STUDY PROTOCOL

Social Behavioral Template

Role Of Non-Specific Effects in The Treatment of depression with Esketamine (ROSETTE)

Protocol Number

2000034829

Protocol Version

Version Date: 3/6/24

Version # 2

Clinical Trials Registration Number (if applicable)
NCT05910775

Confidentiality Statement:

Synopsis

Purpose

We aim to examine the magnitude of non-specific effects in the treatment of depressive episodes with esketamine, by providing patients in the “intervention” group with a pre-treatment presentation and post-treatment “follow up” session, to assess whether non-specific effects can be used effectively to improve the effectiveness of treatment with esketamine.

Objectives

Primary Objective:

To determine whether a positive presentation before first treatment improves expectation of improvement from treatment in patients receiving esketamine for a depressive episode within 24 hours after the first treatment.

Secondary Objectives:

To determine whether a post-treatment follow up session to provide encouragement and reassurance improves expectation of improvement from treatment in patients receiving esketamine for a depressive episode within 24 hours after the first treatment.

To determine whether a positive presentation results in an improved response from treatment in patients receiving esketamine for a depressive episode as measured by MADRS score within 24 hours after the first treatment.

To determine whether a positive presentation before first treatment, combined with a post-treatment follow up session after first treatment, result in an improved response from treatment in patients receiving esketamine for a depressive episode as measured by MADRS score by the end of the acute course of esketamine treatment.,

Study Population

Adult patients with major depressive disorder for whom it has been determined by their primary mental health provider that esketamine is an appropriate treatment and have already been deemed appropriate and scheduled for clinical esketamine treatment at Yale Interventional Psychiatry Service.

Number of Participants

We aim to enroll a total of 34 patients (17 per arm) for this study.

Study Design

Patients who are deemed clinically appropriate for esketamine will be approached for participation in the study. The eligible and consented participants will be randomized at a 1:1 ratio into “intervention” and TAU groups, with the intervention group being presented with the presentation prior to the first treatment, and to receive a “follow up” session within 24 hours after the first treatment. Both groups will otherwise receive treatment as usual during the course. Assessments including treatment expectations and depression severity will be done at baseline, within 24 hours after treatments 1, 2 and 8.

Study Duration 2 years
Outcome Variables Primary outcome: Group difference in change in question 6 of the CEQ-6 from baseline to after the presentation Secondary Outcome: Group difference in change in MADRS score from baseline to 24 hours after first treatment Exploratory outcomes: Group difference in change in CEQ-6 from baseline to 24 hours after first treatment and after follow-up session Group difference in change in MADRS score by the end of the acute series of treatments Group difference in the side effect profile
Locations/Facilities Yale Psychiatry hospital (YPH) Interventional Psychiatry Services (IPS) unit

Abbreviations

Abbreviation	Explanation
AE	Adverse Events
CMP	Clinical monitoring plan
CEQ-6	Credibility and Expectancy Scale
CRF	Case report form
DCC	Data coordination center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Department of Health and Human Services
EC	Ethics Committee
eCRF	Electronic Case Report Forms
GCP	Good clinical practice
HIPAA	Health Insurance Portability and Accountability Act
MADRS	Montgomery-Asberg Depression Rating Scale
NCT	National Clinical Trial
NIH	National Institutes of Health
PI	Principal Investigator

QA	Quality Assurance
QC	Quality Control
QIDS-SR	Quick Inventory of Depressive Symptomatology
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
TAU	Treatment as usual
UP	Unanticipated Problem
YCCI	Yale center for clinical investigation

Glossary of Terms

Glossary	Explanation
Adverse Event	Any event associated with esketamine treatment or the virtual presentation and follow-up sessions whether or not considered therapy related.
Dysgeusia	Altered taste
Serious adverse event	Serious adverse events (SAEs) are defined as AEs that result in death, are life-threatening, require hospitalization, or result in prolongation of existing hospitalization, permanent or significant disability a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

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Protocol Revision History

Include the IRB approved protocol version number and date for each revision of the protocol. All version history should remain in the table and never be deleted. The oldest IRB approved version of the protocol should be listed on the top row. The most recent IRB approved version should be listed on the bottom row.

Version Date	Summary of Substantial Changes

1 Background

1.1 Background

Non-specific treatment effects and more specifically placebo effects have been recognized as major factors contributing to the effectiveness of various therapies for more than two centuries[1] As early as 1955 Beecher noted that placebo effects can be quite beneficial and should be studied further[2]. However, more recently placebo effects have largely been viewed as a nuisance in the conduct of clinical trials and most efforts have been directed at minimizing the effect to better isolate the true specific-treatment effect[3]. Understanding the factors that contribute to the non-specific effects of a treatment, including the placebo and nocebo effects (negative effects experienced in concordance with the expected side effect) could improve our ability to provide effective treatment to patients with little added costs to the health care system[4].

Significant advances have been made in our understanding of the basic factors contributing to the placebo and nocebo effects over last few decades[5]. It is theorized that the culmination of verbal, social and conditioned “cues” create an expectancy for a specific therapeutic response driving the powerful placebo effect[5]. Recent work has begun to elucidate the neurobiological mechanisms underlying this effect. While moderate to large placebo response rates have been observed in a broad range of medical diseases ranging from neurological disorders[6] and depression[7,8] to cardiovascular disorders[9], much of the mechanistic research in this area has been focused on the study of pain management as it is most amenable to studies examining the rapid onset of the effect. The narrow scope of the mechanistic research leaves questions about generalizability and applicability of the findings to other disorders in question. The discovery of rapidly acting antidepressant medications such as ketamine now allows for the efficient investigation of placebo and nocebo effects in patients suffering from depression.

Yale has been a leader in the development of rapidly acting antidepressant treatments and the Interventional Psychiatry Service (IPS) at Yale Psychiatric Hospital (YPH) currently provides over 70 ketamine/esketamine treatments for major depressive disorder (MDD) per week. Throughout the conduct of nearly 20 years of clinical trials and 8 years of clinical care with these treatments, clinicians and investigators working in the program have been increasingly intrigued by the non-specific contributions of the treatments to the clinical response. The data from the existing phase 2 and 3 trials of esketamine[10] have demonstrated much higher than expected rates of response in the placebo treated groups which also suggests a notable non-specific component to the treatment.

