OPTIMUM: Optimizing Outcomes of Treatment-Resistant Depression in Older Adults

Study Protocol: Final Version

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A Introduction

A1 Study Abstract

Background and Significance: One-half or more of older adults fail to remit with antidepressant pharmacotherapy. Treatment-resistant depression (TRD) in older adults is highly deleterious, because persistence of depression is a leading cause of disability, suicide, dementia, and premature mortality. Making it worst is the lack of evidence-supported treatments at a stage in life when medications' benefit vs. risk ratio crucial.

The Optimizing Outcomes of Treatment-Resistant Depression in Older Adults (OPTIMUM) study will provide the evidence that older adults need to get effective treatment that works best for them, improving their quality of life while minimizing risks of medications.

Study Aims: The study aims to close the evidence gap on late-life depression in three ways. First, we will examine the comparative benefits and risks of antidepressant strategies (augmentation and switching) in older adults with TRD. We will focus on the effects on the outcomes that matter most to older adults, like well-being, adverse events, and falls. Secondly, we will explore how aging changes the balance of benefits vs. risks. With aging comes a decline in brain and systemic health that may alter the benefit/risk ratio of antidepressant strategies. Third, we will maximize stakeholder engagement to ensure relevancy to providers and patients alike. Armed with the knowledge of differential benefits and risks, stakeholders could provide personalized precision care that maximizes the benefits of TRD treatment strategies for older adults with minimizing risks.

Study Description: We will randomize 1500 adults aged 60+ to 10 weeks of one of three Step 1 strategies: aripiprazole augmentation, bupropion augmentation, or switch to bupropion. Those who do not attain remission in Step 1 will be randomized to 10 weeks of one of two Step 2 strategies: lithium augmentation or switch to nortriptyline. Those who complete acute treatment will be followed in a one-year continuation. This pragmatic RCT will be carried out in real-world clinical settings. Primary care and mental health clinical partners will provide treatments, with decision support from the study team.

Study population: Participants will be non-demented older adults aged 60+, with equal proportions aged 60-70 and 70+, with current major depression that has failed to respond to 2+ adequate antidepressant trials. We will recruit across five regions: St. Louis and rural Missouri; Los Angeles City and County; Western Pennsylvania; New York City; and Toronto and rural Ontario. Two-thirds of the sample will be women and 70% white, 15% black, 10% Latino, and 5% other racial groups.

Patients will be identified from clinical networks at each of the five participating centers. Our two primary mechanisms of recruitment will be through screening and referrals. We will screen through clinical networks using Electronic Medical Records (EMR) and will contact all patients in practices aged 60 and older who in the recent past were prescribed or are currently taking antidepressants. Referrals will be elicited from practitioners and through in-practice

advertisements to patients and their caregivers specifically asking if the doctor, patient, or caregiver describes the clinical situation as treatment resistant or difficult to treat.

Primary/secondary outcomes: Psychological well-being is the patient-centered effectiveness outcome and remission from depression is the clinician-focused effectiveness outcome. Secondary patient-reported outcomes include physical function and social participation. Safety will be monitored through serious adverse events as well as falls and fall-related injuries. As well, the study will test how aging influences the relative benefits and risks of antidepressants for TRD. Additionally, a qualitative study of patient and clinician partners will provide the lived experience of TRD and antidepressant strategies.

Analytic methods: Repeated measures ANOVA will test effectiveness of antidepressant strategies with respect to the primary patient-centered outcome of psychological well-being, as well as other continuous variables. Then, specific time*group contrasts will compare the changes across pairs of treatment groups. Corresponding generalized linear models with a logit link function will test effectiveness for reaching remission. Cox models examining time to event will test safety of antidepressant strategies in terms of serious adverse events, falls, and fall-related injuries.

Moderator analyses will examine the effect of aging on changing the relative benefits and risks of antidepressants. We will include the treatment by age group (<70 vs >70) by time interaction to the linear models described above to test for both the benefits and risks for the treatment alternatives.

A2 Purpose of the Study Protocol

This study protocol will serve as the shared working document for the study team to ensure that the research is being conducted consistently at all participating sites. Investigators Revisions will be made and shared by the Coordinating Site (Washington University). Changes requiring the approval of local IRB's or the funding agency (PCORI) will not be implemented until such approval is obtained.

B Background

Treatment-resistant depression (TRD) is a major health problem for the growing population of older adults. Older adults with persistent depression experience devastating medical consequences, place high burdens on caregivers, and suffer high suicide rates.[4,5]

TRD is the norm, not the exception in older depressed adults, as most fail to remit with standard antidepressant pharmacotherapy.[6,7] Persistent depression decreases older adults' quality of life more than any other illness.[8] Effective antidepressant treatment would address a leading cause of disability,[9] excess mortality,[10] and cognitive decline.[11-13] Understanding the risks and benefits of antidepressant strategies in older adults could vastly improve the quality of life of seniors and save billions of dollars each year in health care costs.[23] This public health issue will rapidly grow with the aging of the US and world population.[24]

Yet, in spite of the high stakes for public health, the comparative risk/benefit ratio of antidepressants is entirely unstudied in older adults with TRD. This stands in contrast with numerous studies in younger adults.[25-29] This evidence gap was highlighted in critical reviews[30,31]

that found a complete lack of evidence in this age group. The sole exception is our recent randomized controlled trial (RCT) of aripiprazole augmentation in older adults.[2,32]

C Study Objectives

The study aims to close the evidence gap on late-life depression in three ways:

C1 Aim 1: Effectiveness

Examine the comparative benefits and risks of antidepressant strategies (augmentation and switching) in older adults with TRD.

Effectiveness outcomes: psychological well-being and remission from depression
Safety outcomes: serious adverse events, falls, and fall-related injuries

C2 Aim 2: Effects of Aging

Explore how age, and age-related variables (medical comorbidity, cognitive problems) change the balance of benefits vs. risks.

C3 Aim 3: Maximize Stakeholder Engagement

We will maximize stakeholder engagement to ensure relevancy to providers and patients alike.

C4 Rationale for the Selection of Outcome Measures

OUTCOME	WHEN AND HOW MEASURED	RATIONALE
Psychological well-being is the patient-centered effectiveness outcome (Hypothesis 1a [H1a]). Secondary quality of life measures are self-reported physical function and social participation.	In Acute, beginning and end of Step 1 (and Step 2); in Continuation months 4, 8, 12. Measured by NIH Toolbox* (Psychological Well-being) and PROMIS* (Physical function, Social participation). Assessed by independent rater**	Psychological well-being encompasses satisfaction, happiness, cognitive engagement, and meaning/purpose. It is a critical dimension of quality of life, recommended by patient stakeholders in focus groups as an outcome that matters.
Remission is our clinician-focused effectiveness outcome (H1b): reduction of depressive symptoms below a threshold (MADRS≤10). This goal of treatment is a consensus among practitioners.[53,54]	In Acute, beginning and end of Step 1 (and Step 2); in Continuation, months 4, 8, 12 Assessed by independent (blind) rater** via 20-30 minute phone interview.	The MADRS measures 10 areas of depressive symptoms. It is a standard outcome in antidepressant studies. Patient stakeholders described this assessment as "very important" for assessing effectiveness.
Serious adverse events (SAEs) (H2a) This safety outcome encompasses life threatening illness, hospitalization, or need of medical care.	Anytime when a SAE occurs.	Key measure of antidepressant safety in older adults.

Falls and fall-related injuries via self-report are another safety outcome (H2b).	End of Step 1 and Step 2, every 4 months in continuation. Assessed by independent rater**	Patient stakeholders told us that fall risk was very important to them. Clinicians and policy-makers are also concerned about fall risk due to antidepressants.

