Statistical Analysis Plan

1. Administrative information

1.1. Title and Trial Registration

Full study title: Precision medicine with ketamine for older adults with treatment-resistant depression: Pilot Study

Acronym:

ClinicalTrials.gov identifier: NCT04504175

Washington University in St. Louis IRB ID number: 202007085

PCORI Contract number:

SAP version: 1.1 (May 28, 2021)

Study protocol version: 2.3 (May 6, 2021)

SAP version history: Version 1.0 dated May 20, 2021

SAP version justification: - Review by investigators on May 21, 2021 recommended clarification to section 4.2.2 and 3.4.1.

SAP Revision timing: Revision will be conducted after reviewing by PI and biostatistician. This version is the primary draft of the detailed SAPs for each outcome.

1.2. Roles and Responsibility

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Abbreviation

AE	Adverse Event
ATHF	Antidepressant Treatment History Form
AUDIT	Alcohol Use Disorders Identification Test
DAST	Drug Abuse Screening Test
FDA	Food and Drug Administration
IV	Intravenous
MADRS	Montgomery-Asberg Depression Rating Scale
PCP	Primary Care Physician
PHQ-9	Patient Healthcare Questionnaire 9-items
SAE	Serious Adverse Event
SCID-5	Structured Clinical Interview for DSM-5
TRD	Treatment-Resistant Depression

2. Introduction

2.1. Overview

Ketamine is approved by the U.S. Food and Drug Administration (FDA) for anesthesia and pain relief. Ketamine is known to cause side effects such as confusion and hallucinations. While these are temporary, they can be quite uncomfortable. Therefore, along with ketamine, we will administer clonidine to prevent or reduce the uncomfortable side effects of ketamine during the infusion and follow-up injections. Clonidine is approved by the U.S. Food and Drug Administration for treatment of high blood pressure, attention deficit disorder, neuropathic pain, seizure disorder, mood disorder and migraine headaches. The use of ketamine and clonidine are considered investigational in this study.

The Precision medicine with ketamine for older adults with treatment-resistant depression: Pilot Study will assess the safety and feasibility of intravenous (IV) ketamine in older adults with Treatment-Resistant Depression (TRD).

2.2. Objectives

2.2.1. Objectives and study aims

The study aims to learn whether it is feasible to conduct a larger, longer trial in the future to learn about the long-term effects of ketamine infusions. In addition, this study will develop and utilize innovative methodological approaches to demonstrate the feasibility of precision medicine and mHealth approaches in depression treatment.

The study will also provide preliminary data on response and remission rates, adverse events, and cognitive changes with ketamine during a 4-week acute phase, 4-week continuation phase, and 3-month post-infusion follow-up phase.

2.2.2. Hypothesis

Ketamine infusions will show preliminary evidence of acute and continuation efficacy, as assessed by response and remission rates, and changes in MADRS score.

Ketamine infusions will be safe and well-tolerated as measured by adverse events (AEs) and severe adverse events (SAEs).

Ketamine infusions will produce increases in cognitive function as measured by NIH Toolbox and Miro measures.

2.2.3. Scope

This Statistical Analysis Plan will be the guiding document for the quantitative analyses that will be conducted in the Ketamine pilot study.

3. Study Methods

3.1. Study Design and Plan:

The study will enroll approximately 25 participants across 5 sites in the US and Canada.

Participants will receive ketamine infusions twice a week for 4 weeks (acute phase). At the end of the acute phase, those who have a MADRS score <10 or have a MADRS $\geqslant$ 30% reduction from baseline will continue with an additional 4 weeks of weekly ketamine infusions (continuation phase). Participants whose MADRS score was not reduced at least 30% from baseline will not proceed to the Continuation Phase of the study; their participation will end. At the end of continuation phase, those who complete the Continuation phase will be assessed for remission and response using the MADRS.

Participants will be assessed at baseline, end of acute phase, and end of continuation phase for effectiveness, safety, and executive functioning. Participants will be asked to complete daily surveys of

their depression symptoms during their participation. Participants who choose to withdraw from the study early (during acute phase) will be treated as did not respond or remit. Final visit prior to withdrawing early from the study is not required.