1.2 Prior Experience

NA.

2 Rationale/Significance

2.1 Rationale and Study Significance

Based on the available evidence, non-specific effects are thought to be responsible for a notable portion of treatments' effects and side effects. Considering the prevalence of depressive disorders and their significant burden on the society[11], any potential improvements in effectiveness can have far reaching benefits for our patients and the society. This project aims to methodologically examine the magnitude of non-specific effects in the treatment of depressive episodes with esketamine, to explore the moderators and mediators of the effect, and to assess whether the non-specific effects can be used effectively to improve the effectiveness of this treatment.

The data collected in this initial study will be used to provide support for future study proposals designed to more thoroughly evaluate the moderators and mediators of the effect employing the wide range assessment tools and imaging modalities available here at Yale. Furthermore, the laboratory model created through this initial study can be further optimized and modified for use with novel treatments currently under investigation for mental health and other disorders, namely psychedelic treatments.

2.2 Risks

Intervention-specific Risks

The main risk to participants in the current study consists of a change in the level of effectiveness and side effects from treatment as a result of the study intervention. Specifically, the "intervention" group may experience a different rate of response, or notice side effects to a different degree than the "treatment as usual" group.

Although non-specific effects in general are believed to be responsible for a significant portion of the treatment's effects, as the current study only targets a small subcategory of non-specific factors, the magnitude of increased risk will be limited. Furthermore, the study is designed to create a difference between groups mainly by potentially improving the outcomes of the "intervention" group.

The "intervention" group may also experience more dysgeusia which is one of the mild and temporary side effects of esketamine, as a result of intentionally highlighting it in the presentation.

Additionally, the "intervention" group may experience some distress during the "post-treatment" session, particularly if they need to review and discuss distressing or uncomfortable experiences from the treatment.

Psychiatric Assessment and Symptom Rating

Discussing symptoms or past experiences can sometimes be stressful. All included evaluations are non-invasive and have been used without difficulty or adverse events in previous studies and clinical practice.

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

Confidentiality

Loss of confidentiality is another potential hazard of any research protocol. The investigators follow a system of specific precautions to ensure the confidentiality of data in this protocol.

Private identifiable information will be collected (name, date of birth, age, telephone number, address, medical and psychiatric history, diagnoses, laboratory tests, and psychiatric rating scores) but will be kept confidential and will not be divulged in any publication emanating from this work. Please see section 8.1, for the protections in place to mitigate confidentiality risks.

2.3 Anticipated Benefits

Participants may or may not benefit from the study through improvement in their clinical outcomes. Both groups will have extensive contact with the research team in addition to the usual clinical care team, which may provide some additional benefit to patients. Participants will be paid for their participation in the study. They will be paid $50 for completing each non-presentation visit (Screening visit, 24 hours post 1-st treatment, 72 hours post 8th treatment), which makes it up to 150 dollars in total if they complete the study. They will not be paid for the presentation visit. They will receive a debit card upon consenting and completing the screening visit and the reimbursement will be loaded to the card after completing each of the mentioned visits.

The results of this initial study would benefit the field by providing a better understanding of the role of non-specific effects, and whether and to what extent these effects can be optimized.

3 Study Purpose and Objectives

3.1 Purpose

We aim to examine the magnitude of non-specific effects in the treatment of depressive episodes with esketamine, by providing patients in the “intervention” group with a pre-treatment presentation and post-treatment “follow up” session, to assess whether non-specific effects can be used effectively to improve the effectiveness of treatment with esketamine.

3.2 Hypothesis

Hypothesis 1: A positive presentation highlighting the rapid onset effects and positive therapeutic outcomes observed in prior clinical trials and clinical care will increase the expectation of improvement from esketamine treatment compared to the treatment-as usual (TAU) group.

Hypothesis 2: A post-treatment “debriefing” session after first the treatment to provide encouragement and reassurance, will further consolidate the expectation of improvement from esketamine treatment.

Hypothesis 3: A positive presentation highlighting the rapid onset effects and positive therapeutic outcomes observed in prior clinical trials and clinical care combined with a post-treatment “debriefing” session after first the treatment to provide encouragement and reassurance will enhance treatment response compared to the TAU group.

Hypothesis 4: Highlighting a specific side effect during the presentation will result in a difference on the side effect profile of the treatment.

3.3 Objectives

Primary Objective:

To determine whether a positive presentation before first treatment improves expectation of improvement from treatment in patients receiving esketamine for a depressive episode within 24 hours after the first treatment.

Secondary Objective:

To determine whether a post-treatment debriefing session to provide encouragement and reassurance improves expectation of improvement from treatment in patients receiving esketamine for a depressive episode within 24 hours after the first treatment.

To determine whether a positive presentation result in an improved response from treatment in patients receiving esketamine for a depressive episode as measured by MADRS score within 24 hours after the first treatment.

To determine whether a positive presentation before first treatment, combined with a post-treatment debriefing session after first treatment, result in an improved response from treatment in patients receiving esketamine for a depressive episode as measured by MADRS score by the end of the acute course of esketamine treatment.

4 Study Design

Approach and consent:

Patients who are deemed clinically appropriate for esketamine will be approached for participation in the study. They will be provided with information regarding the study, including that they will be randomized into two groups with the “intervention” group receiving an informative presentation prior to the first treatment. They will be informed that the goal is to assess the effect of this presentation with regard to its ability to provide sufficient and appropriate information surrounding the treatment. Participants will not be informed at the time of recruitment that we hypothesize the content to potentially affect the tolerability and effectiveness of the treatment course. They will be informed about the full nature of the study

at a end of treatment debriefing session at the end of their participation (further details below).

Randomization

Participants will be randomized at a 1:1 ratio into “intervention” and TAU groups, with the intervention group being presented with the presentation prior to the first treatment, and to receive a “debriefing” session within 24 hours after the first treatment. Both groups will otherwise receive treatment as usual during the course.