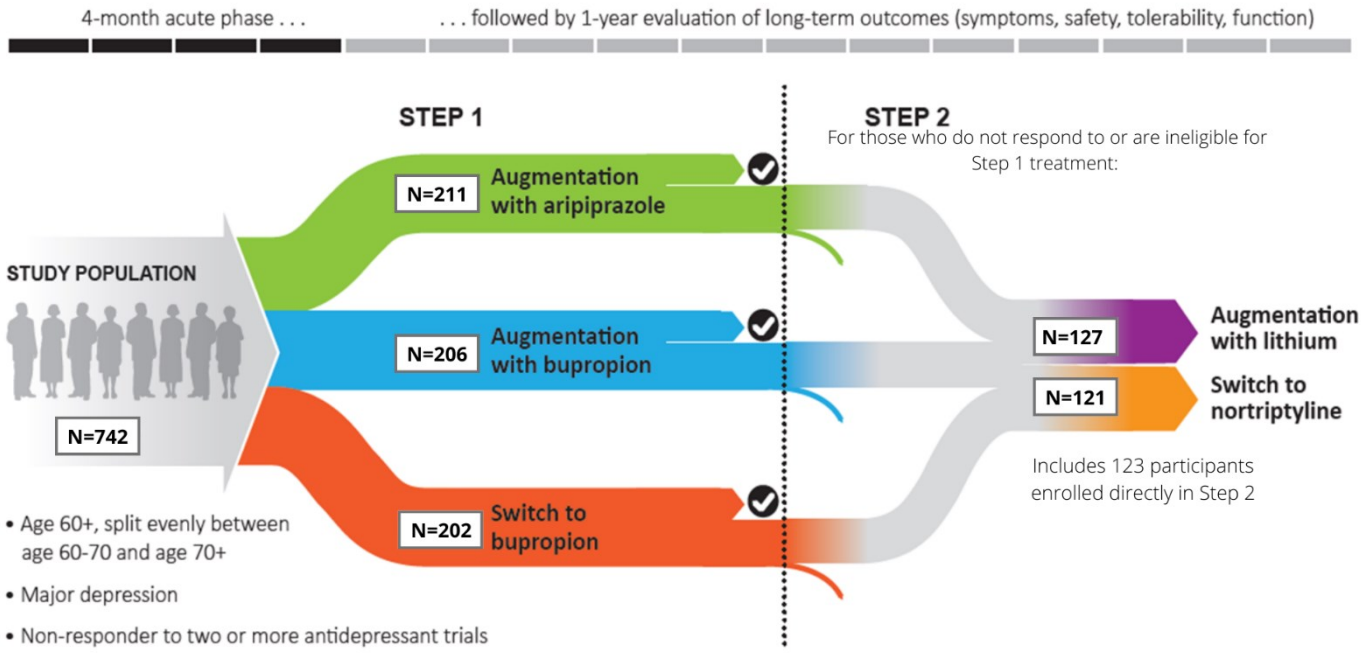
D Study Design

D1 Overview or Design Summary

The study design compares benefits and risks of 3 first-line (simpler to use) strategies: augmentation with aripiprazole, augmentation with bupropion, and switch to bupropion; and 2 second-line (requires more monitoring) strategies: augmentation with lithium and switch to nortriptyline. The step-wise design matches real-world care, in which clinicians go from easier to more challenging management strategies.

This is a collaborative, multi-site study with five sites: Washington University (Coordinating Site) which includes University of Missouri-Columbia, University of Pittsburgh, University of Toronto, University of California Los Angeles, and Columbia University. Each site will randomize 300 eligible participants into Step 1, for a total of 1,500 participants across all sites.

Figure updated after completion of the study to reflect actual sample enrollment numbers.



D2 Subject Selection and Withdrawal

All participants will meet the following eligibility criteria:

1.a **Inclusion Criteria (Steps 1 & 2)**

a) Men and women aged 60 and older, with equal proportions aged 60-70 and 70+.
b) Current Major Depressive Disorder (MDD), single or recurrent, as diagnosed by DSM-5 criteria.
c) Failure to respond adequately to two or more antidepressant treatment trials of recommended dose and length (approximately 12 weeks).
d) PHQ-9 score of 10 or higher.

1.b **Exclusion Criteria (Steps 1 & 2)**

a) Inability to provide informed consent.
b) Dementia, as defined by Short Blessed ≥10 and/or clinical evidence of dementia. Patients screened out due to possible dementia will be referred to a local Memory Clinic or back to their clinician for evaluation to clarify the presence or absence of dementia.
c) Lifetime diagnosis of bipolar I or II disorder, schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, or current psychotic symptoms. A recommendation for psychiatric referral will be made in these cases.
d) High risk for suicide (e.g. active SI and or current/recent intent or plan) and unable to be managed safely in the clinical trial, such as unwilling to be hospitalized). Urgent psychiatric referral will be made in these cases.
e) Contraindication to proposed study medications, as determined by study physician including history of intolerance or non-response to proposed medications.
f) Non-correctable, clinically significant sensory impairment (e.g., cannot hear well enough to cooperate with interview).
g) Unstable medical illness, including delirium, uncontrolled diabetes mellitus, hypertension, hyperlipidemia, or cerebrovascular or cardiovascular risk factors that are not under medical management. This will be determined based on information from the patient's personal physician's and study physician clinical judgement. Referral to the patient's personal physician or to a general practitioner will be made in these cases.
h) Moderate to severe substance or alcohol use disorder, as determined by study physician. Referral to appropriate treatment will be made in these cases.
i) Seizure disorder.
j) Parkinson's Disease

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

1.c **Exclusions to Enter Step 2**

The following conditions are contraindications to Step 2 medications. Participants with them will not be eligible for Step 2 participation (but may be considered for Step 1 provided they meet criteria outlined in Sections 1.a & 1.b.)

a) QTc prolongation or Wide QRS on EKG

b) Active Ischemic Heart Disease as evidenced by angina or requiring treatment (e.g., nitrates) for ischemic attacks. Patients with history of prior MI, stent, or bypass may be included who have had no symptoms of ischemia (e.g., no chest pain) for 2 years.
c) Acute or chronic renal insufficiency (as indicated by creatinine clearance below 30 mL/min; suspected if creatinine above 1.5 mg/dL; per PI and/or clinician discretion)
d) Narrow angle glaucoma

1.d Ethical Considerations

This study will be conducted in compliance with the protocol, United States (US) Food and Drug Administration (FDA) regulations, and all other applicable local laws and regulatory requirements.

Each study site will seek approval by an institutional review board (IRB) according to regional requirements. The IRB will evaluate the ethical, scientific and medical appropriateness of the study. Further, in preparing and handling electronic case report forms (E-CRFs), the investigator, sub-investigator and their staff will take measures to ensure adequate care in protecting participant privacy. To this end, a participant identification number will be used to identify each participant.

1.e Informed Consent

All subjects will have the purpose of the study, study interventions and evaluations, and the potential risks and benefits of participation explained to them and any questions will be answered. If a subject agrees to participate in this study, the subject will review and sign the informed consent form (ICF).

Written informed consent will be obtained from all subjects, themselves, with no proxy consent. If requested by subject, we will be prepared to include others (family members, friends, or their personal physician-making) in the process of informed consent to . Consent will be documented on a written ICF. The ICF will be approved by the same IRB that approves this protocol. Each ICF will comply with the FDA regulations in Title 21 Code of Federal Regulations (CFR) Part 50 ICH, GCP, and local regulatory requirements.

Investigators may discuss study availability and the possibility for entry with a potential subject without first obtaining consent and conduct preliminary pre-screening with the patient's verbal assent, following the process described in section F1.

Written Informed consent will be obtained before any study procedures other than pre-screening are performed.

Once appropriate essential information has been provided and fully explained in layman's language to the subject by the investigator, or a qualified designee, the IRB-approved written ICF will be signed and dated by both the subject and the person obtaining consent (i.e., investigator or designee). The subject will receive a copy of the signed informed consent form; the original shall be kept on file by the investigator.

1.f Subject Recruitment Plans and Consent Process

Study sites will be responsible for developing their site-specific recruitment plans and obtaining IRB approval for the plan and all recruitment materials. In most cases, recruitment will be facilitated through partnerships with community mental health and primary care clinics. Plans for recruitment by referral or via a partial waiver of HIPAA authorization for recruitment purposes must be agreed upon by the appropriate community personnel, and approved by the local IRB, prior to implementing.

1.g Randomization Method and Blinding

Randomization of participants will be implemented in REDCap, using a randomized block design within clinic and age group using variable block size, stratified by institutional site and age strata.

Only assessors of outcome measures will be blinded. Participants, providers, and other research staff will not be blinded to participants' condition.

In this pragmatic design where all levels of adherence are allowed, participants will be considered randomized assuming they meet the eligibility requirements at screening (including any safety screens as applicable) and they and/or their clinician has been given a randomization assignment.

1.h Potential Risks

Study Instruments and measures: The assessments to be conducted as part of this study involving mood assessments, neuropsychological testing, and behavioral and functional assessments are non-invasive and carry with them no more than minimal risk. The most significant risks to the participants related to assessments are those that would follow a breach of confidentiality and the disclosure of clinical information. We also include discomfort in the potential risks. The instruments to be used in this study are brief and pragmatic and have been well-tolerated by older adults in other studies.

Aripiprazole: The most common side effect of aripiprazole (occur in 25% of people) is akathisia.

Common side effects (occur in 1-25% of people) include restlessness, insomnia, fatigue, blurred vision, somnolence, tremor, constipation, sedation, and dizziness. There is a potential that aripiprazole may increase the risk of hyperglycemia (increased blood sugar), diabetes, abnormal cholesterol or increased triglycerides.

We will monitor patients for these symptoms and require that they have a fasting blood glucose and lipid profile obtained prior to start of aripiprazole and as often as clinically necessary.

Neuroleptic malignant syndrome (NMS) has been reported for all atypical antipsychotics, including aripiprazole (albeit rarely -- only 14 cases have been reported, and the aripiprazole dose in these was higher than what is used in this study). Patients who develop this syndrome may have high fevers, muscle rigidity, altered mental status, irregular pulse or blood pressure, rapid heart rate, excessive sweating, and heart arrhythmias.

