Precision medicine with ketamine for older adults with treatment-resistant depression: *Pilot Study*

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I. STUDY OVERVIEW

This pilot study will assess the safety and feasibility of intravenous (IV) ketamine in older adults with Treatment-Resistant Depression (TRD). In addition, this study will develop and utilize innovative methodological approaches to demonstrate the feasibility of precision medicine and mHealth approaches in depression treatment.

II. METHODS

A. Design Overview

Participants will receive ketamine infusions twice a week for 4 weeks (acute phase). Participants who respond or remit will continue with an additional 4 weeks of weekly ketamine infusions (continuation phase). 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.

B. Participant Recruitment

The study will enroll up to 15 participants. Participants will be enrolled from existing studies (WU IRB#201609085, 201202157, and 201811036). In addition we will elicit referrals from our established referral networks of PCPs and specialty mental health practices. Potential participants will undergo pre-screens by phone and then an in-person visit that includes a psychiatric and medical history, blood chemistries, and an ECG.

1. Inclusion Criteria

(1) Community-living men and women age 60 years and older;

(2) 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 Triiodothyroinine

(3) Persistent moderate to severe depressive symptoms determined by Patient Health Questionnaire 9-item (PHQ-9)26 score ≥15 at baseline

(4) Able to provide informed consent.

2. Exclusion Criteria

(1) Dementia per history, score ≥10 on the Short Blessed Test, or determined by clinical interview with geriatric psychiatrist to have high likelihood of dementia;

(2) 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.

(3) Unstable medical conditions such that IV ketamine is not safe or tolerated or that would interfere with participation in a long-term study (i.e., poorly controlled hypertension, life expectancy < 1 year because of terminal illness, unstable angina).

(4) 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.

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

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

(7) Taking more than 2 adequately-dosed oral antidepressants.

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

C. Screening Procedures

After providing informed consent, participants will be assessed for eligibility as follows:

1) SCID-5: *Meet criteria for unipolar Major Depressive Disorder, non-delusional, current. Rule out psychotic and bipolar disorder.*
2) AUDIT: *Rule out current alcohol use disorder (past 3 months)*
3) DAST: *Rule out current substance use disorder (past 3 months)*
4) PHQ-9: *Score must be 15 or higher at baseline.*
5) Short Blessed Test: *Score must 0-9 (excluded if score is 10 or higher).*
6) ATHF: *Must have 2 or more adequate antidepressant trials of different classes in the current episode*
7) 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.*
8) 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.*

D. Schedule of Measures

SCHEDULE OF MEASURES				**FOLLOW – UP +++**		
	BASELINE	ACUTE END (WK 4)*	CONTINUATION END (WK 8)**	1 MONTH	2 MONTH	3 MONTH
Screening						
SCID-5+	X					
PHQ-9	X			X	X	X
ATHF	X					

Short Blessed Test	X					
Blood Pressure	X					
AUDIT	X					
DAST	X					
CIRS-G	X					
Outcomes						
MADRS	X	X	X	X	X	X
Scale for Suicidal Ideation (SSI)	X	X	X			
Psychological well-being (NIH Toolbox)	X	X	X			
Cognitive Battery (NIH Toolbox)	X	X	X			
Miro Health Cognitive Battery	X	X	X			
Pittsburgh Sleep Quality Index (PSQI)++	X	X	X			
Safety						
AE Monitoring	X	X	X			
Medication List	X	X	X			
Medical History	X					
Height/Weight	X		weight			
ECG	X		X			
Blood Chemistries***	X		X			
Craving Scale	X	X	X			
Depression daily self-reports	THROUGHOUT					

*Acute End assessments will take place after at least 4 weeks of treatment or upon early termination from Acute phase. There may be some delays between baseline assessments and the start of treatment.

**Continuation End assessments will take place after the 8th week of treatment or upon early termination from Continuation phase.

*** Blood chemistries may include CBC, BMP (including LFTs); and TSH at baseline if not obtained within the last 6 months.

+Subset of SCID-5 will be administered to assess Bipolar And Related Disorders, Depressive Disorders, Schizophrenia And Other Psychotic Disorders

++Item 6 of PSQI will be administered.