Intervention

The intervention consists of a short presentation provided to the participants within 72 hours prior to the first treatment of the acute course (see study course below). Both groups will receive the information considered necessary for informed consent for esketamine treatment as part of usual clinical care. The presentation will be in addition to this process. The presentation will be factual, however it will emphasize the effectiveness of the treatment, and provide notable encouragement and reassurance. The actual treatments will be provided as usual with no change or alteration in dosing, course or other aspects of the treatment.

The intervention group will additionally receive a follow up session within 24 hours after the first treatment to provide encouragement and reassurance. There are two different versions for the follow up session, with each participant receiving one of the versions depending on whether they have noticed any improvements since the first treatment. The contents of these sessions will remain factual, but with differing emphasis on encouragement and reassurance depending on participants’ experience with the first treatment.

Study course

Participants in the intervention group will receive the presentation within 48 hours before the first treatment of the acute course of esketamine. They will also receive the follow up session within 24 hours after the first treatment, immediately after assessments are completed.

Assessments will be done at baseline, within 24 hours after treatments 1, 2 and 8, as detailed in Table 1. Assessments will be identical for both groups, with the exceptions described below.

Assessments

<u>Intervention group specific assessments:</u>

Participants will provide feedback regarding the presentation using a custom form (Appendix 1) before treatment 1 and at the end of treatment visit.

<u>Assessments received by both groups:</u>

Participants’ expectations will be assessed by Treatment Credibility and Expectancy Scale (CEQ-6).

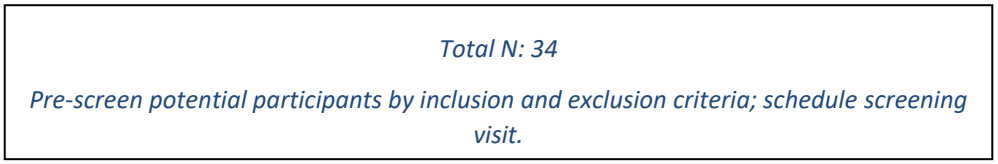
Symptom severity will be assessed by a blinded assessor using a Clinician Rated Outcome questionnaire (MADRS) and a Patient Rated Outcome questionnaire (QIDS-SR16).

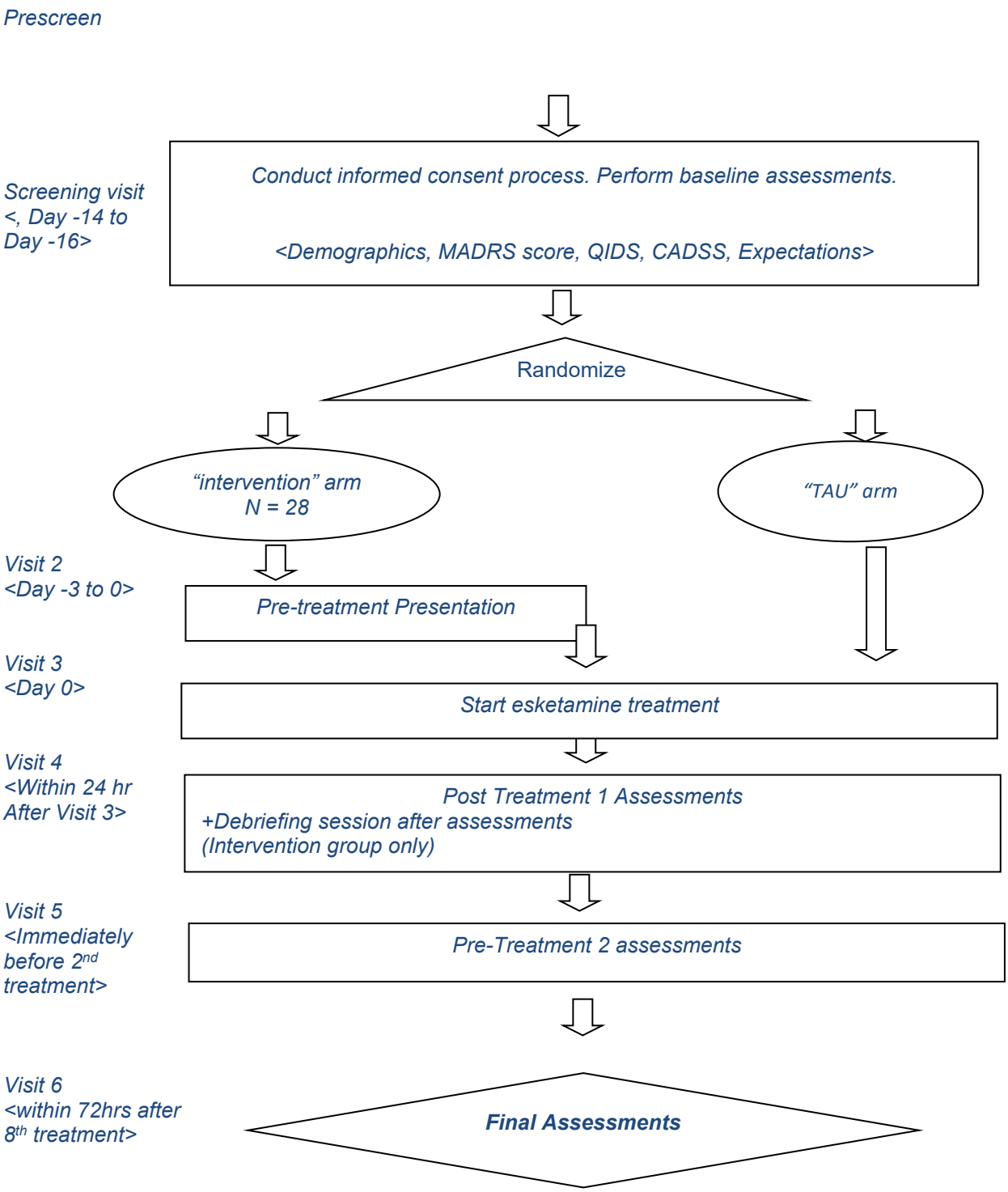
Side effects will be assessed by a custom questionnaire (Appendix 2) based on the side effects reported on the prescription label for esketamine.

