New York State Psychiatric Institute

Institutional Review Board

May 6, 2019

To: Dr. Michael Grunebaum

From: Dr. Edward Nunes, Co-Chair

Dr. Agnes Whitaker, Co-Chair

Subject: Approval Notice: Continuation Expedited per 45CFR46.110(b)(1)(f)Category 8(c)

Your protocol #**6598** entitled: **KETAMINE VS MIDAZOLAM: TESTING RAPID RELIEF OF SUICIDE RISK IN DEPRESSION** Protocol version date 05/06/2019 has been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **June 4, 2019 to June 3, 2020.**

Consent requirements:

√ Not applicable: Data Analysis Only

☐ 45CFR46.116 (d) waiver of consent for secondary data analysis

☐ Signature by the person(s) obtaining consent is required to document the consent process

☐ Documentation of an independent assessment of the participant's capacity to consent is also required.

Approved for recruitment of subjects who lack capacity to consent: ☐ No ☐ Yes

Field Monitoring Requirements: ☐ Routine ☐ Special: _____

✓ Only copies of consent documents that are currently approved by the IRB may be used to obtain consent for participation in this study.

✓ A progress report and application for continuing review is required 2 months prior to the expiration date of IRB approval.

✓ Changes to this research may not be initiated without the review and approval of the IRB except when necessary to eliminate immediate hazards to participants.

✓ All serious and/or unanticipated problems or events involving risks to subjects or others must be reported immediately to the IRB. Please refer to the PI-IRB website at http://irb.nyspi.org for Adverse Event Reporting Procedures and additional reporting requirements.

Cc: RFMH Business Office (NIMH: 1 R01 MH096784-01A1)

EN/AW/kpz4alw

Signed copy on file at IRB

Protocol Title:
Ketamine vs Midazolam: Testing Rapid Relief of Suicide Risk in Depression

Version Date:
05/06/2019

Protocol Number:
6598

First Approval:
06/22/2012

Clinic:
MIND Clinic

Expiration Date:
06/03/2020

Contact Principal Investigator:
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Co-Investigator(s):
Steven Ellis, PHD
J. John Mann, MD
Maria Oquendo,
Barbara Stanley, PHD
Matthew Milak, MD

Research Chief:
J. John Mann, MD

Cover Sheet

Choose ONE option from the following that is applicable to your study
If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.
I am submitting an annual continuation without modifications

Division & Personnel

Division

What Division/Department does the PI belong to?
Psychiatry
Within the division/department, what Center or group are you affiliated with, if any?
MIND

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.

Outside Investigators:
None

Consultant:
Vivek K. Moitra, MD
Associate Clinical Professor of Anesthesiology
Associate Medical Director, Surgical ICU
Associate Program Director, Critical Care Medicine Fellowship
Division of Critical Care, Columbia University College of Physicians and Surgeons

Application for Continuation of Research

Status

Current Status of Study:
Study only involves secondary data analysis or chart record review of data.

Summary of Experiences to Date

Please provide a summary of scientific progress of the study and the experience of research participants, to date. This requirement is designed to allow for the investigator and the IRB to reassess the study's risks and benefits in terms of developments in the field, changing practice patterns, and new IRB policies and procedures.
The study was completed in 2017 and the primary results paper was published in 2018. Currently only secondary data analysis for potential secondary publications is ongoing.

Funding

Have there been any changes in funding status since the prior approval?
No
Have the principal investigator and other investigators made all required disclosures of financial interest in the study sponsor/product?
Yes

Summary

Have there been any study findings, recent literature, or untoward events occuring here or at other sites in the past year which might affect the analysis of the safety, risks or benefits of study participation?
No
Have there been any serious adverse events (serious and/or unanticipated problems involving risks to subjects or others at this site which occured in the past year)?
No
Have all study staff with a significant role in the design or implementation of the human subject components of this study received required training in human research subject protections?
Yes
Is the study covered by a certificate of confidentiality?
No

Approved Sample and Progress

Approved sample size
80
Total number of subjects studied since first approval
80
Have there been any significant deviations from the anticipated study completion estimates?
No
Comments / additional information
None

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures

✓ Psychiatric Assessment
✓ Neuropsychological Evaluation
✓ Collection of Biological Specimens
✓ Medication Trial
✓ Medication-Free Period or Treatment Washout
✓ Administration of Substance of Abuse
✓ Off-label Use of Drug or Device
✓ Somatic Treatment or Intervention

Population

Indicate which of the following populations will be included in this research

✓ Adults
✓ Adults over 50

✓ Substance Users
✓ Inpatients

Research Support/Funding

Will an existing internal account be used to support the project?
No
Is the project externally funded or is external funding planned?
Yes
Select the number of external sources of funding that will be applicable to this study

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?
Yes
Select one of the following
The grant/contract application is a pending review or a funding decision
Source of Funding
Federal
Institute/Agency
NIMH
Grant Name
Ketamine vs Midazolam: Testing Rapid Relief of Suicide Risk in Depression
Grant Number
1 R01 MH096784-01A1
Select one of the following
Single Site
Business Office
RFMH
Does the grant/contract involve a subcontract?
Yes
Subcontracted?
To
Name institution(s)
Columbia University

Study Location

Indicate if the research is/will be conducted at any of the following
✓ NYSPI
✓ Other Columbia University Medical Center Facilities
This protocol describes research conducted by the PI at other facilities/locations

No

Lay Summary of Proposed Research

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We propose a rigorous clinical trial in depressed patients with moderate to severe suicidal ideation to test random assignment to iv infusion of ketamine or midazolam control followed by open continuation treatment with antidepressant medication plus supportive case management. The primary goal is to test ketamine's potential anti-suicidal effects versus a similar sedative control medication not known to reduce suicidal ideation. Exploratory aims include analysis of potential biological (salivary cortisol) and neuro-cognitive correlates as well as systematic assessment of suicidal ideation and behavior during continuation treatment.