+++ Follow-Up assessments (typically phone) will be conducted for participants who begin Continuation Phase at 1, 2, and 3 months after their last study visit (Wk 8, or their last study visit if the participant ends early)

E. Determination of Remission

1. Acute Phase End

Participants who complete the acute phase and reach a MADRS score indicating remission (<10) or response (30% reduction) will continue IV ketamine for 4 weeks. This continuation phase is needed to establish the stability of remission/response.

Participants without a 30% reduction in MADRS score at the end of the acute phase will not proceed to the Continuation Phase of the study; their participation will end.

If needed, a 9th infusion can take place if there is an interruption of infusions during the final week of acute, give one additional so that in the final week prior to assessing response there have been 2 infusions.

2. Continuation Phase End

Participants who complete the Continuation phase will be assessed for remission and response using the MADRS. A second confirmatory MADRS will be obtained at the end of the Continuation Phase to determine final remission status.

F. Intervention: Ketamine Infusions

1. Details of Infusion

To ensure dose accuracy, participants will have weight confirmed prior to each infusion. After safety ratings (see table below) 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 rate 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.

2. Clonidine co-administration

The two most concerning problems observed during infusions are sympathomimetic (blood pressure changes) and psychotomimetic/dissociation. These are a tolerability issue (patients may not tolerate ketamine secondary to these problems), safety issue (transient hypertension or psychosis require additional monitoring and could cause cardiac or psychiatric risks, although to date these have not been seen in our or others' research), and an access issue (hypertension is common in older adults with depression and could prevent many patients from receiving an otherwise effective treatment). Our group showed that co-administered clonidine, an alpha-2 agonist, safely and effectively mitigates both of these concerning side effects of ketamine. Thus, pre-dosing of clonidine can improve the tolerability of ketamine and maximize its potential treatment benefits. Clonidine has not been widely used in ketamine treatment of depression, but it is routinely co-administered with ketamine in chronic pain management to reduce these side effects, and perioperatively as well. Clonidine co-administration does not alter the antidepressant activity of ketamine in either preclinical or clinical studies. If indicated (see human subjects section) participants may receive a 0.1 mg oral clonidine test dose to ensure tolerability, and those who tolerate and accept it will receive pre-dosing with clonidine prior to infusions during the

acute phase. Higher doses of clonidine (up to 0.3 mg) can be used if needed in certain cases to provide greater blood pressure control or prevent distressing neuropsychiatric symptoms (eg, dissociation). The co-administration of clonidine does not introduce excess polypharmacy for older adults because it is used only on days of ketamine infusions, as needed. It may not be needed long-term for most patients, as ketamine's neuropsychiatric side effects decline in most patients with repeat infusions.

INFUSION SCHEDULE To accommodate delays in the infusion schedule for various reasons (e.g. participant travel, illness, or COVID-19 safety guidelines), each phase may be extended by an additional 4 weeks.	
Acute Phase Infusion Schedule	Two infusions per week X 4 weeks (at least two days apart)
Continuation Phase Infusion Schedule	One infusion per week X 4 weeks

Safety Monitoring for Infusions				
	Before Infusion	40 Minutes After	60 Minutes After	90 Minutes After
Weight	X	X	X	X
Vital Signs: Blood Pressure, Pulse rate, oxygen saturation, body temperature	X	X	X	X
Brief Psychiatric Rating Scale - positive (psychotic) symptom subscale (BPRS+)	X	X	-	X
Clinician Administered Dissociative States Scale (CADSS)	X	X	-	X

G. Potential Risks & Risk Mitigation

Interviews/Questionnaires/Surveys:
Participants may experience emotional discomfort with the neuropsychological testing and medical and psychological questionnaires. If any particular question makes the participant uncomfortable, the participant may discuss its importance and the need to answer it with the specially-trained interviewer. These assessments will be administered in private settings. Participants have the right to refuse to answer any question for any reason.

Infusion Procedure/Blood Draws/ Injections:
While rare, participants may experience pain, bruising, and/or bleeding at the site of needle insertion for blood draws, injections and the intravenous catheter. There is a rare risk of infection from a needle insertion. Phlebotomy, IM injection, and IV insertion will be performed by certified and trained staff.

