

STUDY PROTOCOL
Social Behavioral Template

**Using Virtual Reality to control the audio-
visual inputs during Ketamine/Esketamine
Treatment

(VR-KET)**

Protocol Number

2000036184

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Confidentiality Statement:

Synopsis

Purpose

We aim to examine the role of audiovisual inputs during treatment with ketamine/esketamine in affecting tolerability and effectiveness of treatment of depressive episodes, by providing patients with a relaxing environment using virtual reality goggles and noise cancelling headphones, and assessing whether these tools can improve the tolerability and effectiveness of treatment with ketamine/esketamine.

Objectives

Primary Objective:

To determine the feasibility and tolerability of using a custom designed, relaxing VR environment for patients receiving ketamine/esketamine treatment.

Secondary Objectives:

To determine whether a custom designed, relaxing VR environment can improve the acute subjective experience during treatment compared to treatment as usual.

Exploratory Objective

To determine whether there is a change in MADRS score from before the VR session (baseline) and before the post-VR session

Study Population

Patients who are clinically receiving ketamine/esketamine at the Yale IPS, and have completed the acute series of treatment and weekly optimization phases of the treatment, and are currently receiving continuation/maintenance treatment at a frequency of equal or longer than every week will be eligible for participation in the study..

Number of Participants

We aim to enroll a total of 10 patients for this study.

Study Design

This initial study will be an open-label study, during which patients **currently receiving post-acute clinical treatment** with ketamine/esketamine at Yale Interventional Psychiatry Service (IPS) will be approached for participation. Enrolled patients will participate in an initial training session during which they will be familiarized with the study's Virtual Reality Gear (VRG). Subsequently patients will have a single treatment utilizing their preferred relaxing VR environment. Outcome measures will be collected during and after three treatments: the treatment before the VR treatment, the VR treatment session, and the subsequent treatment.

Study Duration

The study is anticipated to conclude by June 30, 2025

Outcome Variables

Primary safety outcome: Tolerability of VR treatment by qualitative report and SAFTEE assessment

Primary efficacy outcome: difference in overall treatment experience satisfaction (via Likert scale) between the pre-VR and VR treatment sessions

Secondary Outcomes:

Difference in the following measures between A) pre-VR and VR treatments, and B) pre-VR and post-VR treatments

- 5D-ASC subscale scores,
- 5D-ASC total score,
- difference in CADSS score
- difference in “pleasant vs unpleasant experience”
- difference in “level of relaxation” scores between the pre-VR and VR treatment sessions, and differences between these outcome measures between pre-VR and post-VR treatment sessions. change in acute subjective experience by ASC

Exploratory outcome:

Difference in MADRS score from before the VR session (baseline) and before the post-VR session

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 ketamine/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

Depression affects more than 264 million people worldwide, and is one of the leading causes of global disability and a significant burden on society¹. Unfortunately, a significant portion of patients with depression do not achieve remission despite multiple treatment trials², pushing the field to explore more novel treatments. In the past couple of decades, there has been an ever-increasing focus on the development and use of rapid-acting antidepressant treatments with dissociative or psychedelic properties. Ketamine, a dissociative agent, has been clearly shown to be an effective treatment for depressive episodes and is now widely used in clinical settings, with intranasal esketamine having been approved by the US FDA for use in treatment-resistant depression (TRD) and major depression with suicidal ideation (MDSI). Other agents are actively being studied for similar indications, including psilocybin, a psychedelic compound for which multiple trials are underway³, 3,4-Methylenedioxy methamphetamine (MDMA)^{3,4}, and others such as LSD and ayahuasca among others with interesting findings from preliminary studies. The importance of the acute subjective experiences elicited by these treatments remains a major issue in the field. Most clinicians studying classical psychedelic agents and many clinicians using ketamine treatments believe the set and setting, and the acute subjective experience induced by the agents are critical to both the mechanism of action, and the clinical response. However, this has not been fully evaluated. In the literature, given the wider availability of ketamine, there has been some attempts to look at factors such as anxiety⁵ and dissociative symptoms⁶⁻⁹ during ketamine treatment and their effects on the treatment outcome, which suggest some of these factors may be associated with a differing trajectory of improvement. While these observational studies do provide critical insight, they did not attempt to alter the outcome by active interventions, nor to control the experience, and as such it is difficult to assess a causal relationship between these factors and antidepressant property of these treatments, thus providing limited clinical insight into how to improve patients' outcomes. A recent randomized study utilizing automated self-assessment training during a single dose ketamine treatment found a significant difference in the duration of effect of the treatment¹⁰. 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. Data from an initial pilot (unpublished) study on the preferences of patients receiving ketamine/esketamine at Yale IPS clearly showed unpleasant auditory and visual stimuli during treatment to be among the most common sources of discomfort (33% and 52%, respectively). The same study showed patients to be open and interested in the idea of using technology such as Virtual Reality (VR) goggles and noise cancelling headphones during treatment to improve their experience (71% open to considering or likely to switch if available).

