Study Title: Bupropion for Depression in Chronic Kidney Disease (CKD) Patients

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1. Purpose and Objectives
The proposed study will evaluate the response and remission rates for major depressive disorder (MDD) in chronic kidney disease (CKD) patients treated with bupropion or fluoxetine for 12 weeks. In addition, the study will document the relative tolerability and safety, and longitudinally contrast the effects of bupropion and fluoxetine on measures of cognitive function, fatigue, inflammation, and tryptophan (TRP) and TRP catabolites in blood. It is hypothesized that both drugs will significantly reduce MDD symptoms from baseline, and be tolerable and safe, but bupropion will be associated with greater reduction in pro-inflammatory cytokines, cognitive impairment, and fatigue compared with fluoxetine.

The Specific Aims of this study are:
Aim 1: Determine the efficacy of bupropion and fluoxetine in treatment of MDD in CKD patients.
Aim 2: Determine whether longitudinal change in MDD symptoms, cognitive dysfunction, and fatigue differ between bupropion and fluoxetine.
Aim 3: Determine whether longitudinal change in MDD symptoms, cognitive dysfunction, and fatigue correlate with change in inflammation, measures of TRP availability to brain, or neurotoxic TRP metabolites.

Hypotheses:
1) Bupropion and fluoxetine will both show efficacy in treating MDD;
2) Bupropion will lead to greater improvement in cognitive dysfunction and fatigue than fluoxetine; and
3) Change in cognition and fatigue over time will correlate with change in C-reactive protein (CRP) and quinolinic acid and change in overall depression score will correlate with measures of TRP availability.

2. Background
Depressive symptoms, major depressive disorder (MDD), fatigue, and cognitive dysfunction are among the most common symptoms in patients with chronic kidney disease (CKD). In one study, 71% of ESRD/HD patients had MDD [1], although lower rates were reported when structured diagnostic interviews were used to diagnose [2]. Even when the full criteria for MDD are not met, most ESRD/HD patients suffer from moderate to severe depressive symptoms. ESRD/HD patients also show high rates of cognitive dysfunction, with up to 87% showing some cognitive impairment and 37% showing severe impairment [3].

There have been few controlled trials for treating MDD in CKD patients [18], although uncontrolled studies are encouraging. The relative safety of selective serotonin reuptake inhibitor (SSRI) drugs such as fluoxetine led to its use in several positive open label studies [19-26]; however the one placebo-controlled trial failed [27]. While SSRIs are efficacious in treating MDD in patients with chronic general medical conditions, symptoms of fatigue and cognitive dysfunction are often unresponsive [28, 29]. Bupropion is a unique antidepressant, being a selective norepinephrine (NE) and dopamine (DA) reuptake inhibitor. These properties may underlie its relative advantage to SSRIs in improving fatigue and cognition. Bupropion is efficacious in MDD [30], attention deficit disorder [31], and improves cognitive dysfunction in MDD patients [30]. Bupropion's selectivity for NE/DA, and the modulation of prefrontal cortex attention/cognition and limbic reward circuits by NE/DA may underlie its favorable profile on cognition, fatigue, energy, weight, and sexual function.

MDD is not a single disease, but a genetically complex syndrome with many causal pathways [4]. While early research focused exclusively on monoamines, pro-inflammatory pathways are now known to play a role, being capable of inducing depressed mood, fatigue, and cognitive impairment [5-7]. This line of research has been complicated in part by the variate sources of inflammation for a given individual, (e.g. age, gender, weight health status, allergies, environment, medications, mental health, substance, etc). For instance the most common cause of inflammation is presence of dental disease. Tryptophan (TRP) depletion, pro-inflammatory cytokines, and neurotoxic TRP metabolites affect the brain circuits involved in depression and cognitive function [8]. Experimental depletion of the essential amino acid TRP can induce depressive symptoms, anorexia, fatigue, and cognitive dysfunction in humans [4, 9] due to reductions in brain serotonin (5-HT) [10] while administration of lipopolysaccharide (LPS) induces depressive

symptoms, fatigue, and cognitive impairment through direct effects of pro-inflammatory cytokines on brain circuits. Many of these effects can be blocked by antidepressants [6].
Elevated levels of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-6 are prominent features of HD [11, 12]. Reduction in total plasma TRP is also a well documented abnormality in CKD patients [11], with plasma levels of total TRP as low as those that are associated with depressive reactions induced by experimental TRP depletion in humans [8]. Elevated TNF-α and IL6 have direct effects on the central nervous system and increase peripheral conversion of TRP to the neurotoxic catabolites kynurenine (KYN) and quinolinic acid [13] [14]; in part by inducing an increase in the activity of the enzyme indoleamine 2,3-dioxygenase (IDO). While total TRP is low, free TRP levels can increase in blood between dialysis treatments [15], further driving its metabolic conversion to KYN and quinolinic acid. KYN and quinolinic acid levels are known to be markedly increased in ESRD/HD patients [16], plausibly contributing to the depressive symptoms, fatigue, and cognitive impairment [17].

Independent of its effects on cognition and fatigue through NE/DA mechanisms, bupropion may have anti-inflammatory actions that could further enhance its efficacy in reducing cognitive dysfunction and fatigue secondary to inflammation. This is suggested by its ability to reduce TNF-α in mice challenged with LPS [33] and to reduce inflammation and improve mood in patients with atopic dermatitis [34]. Bupropion also reduced TNF-α in patients with Crohn's disease and chronic hepatitis B virus infection [35, 36]. While there are no trials of bupropion in ESRD/HD patients with MDD, a retrospective review suggested bupropion might be beneficial [37]. This proposal will obtain preliminary data needed to fully justify and design a definitive trial of bupropion in ESRD/HD patients with MDD.

Lastly, it is well known that depression has a mutually enhancing relationship with pain. As chronic pain is associated with depression and other psychiatric syndromes, and in turn depressed patients endorse somatic symptoms, mainly pain. This is particularly relevant to our study population, since approximately half of the patients with chronic kidney disease suffer from chronic pain, and frequently increased inflammation is the main suspected mechanism.