Ketamine:

Common side effects: Feeling light-headed, "high," exhilarated, having perceptual changes or hallucinations, floating sensations, and/or difficulty concentrating, paying attention, or remembering as many items as usual from a list (like items on a grocery list) Mild and temporary increases in blood pressure.
Less likely: Feeling dizzy, sleepy, anxious, suspicious, nauseated.
Rare side effects: Feeling sad, scared, confused, disoriented, moderate and temporary increases in blood pressure, future abuse of ketamine, prolonged psychosis in individuals with a pre-existing psychiatric condition. It is possible that the use of ketamine could increase interest in the illicit use or abuse of this substance although the fact that individuals with any past or current substance abuse will be excluded makes this highly unlikely.

We will minimize these risks by adhering to all entry criteria, not enrolling participants with uncontrolled hypertension or other unstable medication conditions, having same-room observation of all participants during the infusion and for 2 hours post-infusion that includes blood pressure monitoring, oxygen saturation monitoring, and management of psychotomimetic adverse effects by highly trained and psychologically-informed nursing and medical support staff. We will also use clonidine as needed the day of infusion (if determined to not increase risk of hypotension or orthostasis; see below).

Plans to ensure cardiovascular safety during the ketamine infusions: The most frequent cardiovascular effect of ketamine infusion is increase in blood pressure. A study of 66 patients, mean age 57, 38% with controlled hypertension and excluding patients with either a systolic BP >160 mmHg or diastolic BP > 100 mmHg at baseline, reported blood pressure effects of 684 IV ketamine infusions (Riva-Posse et al, Blood pressure safety of subanesthetic ketamine for depression: a report on 684 infusions. J Affect Disord 2018). In 9% of infusions a blood pressure measurement that was greater than 30 mmHg systolic or 15mmHg diastolic was recorded although there was no measurement that was greater than 45mmHg systolic of 30mmHG diastolic over baseline. The blood pressure increases were transitory. No patient required an intervention to treat blood pressure.

In this study the mean age of the patient group is anticipated to be 10-13 years older than the patient group in the Riva-Posse study and it is also anticipated that the rate of controlled hypertension will be higher. There are several procedures to increase safety in this study.

1. Participants with uncontrolled hypertension, defined as baseline systolic BP > 150 systolic or 90 diastolic, will be excluded.
2. Participants will be routinely pre-treated with clonidine 0.1mg the night before treatment and the morning of treatment, unless otherwise indicated (e.g., baseline BP is below 110 systolic of 70 diastolic).
3. Prior to each infusion BP will be measured after the patient has been lying quietly for 5 minutes. This recording will be the baseline BP. If baseline BP is elevated (Systolic > 160 or Diastolic >95), oral clonidine 0.1 mg will be administered and BP will be re-checked 20-30 minutes later. The dose of clonidine may be increased up to 0.2-0.3 mg depending upon participant benefit and tolerability. If BP continues to be elevated (Systolic > 160 or Diastolic >95), ketamine infusion will not be administered that day.
4. During the IV ketamine infusion BP is recorded every 10 minutes. A measurement that shows a BP increase over 25% from systolic or diastolic baseline and reaches a level of 175 systolic or 105 diastolic will trigger a repeat measurement in two minutes. If the same increase is recorded, then oral clonidine 0.1 mg will be given. If increased blood pressure measurements persist (above 175 systolic or 105 diastolic) the infusion will be discontinued.

5. If BP increases to levels described in #3 or participants experience psychotomimetic/dissociative effects, prior to the subsequent ketamine infusion, oral clonidine 0.1 mg will be taken by participants the night before the infusion and at least 30 minutes prior to the infusion. The dose of clonidine may be increased up to 0.2-0.3 mg, depending upon participant benefit and tolerability, for a maximum total daily dose of 0.6 mg when clonidine is used by the team for pre-treatment (night before/morning of). (Lenze et al, Ninety-six hour ketamine infusion with co-administered clonidine for treatment-resistant depression; World J Biol Psychiatry 2016).
6. An ECG will be done at baseline, at the end of continuation and at the end of the maintenance or at time of reoccurrence of depression

Plans to monitor and minimize psychotomimetic/dissociative effects:

We will measure transient neuropsychiatric changes with the Brief Psychiatric Rating Scale - positive (psychotic) symptom subscale (BPRS+) and the Clinician Administered Dissociative States Scale (CADSS) at baseline, 40 minutes, and 1.5 hours after infusion. Patient participants must be asymptomatic according to these measures and to clinical assessment prior to discharge from the infusion center. To prevent distressing symptoms, clonidine will be prescribed (see above) to take orally the night before and the morning of the subsequent infusion (dose starting at 0.1 mg, increased up to 0.3 mg as needed and tolerated). Nursing and medical support staff will all be trained in the care of patient participants experiencing psychological symptoms in response to a medical treatment, and we will follow best practice nursing approaches to calm and comfort participants by re-orienting them, preventing wandering and falls, assuring them they are safe and their feelings are normal and transient, and by having a psychiatrist on call at all times.

