The Investigator's Protocol

1.Title: Randomized trial of sertraline treatment of depression in Chronic Kidney Disease
2. Principal Investigator: Susan Hedayati, MD, MHSc, Nephrology
3. Sponsor of the Study: No sponsor. **Sources of funds:** NIDDK R01 and VA MERIT Review
4. Investigational New Drug/Device Exemption: N/A
5. Purpose of the Study and Hypotheses to be Tested:

Chronic kidney disease (CKD) is a major public health problem (1) associated with excessive cardiovascular (CV) morbidity and mortality (2, 3). In our previous study of 272 predialysis CKD patients, we discovered that 21% suffer from a major depressive episode (MDE) and that MDE is an independent predictor of dialysis initiation, hospitalization and death. We and others showed that only a minority (16 to 39%) of CKD patients with depression are treated with antidepressant medications (9, 14, 15). Reasons for low treatment rates include a serious lack of published studies that support or refute efficacy and safety of antidepressant medication use in CKD patients. The Sertraline AntiDepressant Heart Attack Randomized Trial demonstrated benefit of antidepressant medication on CV outcomes (16). Unfortunately, this study excluded patients with moderate to severe CKD, precisely those who are at higher risk for both depression and poor CV outcomes. The purpose of the study is to determine the short-term safety and efficacy of antidepressant medications in CKD patients with a MDE as a first step to determine the feasibility of conducting a large-scale trial designed to investigate whether the treatment of depression improves quality of life and survival in patients with CKD.

Hypotheses: We hypothesize that short-term treatment of a major depressive episode (MDE) with serotonin-selective reuptake inhibitor (SSRI) sertraline will improve depression symptom severity in patients with predialysis stages 3-5 CKD and will improve short-term outcomes such as quality of life. We further hypothesize that short-term treatment of MDE with sertraline is safe and tolerable in CKD patients.

Specific Objectives:

1. Determine if treatment with sertraline, as compared with placebo, results in an improvement in depression severity as measured by the Quick Inventory of Depressive Symptomatology Clinician Rated (QIDS-C-16) score in 200 adults with predialysis stages 3-5 CKD and MDE. Subjects will be randomized in a double-blind fashion to placebo or sertraline (beginning at 50 mg/d and escalated by 50 mg every 2 weeks to a maximum of 200 mg/d) and followed for 12 weeks. This study will have 80% power to detect a 0.5 effect size assuming a two-sided-α of 0.05. Secondary outcomes are response to treatment defined as a decline of ≥50% in the baseline QIDS-C-16 and depression remission defined as a QIDS-C-16 score ≤5.

2. Determine if sertraline treatment vs. placebo improves overall function and QOL, as assessed by the Work and Social Adjustment Scale (WSAS) and Kidney Disease QOL Survey (KDQOL-SF), respectively. Aim 2 is also a secondary outcome.

Other exploratory aims are to:

3. Determine if treatment with sertraline, as compared with placebo, is safe and tolerable. This will be assessed by: a. proportion in each group with serious adverse events; b. type, severity and frequency of side effects; c. reduction in platelet aggregation in sertraline vs. placebo group, and whether this reduction correlates with higher plasma sertraline levels.

4. Investigate mechanisms by which sertraline may affect outcomes. We will determine if sertraline treatment vs. placebo will improve: a. nutritional status; b. adherence to prescribed medications; c. cognitive functioning; and d. markers of inflammation.

5. Collect data on death, hospitalizations, and dialysis initiation at 6 and 12 months after randomization for power calculations to determine the feasibility of conducting a large-scale trial designed to investigate whether the treatment of depression improves outcomes in CKD.

6. Background and Results of Previous Related Research:

(a) Background: Depression is more common among patients with CKD as compared to those without CKD. Whereas depression point prevalence is 2-4% in the general community and 5-10% in the primary care setting (18), 20% of CKD patients suffer from depression (9, 13, 27). This prevalence is even higher than that reported for other chronic diseases (24, 25). In addition, depression in CKD patients on chronic hemodialysis (HD) is an independent risk factor for both morbidity and mortality (10-13). HD patients with depression are twice as likely to die or require hospitalization within a year as compared to those without depression (10). Depression in dialysis is associated with a 30% increase in both cumulative hospital days and number of hospitalizations, which in turn contributes to excessive Medicare costs (11). There is a direct relationship between depressive symptoms and non-adherence to diet and interdialytic weight gain in HD patients (48-50). Decreased behavioral compliance is in turn associated with decreased survival (30). It is, therefore, importance to recognize depression as a risk factor for poor outcomes among patients who may not be adhering to medical advice (32) and investigating whether treatment of depression would result in a difference.