Choices of bupropion and fluoxetine for the treatment:
Bupropion is unique amongst antidepressants because it selectively blocks reuptake of NE and DA without having appreciable affinity for postsynaptic receptors including histamine, α- or β-adrenergic, 5-HT, or acetylcholine [30, 88]. This confers a favorable side effect and safety profile [89], absence of weight gain [90] or somnolence [91]; side effects frequently reported by HD patients with other antidepressants [92-95]. Bupropion has no clinically significant effects on the cardiovascular system (e.g., heart rate, blood pressure, QTc interval) in patients with MDD [96]. It can increase the incidence of seizures [97] in a dose-dependent (>450 mg/day) [30] fashion in patients with a history of seizures; therefore it is contraindicated in these patients. Bupropion may preferentially reduce a subset of symptoms of MDD common in medically ill patients, including fatigue, drowsiness, cognitive dysfunction, anhedonia, and mental concentration [98, 99]. In healthy humans, after oral administration, bupropion is rapidly and ~100% absorbed by the intestine, metabolized in the liver, and excreted via kidney. The hepatic cytochrome P450 (CYP) 2B6 catalyzes bupropion to a primary active metabolite, hydroxyl-bupropion. Several studies [62, 100, 101] have provided guidelines and recommendations about antidepressant agents in patients with ESRD/HD. One study [80] determined the PK of bupropion and its active metabolites in HD patients following a single 150-mg oral dose and found comparable PK profile to individuals with normal renal function. Compared with controls, hydroxyl-bupropion demonstrated a >2-fold greater AUC and substantially increased t½, indicating reduced clearance. Based on these data, the authors [80] suggested an oral dose of 150 mg bupropion every 3 days in HD patients.

While it has been suggested that antidepressants may in general reduce inflammation, research data suggests that SSRIs and tricyclic antidepressants may not. Other hand, there has been considerable recent interest in the anti-inflammatory effects of bupropion, although more research is needed [102]. Brustolim et al. [33] demonstrated that bupropion significantly reduced the levels of TNF-α in mice challenged with lipopolysaccharide and suggested that this effect might have important clinical consequences. In case reports, Kast and Altschuler [35, 36] proposed the potential anti-inflammatory

function of bupropion against TNF-α in patients with Crohn's disease and chronic hepatitis B virus infection. Bupropion has been found to be effective at both reducing inflammation and improving mood in patients with atopic dermatitis [34]. While Eller et al [103] found no effect of bupropion on TNF-α when it was added to ongoing escitalopram treatment, this study was in medically healthy MDD patients whose TNF-α levels were not much elevated, suggesting a possible "floor" effect. TNF-α is considered as a "master regulator" of the cytokine cascade in HD [48]. Given the well-established TNF-α elevation in HD, bupropion may be a uniquely well-suited antidepressant for these patients.

Fluoxetine is first SSRI approved by the Food and Drug Administration for treatment of MDD in the US. It is the most studied antidepressant in ESRD/HD patients [18, 20, 23, 27, 60-62] and has been found to be safe, tolerable, and to have some suggestive evidence of being efficacious. It may not reduce inflammation, [60, 104] and therefore will serve as a good comparator for bupropion.

Current Practice

The Food and Drug Administration has approved both drugs proposed in this study (fluoxetine and bupropion) as standard therapy for MDD. The unfortunate reality is that most ESRD/HD patients that develop MDD are never treated. When antidepressants are prescribed for MDD in any patient with another co-occurring condition, they are selected based on the individual prior treatment history and contraindications for the patient. While neither of the medications being studied is contraindicated in ESRD/HD patients, dose adjustments are made due to differences in excretion rates.

3. Study Design

The current study proposes to randomly assign 40 CKD patients with MDD to 12 weeks of open label, flexible dose treatment with either bupropion (N=20) or fluoxetine (N=20).

[NOTE: We are requesting to enroll up to 50 subjects/with 40 completers. One of the outcome measures will be the number of weeks of treatment that a person completes. This is a preliminary feasibility and pilot study, so establishing an estimate of drop out rate will be important for when we design the "definitive" study in the future.]

4. Study population is defined as CKD patients with chronic kidney disease with MDD.

Inclusion Criteria

- age 30-70 yrs;
- meet the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria for MDD;
- have a Ham-D score > 17
- if receiving any of these medications, on a stable or maintenance dose of iron or erythropoietin-stimulating agents, statins, angiotension receptor blockers and/or angiotension converting enzyme inhibitors, phosphate binders and vitamin D receptor analogs as these agents may influence cytokines proposed in the study;
- serum albumin of ≥ 3.2 g/dl, serum phosphate of <6.5 mg/dl, and serum hemoglobin of ≥9 mg/dl in two consecutive blood tests [subjects failing screening due to these blood tests will be allowed to be re-screened in 30 days];

For patients not on HD or Peritoneal Dialysis

- Estimated glomerular filtration rate below 59 mL/min per 1.73 m^2.

For patients on HD

- have patent and non-infected arteriovenous fistula or graft;
- are receiving maintenance HD 2-3 times per week;

For patients on Peritoneal Dialysis

- compliance with outpatient visits for the past two months;

Exclusion Criteria

- meet DSM-IV criteria for Bipolar Disorder or other psychotic disorder in the month prior to screening;
- are taking antidepressants, anti-anxiety medications, or hypnotics (including Zyban for smoking cessation);

- failure to respond to or tolerate bupropion or fluoxetine in the past
- allergic to fluoxetine or bupropion
- known history of HIV/AIDS; No testing will be conducted for screening purposes
- known history of alcohol or drug abuse or dependence within the month prior to screening based on clinical records;
- history of myocardial infarction or heart failure within one month of screening or a history of seizures or stroke at any point;
- history of chronic liver disease and diagnosis of hepatic encephalopathy based on clinical records;
- currently diagnosed with cancer or receiving any cancer treatment;
- history of any infection within the last 2 weeks ;
- currently taking any antibiotics, anti-inflammatory (low dose aspirin is acceptable), and immune-modulator agents;
- recorded noncompliance with dialysis schedules; and
- currently participating in clinical or behavioral intervention studies.

Recruitment Process—Identifying Potential Subjects
Subjects will be recruited from the UAMS Kidney Center, other outpatient UAMS clinics, UAMS Hemodialysis Center and other local dialysis centers using flyers, electronic dissemination of the flyer to UAMS physicians and/or newspaper ads. Referring physicians will be invited to provide the information to patients who they feel are appropriate for the study and, if the patient expresses an interest in participation or obtaining more information, the physician will provide the contact information of the study staff to the patient, who will voluntarily choose whether to contact the study staff for screening. Release of information/consent documents will be obtained prior to accessing patient clinical information. Prior to beginning the protocol and after obtaining patient's consent, study physicians will discuss the merits of a patient's participation in the study with the patient's hemodialysis physician.

Patients seeking information about the study will initiate phone contact with study staff for initial screening regarding inclusion and exclusion criteria. A partial HIPAA waiver will be requested from the IRB for phone screening purposes only. Subsequent access to clinical information will require written release of information/consent by the patient.