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1.2 Prior Experience

While there has been no formal assessment of strategies adjusting audiovisual input in patients, ear plugs and eye masks are provided to patients as part of routine clinical practice; furthermore, **patients have utilized their own virtual reality goggles and headphones during clinical treatment in our clinic with good results.**

2 Rationale/Significance

2.1 Rationale and Study Significance

We believe augmentation and control of audiovisual inputs can improve participants' experience during the acute treatment and improve treatment tolerability. Additionally, and in turn, it is hypothesized to provide a differing trajectory and sustainability of improvement in depression severity.

Furthermore, the findings from this initial study can be used as a foundational tool for further research to understand the effects of sensory inputs and mind states during treatment with dissociative and psychedelic agents. The model devised during this study can be used for future research into various interventions consisting of interactive content such as VR-assisted and AI-assisted therapy, and interactive meditation during treatment with these psychoactive compounds. Finally, any potential treatment tools arising from this model can be easily implemented even in settings with limited resources, addressing the accessibility and equity issues that are among the major challenges of the field.

2.2 Risks

Technology-specific Risks

The devices used during the study are commercially available technology used without limitations by the public. Additionally and as previously mentioned, all of these technologies, including the VR goggles proposed for use during this study (Meta Quest 2) have been previously used by patients during clinical ketamine/esketamine treatment at our clinic without problems. The content used for the study was designed to provide a relaxing environment. As such the technology related risks are considered minimal, and mainly consist of discomfort resulting from effects of the VR content, including anxiety or disorientation, nausea, eye strain and headache. We believe many of these risks can be mediated during the training session where the technology is used outside the treatment setting, to make sure participants are comfortable with the technology and content.

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 the tolerability of the treatment, and in clinical outcomes. Participants will have contact with the research team in addition to the usual clinical care team, which may provide some additional benefit to patients.

The results of this initial study would benefit the field by providing a better understanding of the role audio visual inputs, and whether and to what extent these inputs can be optimized.

3 Study Purpose and Objectives

3.1 Purpose

The overarching purpose of this project is to assess whether purposefully controlling a participants' audiovisual input during treatment with ketamine/esketamine can safely improve the acute subjective experiences, and potentially affect treatment effectiveness.

3.2 Hypothesis

Hypothesis 1: Limiting sensory inputs to controlled, relaxing and positive inputs throughout the treatment will result in a more positive overall acute subjective experience during treatment with ketamine/esketamine.

Hypothesis 2: An improved acute subjective experience during treatment with ketamine/esketamine can result in improved effectiveness of treatment with ketamine/esketamine.

3.3 Objectives

Primary Objective:

To determine the feasibility and tolerability of using a custom designed, relaxing VR environment for patients receiving ketamine/esketamine treatment.

Secondary Objective:

To determine whether a custom designed, relaxing VR environment can improve the acute subjective experience during treatment compared to treatment as usual.

Exploratory Objective

To determine whether there is a change in MADRS score from before the VR session (baseline) and before the post-VR session