Background, Significance and Rationale

Background, Significance and Rationale
Suicide and suicide attempts cost an estimated $33 billion annually in the U.S. and immeasurable pain and suffering. Most suicidal behavior is associated with a depressive disorder, yet medication guidelines for suicidal patients are virtually nonexistent. The evidence base is severely limited because suicidal patients are excluded from most antidepressant clinical trials. Several recent studies show rapid improvement in suicidal ideation, in as little as one hour, in depressed patients after intravenous infusion of sub-anesthetic ketamine, a glutamate antagonist and commonly used anesthetic. The improvement in suicidal ideation appears to last several days, however, depression and suicidality are usually chronic, recurring conditions. Establishing a strong anti-suicidal signal for ketamine in this high-risk population would support an innovative intervention that could change clinical care for a patient population of public health importance. Exploratory assessment of suicidal ideation and behavior during continuation treatment could help target research on strategies to sustain the benefit of ketamine.

Specific Aims and Hypotheses

Specific Aims and Hypotheses
To compare the effect of iv ketamine vs. midazolam infusion on suicidal ideation in a double-blind RCT in MDD during a major depressive episode (MDE) (N=**80**) with moderate to severe suicidal ideation (SSI score = 4 or greater). The study infusion will be given as add-on to current psychotropic medication. Patients will be randomized to iv ketamine (0.5 mg/kg) or midazolam (0.02 mg/kg) infusion. We hypothesize that administration of ketamine will produce greater improvement in suicidal ideation compared to midazolam at 24 hours after infusion.
An exploratory aim of the study is to compare cortisol awakening response (CAR) between the two treatment groups. Hypothalamic-pituitary-adrenal (HPA) axis hyperactivity is associated with cognitive

impairment and suicide risk. Glutamatergic and serotonergic systems are closely associated with HPA activity. We will measure salivary cortisol at baseline and Day 01 post-infusion with 2 saliva samples collected at each time point, the first immediately on waking and the second 30 minutes later. We hypothesize CAR magnitude will be lower on Day 01 after ketamine compared to midazolam.

Description of Subject Population

Sample #1

Specify subject population
Depressed adults with moderate to severe suicidal ideation
Number of completers required to accomplish study aims
80
Projected number of subjects who will be enrolled to obtain required number of completers
115
Age range of subject population
18 - 65

Gender, Racial and Ethnic Breakdown
We expect the following gender and ethnic breakdown: Male (40%); Female (60%); White (67%); Black (24%); Hispanic (16%); Asian (9%).
Description of subject population
The goal is to recruit unipolar depressed patients with current Scale for Suicidal Ideation (SSI) score of 4 or greater, to result in a sample with, overall, moderate to severe suicidal ideation. Based on studies in our clinic, subjects come from the 5 boroughs of New York City and the nearby tri-state suburbs.

Recruitment Procedures

Describe settings where recruitment will occur
Patients are recruited through advertisements, clinician referrals, and the hospital inpatient and emergency services.
How and by whom will subjects be approached and/or recruited?
Subjects will be approached/recruited by study research assistants and psychiatrists.
How will the study be advertised/publicized?
Through local media, internet, mailings to clinicians, outreach to the CPMC and other local emergency departments and clinical facilities.
Do you have ads/recruitment material requiring review at this time?
No
Does this study involve a clinical trial?
Yes
Please provide the NCT Registration Number

NCT01700829

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement
MIND umbrella protocol, IRB #4815.

Inclusion/Exclusion Criteria

Name the subject group/sub sample
Ketamine/Midazolam MDD
Create or insert table to describe the inclusion criteria and methods to ascertain them

INCLUSION	METHOD OF ASCERTAINMENT
1. Unipolar, major depressive episode (MDE), with 17-item HDRS score ≥ 16. Patients may be psychiatric medication-free, or if on psychiatric medication, not responding adequately given current MDE with suicidal ideation (See 2).	DSM-IV criteria by SCID-I administered by trained assessors; Medication history; Clinical evaluation; HDRS.
2. Moderate to severe suicidal ideation as indicated by a Beck Scale for Suicidal Ideation (SSI) score of 4 or greater.	Beck Scale for Suicidal Ideation (SSI) and clinical assessment.
3. 18-65 years old	Interview
4. Patients will only be enrolled if they agree to voluntary admission to an inpatient research unit at NYSPI for up to 72 hours, or longer if clinically necessary, for the infusion.	Clinical interview, informed consent.
5. Female patients of child-bearing age must be willing to use an acceptable form of birth control during study participation such as condoms, diaphragm, oral contraceptive pills.	Clinical assessment, informed consent.
6. Must be enrolled in IRB #4815 (PI: Oquendo)	Informed consent process.
7. Able to provide informed consent	Interview

8. Subjects 61-65 years old must score 25 or higher on MMSE at screening.	Mini Mental State Exam

Create or insert table to describe the exclusion criteria and methods to ascertain them

EXCLUSION	METHOD OF ASCERTAINMENT
1. Unstable medical or neurological illness including baseline hypertension (BP>140/90) or significant history of cardiovascular illness**.**	Baseline medical evaluation including blood pressure, heart rate, physical exam, routine labs, and electrocardiogram (ECG).
2. Significant ECG abnormality (e.g., Ventricular tachycardia, evidence of myocardial ischemia, symptomatic bradycardia, unstable tachycardia, second degree (or greater) AV block).	Baseline ECG.
3. Pregnancy/lactation	Baseline serum pregnancy test.
4. Diagnosis of bipolar disorder or current psychotic symptoms.	Clinical assessment and baseline SCID-I
5. Contraindication to any study treatment.	Medical assessment and history.
6. Current or past ketamine abuse or dependence ever (lifetime); any drug or alcohol dependence within past 6 months; suicidality only due to binge substance use or withdrawal.	Clinical assessment, SCID-!, urine drug screen.
7. Inadequate understanding of English.	Clinical assessment.
8. Prior ineffective trial of or adverse reaction to ketamine or midazolam.	Clinical assessment.
9. Opiate use greater than total daily dose of 20mg Oxycodone or equivalent during the 3 days pre-infusion.	Clinical assessment and medical records.