Each potential subject will contact the study staff by phone for initial screening regarding inclusion and exclusion criteria. Patients, who appear to meet inclusion and exclusion criteria and indicate agreement for the study team to contact their treating physician, will be scheduled to come in for a face-to-face meeting, be provided with study information, sign informed consent/HIPAA Authorization and undergo initial evaluation. After consent/authorization is signed by the subject, the research staff will contact the treating physician to discuss the subject's participation, provide medical records release, and obtain medical information from the treating physician.

5. Consent Process
Patients, who contact the research staff, appear to meet inclusion and exclusion criteria and indicate during this contact that they will agree to allow the study team to contact their treating physician, will be scheduled for a face-to-face meeting for informed consent and initial evaluation either at the UAMS Psychiatric Research Institute (PRI; 4th floor) or their dialysis site. Consent will be obtained prior to any research procedures taking place. The potential subject will be encouraged to bring a family member with them for this appointment. During this meeting, a member of the research staff will describe the study and review the IRB-approved consent form using lay terms with special emphasis on the risks and benefits, in an objective way. The team member will make attempts to answer & clarify or address any questions or concerns the subject (and family member) may have during this process. Ample time will be given to the subject to make a voluntary decision. The study information, inclusion and exclusion criteria, and consent documents will be reviewed. The study team member conducting the consent process will sign and date the consent form. The subject will be given a business card of the study team so that he/she can discuss any further questions or concerns that may arise in the future. A copy of the signed and dated consent form will be given to the subject for his/her record.

Subjects will be encouraged to take the consent form at home to read, understand, and discuss with his/her family members and or primary care physician. In this situation, subject will be contacted after one week to learn his/her decision to participate in the study and a subsequent meeting scheduled to sign the documents. An interested subject must sign the consent form in presence of the study personnel. Patients will be scheduled for consent/initial evaluation appointments during the initial phone screening. This appointment will take place between 1-14 days, giving subjects ample time to make a voluntary decision. There is no specific waiting time limit.

Participation of an eligible subject in this clinical trial is a voluntary process. Subjects will not be coerced or influenced by the study personnel. In order to participate, subjects will have to voluntarily initiate a phone screening and subsequently come to a face-to-face consent/initial evaluation meeting. A research staff member or study investigator will conduct the consent process in order to minimize the possibility of undue influence from the treating physician on their hemodialysis team. Subjects will be informed that participation is voluntary and not participating will not affect the delivery of the routine health care. They and their treating physicians will be informed that the medications being used in the current study are routinely available and relatively inexpensive to obtain. They do not have to participate in this study to receive any of the treatment options.

Subjects are randomly assigned to open label treatment with one of two medications. Therefore, there are two groups:

- Bupropion group:
    - For patient not on hemodialysis, oral administration of bupropion SR tablet at a dose of 150 mg daily. Bupropion SR doses will be adjusted upward or downward based on tolerability and response.
    - For patient on hemodialysis or peritoneal dialysis, oral administration of bupropion SR tablet at a dose of 150 mg on the 1st and the 3rd dialysis day of each week. Bupropion SR doses will be adjusted upward or downward based on tolerability and response.

- Fluoxetine group: Oral administration of fluoxetine tablet will be started at a dose of 10 mg/day for the first week and then increased, as tolerated to 20 mg/day for weeks 2–4. After this, doses will be adjusted based on clinical response and side effects up to a maximum dose of 60 mg/daily by week 10.

Although non-English speaking participants are not anticipated, there is an unlikely possibility that we may recruit a Spanish-speaking individual. If this occurs we will submit the translated materials and certification of translation to the IRB for approval prior to enrolling the subject. The principal investigator is fluent in Spanish (reading, writing, speaking) and will obtain consent from any Spanish speaking subjects. Study staff will assess each subject's understanding of the study procedures, including risks and benefits, during the initial evaluation process. A Spanish-speaking physician will interview Spanish-speaking subjects during the initial evaluation to determine their understanding of the materials, and subjects will be given the option of having study materials in their preferred language. Since the possibility of recruitment of a non-English speaking participant is unlikely in this small population, we will not submit translated materials for approval unless necessary.

6. Research Plan

The current study proposes to recruit up to 50 participants in order to have 40 completers. Eligible CKD patients with MDD will be randomly assigned to 12 weeks of open label, flexible dose treatment with either Bupropion SR (N=20) or Fluoxetine (N=20). Patients will be recruited from the UAMS dialysis center or other local dialysis centers via flyers, referral by their treating physician and/or newspaper ads. Written consent will be obtained before any study procedures. Subjects are randomly assigned to open label treatment with one of the following:

- Bupropion group:

  - For patient not on hemodialysis or peritoneal, oral administration of bupropion SR tablet at a dose of 150 mg daily. Bupropion SR doses will be adjusted upward or downward based on tolerability and response.
  - For patient on hemodialysis or peritoneal dialysis, oral administration of bupropion SR tablet at a dose of 150 mg on the 1st and the 3rd dialysis day of each week. Bupropion SR doses will be adjusted upward or downward based on tolerability and response.
- Fluoxetine group: Oral administration of fluoxetine tablet will be started at a dose of 10 mg/day for the first week and then increased, as tolerated to 20 mg/day for weeks 2–4. After this, doses will be adjusted based on clinical response and side effects up to a maximum dose of 60 mg/daily by week 10.

After consent, subjects will be interviewed by a study staff for eligibility, including a review of medical records (if available), clinical interview, physical examination, routine blood tests, and EKG, if not already available (within one month). Psychiatric diagnosis will be established after interview using the Mini International Neuropsychiatric Interview (MINI) [75], depressive symptoms will be assessed with the Hamilton Depression (HAM-D) Scale [76], and cognitive status will be assessed using the n-back and MSIT tasks [77] and the Modified Mini Mental Status (3MS) Examination [78]. Pain will be characterized with the Physical and Psychological Pain Scale [142]. Pressure pain threshold will be measured with an Algometer [143]. Thermal pain sensitivity will be characterized with Quantitative Sensory Testing (QST). Delay discounting, MSIT and n-back will be the primary measures of cognitive function and the 3MS will be used for comparison to other studies. History of prior antidepressant treatment and response will be obtained using the Antidepressant Treatment Response Questionnaire (ATRQ) [79]. Given the under-recognized role of dental and gum disease in systemic inflammation a basic noninvasive dental evaluation will be performed by Dr. Melissa Efurd at UAMS Dental Hygiene Clinic. Dialysis dose, pre- and post-dialysis body weight and blood pressure, serum urea nitrogen, albumin, serum phosphate hemoglobin, calcium, parathyroid hormone, vitamin D and lipid profile will be extracted. Measures of dialysis adequacy (kt/V) will also be extracted.