4 Study Design

This initial study will be an open-label study, during which patients **currently receiving post-acute clinical treatment** with ketamine/esketamine at Yale Interventional Psychiatry Service (IPS) will be approached for participation. Selection of post-acute patients in this phase reduces the risks associated with participation in the study, while maintaining the objectives of the study. Enrolled patients will participate in an initial training session during which they will be familiarized with the study's Virtual Reality Gear (VRG). Additionally, they will have the opportunity to set up preferences with regards to the contents of the VR experience (While this step creates some heterogeneity, based on our pilot data there is no singular content that would be appropriate for all participants). Subsequently patients will have a single treatment utilizing their preferred relaxing VR environment. Outcome measures will be collected during and after three treatments: one of the treatments before the VR treatment, the VR treatment session, and the subsequent treatment. The primary efficacy outcome for this phase will be the difference in overall treatment experience satisfaction (via Likert scale) between the pre-VR and VR treatment sessions. Secondary efficacy outcomes include difference in 5D-ASC subscale scores, 5D-ASC total score, CADSS score and "level of relaxation" scores between the pre-VR and VR treatment sessions, and differences between these outcome measures between pre-VR and post-VR treatment sessions. Safety will be assessed using the Systematic Assessment for Treatment Emergent Effects (SAFTEE) measure. The findings from this initial study will assist in revising and improving the VR contents, and assure safety and tolerability.

Approach and consent:

Patients who are clinically receiving ketamine/esketamine at the Yale IPS, and have completed the acute series of treatment and weekly optimization phases of the treatment, and are currently receiving continuation/maintenance treatment at a frequency of equal or longer than every week will be approached for participation in the study.

Randomization

This initial study is single-arm and open-label, and as such no randomization will be done.

Intervention

The intervention consists of a utilization of a custom designed VR environment to provide a controlled, relaxing, positive environment for the patients.

The visual aspect of the virtual reality environment consists of multiple nature themed environments that are minimally interactive and patients can explore the environment. No

other form of interaction (e.g. Game like features) will be incorporated at this time. Screen shots from the available environment are included in the appendix.

The auditory aspect of the environment includes options such as corresponding nature sounds, relaxing music, white noise, noise cancellation without any sound, or patient's preferred form of auditory input such as personal playlists etc.

Both the visual and auditory aspects will be selected during the training session based on patient's preference.

During the treatment session, patients will be asked to keep the VRG on for the duration of the treatment (80 minutes to 120 minutes depending on ketamine vs esketamine) but will also be informed that they can remove the devices at any time.

Study course

Pre-VR treatment session (assessments only)

After consent, patients will be asked to complete the assessments (as described above) at the conclusion of a ketamine/esketamine treatment. No other modifications are made to this treatment session. The treatment session may be the immediate next treatment after consent, or a subsequent treatment based on patient preference/availability and recommendation of primary clinical team.

Training Session

The training session can be done before or on the same day of the VR treatment session. During the session patients will have a chance to wear the VRG and get familiarized with the contents, controls and other aspects of the virtual reality environment. They will also have a chance to select the visual environment that they find most appropriate and preferable for them. They will also select their preferred auditory content as described above.

VR treatment session

MADRS score will be collected from patients at the beginning of this session and before treatment. During the VR treatment session, patients will utilize the VRG after start of treatment (for IV ketamine after infusion is started - for esketamine after last insufflation is complete). A member of the research team will monitor the VR contents through a mirrored visual screen at bedside, and provide any assistance as needed. As previously mentioned, patients are instructed to keep the VRG on for the entirety of the treatment duration if tolerable, but that they can take it off (either temporarily e.g. to communicate, use the bathroom etc. or at any point if they no longer want to use the VRG). Once the treatment is complete, patients will be asked to complete the assessments.

Post-VR treatment session (assessments only)