Bupropion: The most frequent (occurs in more than 25% of people) side effects of bupropion include agitation, dry mouth, and headache. Common side effects (occurs in 1-25% of people) include excessive sweating, dizziness, tremor, constipation, nausea, decreased appetite, weight loss, rash, heart pounding, high blood pressure, unsteadiness when walking, confusion, anxiety, increased urination, and difficulty sleeping. Seizures may occur in patients receiving bupropion; however, at the dose range (max 300mg) and once-daily formulation used in this study, only 2 cases of seizures have been reported, and our exclusion of individuals with seizure disorders will minimize this risk. There is a rare (<1%) risk of mania or hypomania associated with antidepressant treatment.

Lithium: Likely side effects (occurs in more than 25% of people) of lithium carbonate include shakiness of the hands, drowsiness, headache, increased urination, increased thirst, and dry mouth. Common side effects (occurs in 1-25% of people) include weight gain, nausea, vomiting, and diarrhea. These are temporary side effects that will usually stop after the body adjusts over 1-2 weeks. Lithium may commonly slow down the functioning of the thyroid hormone (hormone that controls growth and ability to burn energy) and, after years of treatment, it may affects (occurs in less than 1% of people) the functioning of the kidneys. In rare cases, lithium intoxication may occur with muscular weakness and lack of coordination, confusion, altered consciousness. These risks are less likely at the lower serum levels used in this study.

Nortriptyline: The most frequent side effects of nortriptyline include dry mouth and constipation (25-30% of elderly participants in our past studies). Other common (occurs in 1-25% of people) side effects include sedation, sweating, dizziness, rapid pulse, heart pounding, blurred vision, headache, and hypertension (high blood pressure). There is a rare risk of arrhythmia. There is a rare (<1%) risk of mania or hypomania associated with antidepressant treatment.

Potential Risks from Drug Cross-Over: The intent of the study is to move patients onto augmentation and switch strategies; therefore, there is some chance that patients will be switched to a drug that is either ineffective or that the transition will cause side effects (e.g., discontinuation syndrome). In cases of switch, tapering the previous drug while cross-titrating the new drug should minimize any discontinuation risks.

One of our primary aims is to evaluate the safety of these antidepressant pharmacotherapy options. We will closely monitor all participants for any problems (either in low effectiveness, or with side effects) and use this information as part of our "decision support" to inform participants and their clinicians about treatment steps such as increasing or decreasing the medication. Thus, we believe that participants treated in the proposed protocol will actually be safer in than they would in usual care. The potential risks associated with participation (including the risk of medications and the risk of receiving an ineffective treatment) are typical for antidepressant treatment in clinical care, and these will be clearly described to all potential participants as part of the informed consent process.

Suicide: Suicide is not a risk of the study per se but is a risk of having major depression. Patients who are identified as being acutely suicidal will be excluded from the study. 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. Participation in the study does not create or increase the risk of completed suicide;

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 frequently throughout the study. 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, this participant will be referred to a mental health professional for further evaluation and treatment. 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 included a Suicide Risk Management protocol to assess and reduce suicide risk in the manual of procedures as well as a Quick Suicide Safety Screening that may be used during phone pre-screening.

Body Composition Measurement (Washington University site only):
For participants with a pacemaker or a prosthesis that uses any other type of battery-powered or electrical power implant, there is a chance that the measurement of body composition could cause interference with the device. In order to protect from that risk, participants should not take part in the body composition measurement if they have a battery-powered or electrical implant. Participants with a history of abnormal heart rhythms will be reviewed by a medical doctor to make sure that the body composition measurement will not worsen their condition.

1.i Potential Benefits

Participants may or may not benefit from being in this study. Changing medication strategies may provide relief from symptoms of depression. Results from this study will provide doctors and patients with knowledge about the risks and benefits of antidepressant medications for older adults, so that they can make informed choices to manage depression.

1.j Early Withdrawal of Subjects

Participants will be asked to continue in the study for follow-up regardless of their and their physician's adherence to the medication recommendations from the study team. Participants who discontinue study medications for tolerability reasons will be asked to complete the appropriate Acute Phase End Assessments for their phase of the study (see Section F5). Participants who end Step 1 treatment early due to tolerability issues will be invited to proceed to Step 2 after completing Acute Phase End Assessments.

Participants who choose to withdraw from the study early will be asked to complete the appropriate final visit for their phase of the study (Step 1 Week 10, Step 2 Week 20, or Continuation Month 12).

Withdrawal from the study for any reason, including study completion, will be documented in the Electronic Case Report Form.
Participants' reasons for withdrawal will be summarily reviewed by each site's IRB at Continuing Review and at DSMB meetings.

E Medication Strategies and Decisional Support

1.a Description of Decisional Support

The pragmatic, comparative effectiveness design research participants continue to receive ongoing care, management, and prescriptions from their own physicians. The research team will

randomly assign participants to the well-established,evidence-based, standard of care medication strategy conditions. The research team will assess participants for symptoms and tolerability by phone every two weeks during acute treatment. The research team will make a recommendation for medication dosing that the treating physician can override or ignore. The Manual of Procedures for this study will describe how the study team will communicate the randomization assignment and any recommended changes to the treating physician. This decision support is greater than is seen in usual clinical care. Patients highly recommended it, and a similar measurement-based approach has worked well in our prior studies in late-life depression.

- Dose adjustment is done by the treating clinician with support from researchers:
    - If PHQ-9 score is 6 or greater, and side effects are absent or well-tolerated: increase the dose.
    - If PHQ-9 score is 5 or less, or side effects are enough that participant cannot tolerate a dose increase: keep dose the same.
    - If side effects are such that participant needs a dose decrease: decrease dose back to previous.
    - If side effects are intolerable such that participant needs a medication change: end step and move on to the next step (or remove from study if in step 2).
- Clinicians and patients have flexibility: they may decide to exit Step 1 or Step 2 treatment early (e.g., due to tolerability issues). Clinicians are allowed to coprescribe other medications as well. The Manual of Procedures for this study will contain the communication plan for how the treating physician will communicate any changes or new medications back to the study team.
- Decision support will also ask participants their study med adherence. If participants have missed doses, brief counselling about adherence, including the importance of 100% adherence, and solving barriers to adherence, will be provided.

1.b Treatment Group Assignment

In this step-wise design, participants will be randomized 1:1:1 to a Step 1 medication strategy: aripiprazole augmentation, bupropion augmentation, or bupropion switch. Participants whose depression has not remitted at the end of Step 1, will be randomized 1:1 to a Step 2 medication strategy: lithium augmentation or bupropion switch. All medications are being used within their FDA-indicated population (adults), disease (major depressive episode), dosage, and route of administration (PO).

1.c Aripiprazole Augmentation Prescribing Information

Starting Dose	2.5 mg
Maximum Dose:	15 mg
Titration:	Study team will recommend increases approximately every two weeks (5, 7.5, 10, 15) based on symptoms and tolerability.

Potential Side Effects:	-Akathisia, restlessness, insomnia, fatigue, blurred vision, somnolence, tremor, constipation, sedation, and dizziness. -May increase the risk of hyperglycemia, diabetes, abnormal cholesterol or increased triglycerides. -Neuroleptic malignant syndrome (NMS) has been reported for all atypical antipsychotics, including aripiprazole (albeit rarely). Patients who develop this syndrome may have high fevers, muscle rigidity, altered mental status, irregular pulse or blood pressure, rapid heart rate, excessive sweating, and heart arrhythmias.

1.d **Bupropion Switch and Augmentation Prescribing Information**

Starting Dose	150 mg
Maximum Dose:	450 mg
Titration:	Study team will recommend increase to 300 after approximately two to four weeks based on symptoms and tolerability.
Potential Side Effects:	-Agitation, dry mouth, and headache. -Excessive sweating, dizziness, tremor, constipation, nausea, decreased appetite, weight loss, rash, heart pounding, high blood pressure, unsteadiness when walking, confusion, anxiety, increased urination, and difficulty sleeping. -Seizures may occur in 0.4% of patients receiving bupropion. - There is a rare (<1%) risk of mania or hypomania associated with antidepressant treatment.

1.e **Lithium Augmentation Prescribing Information**

Starting Dose:	300 mg QHS
Maximum Dose:	1200* mg *Study team will adherence and accuracy of blood level with patient prior to increasing Lithium higher than 600mg
Titration:	Check blood level 1 week after initiating. adjust dosage linearly to target 0.6 mEq/L. Recheck level 1-2 weeks later. Adjust dose as needed to keep participant in 0.4-0.8 mEq/L

	window. Levels outside of this range may be acceptable per PI discretion.
Potential Side Effects:	-Shakiness of the hands, drowsiness, headache, increased urination, increased thirst, and dry mouth, weight gain, nausea, vomiting, and diarrhea. These are temporary side effects that will usually stop after the body adjusts over 1-2 weeks. -Slowed thyroid functioning -After years of treatment, less than 1% of people it may have kidney functioning affected. -In rare cases, lithium intoxication may occur with muscular weakness and lack of coordination, confusion, altered consciousness.

1.f **Nortriptyline Switch Prescribing Information**

Starting Dose:	25 mg
Maximum Dose:	150 mg
Titration:	Increase by 25 mg approximately every 5-7 days until reaching target dose of 1mg per kg of body weight. Measure blood level 5-7 days after starting target dose. Adjust dose accordingly, targeting therapeutic range of 80-120 ng/ml. Levels outside of this range may be acceptable per PI discretion.
Potential Side Effects:	-Dry mouth and constipation, sedation, sweating, dizziness, rapid pulse, heart pounding, blurred vision, headache, and hypertension. -Rare risk of arrhythmia. -There is a rare (<1%) risk of mania or hypomania associated with antidepressant treatment.