However, serious knowledge gaps exist with respect to depression in the CKD population. Antidepressant treatment rates are low and safety and efficacy are not established. Only a minority of HD patients receive adequate diagnosis and therapy for depression (9, 14, 15, 42). Under-treatment of depression and under-dosing of antidepressants may be due to nephrologists' concerns about adverse effects, since there is a paucity of data regarding the safety of antidepressants as such patients are generally excluded from antidepressant trials due to concerns for safety (16, 43). These include increased risk of drug-drug interactions; accumulation of toxic metabolites with decreased renal clearance; central nervous system depression and increased risk of bleeding, which becomes particularly problematic in patients with advanced CKD and underlying qualitative platelet defects related to uremia (16, 42-46).

There is insufficient evidence to clearly suggest that treatment of major depression is efficacious or changes outcomes in CKD patients (9, 28, 48). Few studies have examined this issue and are fraught with serious problems including insufficient sample size, (48-52), lack of placebo-control (48-50, 52, 53) and lack of DSM IV-based gold-standard criteria for depression diagnosis (50, 51, 53). Nonrandomized observational studies of antidepressant therapy in CKD patients on chronic peritoneal dialysis reported some improvement in depressive symptoms (48); however, major limitations included the lack of a control group, selection and refusal bias, and a 50% drop-out rate. In another study, 14 HD patients with major depression were randomized to fluoxetine or placebo in a double-blind fashion (51). There was a statistically significant improvement in depression at 4 but not at 8 weeks. Further, the sample was too small to clearly identify adverse effects and follow-up was not very long. Finally, non-pharmacological treatment of depression, such as exercise, psychotherapy, and cognitive behavioral therapy have met with very limited success (52, 54-56). The discouraging lack of sufficient published data calls for a randomized placebo-controlled trial where subjects are consecutively recruited and outcomes are blindly assessed. *Our proposed trial will fill this gap in knowledge by establishing the safety, tolerability and efficacy of sertraline for depression treatment in patients with CKD in a randomized double-blinded placebo-controlled trial (Specific Aim 1 and 3).*

Finally, it is not known whether treatment of depression improves outcomes. Given the excessive morbidity and mortality of CKD patients (2, 3) and the failure of interventions to alter mortality (6-8), it is plausible that depression is a crucial component in the causal pathways to morbidity and mortality in the CKD population. This project will provide ground-breaking information needed to determine whether pharmacologic intervention for treatment of depression in CKD patients can improve their dismal outcomes. Importantly, depression also results in substantial decrease in quality of life (QOL) and functional impairment in patients with CKD (53, 57-59), and levels of depression and functional and occupational impairment do not remit spontaneously in untreated depressed patients (60). *Our proposed trial will fill this gap in knowledge by establishing whether the SSRI sertraline treatment of depression in CKD patients will improve overall function and QOL and elucidate mechanisms by which treatment may improve clinical outcomes (Specific Aims 2 and 4).*

(b) Significance: Major depression is a common, under-recognized and under-treated problem that is independently associated with markedly increased risk for both morbidity and mortality in CKD patients. There are no properly controlled trials of safety and efficacy of antidepressant medication treatment and no studies on effects of treatment on outcomes in this population. Treatment of depressed patients after acute coronary syndrome with sertraline was associated with a trend toward improved CV outcomes in the Sertraline AntiDepressant Heart Attack Randomized Trial (SADHART) (16, 41). *Given the excessive rates of CV death in CKD patients (2, 3), and the correlation of depression with increased CV events (20-23), it becomes imperative to not only investigate whether treatment of depression is efficacious in these patients, but also whether it would result in a reduction in CV mortality.* Accomplishing the aims of this proposal will establish the safety and efficacy of SSRI antidepressant medication use in CKD patients and *form the basis of future large trials to investigate whether treatment of depression in this population would impact their poor clinical outcomes.* Dissemination of results would affect clinical practice and encourage SSRI use in depressed CKD patients, with resultant improvement in depressive symptoms and QOL in this chronically ill population. Depression has become a U.S. public health priority. The U.S. Preventive Services Task Force recommends screening adult patients for depression if practices “have systems in place to assure accurate diagnosis, effective treatment and follow-up” (61). Without establishing the efficacy of antidepressants in CKD, screening for depression in this population who is at an increased risk for depression and suffers adverse outcomes resulting from depression would not be feasible.