3.2. Screening data

Potential participants identified from existing studies will be screened for eligibility. After providing informed consent, the following assessments must be conducted prior to randomization to ensure eligibility (see also Section 3.3.1 and 3.3.2 for Inclusion and Exclusion Criteria):

- SCID-5: Meet criteria for unipolar Major Depressive Disorder, non-delusional, current. Rule out psychotic and bipolar disorder.
- AUDIT: Rule out current alcohol use disorder (past 3 months)
- DAST: Rule out current substance use disorder (past 3 months)
- PHQ-9: Score must be 15 or higher at baseline.
- Short Blessed Test: Score must 0-9 (excluded if score is 10 or higher).
- ATHF: Must have 2 or more adequate antidepressant trials of different classes in the current episode.
- Review of current medications: Must not be taking naltrexone memantine, or any medication that could be considered contraindicated with ketamine. Must not be taking more than two adequately-dosed oral antidepressant. Must be stable on antidepressant regimen for at least two weeks.
- Review of medical conditions: Must not have any medical conditions affecting IV ketamine safety or tolerability or that would interfere with participation in a long-term study. (i.e., life expectancy < 1 year because of terminal illness, unstable angina). Must not have inadequately controlled hypertension.

3.3. Eligibility

All participants will meet the following eligibility criteria:

3.3.1. Inclusion Criteria

a) Community-living men and women age 60 years and older.

b) Treatment-resistant depression: defined as unipolar major depressive disorder, non-delusional (diagnosed by SCID-5) that persists despite ⩾ 2 adequate antidepressant trials of different classes in the current episode, including at least one evidence-based second-line treatment in the current episode (including serotonin norepinephrine reuptake inhibitors, bupropion, tricyclics, monoamine oxidase inhibitors, or augmentation with an atypical antipsychotic, stimulant, bupropion, lithium, or Triiodothyronine).

c) Moderate to severe depressive symptoms determined by Patient Health Questionnaire 9-item (PHQ-9) score ⩾15 at baseline.

d) Able to provide informed consent.

3.3.2. Exclusion Criteria

a) Dementia per history, score ⩾10 on the Short Blessed Test, or determined by clinical interview with geriatric psychiatrist to have high likelihood of dementia.

b) Psychotic spectrum or bipolar disorder or severe personality disorder that at the PIs discretion would interfere with safe participation. Anxiety disorders are not an exclusion.

c) Baseline systolic BP > 150 systolic or 90 diastolic at evaluation. Participants who initially present with elevated blood pressure may be re-assessed; and if needed, referred to their healthcare provider for hypertension management. Clonidine is preferred as the agent to control blood pressure, as it will also improve tolerability of ketamine infusion. However, patients' providers are not required to use this drug

(vs. other strategies such as optimizing doses of existing medication). Once blood pressure is adequately managed, they can be reconsidered for study participation.

d) Current alcohol or substance use disorder or lifetime recreational ketamine use or other dissociative agent (e.g., PCP).

e) Use of naltrexone, memantine, or any medication that could be considered contraindicated with ketamine.

f) Taking more than 2 adequately-dosed oral antidepressants.

g) High acute risk for suicide and unable to be managed safely in the clinical trial.

No exclusion criteria are based on race, ethnicity, or gender.

3.4. Intervention

3.4.1. Ketamine Infusion

To ensure dose accuracy, participants will have weight confirmed prior to each infusion. After safety ratings (see table in the protocol) are performed, an IV line will be inserted into upper extremity by research personnel. The ketamine will be infused using an IV infusion pump at a dose of 0.5 mg/kg of body weight over 40 minutes. Heartrate, blood pressure, and pulse-oximetry will be routinely monitored throughout the infusion and for approximately up to two hours after the end of the infusion. Safety ratings will be repeated prior to discharge. After normalization of any psychotomimetic symptoms or blood pressure elevation and IV removal, participants will be discharged. Participants will be provided with transportation to and from infusion visits.

If a participant is unable to receive IV ketamine (e.g., because of lack of IV access), he or she can receive IM ketamine as a bolus. The dosage will be the same (0.5 mg/kg) because its bioavailability is 93% and its plasma half-life is similar to IV.