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)
No
Waiver or alteration of consent
No
Waiver of documentation of consent
No
Waiver of parental consent

No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
Yes
Indicate NYSPI IRB #
4815
Describe Study Consent Procedures

a. Subject is given a detailed, verbal explanation of this study and IRB #4815 and given a signed copy of both consent forms.

b. Subject gives written informed consent to participate in IRB #4815 and this study, IRB #6598.

c. Subject receives medical evaluation under this study. Genetics blood sample is under IRB #4815 (Biological and neuropsychological measures for genetic studies of psychiatric populations—PI: Oquendo).

Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form
✓ Information Sheet

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Grunebaum, Michael, MD
Lan, Martin, MD
Miller, Jeffrey, MD
Sublette, M, MD
Type in the name(s) not found in the above list

Independent Assessment of Capacity

You have indicated that your study involves subjects who MAY LACK capacity to consent.
Does this study require an independent assessment of capacity?
No

Study Procedures

Describe the procedures required for this study
1. Screening
a. We will recruit inpatients or outpatients with a major depressive episode. Referrals generally come from physicians, clinics, the Presbyterian Emergency Department, and ads in media including the internet.
b. Subject completes phone screen, approved under IRB #5880R. If subject appears eligible based on the phone screen, they will be scheduled for an in-person screening visit under Screening Protocol (IRB #5880R) to determine whether inclusion/exclusion criteria (excluding medical screening) are met.
c. Subject is given a detailed, verbal explanation of this study and IRB #4815 and given a copy of both consent forms.
d. Subject gives written informed consent to participate in IRB #4815 and this study, IRB #6598.
e. Subject receives medical evaluation under this study. Genetics blood sample is under IRB #4815 (Biological and neuropsychological measures for genetic studies of psychiatric populations—PI: Oquendo).
f. During the period between enrollment and the infusion, the treating physician will assess the patient weekly in person or by phone, including a Clinical Global Impression (CGI) scale. If concerns are noted during a telephone contact, subjects will be brought in for an in-person visit. If someone has a CGI-I >5 then a repeat CGI-I will be done within 3-4 days and if it remains >5 then the subject will be withdrawn; or 2) their CGI Improvement score is six or seven on one occasion and the treating psychiatrist assesses that they cannot safely continue research participation. If after enrollment a subject refuses inpatient admission that is deemed clinically necessary by the research team they will be withdrawn from research.
2. Prior Psychiatric Medication
a. For insomnia or anxiety, PRN diphenhydramine, hydroxyzine, zolpidem, or a benzodiazepine will be permitted. The goal will be a maximum daily dose of lorazepam 2mg during the week pre-infusion. However, no zolpidem or benzodiazepine will be permitted during the 24 hours pre-infusion. Subjects who at enrollment are taking a higher benzodiazepine dose will be tapered and converted to lorazepam during the pre-infusion week. Subjects who show signs of benzodiazepine withdrawal or cannot tolerate the 24-hours pre-infusion without zolpidem or benzodiazepine will be withdrawn from the protocol.
b. Current psychiatric medications other than benzodiazepines will be maintained at a stable dose until post-infusion treatment. Minor dose adjustments may be made pre-infusion, such as to reduce side effects.
3. Actively Suicidal Patients
a. Patients with imminent (next few days) suicidal plan or intent will only be enrolled as inpatients. The independent treatment team on the inpatient research unit must agree that study participation is clinically reasonable.
b. For patients who require hospitalization because of destabilization or suicidal risk, admission to a NYSPI unit will be available. Hospitalized patients will be discharged from the hospital when stable as judged by the inpatient staff and the treating psychiatrist as not being in imminent risk of harm to self/other.

c. A research psychiatrist will be available by cellphone 24 hours a day, seven days a week. Patients requiring urgent admission will be brought to the CUMC Emergency Dept. by the study physician with security assistance, if needed. Non-emergent admissions will be arranged by the treating psychiatrist, if possible to the 4-Center or 5-South. Patients who are deemed to require hospitalization, but who refuse, will receive all necessary interventions such as contacting the local crisis team, family, or Emergency Medical Services.

4. Pre-Infusion Research Measures

a. Baseline clinical and neuropsychological ratings (See Figure 2, attached).

b. Saliva Cortisol: We will measure salivary cortisol using Salivettes (Sarstedt, Germany) at the following time-points for both the initial infusion and the optional open ketamine infusion: Time-Sensitive (within 72 hours pre-infusion) and 24 HR Post-Infusion Day (i.e., Day 1 Follow-Up). The samples will be collected fasting and before the patient has taken any medication that day. At each time point (Time-Sensitive, 24 HR Post-Infusion Day), patients will be asked to provide two samples, one immediately on waking up in the morning and a second sample 30 minutes later. Samples will be processed in the Nathan Kline Institute laboratory of Thomas Cooper, M.A., who is an expert in these methods.

5. Randomization

a. Patients will be assigned randomly to one of the two treatment conditions: ketamine or midazolam.

b. Randomization will be stratified on two variables: 1) According to time-sensitive pre-infusion Scale for Suicidal Ideation (SSI) score of below 8 vs. 8 or above; and 2) According to whether the subject is currently taking psychiatric medication or not.

c. The infusion medication will be prepared by the NYSPI research pharmacy.

d. Codes linking patient numbers to treatment assignment will be sealed and kept under lockand-key for all study patients.

6. Blinding

a. The patient, study psychiatrist, and assessors will be blind to infusion allocation.

b. An un-blinded pharmacist, who is not part of the research team, will dispense the infusion treatments.

c. To test adequacy of the blind, after completion of post-infusion research assessments, all subjects and research personnel will each complete a brief questionnaire asking them to guess subjects' infusion group status.

d. Infusion responders will be informed by the pharmacy via a letter which infusion they received at the end of their 6-month participation in our clinic or when they stop treatment in our clinic, whichever comes first. Infusion non-responders will be informed which infusion they received after research measures are complete on the post-infusion day. The DSMB may request unblinded data as needed.