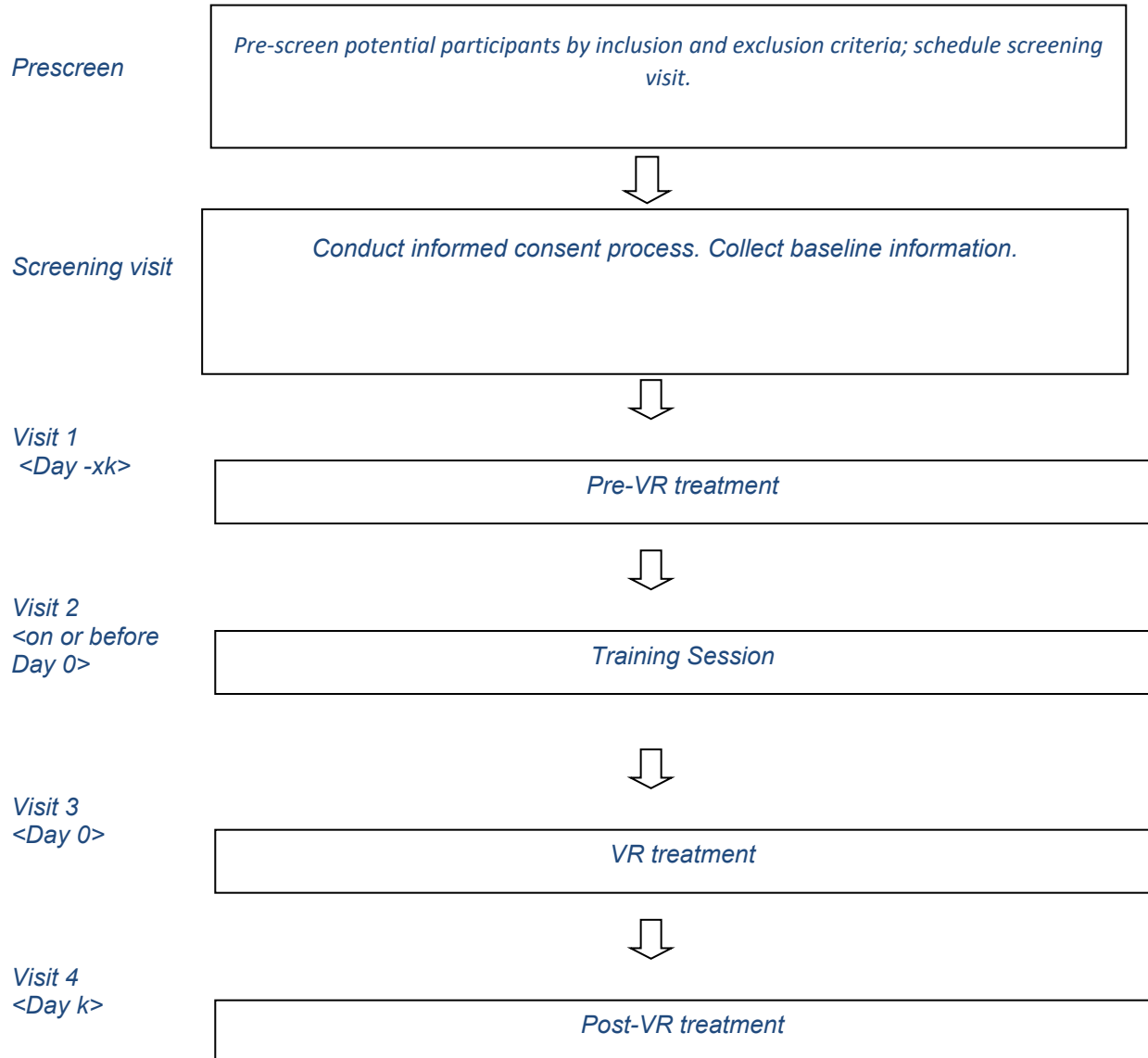
MADRS score will be collected from patients at the beginning of this session and before treatment. Patients will be asked to complete the other assessments after treatment. No other modification are made to this session.

Interval between sessions:

Given the nature of the study, and as patients are in post-acute phase of treatment, the timing between sessions will be mainly dictated by the frequency of clinical treatments as decided by the clinical team (e.g., every 2 weeks, every 4 weeks, etc.) and as such there will not be a set number of days for study course.

Standard of Care during ketamine/esketamine administration:

As part of the standard care patients will be positioned in a comfortable recliner chair or bed for the ketamine/esketamine treatment and in order to maximize the patients' safety, vital signs will be monitored at baseline, 40 minutes after starting the administration of the ketamine/esketamine, and prior to the patient leaving the clinic (approximately 1.5-2 hours after the treatment initiates). Pregnancy tests will be administered before each treatment to rule out pregnancy in patients of child-bearing potential, unless they sign the waiver form. A physician will be present in the IPS area during the treatment, and an RN will be in the same room with the patient throughout their treatment. Subjects will be monitored for up to 2 hours after the start of the ketamine/esketamine administration by the IPS nurse team and overseen by a physician. Patients are allowed to have a break (e.g. to use the restroom) at the discretion of the RN if it is deemed safe for them to do so.

Study Flow Diagram

*k: treatment interval as determined by clinical team (usually between 1 week to 4 weeks)

* x: The number of treatments prior to the VR session where baseline assessment occurs, which could be 1 (treatment immediately before the VR treatment, or a higher number.