Participants will receive the study medication during the baseline assessment and instructed to begin the medication on day 1 (1st dialysis day) of week 1 of the study. For patient on hemodialysis or peritoneal dialysis, generic bupropion SR will be dosed at 150 mg on the 1st and the 3rd dialysis day of each week with doses adjusted upward or downward based on tolerability. The initial dose of bupropion-SR is based on the findings of Worrall et al [80], who measured plasma bupropion levels in a pharmacokinetic study of bupropion in HD patients. For patient not on hemodialysis or peritoneal dialysis, generic bupropion SR tablet will be dosed at 150 mg daily. Bupropion SR doses will be adjusted upward or downward based on tolerability and response. Fluoxetine will be started at 10 mg/day for the first week and then increased, as tolerated to 20 mg/day for weeks 2–4. After this, doses will be adjusted based on clinical response and side effects up to a maximum dose of 60 mg/daily by week 10 [62]. At the week 12 visit, the participants will stop the medication or may undergo a 1-2 week taper (depending on maintenance dose) if they are on a dose of fluoxetine that is higher than 20 mg.

Subjects will be seen during weeks 1, 2, 3, 4, 6, 8, 10, and 12 in face-to-face meetings by a rater blind to study medication and a study physician for Ham-D ratings, CGI, medication accountability, and measurement of adverse events. On weeks 5, 7, 9 and 11, subjects will come in to return the previous week's pill bottles and pick up the current week's medication. Table 1 shows study procedures. Medication will be prepared by UAMS Research Pharmacy, labeled with the directions for use and contact information, and given to participants by study staff on a weekly basis. Compliance will be monitored using the MAFV at each scheduled encounter and by analysis of antidepressant blood levels. Results of a second EKG done during week 4 will be reviewed to ensure QTc interval is less than 500 msec.

In order to control for the potential confound of chronic pain we will characterize it with the physical and psychological pain scale and with two objective measures, i.e. the pressure pain threshold and the Quantitative Sensory Test (QST).

Given that dental disease (gum disease and caries) is the main source of increased inflammation in the general population we aim to control for this confound for our Specific Aim 3 by having a baseline and end of study dental assessment.

Biochemical Measurements:
Plasma for inflammatory markers, TRP, and TRP metabolites will be obtained at mid-week prior to dialysis on weeks 1, 4, and 12. Blood fluoxetine and hydroxyl-bupropion levels will be obtained at weeks 4, and 12. When possible, samples will be taken from pre-filtered blood at the dialysis site and sent to a research laboratory core at UAMS and/or UT San Antonio for analysis. Twenty ml of venous blood will be collected as described in Table 1. Blood for free- and total-TRP and large neutral amino acids (LNAA) will be assayed by high performance liquid chromatography with coulometric detection (HPLC) [105] and expressed in μM. Plasma KYN concentrations will be determined by HPLC [106]. Quinolinic acid will be quantified by electron capture negative chemical ionization gas chromatography/mass spectrometry with [180] QUIN as internal standard [107]. Determinations of plasma concentrations of CRP, IL-1β, IL-6, and TNF-α will be performed by ELISA with the use of Quantikine High Sensitivity kits (intra-assay coefficient of variation for these cytokines 2.0 to 8.6%; interassay coefficient of variation 3.9 to 7.0%; R&D Systems, Minneapolis, MN) following established guidelines [108]. Bupropion and its active metabolites hydroxybupropion and fluoxetine and norfluoxetine will be analyzed using HPLC and mass spectrometry (MS) [109] [110].

The following tools will be utilized:
a) The Mini International Neuropsychiatric Interview (MINI) [75]. Psychiatric diagnosis will be assessed with the MINI, a widely used semi-structured interview for DSM-IV diagnoses. It has high reliability, for MDD and depressive subtypes. (Time - 30 min).
b) The Hamilton Depression (HAM-D) Scale [76]. Depressive symptoms in all phases of this study will be measured with the 25-item version of the HAM-D. (Time – 5 minutes).
c) The Profile of Mood States (POMS) [81, 82]. The POMS is one of the most validated measures for measuring a wide range of clinical and subclinical changes in mood. It has been studied extensively in various clinical samples including psychiatric patients as well as in cancer, drug abuse and addictions, and the broad domain of exercise, fitness, sports psychology, and sports medicine. (Time – 10 min).
d) The Brief Fatigue Inventory (BFI) [83]: It is used to assess the severity of fatigue and the interference of fatigue with daily functioning. The interference items include general activity, mood, walking ability, normal work (includes both work outside the home and housework), relations with other people, and enjoyment of life. The interference items are measured on a 0–10 scale, with 0 being “does not interfere” and 10 being “completely interferes.” (Time – 5 minutes).
e) The Modified Mini Mental Status (3MS) Examination [78]: The 3MS Examination is a validated screening tool to evaluate global cognitive function with components for orientation to time and place, attention, language, immediate recall, short-term verbal memory, calculation, construct ability, and memory. [84]. (Time – 8 minutes).

f) Delay discounting task. It is a decision making task. Subjects will be presented a series of trials in which they will choose between a set of hypothetical rewards or losses to be received in variable time spans. Smaller sooner (SS) hypothetical reward/loss ($X) received today or a larger later reward/loss (LL) ($1000) received at a future delay (1wk, 1mo, 6mo, 1yr). The value of the SS award will be titrated with participant responses so that an equal number of SS and LL choices are selected for each delay. Time - 5 minutes [144].

Table 1. Study Procedures

Measures	Week of Study								
	B	1	2	3	4	6	8	10	12
ATRQ	X								
Vitals	X	X	X	X	X	X	X	X	X
MINI	X								
Dental evaluation	X							X	
Ham-D	X	X	X	X	X	X	X	X	X
POMS	X	X	X	X	X	X	X	X	X
BFI	X	X	X	X	X	X	X	X	X
Blood (20 ml)	X	X			X				X
EKG					X				
CGI		X	X	X	X	X	X	X	X
SAFTEE		X	X	X	X	X	X	X	X
MAFV	X	X	X	X	X	X	X	X	X
Physical and Psychological Pain Scale	X	X	X	X	X	X	X	X	X
Pain threshold	X	X	X	X	X	X	X	X	X
Quantitative Sensory Test (QST)	X					X			X
Delay discounting task	X	X	X	X	X	X	X	X	X
Cognition (MSIT, n-back& 3MS)	X				X				X

MINI: Mini International Neuropsychiatric Interview; HAM-D, Hamilton Depression (HAM-D) Scale; ATRQ: Antidepressant Treatment Response Questionnaire; POMS: Profile of Mood States; BFI: Brief Fatigue Inventory; CGI: Clinical Global Impressions; SAFTEE: Systematic Assessment For Treatment Emergent Events; MAFV: Medication Accountability Form;; 3MS: Modified Mini Mental Status Examination

g) Multi-Source Interference Test (MSIT): MSIT is a non-verbal test of attentional conflict which combines elements of the Stroop, Flanker, and Simon effects. Although designed as a standardized fMRI task for studying attention, MSIT has robust behavioral effects [77]. This task is selected because Dr. James has used it to study cognition in a large normative sample.