7. Inpatient Infusion Phase

a. To participate in the study, patients must agree to inpatient hospitalization at NYSPI (4-Center or 5-South units) for the infusion. Our goal will be for the admission to be as short as possible, approximately 3-5 days, or more if clinically indicated. Patients will be evaluated by a research physician and the inpatient unit's independent clinical team and will be discharged when assessed, according to standard practice, as safe for outpatient treatment in the research clinic. Patients who need to be kept involuntarily for safety reasons will be withdrawn from research and treated clinically.

b. We will attempt to schedule the study infusion as close as possible to the date of enrollment, given time for screening lab results, inpatient admission and BSU scheduling.
c. All patients will be NPO after midnight prior to study infusion and will be escorted by study staff to and from the BSU where the infusion will occur.
d. No zolpidem or benzodiazepine will be permitted in the 24 hours pre-infusion. We will monitor patients for signs of withdrawal, such as severe anxiety, diaphoresis, tachycardia (HR greater than 100), or hypertension (BP greater than 140/90) and if such signs are present then the infusion will be canceled and benzodiazepine restarted.
e. For subjects currently taking psychiatric medication, we will give advance notice of infusion scheduling to anesthesiologist consultant, Dr. Moitra, to confirm his or a backup anesthesiologist's availability for phone consultation during the infusion, if needed.
f. Pre-infusion blood level of BDNF will be measured by drawing a blood sample through the iv site. This will be analyzed in the NKI lab of Tom Cooper.
8. Blinded Ketamine/Midazolam Infusion
a. Dose:
i) Patients randomized to ketamine will receive an intravenous infusion of saline solution with ketamine hydrochloride (0.5 mg/kg; Abbott Laboratories, North Chicago, IL) over the course of approximately 40 minutes in the BSU of NYSPI with continuous monitoring of the subject by a study physician.
OR
ii) Patients randomized to midazolam will receive an intravenous infusion of saline solution with midazolam (0.02 mg/kg) over approximately 40 minutes in the BSU of NYSPI with continuous monitoring of the subject by a study physician.
b. Vital Signs Monitoring: During study infusion(s), blood pressure, heart rate, respiratory rate, and oxygen saturation will be monitored as follows:
i. -5 minutes
ii. 0 (start of infusion)
iii. Post start of infusion: 5, 10, 15, 20, 25, 30, 35, and 40 minutes (end of infusion)
iv. Post end of infusion: Blood pressure will continue to be obtained until there are two measurements at least 15 minutes apart that are within 10 mmHg of the baseline diastolic blood pressure or diastolic blood pressure is below 85. Respiratory rate and oxygen saturation will continue to be obtained until there are two measurements at least 15 minutes apart that are within normal limits (RR of 10 or greater; 02 saturation of 94% or greater).
c. The physician and Research Assistant who remain in the patient’s room during the infusion record the vital signs. After the subject is transferred back to their inpatient unit room, the blood pressure and heart rate will be obtained manually by the unit nursing staff.
d. Intervention for Hypertension: If the systolic blood pressure increases to ≥ 200 or diastolic blood pressure increases to ≥115 mmHg during the ketamine infusion, the infusion will be discontinued. The blood pressure will be monitored and if there is no decrease after 15 minutes, then:
1) One dose of sublingual nitroglycerine, 0.3 mg, will be administered.
2) If there is no response within 10 minutes, clonidine 0.1 mg po will be administered every 30 minutes (total maximum dose 0.6 mg clonidine) until the desired blood

pressure is reached. Desired blood pressure is defined as within normal range or 10 mmHg of baseline diastolic reading.
3) If high blood pressure is symptomatic, i.e., blurred vision, headache, chest pain, the subject will be transferred to the ER. If they do not respond to the above treatment (d.) then they will be transferred to the ER.
e. Intervention for Decreased Oxygen Saturation or Respiratory Rate:
1) If 02 saturation is <94%, the patient will be given oxygen via nasal canula; then if 02 saturation returns to ≥94%, the infusion will be continued. If 02 saturation remains <94% with nasal canula oxygen, then the infusion will be stopped, the anesthesiologist called, the blind broken, and if the infusion drug was midazolam then the patient will be given flumazenil unless the anesthesiologist recommends other treatment.
2) If respiratory rate is <10, the infusion will be stopped, the anesthesiologist called, the blind broken, and if the infusion drug was midazolam then the patient will be given flumazenil unless the anesthesiologist recommends other treatment.
3) If the patient does not respond to the above treatment, they will be transferred to the ER.
9. Post-Infusion Lab Tests
a. BDNF, ketamine and norketamine levels will be measured by drawing blood samples with a blood-draw separate from the iv site. These will be analyzed in the NKI lab of Tom Cooper.
b. Post-infusion saliva cortisol: Same procedure as Pre-Infusion (4b above).
10. Post-Infusion Treatment According to Medications at Enrollment and Responder Status on Day 01 post-infusion (Responder: 50% or greater reduction in SSI score from pre-infusion baseline and score < 4):
1a) Responders already taking an antidepressant will receive open clinical treatment.
1b) Responders not already taking an antidepressant will begin 6-week treatment with open label sertraline as follows: Open-label sertraline will be titrated to a daily dose of 100 mg or higher as tolerated. Fluoxetine, paroxetine ER, or escitalopram may be substituted for sertraline if a subject has had a failed adequate previous trial of the preferred drug due to side effects or lack of response. An adequate trial is defined as at least 2/3 maximum PDR dose for at least 6 weeks. If none of these SSRIs is acceptable, due to previous failed trials as defined, then other medication may be used. The dosing schedule will be as follows, but can be attenuated if required due to side effects:
Week 1: sertraline 50 mg daily (or fluoxetine 20 mg or paroxetine ER 25 mg or escitalopram 10mg).
Week 2: sertraline 100 mg daily (or fluoxetine 40 mg or paroxetine ER 50 mg or escitalopram 20mg).
Week 3-6: Optional increase to sertraline 150 mg (or fluoxetine 60 mg or paroxetine ER 75 mg or escitalopram 40mg) daily, or higher, if indicated by clinical assessment.
Response: Patients not responding adequately to sertraline (CGI Improvement score of 6 or worse 2 weeks in a row) or who develop intolerable side effects will be switched to fluoxetine, paroxetine ER, escitalopram, or if none is acceptable, due to previous failed trials as defined above, then to other medication. Patients who relapse will receive open treatment.
Concomitant medication: For insomnia or anxiety, diphenhydramine, hydroxyzine, zolpidem, or a benzodiazepine (lorazepam up to 4mg total daily dose or equivalent) will be