End of treatment debriefing session:

A debriefing session will be held at the end of the study at the 1-month follow up visit, immediately after the last set of assessments are completed. During this session participants will be informed about the nature of the study in detail, including the hypothesized effects of non-specific factors on overall treatment efficacy, and [for participants in intervention group] the intentional emphasis of a minor side effect (dysgeusia) during the presentation compared to usual care. Participants will be given a chance to ask any questions regarding the study.

Study Flow Diagram




Prescreen
Screening visit <, Day -14 to Day -16>
Conduct informed consent process. Perform baseline assessments.
<Demographics, MADRS score, QIDS, CADSS, Expectations>
Randomize
"intervention" arm N = 28
"TAU" arm
Visit 2 <Day -3 to 0>
Pre-treatment Presentation
Visit 3 <Day 0>
Start esketamine treatment
Visit 4 <Within 24 hr After Visit 3>
Post Treatment 1 Assessments
+Debriefing session after assessments (Intervention group only)
Visit 5 <Immediately before 2nd treatment>
Pre-Treatment 2 assessments
Visit 6 <within 72hrs after 8th treatment>
Final Assessments

4.1 Study Duration

The study is anticipated to be completed in two years

4.2 Outcome Variables/Endpoints

4.2.1 Primary Outcome Variables/Endpoints

Primary outcome: Group difference in change in question 6 of the CEQ-6 from baseline to after the presentation

4.2.2 Secondary and Exploratory Outcome Variables/Endpoints

Secondary Outcome: Group difference in change in MADRS score from baseline to 24 hours after first treatment

Exploratory outcomes:

Group difference in change in CEQ-6 from baseline to 24 hours after first treatment and after follow-up session

Group difference in change in MADRS score by the end of the acute series of treatments

Group difference in the side effect profile

5 Study Participants

5.1 Study Population

Adult patients with a depressive episode for whom it has been determined by their primary mental health provider that esketamine is an appropriate treatment and have already been deemed appropriate and scheduled for clinical esketamine treatment at Yale Interventional Psychiatry Service according to existing FDA REMS that includes diagnoses of treatment resistant depression, or depression with suicidal ideation, will be eligible for participation in the study.

5.2 Number of Participants

We aim to enroll a total of 34 patients (17 per arm) for this study.

5.3 Eligibility Criteria

Inclusion criteria:

To take part in this study, the following eligibility criteria must be met:

- Participants must be either male or female and at least 18 years old
- Deemed clinically appropriate to receive esketamine by a Yale Interventional Psychiatry physician.

- Written consent for the study procedures
- Ability and willingness, in the investigator's judgement, to comply with the study schedule, treatment plan, and other trial requirements for the duration of the study.

Exclusion criteria:
Any individual who meets any of the following criteria will be excluded from participation in this study:

- Hearing or visual impairment to the degree that would interfere with ability to view the presentation
- Difficulty in understanding spoken or written English
- Unable to provide informed consent
- Dementia or other cognitive disorder or intellectual disability that would impair the subject's ability to understand the presentation (per investigator judgment)
- Any other medical or psychiatric comorbidity that the investigator judges would put the participant at additional undue risk due to study participation or would impair subject's ability to participate in the study.
- Previous Esketamine or ketamine treatment
- Unable to give informed consent
- Was previously enrolled/randomized into the trial

Note: Since only patients who have already been deemed clinically appropriate and are planned to receive esketamine are approached, and participation in the study does not influence patients receiving or not receiving esketamine, exclusions for this medication are not included in the study exclusion criteria.

5.4 Recruitment Procedures

Potential subjects will be referred to the study team by the interventional psychiatry physician who has seen the patient in clinical evaluation for esketamine, after ascertaining their agreement to be approached for the study. At this time, the patient will be reached out by a study team member and informed about the study.

5.5 Consent/Assent Procedures/HIPAA Authorization

- Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting procedures/administering study intervention.
- Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The study team member consenting the participant will explain the research study to the participant and answer any questions that may arise. This conversation will take place in a private room.

- Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate.
- Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records.
- Note: Given the nature of the study, the consent form will not provide details about the main objectives of the study, but will provide a general outline, explaining that the goal is to assess various ways of presenting relevant information to patients, and various ways of follow up after the first treatment. The true objectives of the study will be explained in detail during the debriefing session after the conclusion of all study procedures for each participant.

6 Study Methods/Procedures

6.1 Study Procedures

Potential subjects will be referred to the study team by the interventional psychiatry physician who has seen the patient in clinical evaluation for esketamine, after ascertaining their agreement to be approached for the study. At this time, the patient will be reached out by a study team member and informed about the study.

Screening / Intake Visit

It is estimated the screening intake will take approximately 2 hours. It will consist of the following procedures and assessments and can be completed in up to 5 days:

a. Informed Consent: A delegated study team member will discuss risks and benefits of participation and review the study overview with the patient as explained above. The patient will sign the informed consent form prior to any study procedures being performed.
b. Clinical and Demographic Intake (including medical and psychiatric history, medication history, and current medications)
c. Montgomery-Asberg Depression Rating Scale (MADRS) and Quick Inventory of Depressive Symptomatology (QIDS-SR16)
d. CEQ-6 questionnaire regarding upcoming treatment course with esketamine
e. Review of Inclusion/Exclusion Criteria by investigator

Presentation Visit (Intervention group only)

The intervention consists of a short virtual (via Zoom or similar technology) presentation provided to the participants, within 72 hours before the first treatment with esketamine. The presentation includes predetermined slides and content (the presenter will cover the same

slides and topics but will avoid a strict script to retain the personalized feeling of the presentation, an aspect believed to be crucial to the non-specific effects. Further, patients are allowed to engage, ask questions etc.) The presentation will remain factual and provide information from peer-reviewed literature. However, it is designed to convey a strong positive message, highlighting the effectiveness of the treatment. Additionally, a mild and temporary known side effect of the treatment (dysgeusia) will be intentionally highlighted to assess the 4th hypothesis.