4.1 Study Duration

The study, including analysis of identifiable data, is anticipated to be conclude by June 30, 2025

4.2 Outcome Variables/Endpoints

4.2.1 Primary Outcome Variables/Endpoints

Primary safety outcome: Tolerability of VR treatment by qualitative report and SAFTEE assessment

Primary efficacy outcome: difference in overall treatment experience satisfaction (via Likert scale) between the pre-VR and VR treatment sessions

4.2.2 Secondary and Exploratory Outcome Variables/Endpoints

Secondary Outcomes:

Difference in the following measures between A) pre-VR and VR treatments, and B) pre-VR and post-VR treatments

- 5D-ASC subscale scores,
- 5D-ASC total score,
- difference in CADSS score
- difference in “pleasant vs unpleasant experience”
- difference in “level of relaxation” scores between the pre-VR and VR treatment sessions, and differences between these outcome measures between pre-VR and post-VR treatment sessions. change in acute subjective experience by ASC

Exploratory outcome:

Difference in MADRS score from before the VR session (baseline) and before the post-VR session

5 Study Participants

5.1 Study Population

Patients who are clinically receiving ketamine/esketamine at the Yale IPS, and have completed the acute series of treatment and weekly optimization phases of the treatment, and are currently receiving continuation/maintenance treatment at a frequency of equal or longer than every week will be eligible for participation in the study.

5.2 Number of Participants

We aim to enroll a total of 10 patients 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 at least 18 years old
- Patients must have completed the acute series of treatment and weekly optimization phases of ketamine/esketamine treatment, and currently receiving continuation/maintenance treatment
- Written consent for the study procedures
- Ability and willingness, in the investigator's judgement, to comply with the study procedure and study requirements.

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 see or hear VR content.
- 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 study procedure (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.
- Was previously enrolled/randomized into the study

Note: Since only patients who have already been deemed clinically appropriate and have received the acute series and weekly optimization ketamine/esketamine are approached, and participation in the study does not influence patients receiving or not receiving ketamine/esketamine, exclusions for this medication are not included in the study exclusion criteria.

5.4 Recruitment Procedures

Potential subjects will be identified by screening of the list of patients coming to the IPS clinic to receive ketamine/esketamine. Patients who meet the eligibility criteria and do not meet any exclusion criteria 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.

6 Study Methods/Procedures

6.1 Study Procedures

See the Study Course paragraph under the Study Design section.

Table 1: Visit Schedule Table

Timeline	Screening session	pre-VR treatment session	Training Session	VR treatment session	Post-VR treatment session
Day (subject to clinical treatment schedule)	-k	-xk*	0	0	+k

VR events					
VR Training			X		
VR Use during treatment				X	
Assessments					
Demographics	X				
Treatment Experience Satisfaction**		X		X	X
CADSS Baseline	X				
CADSS 40 minutes		X		X	X
CADSS End of Treatment		X		X	X
5D-ASC		X		X	X
Level of relaxation**		X		X	X
MADRS				X	X
SAFTEE		X	X	X	X

*k: Ketamine/esketamine Treatment interval as decided by clinical team (while a singular k is used in this table for simplicity, the interval can be adjusted during the study by the clinical team)

* x: The number of treatments prior to the VR session where baseline assessment occurs, which could be 1 (treatment immediately before the VR treatment, or a higher number.

**Likert scale

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. Additionally baseline CADSS score will be collected.

At the pre-VR treatment session, VR treatment session and post-VR treatment sessions the following will be collected: treatment experience satisfaction, CADSS score at 40 minutes and end of treatment, level of relaxation, and SAFTEE questionnaire. Additionally, MADRS score will be collected before the VR treatment session and before the post-VR treatment session. Vital sign information (collected as part of standard of care at IPS) will also be recorded.

During the VR Training session, participants' preferences for the visual and auditory content will be determined and recorded.

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

Not applicable

6.3 Adverse Events Definition and Reporting

Study investigators will be able to remove participants from the study 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 training session and VR Treatment session, whether or not considered related to the VR content. 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 after each visit (with the exception of the screening visit) utilizing the SAFTEE questionnaire. Additionally, 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 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.

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 study 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.