permitted. If addition of antipsychotic or mood stabilizing medication is required due to agitation, psychosis, or manic symptoms, then the patient will be withdrawn from research and treated openly.
2) Non-responders: For patients who are non-responders at 24 Hrs Post-Infusion (Day 01), the blind will be broken after Day 01 post-infusion research measures are complete. Non-responders who received midazolam will be offered an optional open-label ketamine infusion, following the same procedure as above. Neuropsychological testing will be repeated on Day 01 after the openlabel ketamine infusion, during the inpatient stay.
a) Responders to optional open-label ketamine infusion not already taking an antidepressant will receive the SSRI continuation treatment as above (see 1b). Responders who later relapse will receive open treatment.
b) Non-responders to first infusion who received ketamine (not eligible for second infusion) or who received midazolam but opt not to have a second infusion will receive open treatment.
c) Non-responders to optional open-label ketamine infusion and responders already taking an antidepressant will receive open treatment.
d) Non-responders at Day 01 after ketamine will have an additional Scale for Suicidal Ideation (SSI) rating at Day 03 to assess potential delayed response.
3) All patients receive supportive management according to the NIMH treatment manual of Fawcett et al.6 This condition is similar to what many patients receive in the community when their primary treatment is pharmacotherapy with a psychiatrist as the sole clinician, but is enriched by clinical and ethical necessity with additional monitoring and assessment. This will ensure that patients are being carefully managed. As described in the manual,6 clinical management will emphasize a positive, collaborative doctor-patient relationship through supportive reassurance, rationale for treatment, psycho-education, assessment of target symptoms, side effects, and appropriate dosing, assessment of suicide risk and mental status, and review of procedures to follow if patients become acutely suicidal.
4) Exploratory research assessments of mood, suicidality, and side effects (per Fig. 2) will continue for a six-week continuation phase post-infusion, for all subjects. Non-responders who opt for the open ketamine infusion will start the continuation phase after it. Continuation phase appointments will be weekly for six weeks, then decreasing to at least monthly, as clinically indicated, for the remainder of the six months.
5) In all follow-up treatments, psychiatrists will be available to patients between sessions for consultations and emergencies (a research psychiatrist is on-call at all times). Thus, clinical management will provide careful assessment of the patient's clinical condition to determine clinical changes, safety, and the need for withdrawal from the protocol. Psychiatrists will evaluate mood, suicidality, and treatment course to help determine if a patient's condition warrants removal from the study. Independent, masters or PhD level, raters will systematically assess suicidal ideation and/or behavior and depression weekly during the 6-week continuation phase for exploratory analysis.
6) Week 7-24: All patients will be offered free, open, clinical treatment, and then will be referred for ongoing care.
11. Outcome Measures: See Figure 2, Schedule of Research Procedures and Assessments (attached).
12. Safety Follow-up for Ketamine Abuse/Use:

a. At 3 and 6 months post-ketamine/midazolam, all subjects we can contact will be evaluated to determine the absence of post-exposure ketamine use/abuse.
You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation
13. Withdrawal from Study: Subjects will be withdrawn from the study if:
a. They request it for any reason.
b. The PI judges that it is medically unwise to continue in the study, for example if the subjects are unable to comply with the study procedures.
c. They are unable to tolerate the delay to treatment because of pronounced worsening of symptoms such as marked agitation or psychotic symptoms. Worsening of suicidal ideation will not automatically require discontinuation from research, since this is the primary study aim, as long as the team judges that the patient can be managed safely as an outpatient (e.g. they have no plan or intent), or they agree to inpatient treatment and the inpatient staff agrees that the patient may continue research participation.
d. A rise in systolic blood pressure ≥ 200 mm Hg or diastolic blood pressure to ≥ 115 mm Hg during the infusion.
e. During infusion, if 02 saturation remains <94% with nasal canula oxygen or respiratory rate <10, then patient will be withdrawn from research and treated clinically as described in Section 8.e.
f. Other criteria for discontinuation will be appearance of psychosis, mania, severe agitation, or other deterioration where the treating physician decides that research participation is unacceptable.
g. During the 6-week SSRI trial: 2 consecutive weekly CGI-I's >5.

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens

Sample	Collection Timepoint	Total Collected Per Patient
Blood	Baseline Pre and Post-infusion	59 ml 32 ml total (64 ml if two infusions)
Saliva	Pre-infusion day (2 samples); Post-infusion day (2 samples)	1ml per sample = Total 4 ml

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment

Domain	Instrument	Time
Informed consent	IRB-Approved Form	30–45 min
Diagnosis	SCID I, II	120min
Demographics	Division Baseline Demographic form (BDEMO)	30 min
Clinical State	Hamilton Depression Rating Scale 24-Item (HDRS-24)	10 min
	Beck Depression Inventory (BDI)	10 min
	Profile of Mood States (POMS)	10 min
	Global Assessment Score (GAS)	2 min
	Single Question Anxiety Rating (SQAR)	5 min
	Clinical Global Impressions (CGI)	1 min
Suicidal Ideation and Behavior	Columbia Suicide History (CSH)	10min
	Lethality Rating Scale (LRS)	5 min
	Beck Scale for Suicidal Ideation (SSI)	10 min
	Columbia Suicide Severity Rating Scale (C-SSRS)	5 min
	Beck Suicide Intent Scale (SIS)	10 min
	Brown Goodwin Aggression Inventory (BGAI)	10 min
Life Events	St. Paul Ramsey Scale (SPR)	5 min
Medication	Antidepressant Treatment History Form (ATHF)	20 min
	Systematic Assessment for Treatment Emergent Events-General Inquiry (SAFTEE-GI)	10 min
	Clinician-Administered Dissociative States Scale (CADSS)	15 min
	Brief Psychiatric Rating Scale (BPRS) – *Positive Symptoms Subscale* Only	10 min
	Adequacy of blind questionnaire	1 min
Biomarkers	Neuropsychological testing	45 min
	Salivary cortisol	10 min

