization even beyond the end of the study.

Appropriately qualified and trained medical personnel will conduct an initial assessment of seriousness, severity, and causality when eliciting participant reporting of adverse events. A study physician will review AEs for seriousness, severity, and causality.

Quality Assurance Staff's Role in Monitoring Adverse Events

Quality assurance monitors will review safety documentation on a regular basis and will promptly advise site staff to report any previously unreported safety issues and ensure that the reportable safety-related events are being followed to resolution and reported appropriately. Staff education, re-training or appropriate corrective action plan will be implemented at the participating site when unreported or unidentified reportable AEs or serious events are discovered, to help ensure future identification and timely reporting.

PI Role in Safety Management Procedures of AEs/SAEs

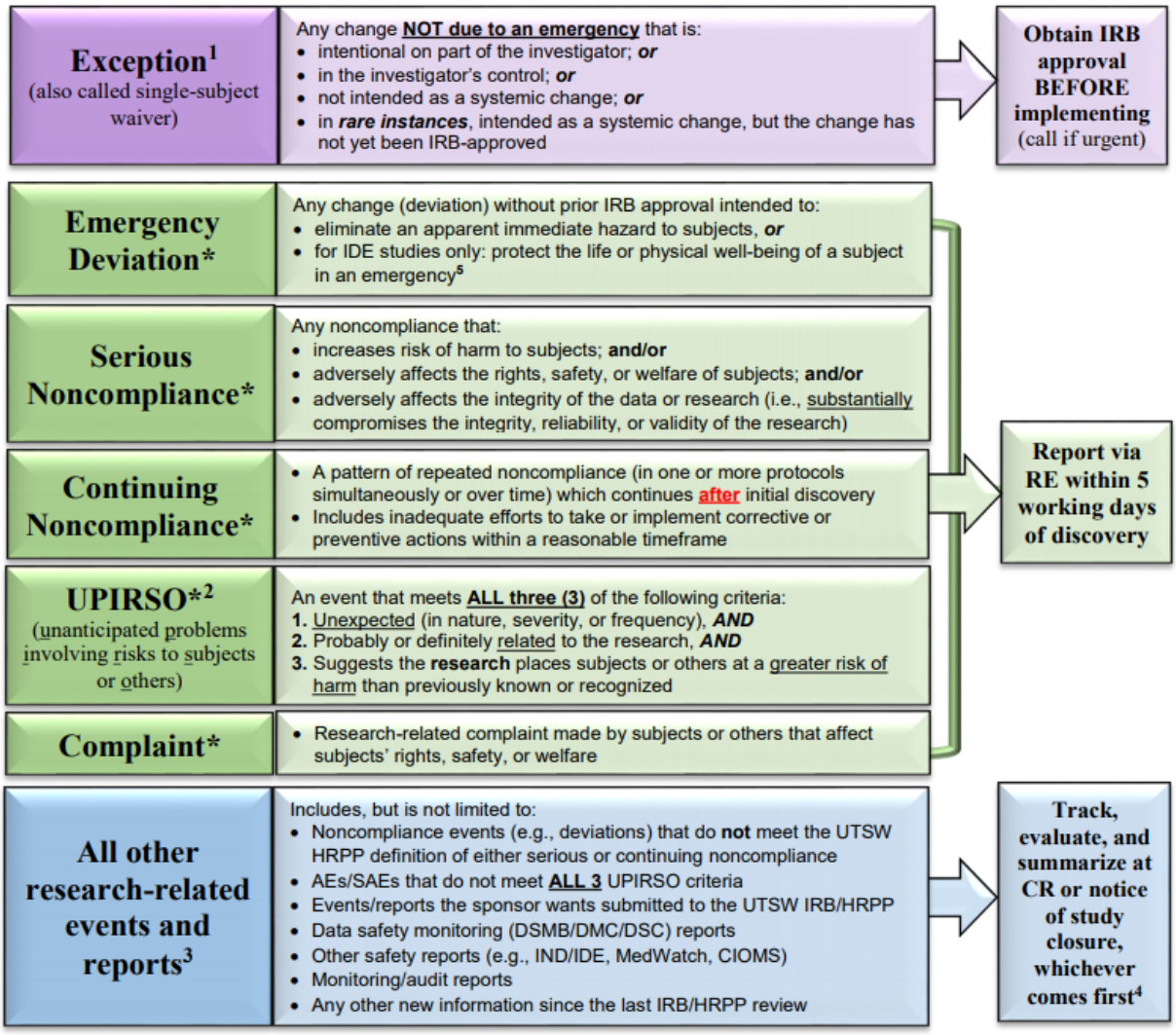
While a study physician will review all SAEs for accuracy, the PI is responsible for SAE oversight to ensure proper reporting procedures are followed and all reportable events are disclosed to the IRB per reporting guidelines.