1.g **Safety Labs and Monitoring**

Safety labs will be obtained from participants in accordance with accepted clinical practice guidelines described below. Participants and their providers will choose a local laboratory to conduct the testing according to their own preferences.

i **Recommended baseline labs**

Study team will recommend that each participant's provider conduct the following laboratory testing if such tests have not been conducted approximately within the last 12 months.

- CBC
- Na*
- K*
- Ca*
- creatinine/BUN*
- liver function tests*
- TSH
- B12
- ECG (to rule out QTc prolongation for Step 2 participants)

**Note that Na, K, Ca, creatinine, BUN, & liver function tests may be obtained efficiently using a CMP.*

ii Recommended labs prior to aripiprazole augmentation

The following laboratory testing is recommended prior to initiation of aripirazole augmnentation if such tests have not been conducted approximately within the last 12 months.

- fasting glucose
- fasting lipid panel

iii Required labs prior to Lithium augmentation

Participants who are randomized to Lithium augmentation in Step 2 must undergo the following laboratory testing prior to initiating lithium treatment. Values obtained at baseline or in the last 12months are acceptable provided they are within the normal limits.

- creatinine
- Sodium (Na)
- Potassium (K)
- TSH

iv Blood Level testing for Lithium Augmentation

Blood level testing is necessary for appropriate titration of Lithium (See also Section E1.e.). Blood levels will be checked approximately 1 week after initiating, and approximately 1-2 weeks following a subsequent dose adjustment.

v Required labs prior to Nortriptyline switch

Participants who are randomized to Nortriptyline switch in Step 2 must undergo an EKG prior to initiating nortriptyline treatment. EKG's conducted at baseline or in the last 12 months are acceptable. Participants whose EKG's reveal the following contraindications to nortriptlyline will be advised *not* to initiate nortriptyline treatment. If these conditions appear after starting notriptyline, participants will be advised to stop nortriptyline treatment.

- QTc prolongation or wide QRS

vi Blood Level testing for Nortriptyline switch

Blood level testing is necessary for appropriate titration of Nortriptyline (See also Section E1.f). Blood levels will be checked approximately 5-7 days after starting target dose.

vii Recommended Follow-up Labs for Continuing on aripiprazole

The following laboratory testing is recommended at Step 1 Week 10, Continuation Month 8, and every 6 months thereafter for participants who continue taking aripiprazole.

- fasting glucose
- fasting lipid panel

Or, alternatively, the following may be collected if preferred by the participant's provider:

- Random blood glucose
- Lipid panel
- Hemoglobin A1C

viii Recommended Follow-up Labs for Continuing on nortriptyline

The following laboratory testing is recommended at Step 2 Week 10, Continuation Month 8 or 12, and yearly thereafter for participants who continue taking nortriptyline.

- EKG
- Nortriptyline level

ix Recommended Follow-up Labs for Continuing on lithium

The following laboratory testing is recommended at Step 2 Week 10, Continuation Month 8, and yearly thereafter for participants who continue taking lithium.

- Creatinine
- Sodium (Na)
- Potassium (K)
- Calcium
- BUN
- TSH
- Lithium level

- Transition from Step 1 to Step 2

		Step 2	
		Nortriptyline Switch	Lithium Augmentation
Step 1	Aripiprazole Augmentation (ADM + Aripiprazole)	(1) D/C Aripiprazole (2) D/C or taper ADM* (3) Start Nortriptyline	(1) D/C Aripiprazole (2) Start Lithium
	Bupropion (ADM + Bupropion)	(1) D/C Bupropion (2) D/C or taper ADM (3) Start Nortriptyline	(1) Patient and their clinician choose whether to D/C Bupropion or D/C or taper as ADM (2) Start Lithium
	Bupropion	(1) D/C Bupropion (2) Start Nortriptyline	(1) Start Lithium

D/C: discontinue
ADM: Antidepressant medication
* Some ADM can be D/C'ed (e.g., fluoxetine) and most needs to be tapered either rapidly (e.g., sertraline) or slowly (e.g., paroxetine or venlafaxine)

1.h Preparation and Administration of Study Drug

In this pragmatic, real-world study, physicians will prescribe these standard of care medications to study participants, who will procure them in the same manner they obtain their other prescriptions. This will include but is not limited to: using health insurance and prescription drug benefit programs, retail pharmacies, and clinic pharmacies.

1.i Subject Compliance Monitoring

Because this is a pragmatic study, all levels of adherence are allowed. Compliance with the study-recommended medication and dosing will be assessed at each decision support call using the Protocol Adherence Form. Reasons for non-compliance will be documented.

1.j Prior and Concomitant Therapy

Patients randomized to an augmentation strategy will continue their previous antidepressant monotherapy. Patients randomized to a switching strategy will be tapered off of their current antidepressant medication with guidance from the research doctors prior to initiating acute treatment. Research doctors will be available 24/7 via exchange in case of issues.

Co-prescription of other medications by the clinician will be permitted, consistent with the pragmatic design. We will recommend limiting benzodiazepine use to ≤2 mg of lorazepam or equivalent each 24 hours as needed.

F Study Procedures

F1 Screening for Eligibility

Potential participants identified through each site's IRB-approved recruitment plans will be screened for eligibility. Staff and PI's at each site are responsible for verifying that participants at their site meet all eligibility criteria before being randomized to acute treatment. We anticipate differences between sites in which assessments may be obtained in pre-screening (pre- written consent) versus screening (post written consent). Despite these potential differences, the following assessments must be conducted prior to randomization to ensure eligibility (see also Section D2 for Inclusion and Exclusion Criteria):

- PHQ-9
- MINI MDE Module
- Screening questions for treatment resistance and medical exclusions
- Short Blessed Test
- ATHF
- CIRS-G

1.a **Screening Log**

Each site will use a phone screening script and screening log as approved by their IRB. In the event that participants do not currently qualify for the study, but may qualify in the near future, research staff will ask the potential participant for permission to keep their contact information on file and follow up with them and/or their doctor at a later date.

F2 Schedule of Measurements

OPTIMUM *Revised 03/30/17 (Changes in Yellow)*	Pre/ Screening	Baseline	Step 1 (10 weeks)						Step 2 (10 weeks)						Continuation (12 months)		
Done by local sites:			wk0	wk2	wk4	wk6	wk8	Step end*	wk0	wk2	wk4	wk6	wk8	Step end*	month 4	month 8	month 12
PHQ-9	X																
Sociodemographics	X																
Screening questions for treatment resistance and medical exclusions	X																
Short Blessed Test	X																
Consent		X															
Confirm Inclusion/Exclusion Criteria		X															
ATHF		X															
CIRS-G		X															
Expectations for Adherence		X															
Height		X															
Weight		X						X						X	X	X	X
Saliva sample for genetic testing		X															
Extra Local MADRS if start of treatment >2weeks since Central MADRS			X						X								
MINI Modules A&C (Depressive and Manic Episodes)		X															
DAST-10 (if indicated by pre-screen)		X															
AUDIT (if indicated by pre-screen)		X		X	X	X	X	X		X	X	X	X	X			
Side Effect Assessment		X		X	X	X	X	X		X	X	X	X	X	X**	X**	X**
Adherence				X	X	X	X	X		X	X	X	X	X	X**	X**	X**
Falls and fall-related injuries		X		X	X	X	X	X		X	X	X	X	X	X**	X**	X**
NIH Toolbox Cognition and Motor batteries -@done if participant able to be seen in person		X						X						X			X
Cognition battery including Attention/exec function (flanker and dimsional change card sort), Episodic memory (Picture seq memory), working memory (List sorting), Processing speed (pattern comparison). Baseline only: Language (Oral reading recognition)																	
Motor battery including Dexterity (pegboard), Strength (using grip dynamometer), Balance, gait speed																	
Psychological well-being (NIH Toolbox self-report measure)		X						X						X	X	X	X
Physical Function (PROMIS)		X						X						X	X	X	X
Social Participation (PROMIS)		X						X						X	X	X	X
AE and SAE collection (collected anytime the event occurs)																	
Anxiety (PROMIS)		X															
Done by central rater pool at WU by phone:																	
MADRS		X						X						X	X	X	X
* Typically Week 10; or upon dropout																	
**Central rater pool will assess side effects, falls, and adherence during continuation; local sites can do additional decision support calls "as needed" during this time																	