h) N-back task. The n-back task is a non-verbal test of working memory, a cognitive process that generally facilitates other cognitions [77]. Dr. James has previously shown this task to have strong construct validity with clinical measures of working memory.

i) Antidepressant Treatment Response Questionnaire (ATRQ;[79]): A scale to determine treatment resistance. It provides criteria for adequate dose duration of a trial for it to be considered a failure.

i) Clinical Global Impressions - Severity and Improvement (CGI-S, CGI-I;[85]) (Time 3-5 minutes): These two instruments are scored 1-7 by the clinician based on assessment of the patient's clinical status. They measure: a) depression severity (CGI-S), and, b) clinical improvement (CGI-I)

k) Systematic Assessment For Treatment Emergent Events (SAFTEE) [86, 87] (Time-5 - 15 minutes)- This measures treatment-emergent events, using both the general and a modified specific inquiry that asks about each symptom found problematic. To this list will be added any item elicited from that patient in response to previous general inquiries and any additional adverse events elicited in at least 10% of the first 50 patients. For each symptom the patient is then asked about onset, intensity, off-set and counteractive measures, and the clinician judges the likelihood it is medication-related.

l) Medication Accountability Record (Time 2-3 minutes). Used to record medication adherence. Pharmacy staff will record number of pills missing from previous week's bottle after each study visit.

m) Physical and Psychological Pain Scale, self-report has 7 items and takes 2-3 minutes to complete. It characterizes psychological pain in comparison with physical pain [142].

n) Pressure Pain Test Patients will be placed supine. A point five inches below the patella in the medial border of the tibia will be identified in both sides. Pressure will be applied using a digital force gauge with a 1-cm^2 rubber tip (J-Tech Medical, Commander Algometer or equivalent) alternately to the left and the right tibia for a total of three times each. Participants are instructed to verbally report when their sensations change from pressure to pain. A mean tender point threshold (kg) is calculated from the six measurements [143]. To prevent any possible tissue damage, stimulation will only be applied to a maximum of 20 Lb.
o) Quantitative Sensory Testing (QST) on untreated skin will be performed using cutaneous hot and cold stimuli via a thermal stimulator (Q-Sense) thermode on the Medoc Pathway System (Medoc Ltd Advanced Medical Systems, Ramat Yishai, Israel). It will be performed via method of limits testing on the right thenar eminence with a program designed to randomly order 5 hot and 5 cold stimuli with random durations (5–35 seconds) between each trial. The Q-Sense thermode will begin at 32°C and increase or decrease by 0.5°C per second. Participants will be instructed to press a button to signify 3 different measures: 1) sensory threshold, or the temperature at which the stimulus becomes noticeable; 2) pain threshold, or the temperature at which the stimulus becomes painful; and 3) pain tolerance, or the temperature at which the stimulus becomes unbearable. The device will be set to stop heating at 51.5°C and stop cooling at 0°C to avoid tissue damage.

Concomitant Clinical Management and Study Termination

Patients will continue to be managed by their treating physician during the study. Acute events that may require hospitalization are expected in this population. These events and possible interruptions of study drugs will be recorded, and if necessary, patients may be discontinued from the study. Patients expressing suicidal ideation or plans will be brought to the attention of the treating physician and treatment options discussed. The PI will be available for consultation on such cases. Depending on the severity and/or wishes of the treating physician and patient, a number of options are available, including transportation to a nearby emergency department, referral to the Psychiatry outpatient clinic, or medical intervention at the dialysis center.

Subjects may terminate the study at any time for any reason. Reasons for early discontinuation will be ascertained by research staff as best possible and recorded in the following categories: 1) unspecified patient request or failure to return, 2) patient request or physician decision due to clinical worsening without meeting relapse criteria: 3) adverse event, 4) protocol violation. Subjects that discontinue prematurely will be given referral options and advice, if possible.

Non-responders to treatment will meet with a physician to review options, including referral to a community clinic or the Psychiatry Department. Subjects that complete the study with no relapse will be given the option to be referred to a physician in the Psychiatry Outpatient Clinic or have their medication managed by their current general physician.

End of study Follow-up Phone call

Participants will be contacted by phone at week 14 (two weeks after concluding the trial) to determine if the participant is experiencing any post-treatment adverse events related to the cessation of study medications. Participants experiencing distress will be referred to the UAMS Walker Family Clinic for further psychiatric care.

Limitations and Alternative Design

The use of peripheral measures rather than measurement of cytokines or biochemical markers in the cerebrospinal fluid (CSF) is a limitation, however, the risks and discomfort involved in CSF measurements is not warranted without stronger justification. The central action of proinflammatory cytokines on the hypothalamic-pituitary-adrenal (HPA) axis has been suggested to be a risk factor for MDD [111]. However, data suggest that the HPA axis function is not markedly altered in HD patients [112, 113]. TNF-α antagonists [114] could be used to test the hypothesis that TNF-α contributes to depressive and cognitive symptoms. However, these compounds are expensive, difficult to administer, and have potentially serious adverse effects [115].

Data Analysis, Statistical Considerations, and Testing of Hypotheses:

Determination of Sample Size: **Hypothesis 1** concerns within-treatment group improvement of

depression. With four post-baseline measures, calculation of power requires an estimate of the matrix of correlations among the repeated measures. We specified a medium effect size averaged across the post-baseline measures (Cohen's d=0.5 SD, 1988), unadjusted alpha of 0.05. We specified compound symmetry among the measures with r=0.50 because the measurements are relatively close in time. With these specifications, it is possible to calculate the standard error of the difference between baseline and the average of the post-baseline measures. With N=20, IBM SamplePower3's (IBM SPSS, 2000) module for the t-test for paired observations indicates power=0.78 with N=20. We confirmed this result with a simulation with 1000 datasets with the structure described, performing mixed effects analyses as described below. The simulation yielded an empirical power estimate of 0.79 for Hypothesis 1. We also evaluated a banded covariance structure in which the correlations fell off from .50 to .32 over time, and found that yielded power=0.75. **Hypothesis 2** concerns between group differences. Power was calculated using Hedeker's RMASS2 software for mixed models with longitudinal data. Specifications were as above but the effect size was adjusted for the use of a baseline covariate and the design involves two groups of N=20 each assessed at four occasions. In this case, power is 0.80 to detect a standardized mean difference (Cohen's d) of 0.6. This is slightly larger than the conventional medium effect size of d=0.50. The analyses for **Hypothesis 3** involves using the TRP/LNAA ratio as a covariate in mixed effects regression models with the same design structure and analytic plan as the between-groups models for Hypothesis 2. Converting Cohen's d to the correlation coefficient equivalent, d=.6 is roughly equal to r=.30, Cohen's convention for a medium correlation. Evidence that these assumptions about effect sizes are probably quite conservative can be found in previously described effects of bupropion [68, 70, 90, 116-120] and fluoxetine [28, 60, 104, 116, 121] on symptoms of major depression, cognition, and inflammation.