6.6 Locations/Facilities

This is a single-site study that will take place at Yale University (New Haven, CT). Treatments and clinical assessments will take place at Yale Psychiatric Hospital (YPH, part of Yale New Haven Hospital; YNHH), Interventional psychiatry services (IPS).

7 Statistical Design

7.1 Sample Size Considerations

Given the pilot/feasibility nature of this study, no formal sample size calculations has been made, but our goal is to recruit a minimum of 10 participants.

7.2 Planned Analyses

Data will be examined using descriptive statistics, presented as means $\pm$ SD or median (interquartile range) for continuous characteristics, and as frequencies (%) for categorical characteristics.

7.2.1 Safety Objective Analyses

To examine the safety and tolerability, 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 $\pm$ SD or median (interquartile range) for continuous characteristics, and as frequencies (%) for categorical characteristics. Baseline characteristics include age, sex, ethnicity, socioeconomic status, diagnosis and number of previous series and treatments with ketamine/esketamine.

7.2.3 Interim Analysis

NA

7.3 Data Relevance

In the study, the primary efficacy question is whether VRG can improve the treatment experience satisfaction score compared to treatment without VRG.

The primary safety question is whether the study's VR contents are well tolerated by the participants.

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 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 these scores can be transformed into categorical or continuous variables for analysis. For the side effects, SAFTEE questionnaire will be used.

7.5 Data Analysis Tools

R version 3.3 will be used.

7.6 Data Monitoring

A Data and Safety Monitoring Plan (DSMP) has been devised for the study, and is submitted as an additional document.

7.7 Handling of Missing Data

Our primary analyses will be intent-to-treat using all available data. Given the nature of the study and as no formal comparative analysis is being done, sensitivity analyses are not necessary.

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 (e.g., MADRS), training of assessors 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.

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 six months. The expected completion date is 4/2024. IRB 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 unfunded.

9.9 Publication Plan

Every attempt will be made to publish the results in peer-reviewed journals.

10 Appendices

Appendix #	Title	Section	Topic
Appendix 1	VR environment screenshots	4	Study design