F3 Baseline

- Participant signs (or returns signed) informed consent form; all elements of informed consent have been discussed and participants' questions answered.
- Local Research Team Assessments: (in person if possible; approximately 3 hours)
    - MINI MDD & Bipolar Modules
    - PHQ-9 (If more than 7 days has elapsed since the PHQ-9 was done at pre-screen.)
    - Suicide History, Risk & Protective Factors
    - Baseline Side Effects
    - Expectations for Adherence
    - Behavioral Therapy Assessment
    - Falls & Related Injuries (history)
    - Height and Weight (self-reported)
    - If indicated by pre-screen: DAST-10
    - If indicated by pre-screen: AUDIT
    - NIH Toolbox Psychological Well Being
    - PROMIS Physical Function
    - PROMIS Social Participation
    - PROMIS Anxiety
    - NIH Cognition and Motor Batteries (in person assessments - may be foregone for participants living in remote locations)
    - ATHF
    - CIRS-G
    - Medical Conditions and Medication List (study doctor to review before randomization)
    - Confirm inclusion/ exclusion criteria are met
    - Randomize participant; provide initial decision support per randomization status to participant's doctor.
- Central Rater Assessments (by phone; approximately 30 minutes)
    - MADRS

F4 Decision Support Calls

- Every 2 Weeks During Acute Treatment: Step 1 Weeks 2, 4, 6, 8, 10* & Step 2 Weeks 2, 4, 6, 8, 10*
- Phone Call with Local Research Team (approximately 10 minutes)
    - PHQ-9
    - Spontaneous side effect report & severity
    - Falls Assessment
    - Adherence
    - Counselling about adherence and management of side effects.
    - AE reports done as needed.
    - Decision support staff contact study MDs when needed (e.g. if confusion about whether to increase antidepressant dose).
    - Decision support staff contact participant's clinical provider with recommendations; also will typically tell patient the recommendations.

F5 Acute Phase End Assessments

- Step 1 Week 10, Step 2 Week 10, or upon early withdrawal (if possible)
    - If there is a long delay between the Step 1 Week 10 assessment and the initiation of Step 2, the participant may be asked to repeat some or all of the Step 1 End assessments.
- *In addition to Decision Support assessments, local research team will conduct the following assessments (in person if possible; approximately 1 ½ hour):
    - NIH Toolbox Psychological Well Being (may be conducted via phone or Redcap survey)
    - PROMIS Physical Function (may be conducted via phone or Redcap survey)
    - PROMIS Social Participation (may be conducted via phone or Redcap survey)
    - NIH Cognition and Motor Batteries (may be foregone for participants living in remote locations)
    - Weight (self-reported)
- Central Rater Assessments (by phone; approximately 30 minutes. WU participants may do in person or by phone)
    - MADRS

F6 Continuation Assessments

- Months 4, 8, and 12 after completing acute treatment in Step 1 and/or 2 as indicated.
- Participants who relapse in Continuation after Step 1 may be invited to participate in Step 2; and then continuation subsequently.
- Local Research Team Assessments (in person if possible; approximately 1½ hour)::
    - NIH Toolbox Psychological Well Being (may be conducted via phone or Redcap survey)
    - PROMIS Physical Function (may be conducted via phone or Redcap survey)
    - PROMIS Social Participation
    - Weight
    - NIH Cognition and Motor Batteries (Month 12 only; may be foregone for participants living in remote locations)
- Central Rater Assessments (by phone; approximately 30 minutes)
    - MADRS
    - Falls & Related Injuries
    - Spontaneous side effects and severity(discuss with local sites if needed)
    - Adherence

F7 Genetic Testing

The proposed study will be a robust clinical trial platform for translational research, and the primary aims of this study, regarding effectiveness and safety of augmentation and switch strategies, lend themselves to pharmacogenetic studies. For example, these methods can address whether efficacy or tolerability are associated with genetic variability at the medication target receptors (producing pharmacodynamic variability at serotonin, norepinephrine, and dopamine receptors).

We will collect DNA from all participants at baseline. As the study approaches completion **(or after completion)**, we will select specific hypotheses based on pharmacogenetics advances expected during the next 5 years. Resources such as the Human Genome Center at Washington

University or the Centre for Pharmacogenetics in Toronto will provide cutting-edge testing and analytical methods leading to precision and patient-centered medicine.

7.a **Processing of DNA:**

Saliva samples will be obtained approximately at baseline for each subject. Each site will ship samples (typically in batches) to WU for DNA isolation and long-term storage.

F8 Qualitative Interviews

A subset of randomly selected participants will be asked to participate in a semi-structured qualitative phone interview to fulfill Aim 3. These interviews will be conducted by trained research staff at the University of Pittsburgh. Interviews will be audio recorded and transcribed. They will take approximately 60 minutes. Interviews will assess patient experiences with depression, treatment, and the study. Participants may choose whether or not to take part in the interview. Those that do take part in the interview may choose to skip any questions they would prefer not to answer. Participants who take part in the phone interview will be offered additional compensation for their time.

G Safety and Adverse Events

1.a **Safety Monitoring**

Safety will be assessed by AE reporting, assessment of side effects, falls, and falls-related injuries, and blood level monitoring for participants taking lithium or nortriptyline. Suicide risk will also be assessed and managed.

The primary mechanism for ensuring safety of participants, over and above their usual clinical care, is the bi-weekly Decision Support Calls. This will ensure we have contact with participants that is much more frequent and structured than routine clinical care.

In addition, we will ask each participant and their physician to notify us of new symptoms, illnesses, or other problems.

1.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 e-E-CRF. 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. Serious AEs will be collected for 30 days after the last dose or at the Follow up Visit, whichever comes later.

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.

1.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.

i 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

ii 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 in step 1 is started on bupropion augmentation which is increased to 300mg. They report severe insomnia that reduces their day-time functioning (moderate AE). Bupropion is reduced to 150mg and insomnia is no

longer present. Patient and clinician make a decision not to try higher dose of bupropion again.

- Possibly Related: There is a reasonable causal relationship between the study drug and the AE. Dechallenge is lacking or unclear.
    - Example: patient in step 2 is switched to nortriptyline. They report constipation which is uncomfortable but does not disrupt their daily activity (mild AE). They are willing to continue the medication at the current dose; no dose reduction is made.

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 in step 2 is started on lithium augmentation. One day after taking the first dose, they are driving and are hit by another car, necessitating hospitalization (severe and serious AE). The accident is the fault of the other driver.

iii 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.

iv Assessing Seriousness of Adverse Events

An **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

1.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 e-CRF. All Adverse Events will be collected from the time of informed consent through the last assessment.

1.e Reporting Procedures for Adverse Events

- **Serious Adverse Events:** Must be reported to Coordinating Site via e-mail as soon as possible, within 24 hours of the occurrence of the event or notification to the investigator or research team of the event.
- **All other Adverse Events:** Report to Coordinating Site 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 DSMB, IRB, FDA, and PCORI as required by each institutional policy.

G2 Data Safety and Monitoring Board

We will convene a Data Safety and Monitoring Board (DSMB) to examine safety data.
The DSMB will:

- Meet PCORI's guidelines for Data Safety and Monitoring Plans.
- Meet approximately every 6 months (more frequently – or perhaps less frequently, per DSMB determination) via teleconference.
- Include a psychiatrist, a statistician, and a psychopharmacological expert. DSMB members will not be otherwise involved in the conduct of the study.
- Have a charter approved by the DSMB.
- Approve the study protocol, including the DSMP, informed consent template, reporting templates for data to be presented to the DSMB, and other materials as requested by the DSMB prior to the initiation of study enrollment.
- Monitor the progress of subject recruitment and data acquisition, data confidentiality procedures, validity, and integrity of the data, the conduct of the protocol and deviations from the protocol, and any untoward or unexpected effects of protocol participation which might lather the brisk to benefit ratio of subject participation.
- Take meeting minutes to summarize the topics discussed and list DSMB recommendations. Meeting minutes must be signed by the DSMB Chair.

The Coordinating Site will:

- Be responsible for preparing reports for the DSMB.

- Submit DSMB meeting minutes to PCORI with Interim Progress Reports as laid out in the Milestone Schedule.
- Arrange for a summary of DSMB recommendations to be sent to each participating IRB at the time of Continuing Review (or earlier if required by local institutions or recommended by the DSMB)

H Statistical Plan

H1 Analysis Plan from OPTIMUM grant

A priori, specific plans for data analysis correspond to major aims and will be directed by Co-I J. Philip Miller, professor of biostatistics at the coordinating site.
We will follow the intention-to-treat (ITT) principle. In other words, patients who receive co-prescribed medications stop randomized medication, or switch to a different medication will continue to be followed. To confirm that ITT findings represent the "true" data on effectiveness, safety, and tolerability of management strategies, we will conduct a sensitivity analysis that will compare ITT to per-protocol findings.

H1a (Psychological Well-Being): We will use a repeated measures 2*2*3 ANOVA with age (60-70, >70), time (baseline, end of Active phase of Step 1) by treatment group (3 levels). Specific time* treatment group contrasts will compare the changes across pairs of treatment groups. These tests will be conducted with a significance level of .05/3. We will include site as a strata in all analyses.[63] For those who proceed to Step 2, analogous repeated measures 2*2*2 ANOVA will be used with a significance level of .05 for the time*treatment group comparison.

H1b (remission): Corresponding 2*3 (age by treatment group) generalized linear models with a logit link function will be computed for the dichotomous outcome of remission.

In the **continuation phase** we will explore the long-term effectiveness of antidepressants:
We will test for preservation of psychological well-being and other quality of life variables, and sustained resolution of depressive symptoms, by mixed effects repeated measures models.