Treatment visits:

Both groups will receive the usual treatment and care. Immediately before first and second treatments both groups will complete the CEQ-6 questionnaire. Additionally, the intervention group will complete the presentation feedback form prior to the first treatment. The rest of the treatments (i.e. treatments 3 to 8) will be done without any assessments.

Follow-up visit:

Twenty-four hours after the first treatment, CEQ-6, MADRS, QIDS, side effects, and adverse effects will be collected. Additionally, patients in the intervention group will receive a follow-up session after their first esketamine treatment. The follow up session will utilize one of two versions: “early-responder” content will be presented to patients with a noticeable improvement after first treatment, providing encouragement. “Early non-responder” content will be presented to patients with no noticeable improvement after first treatment, providing reassurance.

End of study visit:

During the end of study visit, MADRS, QIDS and side effects information will be collected. Additionally, a debriefing session will be held, immediately after the last set of assessments are completed. During this session participants will be informed about the nature of the study in detail, including the hypothesized effects of non-specific factors on overall treatment efficacy, and [for participants in intervention group] the intentional emphasis of a minor side effect (dysgeusia) during the presentation compared to usual care. Participants will be given a chance to ask any questions regarding the study.

Table 1: Visit Schedule Table

Timeline based on ketamine/esketamine treatments	Screening session	Within 72h before treatment 1 (intervention group only)	Immediately before Treatment 1	24hr post dose 1	Immediately before Treatment 2	Within 72 hours after 8th treatment
Day (subject to clinical treatment schedule)	-16±14	-3	0	1	5±3	30±3
Interventions						
Presentation		**X**				
Follow up session				**X**		
End of Treatment Debriefing						**X**
Assessments						
Demographics	**X**					
MADRS	**X**			**X**		**X**
QIDS	**X**			**X**		**X**
Presentation quality feedback*			**X**			
Side effects*				**X**		**X**
Expectations**	**X**		**X**	**X**	**X**	

6.1.1 Data Collection

Data collection for the study will be conducted in several stages. Firstly, the eligible participants will be approached and consented to participate in the study. A delegated study team member will discuss risks and benefits of participation and review the study overview with the patient as explained above. The patient will sign the informed consent form prior to any study procedures being performed. After that a trained research study team member will collect clinical and demographic information (including medical and psychiatric history, medication history, and current medications) using a custom questionnaire. After that symptom severity will be assessed by a trained and blinded assessor using a Clinician Rated Outcome questionnaire (MADRS) and a Patient Rated Outcome questionnaire (QIDS-SR16). Then participant expectations regarding upcoming treatment course with esketamine will be accessed using the Treatment Credibility and Expectancy Scale (CEQ-6) questionnaire. After this visit the investigator will review the Inclusion and Exclusion Criteria. If the participant is eligible, randomization will take place.

After randomization and within 72 hours before first treatment, participants in the intervention group will receive a virtual presentation on the benefits and potential side effects of esketamine. The presentation will be factual, however it will emphasize the effectiveness of the treatment, and provide notable encouragement and reassurance. The actual treatments will be provided as usual with no change or alteration in dosing, course or other aspects of the treatment.

Participants in intervention group will provide feedback regarding the presentation using a custom form before treatment 1. (See appendix 1)

Twenty-four hours after the first treatment, participants' expectations will be assessed by Treatment Credibility and Expectancy Scale (CEQ-6).

Symptom severity will be assessed by a trained and blinded assessor using a Clinician Rated Outcome questionnaire (MADRS) and a Patient Rated Outcome questionnaire (QIDS-SR16).

Side effects will be assessed by a custom questionnaire based on the side effects reported on the prescription label for esketamine. (See appendix 2)

All data collected will be stored and managed securely and will be regularly monitored to ensure its quality and accuracy.

6.2 Method of Assignment/Randomization

The randomization process in the study will occur after the screening visit and once the eligibility criteria have been checked and it has been determined by the PI that the subject qualifies. The eligible patients will be randomly assigned to either the intervention group or the TAU group with a 1:1 ratio. Randomization will be conducted using the sequentially numbered, opaque sealed envelopes (SNOSE)[12].

6.3 Adverse Events Definition and Reporting

Study investigators will be able to remove patients from the trial based on their clinical discretion and specific patient outcomes. Any adverse events, including grading of severity and attribution to research will be reported.

In this study, AEs will be defined as any event associated with virtual presentation and follow-up sessions whether or not considered intervention related. This includes any physical, psychological or emotional harm, or any other unintended effects experienced by the participant. Adverse events will be considered from the time of consent and will be monitored and recorded throughout the study. AEs evaluation will be done 24 hours after the first treatment and within 72 hours after 8th treatment. Participants will be asked to report any AEs they experience, either spontaneously or during the study visits. AEs will be recorded on the appropriate CRF. Patients will be closely monitored for adverse events.

The following adverse events will be collected from the time of randomization for the study:

- Adverse events that are not listed in the current labeling for esketamine. This includes events that are similar to those on the labeling but differ from the event because of greater severity or specificity.
- Study Treatment Discontinuation Adverse Events
- Events that lead to the discontinuation of esketamine will be collected for the study. These events will be recorded on either an AE or an SAE form.

The study team will document the AEs, its severity, relationship to the intervention, and the actions taken to address it.

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

Note: In addition to AEs as described above, a separate side effect form will be collected during the trial which will solely focus on known side effects of esketamine as per the current labeling (See appendix 2).

6.4 Reaction Management

Reaction management refers to the actions taken to manage any adverse events (AEs) that occur during the study. In the event that a participant experiences an AE, the study team will take appropriate measures to manage the reaction, minimize harm, and ensure the safety and well-being of the participant.

The first step in reaction management is to identify and document the AE. Participants will be asked to report any AEs they experience, either spontaneously or during the study visits.