General Methods: Given that a primary goal of the current study is to obtain data to justify and support the feasibility of a future definitive trial, a variety of data necessary for this, including data on tolerability and safety (see below), will be obtained. For example, subject disposition will be summarized with a table indicating the number of subjects screened, the number of screen failures by reason, the number enrolled, the number who dropped out (by reason), and the number completing the study. Random double-blind assignment of patients to fluoxetine or bupropion is expected to yield similar distributions of measured and unmeasured variables of interest. This design provides a strong basis for making inferences about causal relationships between variables by controlling a priori for a wide range of patient and situational factors, thereby increasing the validity of estimates and inferential tests. In between-groups analyses, variables that are related to outcome which differ between groups will be included as predictors in a logit model predicting group assignment, and the predicted values of this model will be incorporated as a covariate in all subsequent analyses. This includes factors that could influence treatment response [125-127], including number of prior episodes (>2 or not), treatment response vs. remission during treatment, and sex [128]. Continuously distributed outcomes will be summarized with the sample size, mean, standard deviation, median, minimum and maximum and categorical or binary outcomes with counts and percentages. Distributions will be examined to identify potentially influential observations (outliers) and suggest transforms (e.g., log) to normalize. The final report containing formatted tables and embedded graphics will be produced in Microsoft Word directly from the database using the SAS Output Delivery System. Analyses will use all subjects with usable data. All statistical testing will be two-sided with a significance level of 5%. The Holm-Bonferroni step down method will be applied as necessary to correct for multiple testing. SAS Version 9.2 for Windows (SAS Institute, Cary, North Carolina) will be used throughout.

Tolerability and Safety: We will determine incidence rates for all adverse events and treatment emergent adverse events will be determined using the SAFTEE. Treatment emergent adverse events will be defined as those that were not present before the first administration of drug, but occurred after the first administration, or that were present before the first administration but increased in severity or frequency after the first administration. Incidence rates for all adverse event and treatment emergent adverse events will be compared between medication groups using chi-square for frequencies with any events or Poisson regression for counts of numbers of events adjusting for time at risk using log time as an offset variable. The numbers of subjects withdrawing from the study for each reason will also be compared across groups using survival analysis on time to study discontinuation.

Testing Hypothesis 1. Both antidepressants will be efficacious based on change in Ham-D scores over time. The primary analyses will be mixed effects regression models with repeated measures (baseline, 1, 4, 8, 12 weeks) performed separately in the medication groups. The fixed effect is time, and the hypothesis test is an *a priori* contrast comparing the baseline value with the average of the four post-baseline values. In secondary analyses, patients will be categorized as responders and remitters, with response defined as a 50% or greater improvement in Ham-D score with total score ≤ 15 at the 12 weeks compared with baseline and remission [129] as having had a treatment response plus a final Ham-D score ≤7.
Testing Hypothesis 2. Changes in cognition, fatigue, and depression will be evaluated between and within treatment groups. Changes in BFI and cognition should be greater in bupropion SR-treated patients [30, 32, 89, 130-140]. These analyses will use mixed effects regression models with repeated measures. Treatment group, time and their interaction are the fixed independent variables. Change in Ham-D, BFI and cognitive dysfunction (3MS, MSIT, and n-back performance) are the time-varying dependent variables. All subscales of the BFI will be summarized by time point.
Testing Hypothesis 3. These analyses will measure the association between CRP, TRP availability, and quinolinic acid to Ham-D score, BFI, and cognitive measures over time. Because the effects of TRP on brain 5-HT is best estimated by the ratio of free TRP to LNAA, this ratio will be calculated and used as the primary measure of possible brain 5-HT depletion. The analyses will use mixed effects regression with time, the TRP/LNAA ratio, and their interaction as independent variables and measures of depressive symptoms (HAMD) and cognitive dysfunction (3MS, n-back accuracy, and MSIT reaction time) serving as dependent variables. Supplemental analyses will be done using the presence of residual depressive symptoms (yes: HAM-D>15; no: HAM-D<=15) and presence of cognitive impairment (yes: 3MS <80, no: 3MS ≥80), presence of dental disease (yes/ no) over time (1, 4, 8 and 12 weeks) using the generalized linear model (GEE) with the same fixed effects and binomial error.
Exploratory Analyses: Additional analyses will explore age, sex, baseline depressive symptoms (HAMD), baseline dental disease and interactions of these covariates with the fixed effects in the models described above. McNemar's test will be used to compare the proportion of subjects meeting criteria for cognitive dysfunction at baseline compared with study end, and chi-square tests to compare these proportions with population rates. Pearson correlations will be used to assess the strength of associations between variables at each assessment. Correlations between the measures of depression, cognitive function, and fatigue will be tabled and summarized with scatter plots across all time points and by time point. Exploratory analyses will also substitute individual cytokines and the ratio of pro- to anti-inflammatory cytokines for inflammation in relevant analyses and also seek to define whether there is a threshold for individual cytokines or the pro/anti-inflammatory ratio before depressive symptoms (HAM-D>8) or cognitive dysfunction occur. The threshold analysis will utilize traditional receiver-operator characteristics (ROC) analyses. Both buproprion SR and Fluoxetine are local standard practice.

Source of Funds
This study is funded by UAMS Department of Psychiatry.

Probable Duration
The study will be completed in 1 year.

Risks and Benefits:

Study Intervention #1 Benefits Bupropion SR Group	
Bupropion SR Group	Possible improvement in depression status

Reasonably foreseeable risks:		
	Not serious	**Serious**
Likely These risks are expected to occur in more than 10 out of 100 subjects.	• Dizziness • Agitation • Blurred vision • Tremor • Sweating • Headache/migraine • Inability to get adequate sleep • Increased heart beat • Dry mouth • Constipation • Decreased appetite • Nausea, vomiting • Weight gain	• None
	Not serious	**Serious**
Less likely These risks are expected to occur in 2-9 subjects or less out of 100 subjects.	• High blood pressure (Hypertension) • Low blood pressure (Hypotension) • Skin rash and itching • Impotence • Urinary frequency • Arthritis • Slowness in movement (bradykinesia) • Upper respiratory complaints • Fatigue • Anxiety • Decreased sexual desire (libido)	• Abnormal heart rhythm
		Serious
Rare These risks are expected to occur in less than 1 subject in 100.	• Urinary retention	1) Suicidal ideation 2) Suicide 3) Faint (syncope) 4) Seizures. In doses over 400mg per day, bupropion SR can be associated with seizures. The incidence of seizure with bupropion SR at the usual daily dose of 300 mg is approximately 0.1%, (or 1 out of every 1000 patients), which increases to approximately 0.4% at the maximum dose of 400 mg/day. The dose of 150 mg twice per week used in this study was previously shown to lead to blood levels in hemodialysis patients comparable to those obtained during routine treatment of non-hemodialysis patients treated with 300 mg daily.