We will also test for sustained remission by measuring relapse in each arm. Relapse will be defined as meeting DSM 5 criteria for a major depressive episode, as determined by an Independent Evaluator who will confirm the diagnosis by conferring with a study investigator. We will carry out Cox models examining time to relapse and time to dropout, to examine for treatment inferiority (i.e., whether one antidepressant strategy produces poorer long-term outcomes). Based on our prior research we don't have an empirical basis to posit a specific arm as inferior. Therefore, although these analyses are important to our stakeholders, we describe them as exploratory.

We will also examine **exploratory hypotheses**, such as whether there are baseline covariates which will help to significantly enhance the prediction of response to treatments, e.g., gender, race, treatment site (primary care vs. specialty clinic), social support, co-treatments. This will enhance the precision medicine implications of the study.

H2: serious adverse events, falls, and fall-related injuries are the safety outcomes. Cox models examining time to event (with Anderson & Gill[64] extensions for repeated events) will compare the treatment arms during both the acute phase and the continuation in terms of serious adverse events, falls, and fall-related injuries.
We will also compute rates of side effects in each arm, as specifically recommended by patient stakeholders. These data are not hypothesis-testing, but they support the patient-centered goal of allowing clinicians and patients to know what to expect in terms of side effects from treatment.
H3: Moderator analyses (Heterogeneity of Treatment Effects).
Confirmatory analysis (HT-1): Effectiveness and safety differences between treatment arms will be moderated by age. Specifically, with increasing age effectiveness differences between treatment arms will decrease, and safety differences between treatment arms will increase.

Rationale: Our stakeholders demand that we move past the current "one size fits all" paradigm of antidepressant prescribing. Precision treatment would greatly improve older adults' quality of life.

Data analysis plan for moderator testing: We will include the treatment by age group (<70 vs >70) by time interaction to the linear models described above to test for both the benefits and risks for the treatment alternatives.

We are well-powered for a confirmatory moderator analysis examining how age modulates the differences between treatment arms in comparative benefits and risks, because of our recruitment strategy aiming for equally-sized strata of ages (60-70 and >70). Age will be treated as a categorical variable, comparing relative benefits and risks of antidepressants in those aged <70 to those aged >70.

Here are some scenarios of the types of treatment modulators by age that we will be able to detect with a power > 85% (using SAS's GLMPOWER): (1) If treatment arm A has superior effectiveness over arm B by 2.3 points more than what would be predicted based on age and treatment effects on Psychological Well-being for age 60-70 but no difference between arms for age >70; (2) If treatment arm A has a superior effectiveness over arm B in terms of 13% higher remission rate for age 60-70, but there is no difference between arms for age>70.
Exploratory moderator analyses based on aging-related brain and systemic health variables: Our next step will be to analyze three aging-related variables –impairment in executive cognitive function, frailty, and medical complexity – treated both as continuous variables and categorical variables, using the same models as with chronological age.

Finally, we will examine the relative strength of these moderator variables by performing a combined moderator test.[76,77] This exploratory analysis incorporates all of the age-related variables into models of each effectiveness and safety finding from hypothesis-testing.

Notes regarding these Heterogeneity of Treatment Effect (moderator) analyses: We will perform statistical contrasts between treatment arms as a function of thee pre-specified moderator variables, and we will report all of these prespecified analyses, as well as post-hoc analyses, in published reports.

H2 Sample Size Determination and Power

Power to detect Effect Size of the benefits and risks of antidepressants: As a conservative method for computing the detectable effect size we used simple t-tests for comparing change scores between groups. The research on minimally clinically relevant changes for Toolbox or PROMIS measures suggests that they are between 2-3 T-score points (personal communication, David Cella, PI of PROMIS Statistical Center). The table below shows that we have power > 0.80 to detect changes smaller than minimally clinically relevant changes (e.g., we can detect changes < 2 T-score points). For proportional outcomes we used the conservative approach of a simple comparison between proportions for remission. Difference of 10 percentage points around a remission rate of 40%[1,2] are generally considered clinically meaningful. Secondary tests of effectiveness will examine changes in other aspects of quality of life: physical function, social participation, and changes in depressive symptoms (i.e., MADRS scores). Detectable differences for these endpoints are also included in the power table below

We have robust power for detecting clinically significant differences even if we only recruit 400 in each group: we would still have a power of .9 to detect a difference of 2.0 in Step 1 on our primary outcome (Psychological Well-being) and a difference of 13 percentage points on our primary clinical outcome (remission rate).

	Step 1 Effect[1]		Step 2 Effect[2]	
Power	**.8**	**.9**	**.8**	**.9**
Toolbox Psychological Well-being[3]	1.6	1.9	1.6	1.8
PROMIS Physical Function[3]	1.6	1.9	1.6	1.8
PROMIS Social Participation[3]	1.6	1.9	1.6	1.8
Remission[4,5]	10.2%	11.5%	9.8%	11.4%
Serious Adverse Events[6,5]	5.0%	5.9%	4.8%	5.8%
Falls[7]	8.8%	10.0%	8.5%	9.9%
Fall-related injuries[8]	5.0%	5.9%	4.8%	5.8%
MADRS[9,5]	1.8	2.1	1.8	2.1

[1] n=500 each for 3 groups, p=.05/3
[2] n=400 each for 2 groups, p=.05
[3] Points on T-score; sd=8 beginning and end of phase, r=.5 between scores
[4] Difference in proportion remitting, around a 40% remitting point
[5] Based on aripiprazole group in [1,2]
[6] Increase in proportion experiencing an SAE, around a 4% baseline rate
[7] Increase in proportion experiencing a fall, around a 20% baseline rate
[8] Increase in proportion experiencing an injurious fall, around a 4% baseline rate
[9] Scale point change, sd=9

H3 Interim Analysis

No interim analysis is planned.

H4 Missing Outcome Data

The primary analysis will be intent-to-treat; therefore, all data will be utilized and, as appropriate, a data imputation technique will be used for missing outcome data.

I Data Handling and Record Keeping

I1 Confidentiality and Security

Participant confidentiality and data security will be facilitated with the following tools and processes:

The primary data collection and management tool for this study will be REDCap (Research Electronic Data Capture) databases created and maintained by the Data Management team at the Coordinating Site.

REDCap's features support best practices for data confidentiality and security. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: • user authentication and role-based security • collaborative access to data across academic departments and institutions • intuitive electronic case report forms (CRFs) • real-time data validation, integrity checks and other mechanisms for ensuring data quality (e.g. double-data entry options) • data attribution and audit capabilities • protocol document storage and sharing • central data storage and backups • data export functions for common statistical packages • data import functions to facilitate bulk import of data from other systems. Data that is imported and/or exported will be kept on a secure department network.

Secure data collection in sites with inconsistent internet connections will be facilitated by using the REDCap Mobile App on password-protected tablet devices. The REDCap Mobile App allows for secure data transmission (using SSL/HTTPS), secure data storage, secure user authentication, and remote lockout capability. Details of the security features for the REDCap Mobile App can be located here: https://projectredcap.org/security.pdf

Washington University Security Architecture: To ensure patient privacy and compliance with HIPAA regulations, data is stored behind the university approved, hardware firewalled network. Access is context specific to each user and individual collection protocols such that it supports both the regulatory guidelines (e.g. HIPAA and patient privacy) and proprietary (intellectual property) concerns.

Hard copy records will be stored in a locked drawer/cabinet in a locked office/suite. The study team will treat all subject/patient data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations, including all applicable provisions of HIPAA and its implementing regulations. Study records sent to the sponsor will not include participant's name to protect patient confidentiality.

I2 Training

The Coordinating Site will ensure that the PI and Study Coordinator at each site have access to appropriate training materials in study procedures, assessments, and recordkeeping. The PI and/or Study Coordinator at each site are responsible for ensuring and documenting that all research team members at their respective sites are trained and supervised appropriately prior to conducting any study procedures.

Training of each treating physician will be the responsibility of each site working with the treating physician's patient and will be done according to the training plan outlined in the manual of procedures.

I3 Case Report Forms and Source Documents

This study will utilize REDCap-based electronic Case Report Forms (e-CRF's) for data capture and storage. 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.

I4 Records Retention

The investigator will maintain records in accordance with state and federal government regulations standards of Good Clinical Practice, and applicable institutional research policies and procedures. All electronic and hard copy research records and imaging data are stored for at least seven years beyond the close of the study.

J Study Monitoring, Auditing, and Inspecting

J1 Study Monitoring Plan

In order to fulfill our ethical, legal, and scientific obligations to conducting this study in a detailed and orderly manner, the Coordinating site may visit the other participating sites during the study, as well as communicate frequently via telephone and written communications.

J2 Auditing and Inspecting

The Coordinating site may conduct study site audits. Audits would typically include, but are not be limited to, presence of required documents, the informed consent process, and review of research records. Most auditing will be done remotely via review of REDCap records.

Regulatory authorities may inspect the investigator during or after the study. The investigator will cooperate with such inspections and will contact the Coordinating site immediately if such an inspection occurs.