The study team will document the AE, its severity, relationship to the intervention, and the actions taken to address it.

Based on the severity of the AE, the study team may take various actions to manage the reaction. For minor AEs, such as mild nausea or headache, the study team may provide advice or over-the-counter medications to alleviate the symptoms. For more serious AEs, such as hospitalization, the study team will take immediate action to ensure the safety and well-being of the participant.

If necessary, the study team may discontinue the intervention for a participant experiencing a serious adverse event. Participants who experience a serious adverse event will be referred to their treating physician or a specialist for further evaluation and management.

6.5 Withdrawal Procedures

The withdrawal procedure refers to the process for removing a participant from the study if they decide to discontinue their participation or they may be withdrawn at the discretion of the investigator at any time.

Participants may withdraw or be withdrawn from the study for various reasons, including adverse events, dissatisfaction with the study, personal circumstances, or inability of the subject to comply with the protocol-required schedule of study visits. In the event of a participant wishing to withdraw from the study, they will inform the study team.

The study team will inquire about the reason for withdrawal and document the reason and any relevant information related to the participant's decision. The investigator should also request the subject to return for an end-of-study visit to assess AEs/SAEs, safety endpoints, outcome events, and vital status. The investigator should also follow-up with the subject regarding any unresolved adverse events. Any unresolved events at the end of study or withdrawal should be followed for 2 weeks, until resolution, or until an adequate treatment plan is in place.

If the subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. Adequate documentation of this request should be obtained and retained in the subject's source file. True withdrawal of consent should be initiated by the subject and in writing. Data collected before the withdrawal of consent may be retained and used for analysis.

Patients who Withdraw from Treatment but not study

Participants may also decide to withdraw from the intervention but not the study for any reason. Or an investigator may withdraw a participant from the intervention for the following reasons:

- Significant study intervention non-compliance

- If any clinical adverse event (AE), or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Medical condition 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
- Study termination

Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

For participants who withdraw from treatment prior to 8th esketamine treatment and are not replaced, we will try to continue to collect the MADRS, the QIDS, and adverse events as indicated by study protocol.

If a participant withdraws from the study, they will no longer receive the intervention and he study team will ensure that the participant's privacy and confidentiality are maintained and that all personal information is handled in accordance with relevant regulations.

The study team will also ensure that any data collected from the participant up to the point of withdrawal is analyzed and reported in accordance with the study protocol.

6.6 Locations/Facilities

This is a single-site trial that will take place at Yale University (New Haven, CT). Treatments will take place at Yale Psychiatric Hospital (YPH, part of Yale New Haven Hospital; YNHH), Interventional psychiatry services (IPS). Clinical assessments will take place at YPH or virtually via HIPAA compliant technology (e.g. Yale Zoom), as applicable.

7 Statistical Design

7.1 Sample Size Considerations

While to our knowledge there are no analogous studies in the literature to use as a basis for sample size calculation, we used the data from the two active groups of a relatively similar study of open-label vs placebo-controlled citalopram[7] to calculate sample size for the current study. Based on this data, sample size per arm was calculated as follows[13]:

$$N = 2 \times \left(\frac{z_{1-\alpha} + z_{1-\beta}}{\delta - \delta_0} \right)^2 \times s^2$$

To account for dropouts, we have chosen a sample size of 34 participants (17 per arm) during the two years of the study.

7.2 Planned Analyses

Data will be examined prior to analysis using descriptive statistics, presented as means ± SD or median (interquartile range) for continuous characteristics, and as frequencies (%) for categorical characteristics.

Where appropriate, randomized groups will be compared on baseline continuous characteristics (e.g. age) using two-sample Welch's t-test or Wilcoxon rank sum test, and on categorical characteristics using the chi-square test or Fisher's exact test as appropriate. Continuous outcome measures will be assessed for normality using histograms and Q-Q plots, and transformations will be applied as necessary. Between groups primary and secondary outcomes (CEQ-6, MADRS and QIDS) will be considered significant using a two-tailed alpha threshold of 0.05.

The primary and secondary outcomes (CEQ-6, MADRS, QIDS) will be compared between groups using a linear mixed model with group (intervention, TAU) included as a between-subjects factor and time (see study timepoints) included as a within-subjects factor. The group by time interaction will be modeled. The correlation between multiple measurements in different timepoints within each subject will be modeled with random effects with the best-fitting model determined using information criteria.

7.2.1 Secondary Objective Analyses

Please see above for the analysis of secondary efficacy outcomes (MADRS and QIDS). To examine the safety and tolerability of the intervention for the duration of the study, we will use descriptive statistics to characterize the rates of these events in the intervention group.

7.2.2 Analysis of Subject Characteristics

Baseline characteristics will be examined using descriptive statistics, presented as means ± SD or median (interquartile range) for continuous characteristics, and as frequencies (%) for categorical characteristics. Baseline characteristics include age, sex, ethnicity, socioeconomic status, treatment expectation (CEQ-6) and psychiatric symptoms (MADRS, QIDS).

7.2.3 Interim Analysis

NA

7.3 Data Relevance

In the study, the primary research question is whether a positive presentation highlighting the rapid onset effects and positive therapeutic outcomes of esketamine treatment, before first treatment improves expectation of improvement from treatment in patients receiving esketamine compared to the treatment-as-usual (TAU) group.

The secondary research question is whether a positive presentation results in an improved response from treatment in patients receiving esketamine for a depressive episode as measured by MADRS score within 24 hours after the first treatment.

To answer these questions, the data collected will include expectations of improvement assessed by the Treatment Credibility and Expectancy Scale (CEQ-6), symptom severity assessed by Clinician Rated Outcome questionnaire (MADRS) and Patient Rated Outcome questionnaire (QID-SR16), and side effects assessed by a custom questionnaire. These data points will be analyzed and compared between the intervention and TAU groups to determine if there is a difference in treatment response and whether the non-specific effects of the positive presentation and follow-up session have an impact.

7.4 Data Coding

In this study, data coding will be necessary for several aspects of the data collection, including participant characteristics, treatment groups, and outcome measures.