Clonidine:

Common side effects: Dry mouth, constipation, nausea, vomiting, mild abnormalities in liver function blood tests; salivary gland pain, leg cramps pain or musculoskeletal pain or joint pain, and feeling weak.
Less likely side effects: Dry throat, low blood pressure, dizziness, tremor; feeling nervous or irritable, having trouble sleeping or feeling drowsy, tired, or sedated; dry or blurred eyes or feeling tearful.
Rare side effects: Lack of appetite, transient elevation of blood glucose or blood serum creatinine tests, fluid retention, sexual dysfunction, genitourinary effects, headache, abdominal pain, change in taste, unpleasant dreams, ECG abnormalities, and palpitations have also been reported. We will only use clonidine in participants who experience infusion-related blood pressure elevations or psychotomimetic effects (e.g., dissociation). Prior to using low-dose clonidine, frequently prescribed for older adults with hypertension, and which we observed to be well-tolerated when administered prior to ketamine infusions to minimize these adverse effects, we will assure there are no pharmacodynamic interactions which would preclude its safe use, and as needed, consult with the participant's primary care physician or the study's PCP consultant, Dr. Bruce Rollman.

Suicide:

Patients who are identified as acutely suicidal will be excluded from the study and referred for acute psychiatric evaluation and care. Nevertheless, since the rate of completed suicide in the USA remains high (i.e., about twice the rate of homicide) and most Americans who commit suicide suffer from depression, all participants eligible to participate in this study are statistically at a relatively higher risk for suicide than the general population. However, the participants' absolute risk for completing suicide during this study remains very low (i.e., about 1 in 3,000 to 10,000) and participation in the study does not create or increase the risk of completed suicide. Actually, most experts believe that one of the most efficient ways to decrease suicidal risk in older depressed individuals is to treat their depression. Furthermore, all

participants will be formally assessed at least every two weeks for the duration of the study, and we will make efforts to engage family caregivers and obtain an emergency phone number for all participants. All sites have a 24/7/365 on-call system with geriatric psychiatry back-up. If the study personnel identify that a participant has become acutely suicidal, the local study team will take all necessary efforts to assure the participant is safe (i.e., escort them to the emergency room for evaluation, activate emergency medical services, speak with PCP or family members). This may lead to a clinical intervention that is lifesaving and may not have occurred had the participant not been participating in the study. We have published about our suicide safety risk management protocol (Herbeck Belnap et al, Electronic protocol for suicide risk management in research participants, J Psychosom Res 2015) and will follow this algorithm at every clinical assessment if it is triggered. This protocol has already been used successfully by this team to manage acutely suicidal patients in the ongoing OPTIMUM study. Briefly, the protocol entails a specific determination of the suicidal risk and prescribes a set of actions. For instance, when a participant is determined to be at high and immediate risk, the rater is instructed to stay with the participant until he or she has contacted a clinician to discuss the situation and to devise a plan. For this reason, raters will have cell phones and a study clinician will be reachable via cell phone. In case of extreme emergency, raters are instructed to call their hospital security team or 911 for immediate help and in order to have the participant escorted to the emergency department for further safety evaluation.

Breach of Confidentiality:
One risk of participating in this study is that confidential information may be accidentally disclosed. We will follow our established best-practice procedures to keep the information about participants secure. All private information is stored in secured areas and on encrypted and password-protected servers.

Other risks:
Participants may experience all or some of the risks listed above. There may also be unknown risks**.** We will adjust the informed consent process if new risks are identified. We will monitor adverse events and serious adverse events to determine if an emerging pattern suggests a re-evaluation of the risk/benefit ratio.

III. SAFETY AND ADVERSE EVENTS

A. 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.

B. Definitions of Adverse Events

An Adverse Event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a drug under study. An AE does not necessarily have a causal relationship with the study drug.