Reporting of AEs, SAEs, and UPIRSOs

UTSW IRB reporting timelines will be followed for all qualifying events. The below summarizes current HRPP reportable Event Guidelines. See appendix C for NIMH reporting guidelines.

UTSouthwestern Medical Center

HRPP Reportable Event Guidance#



15.0 APPENDIX B – NIMH REPORTABLE EVENTS POLICY

Purpose
Timely reporting of significant research events to the National Institute of Mental Health (NIMH) is necessary for the NIMH's oversight of the protection of the rights and welfare of participants in funded research. The purpose of this policy is to outline the NIMH's expectations of NIMH-funded researchers relating to the submission of reportable events (i.e., Adverse Events (AEs); Serious Adverse Events (SAEs); Unanticipated Problems Involving Risks to Subjects or Others; protocol violations; non-compliance (serious or continuing); suspensions or terminations by monitoring entities (e.g., Institutional Review Board (IRB), Independent Safety Monitor (ISM)); and suspensions or terminations by regulatory agencies (e.g., Office for Human Research Protections (OHRP) or the Food and Drug Administration (FDA)).

Scope and Applicability
This policy applies to the reporting of AEs, SAEs, Unanticipated Problems, protocol violations (significant divergences from the IRB-approved protocol), serious/continuing non-compliance, and suspensions and terminations for clinical research funded (in whole or in part) by the NIMH. This policy is specific to reporting to the NIMH and does not replace regulations or policies requiring reporting of these events to other monitoring entities or regulatory agencies.

General Reporting Policy
Consistent with NIH policy, the Principal Investigator is responsible for the clinical management of the participant and accurate written documentation, investigation, and follow-up of all possible study-related AEs. The investigator is also responsible for describing and adhering to the procedures for identifying, monitoring, and reporting reportable events outlined in the study's Human Subject's section of the application. AEs, SAEs, death, Unanticipated Problems, protocol violations, non-compliance, suspensions, and terminations should be reported to the NIMH (as the funding sponsor) according to the expectations and timeframes described below. The NIMH Reportable Events Policy remains unchanged and the version included in the protocol reflects the NIMH DSMB-E request to update how reportable events are reported to this specific Board. The below table summarizes NIMH DSMB-E reportable events timelines.

Reportable Event	When is Event Reported to the NIMH	Reported By
IRB/ISM/DSMB/OHRP/FDA Suspensions or Terminations	Any suspension or termination of approval must include a statement of the reason(s) for the action and must be reported promptly to the NIMH PO **within 3 business days of receipt.**	Regulatory or Monitoring Entity and Investigator
Deaths related to study participation	Deaths must be reported immediately (**no later than within 5 business days**) of the principal investigator first learning of the death.	Investigator
Unexpected Serious Adverse Events related to study participation	Reported to the NIMH PO **within 10 business days** of the study team becoming aware of the SAE.	Investigator
Unanticipated Problems Involving Risks to Subjects or Others	Reported to the NIMH PO **within 10 business days** of the investigator learning of the event.	Investigator
Serious or Continuing Noncompliance	Reported to the NIMH PO **within 10 business days** of IRB determination	Institution
Adverse Event	For all AEs that are deemed expected and/or unrelated to the study, a summary should be submitted in the **annual data report**. SAEs that are deemed expected and/or unrelated to the study will be submitted in each data report.	Investigator
Protocol Violations	With the **annual data report**.	Investigator

All reports must be made in writing to the NIMH Program Official (PO) and DSMB Liaison. These reports should indicate that the monitoring entities (i.e., the PI and IRB, ISM and/or DSMB) and appropriate regulatory entities (e.g., OHRP, FDA) have been notified in accordance with the approved monitoring plan and federal regulations. Reports should be submitted to the monitoring entity (e.g., a DSMB or ISM) at least annually on a schedule determined by the monitoring entity's policy. Monitoring entities may require more frequent reporting.