Please attach copies, unless standard instruments are used

Off label and investigational use of drugs/devices

Choose from the following that will be applicable to your study
✓ Drug
Select the number of drugs used in this study
2

Drug #1

Name of the drug
Ketamine
Manufacturer and other information
Multiple generic manufacturers.
Approval Status
No IND is required
Choose one of the following options
FDA conditions are met (see 'Rules')
Explain

This is a clinical study involving two marketed drugs and the study meets all of the following conditions:
1. It is not intended to be reported to the FDA in support of a new indication for use or to support any other significant change in the labeling; and
2. It is not intended to support a significant change in the advertising for the product; and
3. It does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the product; and
4. It is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 50 and 56 respectively]; and
5. It is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7].

Drug #2

Name of the drug
Midazolam
Manufacturer and other information
Multiple generic manufacturers.
Approval Status
No IND is required
Choose one of the following options
FDA conditions are met (see 'Rules')
Explain

This is a clinical study involving two marketed drugs and the study meets all of the following conditions:
1. It is not intended to be reported to the FDA in support of a new indication for use or to support any other significant change in the labeling; and
2. It is not intended to support a significant change in the advertising for the product; and
3. It does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the product; and
4. It is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 50 and 56 respectively]; and
5. It is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7].

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
Yes
Maximum duration of delay to any treatment
Patients will continue their current psychiatric medication. The delay to inpatient admission will not exceed 2 weeks; if a subject needs a longer delay between consent and beginning treatment, it will be determined by the study clinician on a case-by-case basis based on need for delay, clinical stability, and ability to comply with the plan for monitoring. This period allows the time required for processing lab samples, completion of baseline research measures, and scheduling inpatient admission for the infusion procedure in the BSU. We will attempt to minimize this delay period. During this time period the treating physician will stay in contact with the participant and assess their clinical condition weekly, either in person or via phone, including the Clinical Global Impressions (CGI) scale. If items of concern are noted during a telephone contact, the participant will be brought in for an in-person visit. If someone has a CGII >5 then a repeat CGI-I will be done within 3-4 days and if it remains >5 then the subject will be withdrawn from research and start clinical treatment. Additionally, if the team judges that this delay is not clinically acceptable or the participant does not agree to the delay, then the patient will be withdrawn from research.
Maximum duration of delay to standard care or treatment of known efficacy
As described above, for subjects not already taking an antidepressant, treatment with standard antidepressant medication plus supportive clinical management will begin on the day after the ketamine/midazolam infusion, after 24-hour research assessments are completed. This adds 1 day to the delay described above. Non-responders who received midazolam and who choose to receive a clinical ketamine infusion prior to beginning standard clinical treatment will have an additional delay of a few days for BSU scheduling, which we will attempt to minimize.
Treatment to be provided at the end of the study
Described in Procedures (Section 10) above.

Clinical Treatment Alternatives

Clinical treatment alternatives
This is a study of sub-anesthetic ketamine's effect on suicidal ideation in suicidal depressed patients, with midazolam as an active control. Many treatments for major depressive disorder exist, such as numerous approved antidepressant medications, ECT, and various psychotherapies. Relatively little is known about best practices for more suicidal depressed patients.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period
Potential Risks to Subjects and Procedures for Minimizing Risks:
Risks associated with participation in this study are related to 1) side effects of the medications; 2) other medication related risks; 3) intravenous catheters; 4) blood drawing; and 5) pregnancy. Dr. Milak, a co-investigator on this study, has experience with this ketamine dose in our institution and will consult and supervise on this study's infusion procedures. Dr. Vivek Moitra, MD, Associate Clinical Professor of Anesthesiology, Associate Medical Director Surgical Intensive Care Unit, Associate Program Director, Critical Care Medicine Fellowship, Division of Critical Care, Columbia University College of Physicians and Surgeons, is experienced with both ketamine and midazolam, has reviewed this protocol, and is a consultant on this study.
1. Side effects of medications:
1.A. Side Effects of Intravenous Ketamine.
i) Medical Risks. Administration of sub-anesthetic doses of ketamine i.v., such as the 0.5 mg/kg dose to be used in this study, may induce a modest rise in blood pressure. We have administered sub-anesthetic doses of ketamine i.v. (0.5mg/kg over 40 minutes) in the setting of a currently approved MRI/MRS brain imaging protocol at this institution (IRB #5786, PI: J. Mann). The resulting effects on vital signs for the eleven patients scanned under protocol #5786 are presented as a function of time in Table 1 below for the duration of the ketamine injection. These modest increases all peaked and largely resolved by 75 minutes, with vitals returning to near baseline.

Table 1. Effects of ketamine on systolic and diastolic blood pressure in a group of patients (n=11). The dose of ketamine was 0.5 mg/kg given over 40 minutes.

Time (min)	Systolic Blood Pressure during Ketamine (mm Hg)	Diastolic Blood Pressure during Ketamine (mm Hg)	Pulse during Ketamine (min^{-1})
0	111	70	69
5	113	72	63
10	116	73	69
15	116	73	72
20	121	75	68

25	121	78	73
30	120	77	72
35	124	78	73
40	122	78	79
45	122	78	74
50	116	75	73
55	121	76	74
60	123	76	75
65	124	79	75
70	121	81	76
75	114	75	76