For participant characteristics, such as age, gender, and baseline symptom severity, appropriate codes can be assigned to easily categorize and analyze the data. For example, age can be coded as continuous or categorical (e.g., 18-25, 26-35, 36-45, etc.), and gender can be coded as binary (male/female).

For treatment groups, a binary code can be assigned to each participant, with 0 representing the treatment-as-usual group and 1 representing the intervention group. This will allow for comparison between the two groups.

For outcome measures, such as symptom severity and side effects, appropriate scoring systems or coding will need to be established. The symptom severity can be measured using the Clinician-Rated Outcome questionnaire (MADRS) and Patient-Rated Outcome questionnaire (QID-SR16), and these scores can be transformed into categorical or continuous variables for analysis. For the side effects, a custom questionnaire based on the side effects reported on the prescription label for esketamine will be used and side effects can be coded as present or absent.

7.5 Data Analysis Tools

R version 3.3 will be used.

7.6 Data Monitoring

Given the minimal-risk nature of the study, and as patients are simultaneously receiving treatment as part of usual clinical care, no external monitoring will be done.

7.7 Handling of Missing Data

Our primary analyses will be intent-to-treat using all available data. We will undertake sensitivity analyses to assess the impact of the missing response data on our conclusions. We will perform single-step (e.g., missing values on the response variable replaced by predicted values from linear or generalized linear models of the longitudinal data over time) or multiple imputation and compare the performance of the imputed data results compared to complete case analyses. It is important to note that the linear mixed model method we propose to use is valid under the assumption that missing data is missing at random (MAR). Since it is not possible to test the MAR assumption and since for every MNAR model there is an equally well-fitting MAR model, we believe that the only suitable approach is to perform sensitivity analyses according to different plausible scenarios for missing data and make sure the conclusions are consistent. If the results are not consistent depending on the assumptions for missing data we will report the conclusions based on each set of assumptions.

8 Data/Specimen Handling and Record Keeping

8.1 Subject Data Confidentiality

Participant confidentiality and privacy is strictly held in confidence by the participating investigators, their staff, and the sponsor(s)/funding agency. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

All research activities will be conducted in as private a setting as possible.

Representatives of the Institutional Review Board (IRB), regulatory agencies or study sponsor/funding agency may inspect all documents and records required to be maintained by the investigator for the participants in this study. The study site will permit access to such records.

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

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

the study, all study databases will be de-identified and archived on the server used by the PI's lab.

8.2 Data Quality Assurance

Data quality assurance is a crucial aspect of this study to ensure the validity and reliability of the results. A number of steps will be taken to maintain data quality, including the use of standardized and validated assessment tools (CEQ-6, MADRS, QID-SR16, and custom questionnaire), training of the blinded assessor to ensure consistent administration of the assessment tools, regular monitoring of data collection to identify and address any discrepancies, and proper storage and management of the collected data.

We will perform internal quality management of study conduct, data collection, documentation and completion.

8.3 Data or Specimen Storage/Security

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

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

Data collection is the responsibility of the clinical trial staff under the supervision of the primary investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

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

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) will be entered into an online database approved for high-risk data as per Yale's data classification). Clinical data will be entered directly from the source documents.

8.4 Study Records

The following documents will be considered study records:

- Consent forms
- Case report forms
- Subjects' medical records

- Protocol
- Regulatory documents

Study records will be securely stored in the PI's office for internal use during the study. The PI is responsible for maintaining the study documentation. All study research members will have access to study records. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, regulatory, or sponsor/funding agency requirements.

The study records will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used will be secured and password protected. At the end of the study, all study databases will be de-identified and archived on the server used by the PI's lab.

8.5 Access to Source

Source data include all information and original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial.

Source documentation include:

- Study records
- Electronic medical records
- Laboratory reports
- Memoranda
- Subject diaries
- Subject questionnaires
- Recorded data from automated instruments.

Source documents should be neat and legible. When making changes or corrections, the original entry should be crossed out with a single line, initialed and dated.

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

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) will be entered into an online database as described above.

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

8.6 Retention of Records

Study documents will be retained for a minimum of 2 years after the completion of the study. These records will be securely stored and accessible to authorized individuals, such as study personnel and regulatory agencies, when needed.

8.7 Data and Safety Monitoring Plan

We do not anticipate any adverse events. The principal investigator (PI) will monitor the data, assure protocol compliance, and conduct the safety reviews at least annually. The PI evaluates whether the study should continue unchanged, require modifications, or close to enrollment. Any Reportable Events (which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related) Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO) will be reported to the IRB and any appropriate funding and regulatory agencies. Unanticipated Problems Involving Risks to Subjects or Others that may require a temporary or permanent interruption of study activities (if possible) will be reported, followed by a written report within 5 calendar days of my becoming aware of the event to the IRB and any appropriate funding and regulatory agencies. The PI will apprise fellow investigators and study personnel of all UPIRSOs and adverse events that occur during the conduct of this research project. The PI will report all UPIRSOs and adverse events that occur during the conduct of this research project to other applicable oversight bodies as required within applicable reporting timeframes.

9 Study Considerations

9.1 Institutional Review Board (IRB) Review

The protocol will be submitted to the IRB for review and approval. Approval of the protocol must be obtained before initiating any research activity. Any change to the protocol will require an approved IRB amendment before implementation. The IRB will have final determination whether informed consent and HIPAA authorization are required.

Study closure will be submitted to the IRB after all research activities have been completed.

Other study events (e.g. data breaches, protocol deviations) will be submitted per Yale policies.

9.2 Research Personnel Training

The training will cover all aspects of the study design, protocol, and procedures, including ethical considerations, informed consent and data collection. The training will be documented and kept on file for future reference and potential audits.

The training process will cover the following key areas:

- Study objectives and hypotheses - The research assistants will have a clear understanding of the overall aim and specific hypotheses of the study.