Documentation to be Submitted for Reportable Events

- Identifying information for the research protocol (e.g., project title, investigator's name, and the grant/contract number);
- The date on which the event occurred and the date at which the PI became aware of the event;
- A detailed description of the event and impact on the participant(s);
- A detailed description of the measures taken (including clinical) in response to the event (if any);
- Confirmation that the appropriate monitoring entities and regulatory bodies have been notified as needed; and
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the event.

16.0 APPENDIX C – DATA AND SAFETY MONITORING PLAN

OVERSIGHT OF CLINICAL RESPONSIBILITIES

PI

The study is designed to carefully monitor patient safety. The PI is ultimately responsible for ensuring the safety of participants. Active participants will be reviewed at a weekly meeting, including information about ongoing symptoms of suicidality, course of psychiatric illness, and adverse events. All serious adverse events (SAEs) will be reported to the UTSW Institutional Review Boards (IRBs) according to the regulations set forth by the IRB and NIMH DSMB.

Overall data monitoring will be the responsibility of the PI. In addition to provisions to maintain confidentiality and safety, the PI will carefully monitor recruitment, accrual, and retention, as well as the quality of the data. During the course of the study, the PI will follow the progress of the clinical study and data entry to ensure utmost accuracy of the data and to detect any possible errors at an early time point. The Study Coordinator will verify the data with the participant's medical chart, evaluate the data for accuracy, completeness, and consistency, and will assure that all forms with missing data and/or errors are corrected, accurate, and complete. In addition, the Study Coordinator will generate weekly reports, which will include suicidality, psychiatric symptomatology, and adverse events for each subject for review during weekly project meetings as well as an ongoing CONSORT diagram.

NIMH DSMB

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) convened by NIMH. The DSMB includes experts in scientific disciplines needed to monitor the data and ensure patient safety during the conduct of this study, including addiction and mental health experts, clinical trial experts, biostatisticians, and bioethicists. DSMB members have no association with the project investigators, and no conflicts of interest with study outcomes. The DSMB will meet at least three times a year to assess safety and data of the study. The DMSB will operate under the rules of an approved charter. The DSMB will provide its input to NIMH staff.

DSMB procedures conform with usual standards, including reviewing emerging trial data and maintaining confidentiality. The main responsibilities of the NIMH DSMB include, but are not limited to the following: (1) reviewing the research protocol, consent form(s) and plans for data and safety monitoring prior to the initiation of the study; (2) monitoring of the progress of the study, including data quality, timeliness, recruitment and retention of study participants, adverse events, serious adverse events (SAEs), reasons for participant withdrawal, adherence to the timeline of the study, protocol deviations, performance across study sites, and factors that may affect the risks and benefits of the study such as emerging literature; and (3) making directives about the continuation, modification, or termination of the study, based on the balance of adverse events and beneficial outcomes. Throughout the study, notification of SAEs as well as any proposed investigator-initiated changes in the protocol will be submitted to the NIMH DSMB. Based on its review of the protocol, the NIMH DSMB will identify the data parameters and format of the information to be regularly reported. The NIMH DSMB may at any time request additional information from the Principal Investigators.

All SAEs and adverse events (AEs will only be reported to the NIMH DSMB annually) will be tabulated and submitted to the NIMH DSMB in the triannual DSMB data reports. Based on review

of safety data, the NIMH DSMB will issue directives concerning the conduct of the study. Recommendation/directives made by the DSMB may include amending safety monitoring procedures, modifying the protocol or consent, terminating the study, or continuing the study as designed.