Describe procedures for minimizing risks
ii) Specific measures and precautions
Any medical risks from increased blood pressure will be minimized through the careful screening of potential subjects. Subjects will be excluded for baseline hypertension or any history of cardiovascular illness. A physician, Dr. Michael Grunebaum (ACLS certified 05/22/2012; copy of certification attached), will be present during the procedure. If physician coverage for Dr. Grunebaum is needed (such as vacation), then another ACLS-certified MIND physician (Drs. Matthew Milak or Martin Lan), who has been trained in the infusion procedure, will be present. Procedures for hypertension that occurs during the infusion are described above under Study Procedures. Nausea and vomiting will be treated supportively and, if severe, with anti-emetic agents; if necessary, administration of ketamine will be discontinued. Subject will be informed that they should be fasting (12 hours no food, 4 hours no liquids) prior to the ketamine infusion. For these reasons, the medical risks involved in participation in this study will be minimized.
iii) Psychiatric or Behavioral Risks. Ketamine is an FDA-approved dissociative anesthetic. Ketamine exposure at the sub-anesthetic dose to be used in this study can be associated with a moderate dissociative state, which is well tolerated in the majority of cases and is spontaneously reversible (7). There is extensive clinical experience with ketamine used at anesthetic doses, and no long-term detrimental effects of ketamine exposure have been reported. It is possible that ketamine administration will increase the risk of psychosis, even in normal subjects. Ketamine is a street drug of abuse. As such, it poses the risk that exposure during this study may predispose subjects to subsequent abuse of this drug. To minimize this risk, current drug or alcohol dependence or any history of ketamine abuse or dependence will be excluded. We will follow patients while they are receiving clinical treatment and review any evidence of abuse that may appear after the ketamine infusion. This dose of ketamine has been safely administered in similar settings to depressed patients with clinically significant suicidal ideation at least 23 times without
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any serious side effects (8, 9).
iv) Specific measures and precautions
The experiment will be carried out in the presence of at least one psychiatrist. In case of severe

agitation, hyperarousal, or psychosis, the blind will be broken. If the patient received ketamine, they will be treated with benzodiazepine (lorazepam) or neuroleptics, as indicated (see below for midazolam). The risks of exposing subjects to a drug of abuse potential will be minimized by explaining this risk to prospective subjects, and by excluding from the study any subjects with documented or suspected current substance or alcohol dependence.

2.A.2. Side Effects of Intravenous Midazolam

Midazolam is an imidazobenzodiazepine derivative in common use as a sedative and, like ketamine, anesthetic induction agent, including for routine outpatient procedures such as colonoscopy (10-12). It is the control medication at a dose of 0.045 mg/kg in the ongoing NIMHfunded ketamine RCT, "Optimization of IV Ketamine for Treatment Resistant Depression" (ClinicalTrials.gov Identifier NCT00768430; PI: SJ Mathew). We will use a lower dose of 0.02 mg/kg, which was found in a double-blind RCT of anesthesia pre-medication to produce equal anxiolysis, but fewer sedative and cardio-respiratory effects compared to 0.06 mg/kg (13). The lower dose was recommended by our anesthesiologist consultant, Dr. Moitra, as being less likely to make subjects sleepy, which would make it a less effective control medication.

i) Medical Risks.

a. Midazolam is an imidazobenzodiazepine derivative in common use as a sedative and, like ketamine, anesthetic induction agent (10-12). It has anxiolytic, hypnotic, muscle relaxant, and antegrade amnestic effects (10-12). Midazolam is not known to have direct effects on glutamate or NMDA receptors (10,11). To investigate the potential relationship of anxiety or anxiolysis to infusion effects on suicidal ideation, we will systematically assess anxiety using a visual analog scale (14).

b. Midazolam may cause respiratory depression, decreased systolic and diastolic blood pressure and increased heart rate (10-12) The sub-anesthetic dose we plan to use requires the presence of a physician, but not an anesthesiologist (personal communication from Eric Heyer, MD, Chief of Neuro-Anesthesiology, Columbia University Medical Center).

c. Cardio-respiratory effects are usually absent at intravenous sedative doses (0.05-0.15 mg/kg) and our planned dose is below the low end of this range (10-12). Midazolam has an onset of CNS activity within minutes, a half-life of 2-4 hours, and psychomotor performance returns to normal approximately 2 hours after administration (10-12) It is relatively free of other side effects such as nausea, vomiting, or venous irritation.10-12 Midazolam may cause confusion, but an RCT found it to be safe even in the elderly (15).

ii) Specific measures and precautions

The risk of respiratory depression with the midazolam dose in this study is expected to be "miniscule" (personal communication, Dr. Moitra, study consultant). Adverse effects of midazolam can be reversed with administration of the benzodiazepine antagonist flumazenil (10-12). Specific

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interventions for respiratory depression or low oxygen saturation are described under Study Procedures.

iii) Psychiatric or Behavioral Risks. Midazolam has anxiolytic, hypnotic, muscle relaxant, and antegrade amnestic effects substantially mediated by its binding to CNS benzodiazepine receptors and increased GABA activity (10-12). It is not known to have direct effects on glutamate

or NMDA receptors (10-12). Midazolam may cause confusion, but an RCT found it to be safe even in the elderly (15) Paradoxical excitation has approximately a 10% incidence after midazolam doses twice as high as the dose we plan to use, is more common among older patients, and is reversible within 30 seconds with administration of flumazenil (16).
iv) Specific measures and precautions
The experiment will be carried out in the presence of at least one psychiatrist. In case of severe agitation or hyperarousal, the blind will be broken and if the patient received midazolam, then they will be treated with neuroleptics and or flumazenil. The risks of exposing subjects to a drug of abuse potential will be minimized by explaining this risk to prospective subjects, and by excluding from the study any subjects with documented or suspected current substance or alcohol dependence.