Appendix 1 – VR environment screenshots

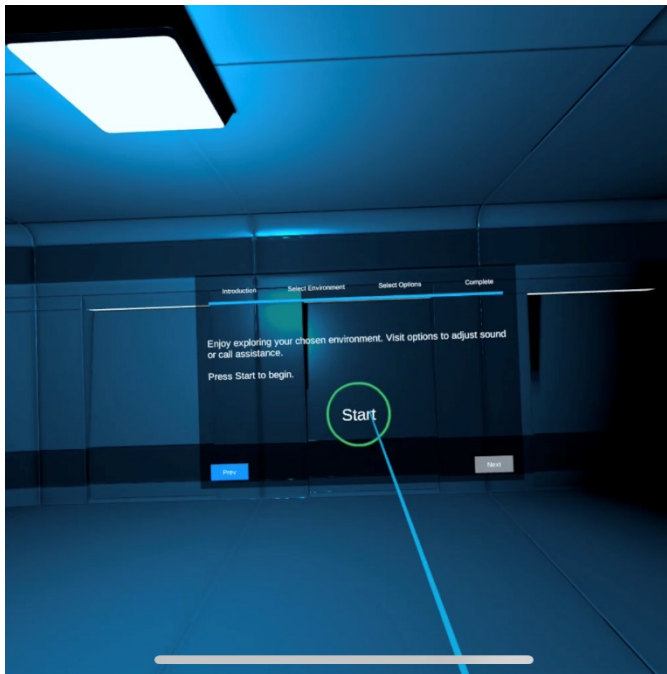


Figure 1 – Lobby – Introduction

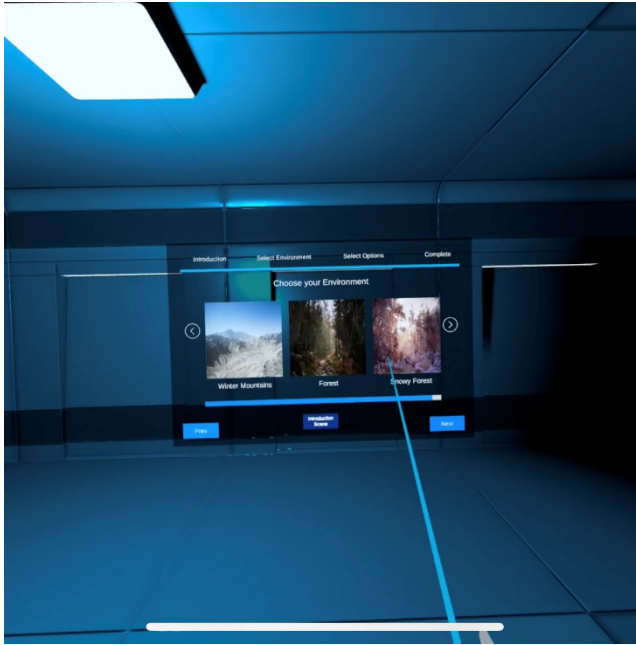


Figure 2 – Lobby – Preferred environment selection

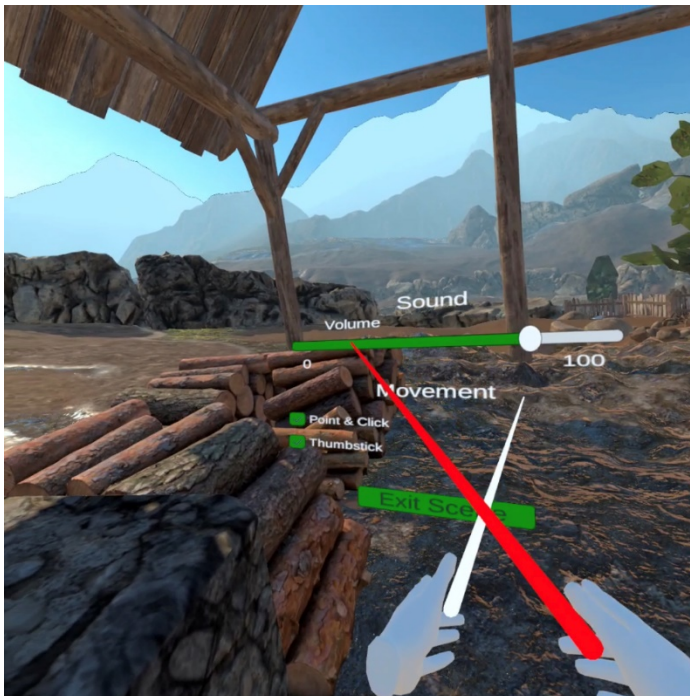


Figure 3 –Heads up display (HUD)

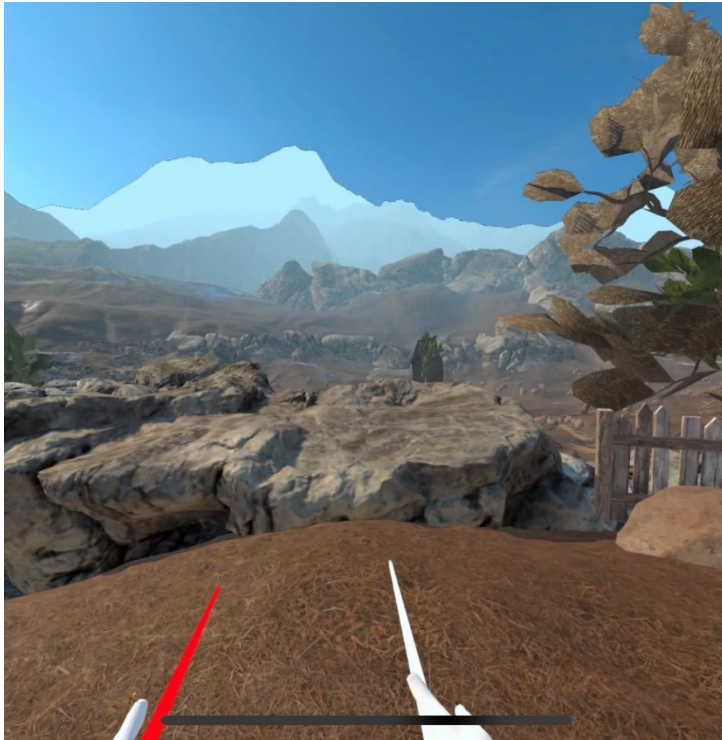


Figure 4 – One of available environments



Figure 5 – One of available environments

11 List of Tables

1 Table 1: Visit Schedule Table

12 References

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