The criteria for identifying AEs are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug under study, whether or not considered related to the drug under study
- Any new disease or exacerbation of an existing disease

- Any deterioration in nonprotocol required measurements of a laboratory value or other clinical test (e.g., ECG or x ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (e.g., headache) not present pretreatment (i.e., baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, whether prescribed in the protocol or not.
- A laboratory result should be considered by the investigator to be an AE if it:
    - Results in the withdrawal of study drug
    - Results in withholding of study drug pending some investigational outcome
    - Results in an intervention, based on medical evaluation (e.g., potassium supplement for hypokalemia)
    - Results in any out of range laboratory value that in the investigator's judgment fulfills the definitions of an AE with regard to the subject's medical profile.

All AEs observed during the study will be reported on the Redcap AE form. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. Any laboratory abnormality considered to constitute an AE should be reported as an AE on the E-CRF.

It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

C. Classification of Events

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

1. Assessing Severity of Adverse Events

AEs will be graded on a 3 point scale (i.e., mild, moderate, and severe) and reported in the detail indicated on the CRF. The definitions are as follows:

- Mild: Discomfort noticed, but no disruption of normal daily activity
- Moderate: Discomfort sufficient to reduce or affect normal daily activity
- Severe: Incapacitating, with inability to work or to perform normal daily activity

2. Assessing Relationship of Adverse Events

The causal relationship of the study drug to an AE will be assessed as related or unrelated, as follows:

- Probably Related: There is a reasonable causal relationship between the study drug and the AE. The event responds to dechallenge. Seeing a recurrence of the AE with study medication rechallenge is not required.
    - Example: patient receives a ketamine infusion. They report vertigo that starts during their infusion and persists for 2 days afterwards, interfering with their day-time functioning (moderate AE). At the next infusion, the vertigo occurs again.

- Possibly Related: There is a reasonable causal relationship between the study drug and the AE. Dechallenge is lacking or unclear.
    - Example: patient reports new-onset insomnia the night after their first infusion but does not disrupt their daily activity (mild AE). They continue with the infusions and insomnia does not reliably occur after subsequent infusions.

Unrelated:

- Not Likely Related: There is a temporal relationship to study drug administration, but there is not a reasonable causal relationship between the study drug and the event.
    - Example: patient is started on ketamine infusions. One day after the first infusion, they are driving and are hit by another car, necessitating hospitalization (severe and serious AE). The accident is the fault of the other driver.

3. Assessing Expectedness of Adverse Events

An **Unexpected Adverse Event** is an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

4. Assessing Seriousness of Adverse Events

A **Serious Adverse Event (SAE)** is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (i.e., the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect in the child of a subject who was exposed to the study drug

Other important medical events that may not be immediately life threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

The following hospitalizations are not considered to be SAEs because there is no “adverse event” (i.e., there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Hospitalization planned before informed consent where the condition requiring the hospitalization has not changed post study drug administration
- Hospitalization for routine maintenance of a device (e.g., battery replacement) that was in place before study entry

D. Data Collection Procedures for Adverse Events

Participating sites are responsible for gathering and documenting data pertinent to Adverse Events occurring at their sites and for collecting Adverse Event information from each treating physician, including but not limited to:

- Description of the event, including onset and duration
- Treatment assignment, dose recommendation, and adherence
- Relevant medical and laboratory findings and reports
- Correspondence regarding the event
- Action taken in response to the event
- Classification of the Adverse Event (Severity, Relationship, Expectedness, Seriousness)

All Adverse Events observed during the study will be recorded on the Redcap AE form. All Adverse Events will be collected from the time of informed consent through the last assessment.

1.a Reporting Procedures for Adverse Events

- **Serious Adverse Events:** Must be reported to local site IRB as per each institutional policy.
- **All Adverse Events:** Document promptly via Redcap AE form, within 5 working days of the occurrence of the event or notification to the investigator or research team of the event.
- **Other Reporting Requirements:** Adverse Events will be reported per relevant reporting criteria and timeframes to IRB and FDA as required by each institutional policy.

E. Data Management & Analysis

The study is a pilot, feasibility study in that sample size is determined by feasibility, not a power calculation. If the study demonstrates feasibility of methods and a positive signal, then pilot data would be used to construct a larger, adequately-powered clinical trial with federal funding.

Study data are collected and managed using REDCap electronic data capture tools hosted in the Washington University School of Medicine Institute for Informatics (I2), Informatics Core Services (ICS). REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

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.

IV. REFERENCES

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