2.A.3. Side Effects of Other Medications
Sertraline (or Fluoxetine, Paroxetine, Escitalopram): The potential side effects of SSRIs include nausea, sexual function change (orgasmic delay), weight loss or gain, headache and diarrhea, drowsiness or stimulation, nervousness and/or insomnia, and allergic reactions.
Zolpidem: The potential side effects are diarrhea, dizziness, drowsiness, a drugged feeling, and dry mouth.
Lorazepam: The potential side effects are dizziness, drowsiness, a drugged feeling, and some potential for tolerance and withdrawal symptoms.
Diphenhydramine, hydroxyzine: The potential side effects are dizziness, drowsiness, a drugged feeling, and dry mouth.
2.B. Other medication related risks:
Delay to Infusion: We will schedule the infusion as soon as possible. Patients on psychotropic medications may continue them. Patients may experience worsening of their depressive symptoms during this period and this will be discussed with all subjects as part of the consent process.
Non-response: There is a chance that the medications and/or dosages used in this study will not be helpful or that a participant may feel worse during participation in the study. Participants will be encouraged to tell their doctor if they feel worse during the study.
Other Risks Associated with Antidepressant Use:
The Food and Drug Administration (FDA) has issued a public health advisory concerning a possible link between worsening depression, and, in rare cases, suicidal thoughts or behavior in adults younger than 25 years of age treated with certain antidepressant medications (including those in this study). This FDA advisory will be discussed with all subjects as part of the consent
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process.
2.C. Risks from Intravenous Catheters. There is a small risk of infection and bleeding associated with intravenous catheters, which are prevented by proper techniques. Placement of IVs will be by a physician, nurse, or technician trained and certified in aseptic technique for catheter placement to minimize this risk.
2.D. Blood Drawing: The risks associated with drawing blood are slight discomfort and

occasional bruising. There is no risk of anemia in a physically healthy person with the amounts of blood drawn in this study.
2.E. Interviews: Psychiatric interviews and neuropsychological testing can sometimes be stressful, but some people find talking to a physician or psychologist helpful. The interviewers will all be experienced personnel. The research team may request permission to record the interview for teaching purposes with audiotape and/or videotape. In this event, a separate consent process will occur for this.
2.F. Saliva sampling: This procedure has no significant risks other than minor inconvenience.
2.G. Pregnancy: Pregnancy is one of the study's exclusion criteria and will be ascertained at screening with a pregnancy test. Patients must agree at the time of consent to use an effective form of birth control and to inform the treating psychiatrist in the event of pregnancy while in the study. A pregnancy test will be repeated on the pre-infusion day. If a patient becomes pregnant during the study, they will be withdrawn from research and treated clinically.
2. H. Electrocardiogram
An electrocardiogram has no serious risks. On rare occasions a rash may develop where the electrodes are placed which usually resolves without treatment.
3. Data and Safety Monitoring Plan: The Principal Investigator will be responsible for monitoring the safety and sound clinical care of all study participants through a weekly team meeting and as needed.
3.a. Adverse events. Serious adverse events will be reported per regulatory requirements. Other adverse events will be monitored using the SAFTEE-GI (17) and a weekly meeting of the research team.
3.b. Data and Safety Monitoring Board
i) Membership: A Data Safety Monitoring Board (DSMB) will consist of three members, all experienced psychiatric researchers in depressive disorders. None will be affiliated with the research team conducting this project.
ii) Responsibilities: The initial tasks include review of the protocol and study forms documenting adverse effects, laboratory results, and clinical research forms. If any modifications are indicated, they will be instituted. Throughout the study, notification of any Serious Adverse Events (SAEs) as

well as any investigator-initiated changes in the protocol will be submitted to the DSMB when they are submitted to the IRB. Based on its review of the protocol, the DSMB will identify the data parameters and format of the information to be regularly reported. The DSMB may at any time request additional information from the Principal Investigator. The DSMB may monitor study charts or delegate this task to the personnel of the New York State Psychiatric Institute IRB.
Other than SAEs, adverse events will be tabulated and submitted to the IRB and DSMB annually. SAEs are also reviewed by the Incident Review Committee of the New York State Psychiatric Institute. The DSMB will initially be given data blinded to treatment status but may request unblinding if there is a safety concern.
Based on review of safety data, the DSMB will make recommendations concerning the conduct of the study. These may include amending safety monitoring procedures, modifying the protocol or consent, terminating the study or continuing the study as designed.

iii) Initially, one DSMB member will review the study books of the first two patients to be enrolled to make sure that all necessary forms are included and are being filled out correctly. In addition, the DSMB will meet in person or by conference call after three and six months of enrollment and then on a semi-annual basis but can determine that more frequent meetings are indicated.
Meetings:
iv) Reports: The discussions and decisions of the DSMB will be summarized in written reports and provided to the NIMH Program Officer in annual reports.
v) HIPAA Procedures: This grant will go through Columbia University and will be conducted at the New York State Psychiatric Institute and Columbia University Medical Center. All HIPAA requirements will be followed including forms for patients to sign and receive a copy to keep as part of the informed consent process.

Methods to Protect Confidentiality

Describe methods to protect confidentiality
Records will be kept in locked files and access will be allowed only to members of the research team or institutional personnel as part of a routine audit. Research records, like other medical and clinical records, will be kept confidential to the extent permitted by law. Once a patient enrolls in the project they are given a code number for all subsequent computer data and/or lab forms. The code list and patient names as well as all data are kept in locked files in locked offices with access limited to those directly responsible for maintenance of these files by the research team. The data capture system we will use in this study, StudyTRAX, has been used as a data repository for NIH sponsored projects at NYSPI and is HIPAA compliant. Data sets are de-identified as defined in HIPAA 45 C.F.R. §164.514 (b)(2).
Will the study be conducted under a certificate of confidentiality?
Yes, we have already received a Certificate of Confidentiality

Direct Benefits to Subjects

Direct Benefits to Subjects

Subjects will receive a complete medical, neurological and psychiatric evaluation, results of which will be communicated to them. Subjects are not expected to benefit directly from participation in this study, however, they will be offered a total of six months of medication based treatment for depression.

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
Yes

Please describe and indicate total amount and schedule of payment(s).
Include justification for compensation amounts and indicate if there are bonus payments.

We will give participants a modest inconvenience payment of $20 cash for each outpatient visit at which research data are collected, which we believe will not be coercive but will help recruitment and decrease attrition. Subjects will not receive payment for research assessments or procedures during the inpatient stay.

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Uploads

Upload the entire grant application(s)
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Upload copy(ies) of unbolded Information Sheet(s)
Upload copy(ies) of bolded Information Sheet(s)
Upload a copy of Certificate of Confidentiality
Upload copy(ies) of the HIPAA form
Upload any additional documents that may be related to this study