- Study protocol and procedures - The research assistants will be familiar with the study protocol and procedures, including patient enrolment, data collection, and adverse event reporting.
- Data collection instruments - The research assistants will be trained on the use of the study's data collection instruments, including the clinician-rated and patient-rated outcome questionnaires and the custom side effect questionnaire.
- Patient interaction - The research assistants will be trained on how to interact with patients during the study, including how to approach patients for participation, explain the study's aims and procedures, and handle any questions or concerns that may arise.
- Confidentiality and ethics - The research assistants will be trained on the importance of maintaining patient confidentiality and adhering to ethical standards in research.
- Data management and analysis - The research assistants will be familiar with the data management including data coding, data entry, data monitoring, and handling of missing data.

The training process will also include a hands-on component, such as role-playing or mock data collection, and then doing real data collection with supervision for the first two times to help the research assistants gain practical experience and ensure they are confident in their role.

9.3 Study Monitoring

Study monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, that the facilities and staffing are adequate for continued study conduct, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Council for Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s) including federal, state and local regulations and institutional policies and procedures. In addition to all applicable regulatory bodies, the Yale Center for Clinical Investigation (YCCI), as the sponsor of the study, will oversee the study.

9.4 Unanticipated Problems and Protocol Deviations

A protocol deviation is any noncompliance with the protocol. The noncompliance may be either on the part of the participant, the investigator, or the study staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the investigator to identify and report deviations within five working days of identification of the protocol deviation. All deviations must be addressed in study source documents, reported to the study sponsor, and the reviewing Institutional Review Board (IRB) per their policies.

Unanticipated problems involving risks to participants or others include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

If the study team becomes aware of an unanticipated problem (e.g. data breach, protocol deviation), the event will be reported to the IRB by email.

The UP report will include the following information:

Protocol identifying information: protocol title and number, PI's name, and the IRB project number;

- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

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

- UPs will be reported to the IRB within five of the investigator becoming aware of the event.

9.5 Study Discontinuation

The study might be discontinued in several circumstances, including if there are any adverse events or safety concerns that put the participants at risk, if the enrollment rate is significantly lower than expected and impacts the validity of the results, or if there are changes in regulations or ethical guidelines that make it necessary to discontinue the study. Additionally, the principal investigator may choose to discontinue the study if it is found to be ineffective or if funding for the study is withdrawn. In any of these circumstances, the participants will be informed and appropriate measures will be taken to ensure their safety and wellbeing.

9.6 Study Completion

This study is expected to continue for two years. The expected completion date is 5/2025. IRB and the sponsored will be notified if the completion date of the study is expected to changed, as applicable.

9.7 Conflict of Interest Management Plan

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

All investigators will follow the applicable conflict of interest policies.

9.8 Funding Source

The study is funded by YCCI by a UL1 Clinical Junior Faculty Pilot Award.

9.9 Publication Plan

This study will be conducted in accordance with the following publication and data sharing policies and regulations: National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

10 Appendices

Appendix #	Title	Section	Topic
Appendix 1	Feedback form	4	Study design
Appendix 2	Adverse events form	4	Study design

Appendix 1 – Presentation Feedback Form

With regards to the presentation you just received, please answer the following questions:

- The overall information provided was informative

Fully disagree Fully agree

0 1 2 3 4 5 6 7 8 9 10

- The slides were helpful

Fully disagree Fully agree

0 1 2 3 4 5 6 7 8 9 10

- The presenter was able to relay the information effectively

Fully disagree Fully agree

0 1 2 3 4 5 6 7 8 9 10

- My questions were satisfactorily addressed either during the presentation or afterwards by the presenter

Fully disagree Fully agree

0 1 2 3 4 5 6 7 8 9 10

- I wish I could receive a similar presentation for any treatments I receive in the future (psychiatric or non-psychiatric)

Fully disagree Fully agree

0 1 2 3 4 5 6 7 8 9 10

Appendix 2- Side Effects Questionnaire

Please ask each of the items below from the participant. Provide explanation for items as appropriate (e.g., for tachycardia you can mention “heart racing” or “rapid heartbeat”)

Tachycardia

☐None ☐Mild ☐Moderate ☐Severe

Vertigo

☐None ☐Mild ☐Moderate ☐Severe

Nausea

☐None ☐Mild ☐Moderate ☐Severe

Vomiting

☐None ☐Mild ☐Moderate ☐Severe

Diarrhea

☐None ☐Mild ☐Moderate ☐Severe

Dry Mouth

☐None ☐Mild ☐Moderate ☐Severe

Constipation

☐None ☐Mild ☐Moderate ☐Severe

Feeling drunk

☐None ☐Mild ☐Moderate ☐Severe

Feeling abnormal

☐None ☐Mild ☐Moderate ☐Severe

Increased blood pressure

☐None ☐Mild ☐Moderate ☐Severe

Dizziness

☐None ☐Mild ☐Moderate ☐Severe

Sedation

☐None ☐Mild ☐Moderate ☐Severe

Headache

☐None ☐Mild ☐Moderate ☐Severe

Dysgeusia

☐None ☐Mild ☐Moderate ☐Severe

Hypoesthesia

☐None ☐Mild ☐Moderate ☐Severe

Lethargy

☐None ☐Mild ☐Moderate ☐Severe

Dysarthria

☐None ☐Mild ☐Moderate ☐Severe

Tremor

☐None ☐Mild ☐Moderate ☐Severe

Mental impairment

☐None ☐Mild ☐Moderate ☐Severe

Dissociation

☐None ☐Mild ☐Moderate ☐Severe

Anxiety

☐None ☐Mild ☐Moderate ☐Severe

Insomnia

☐None ☐Mild ☐Moderate ☐Severe

Euphoric mood

☐None ☐Mild ☐Moderate ☐Severe

Pollakiuria

☐None ☐Mild ☐Moderate ☐Severe

Nasal discomfort

☐None ☐Mild ☐Moderate ☐Severe

Throat irritation

☐None ☐Mild ☐Moderate ☐Severe

Oropharyngeal pain

☐None ☐Mild ☐Moderate ☐Severe

Hyperhidrosis

☐None ☐Mild ☐Moderate ☐Severe

11 List of Tables

12 References

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