K Study Administration

K1 Organization and Participating Centers

This is a collaborative, multi-site study with five academic sites: Washington University (Coordinating Site), University of Pittsburgh, University of Toronto, University of California Los Angeles, and Columbia University.

Ongoing communication and coordination between sites will be facilitated by regular conference calls attended by PI's and appropriate personnel. Records of these conference calls will be maintained by the Coordinating Site.

A Manual of Procedures will be provided to sites and updated as needed to ensure consistent conduct of the trial across sites.

K2 Funding Source

This project is funded by the Patient Centered Outcomes Research Institute (PCORI).

K3 Participant Compensation

Compensation plans for participants will be determined by each study site and approved by their respective IRB's. Compensation plans must adhere to the following guidelines:

- All participants should receive equal compensation for equivalent time and effort..
- The compensation amount should be reasonable for the time and effort of the participant.
- Compensation may not be held until completion of all study activities. If there are multiple visits or study procedures compensation must be pro-rated for the completion of each visit or part of the study.
- Information about compensation must be included in the Consent Document.

K4 Milestone Schedule

The overall timetable for the study will follow the milestone schedule agreed upon in the PCORI contract. Any barriers or delays to completing milestones per the schedule should be discussed with the Coordinating Site, who will bring significant issues to the attention of the PCRI program officer as needed.

	Milestone Name	Description	Projected Completion Date
A	**Effective Date**	-	10/1/2016
B1	IRB Approval Obtained	Obtain local IRB approval	1/1/2017
B2	Formation of Stakeholder Advisory Board (SAB)	Finalize the composition of the SAB to include members recommended by PCORI. Document the members of the SAB including the organization, title, and stakeholder group they represent. Deliverable: Complete SAB roster (including the organization, title, and stakeholder group they represent).	1/1/2017
B3	In-person Kickoff Meeting. Initiate implementation and start recruitment	Study startup meeting. Launch study and begin recruitment in some practices once approved by DSMB. Kickoff meeting to include investigators, research coordinators, and other key partners. Train staff and clinicians from each site on the study protocol.	1/12/17-1/13/17
B4	Stakeholder Advisory Board Kickoff Meeting	Kick off meeting for the Stakeholder Advisory Board. Deliverable: Meeting minutes and/or summary of the meeting discussion should document the input of the patient/stakeholder members and should be submitted with the Interim Progress Report	1/12/17-1/13/17
B5	Protocol Complete	Complete the final study protocol and submit to fundedpfa@pcori.org and cc the Program Officer and Associate	2/1/2017
B6	Finalize study	Finalize assessments, materials, study protocol, and statistical analysis plan in collaboration with SAB. Submit materials as attachment in next Interim Progress Report. Design database and implement data entry process.	2/1/2017

B7	Select and register project at appropriate site for the study design (Clinicaltrials.gov, RoPR, or other as approved by PCORI before study start date)	Study Identification Number and the Primary Research Completion Date must be sent to PCORI.	3/1/2017
B8	IRB approval	Approval by all sites' IRBs	4/1/2017
B9	DSMB meeting	Minutes from 1st DSMB meeting. Review and discuss subject data collected to date. In the interim progress report, include any significant data & safety monitoring issues that occurred in the reporting period. If there are any serious unanticipated problems (e.g., serious adverse event, serious safety issue, or other serious problem) relating to the research study, awardee institutions must notify PCORI promptly, but no later than 10 days after.	4/1/2017
B	**Report Submission**	**Submit Progress Report, Using Interim Progress Report Template**	4/1/2017
C1	Complete implementation	Launch study and begin recruitment in all practices. Recruit and randomize 125 participants each quarter for 12 quarters (total randomized N=1,500; approximately 42 participants recruited per month).	7/1/2017
C2	Stakeholder Advisory Board Meeting	Stakeholder Advisory Board Meeting. Deliverables: Meeting minutes and/or summary of the meeting discussion should document the input of the patient/stakeholder members and should be submitted with the Interim Progress Report	7/1/2017
C3	DSMB meeting	Minutes from 2nd DSMB meeting. Review and discuss subject data collected to date. In the interim progress report, include any significant data & safety monitoring issues that occurred in the reporting period. If there are any serious unanticipated problems (e.g., serious adverse event, serious safety issue, or other serious problem) relating to the research study, awardee institutions must notify PCORI promptly, but no later than 10 days after.	10/1/2017
C	**Report Submission**	**Submit Progress Report, Using Interim Progress Report Template**	10/1/2017
D1	Complete 25% of recruitment	Recruit 375 participants in total (approximately 42 participants recruited per month). Document and send to PCORI Program Officer and Associate.	1/1/2018
D2	DSMB meeting	Minutes from 3rd DSMB meeting. Review and discuss subject data collected to date. In the interim progress report, include any significant data & safety monitoring issues that occurred in the reporting period. If there are any serious unanticipated problems (e.g., serious adverse event, serious safety issue, or other serious problem) relating to the research study, awardee institutions must notify PCORI promptly, but no later than 10 days after.	4/1/2018
D3	Stakeholder Advisory Board Meeting	Stakeholder Advisory Board Meeting. Deliverables: Meeting minutes and/or summary of the meeting discussion should document the input of the patient/stakeholder members and should be submitted with the Interim Progress Report	4/1/2018
D	**Report Submission**	**Submit Progress Report, Using Interim Progress Report Template**	4/1/2018
E1	Start follow-up data collection	250 participants finish 4-month acute phase and begin 12-month continuation phase (based on 45% remission rate and 8% attrition in each of steps 1 and 2).	7/1/2018
E2	Complete 50% of recruitment	Recruit 750 participants in total (approximately 42 participants recruited per month). Document and send to PCORI Program Officer and Associate.	10/1/2018

E3	Stakeholder Advisory Board Meeting	Stakeholder Advisory Board Meeting. Deliverables: Meeting minutes and/or summary of the meeting discussion should document the input of the patient/stakeholder members and should be submitted with the Interim Progress Report	10/1/2018
E4	Begin semi-structured interviews	Begin semi-structured interviews (goal N=150)	10/1/2018
E5	DSMB meeting	Minutes from 4th DSMB meeting. Review and discuss subject data collected to date. In the interim progress report, include any significant data & safety monitoring issues that occurred in the reporting period. If there are any serious unanticipated problems (e.g., serious adverse event, serious safety issue, or other serious problem) relating to the research study, awardee institutions must notify PCORI promptly, but no later than 10 days after.	10/1/2018
E	**Report Submission**	**Submit Progress Report, Using Interim Progress Report Template**	10/1/2018
F1	DSMB meeting	Minutes from 5th DSMB meeting. Review and discuss subject data collected to date. In the interim progress report, include any significant data & safety monitoring issues that occurred in the reporting period. If there are any serious unanticipated problems (e.g., serious adverse event, serious safety issue, or other serious problem) relating to the research study, awardee institutions must notify PCORI promptly, but no later than 10 days after.	4/1/2019
F2	Stakeholder Advisory Board Meeting	Stakeholder Advisory Board Meeting. Deliverables: Meeting minutes and/or summary of the meeting discussion should document the input of the patient/stakeholder members and should be submitted with the Interim Progress Report	4/1/2019
F	**Report Submission**	**Submit Progress Report, Using Interim Progress Report Template**	4/1/2019
G1	Complete 25% of follow-up data collection	225 participants finish 4-month acute phase and begin 12-month continuation phase (estimate of 12-month completers = 225, based on 45% of participants remitting at each of steps 1 and 2, 8% of participants dropping out during each of steps 1 and 2, and additional 10% dropping out during the 1-year continuation phase). The Interim Progress Report should include summary of data collected to date for review of patient accrual, patient characteristics and data quality.	7/1/2019
G2	Complete 75% of recruitment	Recruit 1125 participants in total (approximately 42 participants recruited per month). Document and send to PCORI Program Officer and Associate.	7/1/2019
G3	Complete semi-structured interviews	Complete semi-structured interviews (goal N=150)	7/1/2019
G4	DSMB meeting	Minutes from 6th DSMB meeting. Review and discuss subject data collected to date. In the interim progress report, include any significant data & safety monitoring issues that occurred in the reporting period. If there are any serious unanticipated problems (e.g., serious adverse event, serious safety issue, or other serious problem) relating to the research study, awardee institutions must notify PCORI promptly, but no later than 10 days after.	10/1/2019
G5	Stakeholder Advisory Board Meeting	Stakeholder Advisory Board Meeting. During this meeting, findings from semi-structured interviews analyzed and provided to SAB. Deliverables: Meeting minutes and/or summary of the meeting discussion should document the input of the patient/stakeholder members and should be submitted with the Interim Progress Report	10/1/2019
G	**Report Submission**	**Submit Progress Report, Using Interim Progress Report Template**	10/1/2019
H1	Complete recruitment	Recruit 1500 participants total (approximately 42 participants recruited per month). Document and send to PCORI Program Officer and Associate.	1/1/2020