3.4.2. Clonidine Co-administration

In order to prevent or reduce the severity of the psychotomimetic/dissociative and hypertensive effects of ketamine, Clonidine(0.1mg) is recommended to be routinely co-administered with ketamine. Clonidine co-administration does not alter the antidepressant activity of ketamine in either preclinical or clinical studies.

We will measure doses of clonidine co-administration and, if not used, reasons why it is declined.

4. Statistical principles

4.1. Confidence intervals and p values

The primary focus of all analyses of this pilot study will be descriptive and thus summary estimates will be accompanied by 95% confidence intervals.

4.2. Adherence and protocol deviations

4.2.1. Definitions of protocol deviations

Any alteration or modification to the IRB-approved research without prospective IRB approval. The term research encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

4.2.2. Adherence and protocol deviations to be summarized
Actual doses and infusion duration will be captured using the Infusion Visit Log. Reasons for not completing infusion per protocol will also be documented using the Infusion Visit Log. Follow-up data will be collected regardless of treatment adherence.

4.2.3. Electronic Data Capture
This study will utilize MyCap smartphone app as the primary data collection method for daily depression surveys. Data collected in MyCap is recorded and stored in REDCap, hosted in the Washington University School of Medicine Institute for Informatics (I^2), Informatics Core Services (ICS). Study data will also be collected using paper CRFs and then entered into REDCap. Study data will also be collected using NIH Toolbox and Miro Health iPad applications which use recognized security features. Study devices will be kept secured and passcode-protected.

Source documents, including laboratory values, medical records and physician communications will be maintained at each site to verify adherence to protocol, inclusion/exclusion criteria, and data accuracy.

4.3. Analysis populations
All participants who receive at least one infusion will be part of the analyzed sample.

5. Analysis
5.1. Outcome definitions
Remission from depression is defined as MADRS score 0-9 at Week 4(acute phase end).

Response to treatment is defined as ≥ 30% reduction in depressive symptoms on the MADRS from baseline to Week 4.

5.1.1. Primary outcomes
Remission from Depression at Week 4.

5.1.2. Outcome measurements
Change in Depression Severity as measured by MADRS at Week 4 and 8.

Change in Psychological Well-Being as measured by NIH Toolbox Psychological Well-Being Surveys, Positive Affect and General Life Satisfaction at Week 4 and 8.

Change in Cognition as measured by NIH Toolbox and Miro Health Cognitive Batteries at Week 4 and 8.

Change in Executive Function as measured by NIH Toolbox and Miro Health Cognitive Batteries at Week 4 and 8.

Change in Suicidal Ideation as measured by Scale for Suicidal Ideation at Week 4 and 8.

5.2. Analysis methods
Data analysis will be mostly descriptive, including rates of response and remission and AEs.

Continuous changes in depressive symptoms and cognitive changes will also be measured with mixed-effect model.

5.3. Missing data
Reasons for missingness will be collected.

5.4. Interim analyses and stopping rules

No interim analysis is planned due to the nature of the trial. As there is no control arm and all treatments are FDA-approved and frequently used in older adults, no contingency plans for early stopping because of futility or safety are planned.

5.5. Safety and Adverse Events

5.5.1. Safety Monitoring

Safety will be systematically monitored during infusions according to the Safety Monitoring for Infusions schedule. In addition, we will ask each participant to notify us of new symptoms, illnesses, or other problems.

5.5.2. Recording Adverse Events

During the study, regular assessments for AEs will be conducted and recorded in REDCap. Participating sites are responsible for gathering and documenting data pertinent to AEs occurring at their sites and for collecting AE information, including but not limited to:

a) Description of the event, including onset and duration.
b) Doses of study medications and adherence.
c) Relevant medical and laboratory findings and reports.
d) Correspondence regarding the event.
e) Action taken in response to the event.
f) Classification of the AE (Severity, Relationship, Expectedness, Seriousness).

5.6. Statistical software

Data cleaning and statistical analyses will be performed using SAS (SAS Institute, Cary NC) and R (The R Foundation for Statistical Computing; Vienna, Austria).