Study Intervention #2 Benefits Fluoxetine Group		
Fluoxetine group	Possible improvement in depression status	
Reasonably foreseeable risks:		
	Not serious	**Serious**
Likely These risks are expected to occur in more than 10 out of 100 subjects.	• Decreased appetite • Anxiety • Nervousness • Inability to obtain adequate sleep (insomnia)	• None
	Not serious	**Serious**
Less likely These risks are expected to occur in 2-9 subjects or less out of 100 subjects.	• Impaired thinking	• Alteration in blood glucose • Abnormal bleeding • Weight loss
		Serious
Rare These risks are expected to occur in less than 2 subjects out of 100		• Suicidal ideation • Suicide • Serotonin syndrome symptoms (mental status changes [agitation], increased heart beat, change in blood pressure, dizziness, tremor, seizures, and/or nausea, vomiting, diarrhea) • Allergic reactions (Anaphylactoid reactions - including bronchospasm, angioedema, laryngospasm, and urticarial) and skin rash

Risks associated with stopping the study medication. To our knowledge, there are no known risks to stopping bupropion abruptly. In addition, although abrupt termination of selective serotonin reuptake inhibitors (SSRIs) have been associated with a SSRI discontinuation syndrome (consisting of symptoms described as "head shocks," dizziness, electric shock-like sensations, sweating, nausea, insomnia, tremor, confusion, nightmares, and vertigo), fluoxetine has been associated with only mild dizziness and vertigo in patients maintained on fluoxetine at 20 mg/day that was abruptly terminated in a randomized double blind trial (141).

Procedures to Minimize Risks

- All side effects will be closely monitored;
- Physical examination and blood test results will be performed reviewed to help detect an increased risk of developing side effects;
- Aseptic precautions to minimize risks associated with blood draw;
- Subjects will be educated to share any unusual event or change in their health with the study staff;
- Study staff will ask questions to elicit any new event or change in their health during each encounter;
- The study procedures to be performed on subjects are consistent with sound research design.
- Participants maintained on fluoxetine at doses higher than 20 mg/day will undergo a 1-2 weeks taper depending on the maintenance dose.
- The researchers have taken steps to minimize the known or expected risks. However, appropriate medical treatment will be provided for any adverse event (anticipated or un-anticipated) as per standard medical practice and guidelines. In addition, the event will be documented for proper notification. In addition, following measures will be implemented:
  - All patients will continue to be managed by their treating physician during the study. Acute events that may require hospitalization for reasons unrelated to the study are possible in this population. These events and possible interruptions of study drugs will be recorded, and if necessary, patients may be discontinued from the study. Patients expressing suicidal ideation or plans will be brought to the attention of the treating physician and treatment options discussed. The PI will be available for consultation on such cases. Depending on the severity and/or wishes of the treating

physician and patient, a number of options are available, including transportation to an emergency department medical facility, referral to Psychiatry outpatient clinic, or medical intervention at a nearby dialysis center.

Minimize Risks From Loss of Privacy:
All participant information (clinical and research information) will be maintained in a research file separate from hospital medical records. In addition to current measures, the present study will comply with the Health Insurance Portability and Accountability Act of 2003. No biological result or data are released to subjects or third parties under any circumstances.

Data at each visit will be recorded using a standardized clinician assessment forms, a set of patient rating scales and/or computer-delivered tasks. To protect participants' confidentiality, minimal identifying information will be collected, and any information collected will be stored securely. Paper-based and electronic records will be stored in a locked cabinet located in an office at the Psychiatric Research Institute at UAMS, Little Rock, AR 72205 and a secure server, respectively. Only the PI, Co-PI and the study coordinator will have access to the locked cabinet. Only the Principal Investigator and research staff will have access to these files. Electronic records will be encrypted and stored on password-protected computers accessible only to members of the research team. All data will be double entered and compared using automated comparison programs. Inconsistent data entry will be resolved against the raw data and comparisons will continue until all inconsistency is removed. Edited and corrected data will be added to a database that is ready to be used as input to statistical software. All data will be kept in password-protected files separate from the data for analyses or stored in locked file cabinets. No identifiers other than study patient number assignment will be included in the dataset. In the reporting of results, only aggregate group information will be presented. No unique personal identifiers that could disclose the identity of the research participants will be presented or published Clinical and research information will be maintained in a research file separate from hospital medical records.

Data will be kept in accordance with FDA, UAMS, and NIH guidelines. When the study is complete, data will be stored at a secure long-term storage facility managed and operated by UAMS. Only limited staff will have access to the stored data. Where policies overlap, the longest retention policy will be followed, and then the most stringent destruction policy will be followed.

Biological materials for will be identified by bar code or study ID rather than by name. Any records (either hard copies or removable electronic files) with identifiable patient information are kept in a locked file in the Department of Psychiatry and can only be accessed by the investigators and study staff. Biological specimens will be analyzed as per Protocol. Specimens collected during this study, if any are remaining, will be destroyed by the end of the study.

Payment.
A subject will receive a small reimbursement for time/travel for being in this study. S/he will be compensated with a check for $25.00 for every study visit completed that involves assessments. Subjects can earn up to a total of $250.00 upon completing 10 study visits that involve assessment. Subjects will not be compensated for visit that involve only picking up meds. However, subjects can be provided taxi rides for the visits to pick up meds. If a subject does not finish all the study visits, he/she will be paid only for the visits completed.

Costs to Subjects.
The Investigator will provide the study drug free of charge during this study. In addition, all tests, examinations, and medical care required in this study are provided to a participant at no cost. There will be no costs for the subject participation

The researchers will take steps to minimize the known or expected risks. However, the subject may still experience problems or side effects, even though the researchers are careful to avoid them. If the subject believes that he/she has been harmed, she/he will be instructed to notify the researchers as soon

as possible. In the event of a research-related injury or if the subject experiences an adverse reaction, he/she will be instructed to immediately contact the study doctor.

If the subject is injured as a result of the research procedures, the injury will be treated.