H2	Complete 50% of follow-up data collection	450 participants finish 4-month acute phase and 12-month continuation phase (estimate of 12-month completers = 450, based on 45% of participants remitting at each of steps 1 and 2, 8% of participants dropping out during each of steps 1 and 2, and additional 10% dropping out during the 1-year continuation phase). The Interim Progress Report should include summary of data collected to date for review of patient accrual, patient characteristics and data quality.	4/1/2020
H3	DSMB meeting	Minutes from 7th DSMB meeting. Review and discuss subject data collected to date. In the interim progress report, include any significant data & safety monitoring issues that occurred in the reporting period. If there are any serious unanticipated problems (e.g., serious adverse event, serious safety issue, or other serious problem) relating to the research study, awardee institutions must notify PCORI promptly, but no later than 10 days after.	4/1/2020
H4	Stakeholder Advisory Board Meeting	Stakeholder Advisory Board Meeting. Deliverables: Meeting minutes and/or summary of the meeting discussion should document the input of the patient/stakeholder members and should be submitted with the Interim Progress Report	4/1/2020
H	**Report Submission**	**Submit Progress Report, Using Interim Progress Report Template**	4/1/2020
I1	Complete acute phase	All participants finish 4-month acute phase	10/1/2020
I2	DSMB meeting	Minutes from 8th DSMB meeting. Review and discuss subject data collected to date. In the interim progress report, include any significant data & safety monitoring issues that occurred in the reporting period. If there are any serious unanticipated problems (e.g., serious adverse event, serious safety issue, or other serious problem) relating to the research study, awardee institutions must notify PCORI promptly, but no later than 10 days after.	10/1/2020
I3	Stakeholder Advisory Board Meeting	Stakeholder Advisory Board Meeting. Deliverables: Meeting minutes and/or summary of the meeting discussion should document the input of the patient/stakeholder members and should be submitted with the Interim Progress Report	10/1/2020
I	**Report Submission**	**Submit Progress Report, Using Interim Progress Report Template**	10/1/2020
J1	Complete 75% of follow-up data collection	675 participants finish 4-month acute phase and 12-month continuation phase (estimate of 12-month completers = 675, based on 45% of participants remitting at each of steps 1 and 2, 8% of participants dropping out during each of steps 1 and 2, and additional 10% dropping out during the 1-year continuation phase). The Interim Progress Report should include summary of data collected to date for review of patient accrual, patient characteristics and data quality.	1/1/2021
J2	DSMB meeting	Minutes from 9th DSMB meeting. Review and discuss subject data collected to date. In the interim progress report, include any significant data & safety monitoring issues that occurred in the reporting period. If there are any serious unanticipated problems (e.g., serious adverse event, serious safety issue, or other serious problem) relating to the research study, awardee institutions must notify PCORI promptly, but no later than 10 days after.	4/1/2021
J3	Stakeholder Advisory Board Meeting	Stakeholder Advisory Board Meeting. Deliverables: Meeting minutes and/or summary of the meeting discussion should document the input of the patient/stakeholder members and should be submitted with the Interim Progress Report	4/1/2021
J	**Report Submission**	**Submit Progress Report, Using Interim Progress Report Template**	4/1/2021

K1	Complete follow-up data collection	All (n=900) participants finish 12-month continuation phase (estimate based on 45% of participants remitting at each of steps 1 and 2, 8% of participants dropping out during each of steps 1 and 2, and additional 10% dropping out during the 1-year continuation phase). The Interim Progress Report should include summary of data collected to date for review of patient accrual, patient characteristics and data quality.	9/1/2021
K2	Primary Research Completion Date	A Primary Research Completion Date must be provided when registering the study in Clinicaltrials.gov. For studies that are not clinical trials or observational studies registered on ClinicalTrials.gov, the Awardee and PCORI shall agree on a primary completion date as a milestone that precedes the agreed-upon date to submit a Draft Final Research Report.	9/1/2021
K3	Initiate data analyses	Clean database and set up analytic files	9/1/2021
K4	Complete data analyses	"Break blind" and run analytic files	9/1/2021
K5	Final DSMB meeting	Minutes from 10th DSMB meeting. Review and discuss subject data collected to date. In the interim progress report, include any significant data & safety monitoring issues that occurred in the reporting period. If there are any serious unanticipated problems (e.g., serious adverse event, serious safety issue, or other serious problem) relating to the research study, awardee institutions must notify PCORI promptly, but no later than 10 days after.	9/30/2021
K6	Stakeholder Advisory Board Meeting	Stakeholder Advisory Board Meeting. Deliverables: Meeting minutes and/or summary of the meeting discussion should document the input of the patient/stakeholder members and should be submitted with the Interim Progress Report	9/30/2021
K7	Dissemination and implementation	Prepare findings for D&I	9/30/2021
K8	Data sharing	Begin preparation of de-identified final dataset for replication and data-sharing. Prepare results for publication in peer-reviewed journals and submission of results to clinicaltrials.gov	9/30/2021
K	**Final Progress Report**	**Submit Final Progress Report, Using Final Progress Report Template**	9/30/2021
L	**Research Project Period End Date**		**9/30/2021**
M	Results submitted to ClinicalTrials.gov or appropriate database.	Awardee ensures results are submitted to ClinicalTrials.gov or appropriate database. For ClinicalTrials.gov, the generated tables are a required section in the Draft Final Research Report.	12/1/2021
N	**Draft Final Research Report Submission**	**Submit Draft Final Research Report according to instructions found at** *http://www.pcori.org/awardee-resourcesx* ***Draft Final Research Report must be submitted no later than 30 days from when results are posted to clinicaltrials.gov or other applicable website.***	**1/1/2022**
O	**Final Research Report**	**Upon receipt of written summary, and as applicable, PI will make revisions and submit revised Draft Final Research Report for acceptance as directed by PCORI.**	**See Description**
P	**Approval / sign off of the Lay Abstract**	**Sign off must be no later than 90 days beyond the date PCORI accepts the final report**	**See Description**
Q	**Contract Term Date**	-	**5/31/2022**
R	**Final Expenditure Report**	**Submit Final Expenditure Report (See Contract for Instructions)**	**90 days from Contract Term Date**
S	**Notification of Publication Acceptance**	**See Contract for Instructions**	**Within 30 Days of Acceptance**

K5 History of Changes to Study Protocol

Version number and date	Description of changes
V2.3: 1/19/17	Originally approved version of the study protocol.
V2.4: 3/31/17	1) Participants who do not qualify for Step 1 due to a contraindication to a Step 1 medication, but otherwise meet eligibility criteria, may participate and proceed directly to Step 2. 2) Increase in maximum dose of bupropion from 300 mg to 450 mg to be consistent with the FDA approved maximum dose. 3) Additional baseline assessments. 4) Assessment of falls at every decision support. 5) Collection of self-reported weight at baseline, acute phase end, and continuation time points. 6) All participants followed in Continuation, not just remitters. 7) NIH Cognitive and Motor Batteries assessed at Continuation Month 12 but not at 4 or 8. 8) DNA samples collected via saliva sample instead of blood.
V2.5: 6/26/17	1) Changes to eligibility criteria. Seizure disorder and Parkinson's disease are exclusions for Step 1 but not for Step 2. 2) Clarification to Step 2 exclusions indicating that participants may still be considered for Step 1 participation even if ineligible for Step 2. 3) Clarification to lithium augmentation prescribing information that levels outside of 0.4 – 0.8 mEq/L window may still be acceptable per PI discretion. 4) Clarification to nortriptyline switch prescribing information that levels outside 80-120 ng/ml window may still be acceptable per PI discretion. 5) Removed fasting glucose from (generally) recommended baseline labs and added new section for recommended labs prior to aripiprazole augmentation including fasting glucose and fasting lipid panel.
V2.6: 10/2/17	1) Clarified Step 2 exclusion of Acute or chronic renal insufficiency with the addition of the following language: as indicated by creatinine clearance below 30 mL/min; suspected if creatinine above 1.5 mg/dL; per PI and/or clinician discretion.
V2.7: 10/31/17	1) Updates to assessment procedures: a. If there is a long delay between the Step 1 Week 10 assessment and the initiation of Step 2, the participant may be asked to repeat some or all of the Step 1 End assessments. b. Participants who relapse in Continuation after Step 1 may be invited to participate in Step 2; and then continuation subsequently. 2) Addition of qualitative interviews for randomly selected subset of participants to fulfill Aim 3.
V2.8: 12/5/17	1) Narrowed Step 2 exclusion criteria to identify and exclude patients with active ischemic heart disease while including patients with history but no symptoms for the past 2 years.

V2.9: 3/26/18	1) Addition of body composition measurement at WU.
V3.0: 3/4/19	1) All participants are to begin the study in Step 1. Following their participation in Step 1, they will be considered for Step 2 (as in the current protocol). However they will not be invited to participate in Step 2 without first participating in Step 1. a) Accordingly, because direct entry into Step 2 is disallowed, the Step 1 exclusions of Seizure disorder and Parkinson's Disease are exclusions to the study as a whole. 2) Increasing the inclusion criteria for the PHQ-9 from 6 to 10 to include participants with higher degree of symptom severity. 3) Recommended schedule for standard of care follow-up labs is being standardized in the protocol. 4) Removal of body composition measurement. This was exploratory and is not safety related.

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