17.0 APPENDIX D – PROHIBITED AND ALLOWED CONCOMITANT MEDICATIONS

Except where specifically noted, the prohibited medications listed in the following table are prohibited from 1 week (or 5 half-lives, whichever is longer) prior to the first dose of study medication until after the last dose of study medication.

Note in the following table: N, Prohibited; Y, Permitted, with restrictions (please refer to the column labeled “Comments” for additional guidance).

Drug Class	Episodic Use (as needed)	Continuous Use	Comments	Reasons for Prohibition
ADHD medications (e.g., atomoxetine, guanfacine)	N	Y	Can be continued but must not be taken within 12 hours prior to the treatment session or for 2 hours after the treatment session.	Safety
Amantadine	N	N		PD interaction
Anorexiants **(e.g., phentermine, phendimetrazine)**	N	N		Safety
Anticholinesterase inhibitors	N	N		Subject population is excluded
Anticonvulsants	Y	Y	Subjects with seizures are excluded. Note: Anticonvulsants used for indications other than seizures may be allowed (e.g., valproate for migraine; pregabalin)	Safety and PD interaction
MAO-I Antidepressants	N	N	There must be a minimum washout interval of 2 weeks prior to the first dose of study medication and MAO-I antidepressants are prohibited throughout the study.	Safety
Antipsychotics	N	Y		PD interaction

Benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day lorazepam) and non-benzodiazepine sleeping medication (including: zolpidem, zaleplon, eszopiclone, and ramelteon)	N	N	Episodic use of benzo is prohibited for at least 1 week (or 5 half-lives, whichever is longer) prior to the first dose of study medication until after the last dose of study medication. Chronic use of benzodiazepine is prohibited for at least 3 months prior to the first dose of study medication until after the last dose of study medication.	Safety and PD interaction
Benztropine	Y	N	Prohibited if use is continuous and prohibited within 12 hours	Safety and PD interaction
Chloral hydrate, melatonin, valerian	N	N		Safety and PD interaction
Clonidine	Y	Y	Use for blood pressure control is allowed.	
Corticosteroids (systemic)	Y	N	Inhaled, intranasal, topical, and ophthalmic steroids are not prohibited. Intermittent IM/IV/PO corticosteroids are permitted with investigator approval (chronic use prohibited).	PD interaction
Cough/cold preparations/nasal solutions containing vasoconstrictors, decongestants	Y	Y	Intranasally-administered decongestants (vasoconstrictors) should not be used from 1 hour prior to each study medication administration. Pseudoephedrine-containing products should not be used within 12 hours prior to a treatment session.	Safety and PD interaction
CYP3A4 inducers - Potent	N	N	Subjects may not take a known potent inducer of hepatic CYP3A activity within 2 weeks of the first administration of study medication until at	PK

			least 24 hours after the last dose of study medication. Examples (not all-inclusive): Efavirenz, nevirapine, barbiturates, carbamazepine, glucocorticoids, modafinil, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort	
Dextromethorphan	N	N		PD interaction
Diphenhydramine	Y	N	Prohibited within 12 hours prior to the start of each treatment session	Safety
Ketanserin	N	N		Safety
Memantine	N	N		PD interaction
Methyldopa	N	N		Safety and PD Interaction
Metyrosine	N	N		Safety and PD interaction
Non-vitamin K antagonist oral anticoagulation agents (e.g., dabigatran, rivaroxaban, apixaban)	N	N		Safety
Opioids	N	N	With investigator approval, brief treatment with opiates may be allowed for treatment of acute injuries, etc.	PD interaction
Naltrexone	N	N		May affect the antidepressa

				nt effects of ketamine
Psychostimulants (e.g., amphetamines, methylphenidate)	N	Y	Prescribed psychostimulants can be continued or newly initiated but must not be taken within 24 hours prior to the treatment session or for 2 hours after the treatment session.	Cardiovascular safety
Reserpine	N	N		PD interaction
Thyroid hormone supplement for treatment of thyroid condition only (not for depression)	N	Y		Safety
Thyroxine/ triiodothyronine (T3), thyroid hormone prescribed for depression	N	N		PD interaction
Warfarin	N	N		Primary condition where used is excluded