The subject/insurance company will be responsible for any charges. We have no plans to give the subject money if he/she is injured.

Subjects are informed that they do not give up any of legal rights by signing the Consent Form.

Data and Safety Monitoring Plan.

The current study is a Clinical Trial and includes procedures that could pose a risk to subjects. A data and safety monitoring plan has been developed.

Data Acquisition, Collection, Transmission, and Entry:
Procedures in Place to Ensure the Validity and Integrity of the Data

Written standard operating procedures will be used to protect data from error, negligence, misconduct, conflict of interest, malicious acts, and catastrophe. The principal investigator will maintain all research records. They will not be mingled with or co-located with medical records. To insure an adequate archive, data will be collected on paper forms and stored in folders unique to each participant. Calculations of test scores will be made by the test administrator and independently verified by the principal investigator. The test administrator will enter data into a dedicated computer database within one week of collection. The principal investigator will independently verify accuracy of data entry. Computer files will be backed up daily. The principal investigator and test administrator will verify data integrity weekly. To safeguard patient anonymity and the confidentiality of research records, all data collection forms and computer databases will identify patients by subject identification number only. Computers and computer databases will be password protected with independent passwords known only to the principal investigator and test administrator. Computers used for data storage and analysis will be not be networked to public access servers. Original paper files and backup disks will be archived in locked file cabinets in a locked room in a secure building. Access to combinations/keys will be limited to the principal investigator and test administrator. The UAMS Institutional Review Board (IRB) will monitor the conduct and progress of the study at least annually and may audit data collection and management procedures without notice.

The entire study team is responsible for collecting study data including safety data during each encounter (e.g., scheduled clinic visit, telephone contact, subject's reporting). Data will be entered in the Source Document as a narrative. PI and the Sub-Investigators will review the data and additional information will be collected or verified through medical records, electronic medical data sources, further subject interview etc. The CRF (or the electronic data capturing) will be updated as per verified Source Document. All data will be maintained and kept confidential in a locked cabinet (or electronic devise) with authorized access.

The research assistants will have at least a bachelor's level education (or relevant experience) and previous experience in clinical rating and/or interviewing. One of the investigators or designee will give a training session on the background of the particular scale and how it is to be completed. Then the staff member will observe completion of the assessment by an experienced rater on at least three occasions. Afterward, the staff member will complete the assessment in the presence of an experienced rater on at least three occasions, with feedback given each time, until the trainer is confident that the person understands the assessment and completes it properly. Thereafter, assessments will be checked on a continuous basis for appropriate completion, and constructive criticism will be given as necessary. Staff members will also undergo a refresher on assessments every 4 months.

Each research staff member will be instructed on the timing of assessments for each individual. Checklists will be used to ensure that assessments are obtained at the time indicated. The PI or designee also will review assessments. For the computerized assessments, the research assistants will create each subject's template. The computer data will be backed up on a secure server and checked by the PI

or designee, for missing data. The computer(s) used to collect data will be kept in a locked office when not in use and will not be networked.

For paper assessments, the research assistants will review the assessments for missing/out-of-range values. If any missing or inaccurate values are found, the participant will be asked to complete those again. Paper data will be entered into the computer by trained research staff within one week of the assessment.

Prior to statistical analyses, the Data Manager will check the data for mislabeling, missing data, out-of-range data, etc., and will change/correct as appropriate based on source data. The Data Manager will also assign study condition per study ID for analysis purposes. A master data set will be created with at least two backups. One of these backup disks will be given to the statistician, with a data assessment dictionary, for analysis.

Collection and Reporting of Adverse Events (AEs), Serious Adverse Events (SAEs) and Unanticipated Problems involving Risks to Subjects or Others (UPIRTSOs)

Any adverse event (AE) or serious adverse event (SAE) or unanticipated problem involving risk to subjects or others (UPIRSO) or any change in health from the baseline including injuries, accidents or hospitalizations will be reported. Safety data or events will be captured by interviewing the study participants with specific questions asking any changes in health and functionality since the previous visit and/or by reviewing the following in the participant's medical chart (if available): physical examinations, vital sign measurements, 12-lead electrocardiograms, clinical laboratory measurements, and concomitant medications.

All adverse events (AEs) occurring during the course of the study must be collected, documented, and reported to the PI. The occurrence of AEs will be assessed in an ongoing way. Each week the PI and study personnel will review and discuss the AEs from the previous week for events that were reported as new or continuing and discuss appropriate measure to address each event – such as notification to the proper authority, prevention and treatment of the event, notification to the study subjects, suspension of enrollment, and termination or suspension of the study. The study team will follow all AEs to the point of satisfactory resolution.

The PI and sub-Investigators will determine whether an event meets the criteria of a serious adverse event (SAE) and/or an unanticipated problem involving risks to subjects or others (UPIRTSO). The PI will report AEs and SAEs on an annual basis and UPIRTSOs to the IRB in a timely fashion

The study investigators will follow all AEs to the point of a satisfactory resolution. A study participant may be withdrawn from the study if the study physician determines it is the best decision in order to protect the safety of the participant. In the event that a participant either withdraws from the study or the investigator decides to discontinue a patient due to an SAE, the participant will have appropriate follow-up medical monitoring. Monitoring will continue until the problem requiring hospitalization has resolved or stabilized with no further change expected, is clearly unrelated to study interventions, or results in death.

The IRB communicates recommendations and decisions to the PI in a timely manner. The decision to terminate the study early for suspected or actual benefit or risk will be made by the principal investigator in consultation with the Chair of the IRB.

DSM Plan

The PI will be ultimately responsible for monitoring the safety and efficacy of the trial, executing the DSM plan, and complying with reporting requirements. Any adverse events that occur will be monitored in an ongoing way, as well as being formally reviewed by investigators after 50% and 100% of participants have been enrolled. Whether risks of participation remain acceptable under the present protocol or modifications to the protocol are necessary while still maintaining scientific integrity of the project will be

determined. Any data accrued will be summarized and reviewed by the study investigators after 50% and 100% of participants have been enrolled. In addition, the PI will submit a report of recruitment and retention, protocol deviations, adverse events (summary), serious adverse events (individually), and reasons for study discontinuation to the IRB on at least an annual basis. Interim analyses will not be performed unless clinically indicated. All SAEs, such as death, hospitalization, and unexpected toxicity, will be reported to the IRB under expedited reporting, as appropriate. The procedures for this reporting include written documentation using the clinical notes related to the adverse event and specific forms detailing the event with a sign-off by all appropriate supervisory personnel. According to SF 424 guidelines, a Data and Safety Monitoring Board is required only for multi-site clinical trials; thus, there is no current plan to form a DSMB for this trial.

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