(c) Relevance to Veterans Health: Prior research has shown that deployment stressors and exposure to combat result in considerable risks of mental health problems, including major depression, post-traumatic stress disorder (PTSD), substance abuse, and impairment in social functioning and in the ability to work among Veterans (62-64). In one study of 602 first Gulf War Veterans, 32% met criteria for current or lifetime depressive disorder (65). Given the high prevalence of both depression and cardiovascular disease in Veterans, the Veterans Affairs (VA) patient population provides a unique opportunity to address the research questions proposed above. Mental health disorders are not only prevalent among Veterans, but result in increased utilization of health care services (62, 66, 67) and, therefore, health care-related costs. Efficacious treatment of depression with SSRIs in these patients by primary care physicians and nephrologists in turn may lessen the use of health care resources and perhaps lead to overall decreased health care costs.

(d) Works Accomplished:

1)Knowledge Gap: To our knowledge, there are no published data using a DSM IV-based gold standard to define the prevalence of a MDE blindly and consecutively in predialysis CKD patients. Knowing the disease point prevalence becomes important in determining the feasibility of recruitment and conducting power calculations for clinical trials of depression treatment.

Methods: We consecutively recruited 272 patients with predialysis Stages 2-5 CKD from the Dallas VA outpatient CKD clinic to define the point prevalence of a current MDE using the DSM IV-based Mini International Neuropsychiatric Interview (MINI) (72).

Table 1 Unemployment, diabetes and co-morbid psychiatric illness are associated with a major depressive episode in CKD

Variable	Odds Ratio (95% CI)
Age, per year increase	0.97 (0.94, 1.01)
Employed	0.19 (0.05, 0.66)
Diabetes mellitus	2.17 (1.06, 4.45)
Co-morbid psychiatric illness	11.40 (4.64, 27.98)
History of drug or alcohol abuse	1.30 (0.62, 2.74)

Results: Fifty-seven of the 272 subjects or 21% met criteria for a current MDE. The presence of a MDE did not vary based on severity of kidney disease (CKD stage). **Table 1** lists variables associated with a MDE.

Conclusions: Twenty percent of patients with predialysis CKD has a current MDE and the prevalence does not vary based on CKD stage. Unemployment, presence of diabetes, and other psychiatric illness are associated with a current MDE in CKD patients.

2)Knowledge Gap: There are limited data regarding the psychometric properties and validation of self-report depression screening tools among patients with predialysis CKD. This makes it not only difficult to formally screen and diagnose patients in the clinical setting, but also accurately identify subjects with a MDE for enrollment into trials.

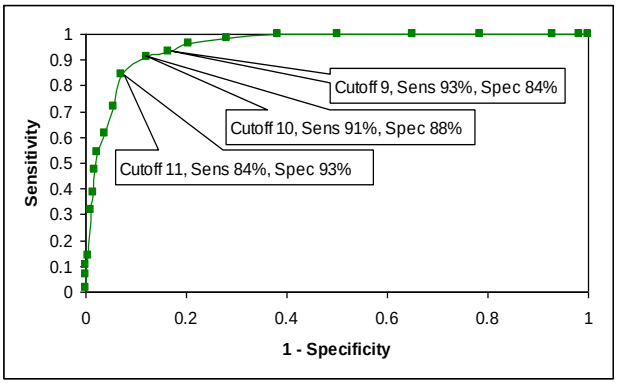


Figure 1 The best QIDS-SR-16 cutoff for major depressive episode is 10 in CKD patients by ROC curve analysis.

Methods: All the 272 CKD subjects completed the Beck Depression Inventory (BDI) and 16-item Quick Inventory of Depressive Symptomatology–Self-report scale (QIDS-SR-16) (115). The MINI was administered to all by trained persons blinded to self-report scores. ROC curves derived optimal cutoffs on BDI and QIDS-SR-16 for ascribing a MDE by MINI.

Results: The cutoff with the best diagnostic accuracy was ≥10 for the QIDS-SR-16 and ≥11 for the BDI. See **Figure 1** for QIDS-SR-16 ROC curve, and **Table 2** for the sensitivities and specificities, positive and negative predictive values and positive and negative likelihood ratios. The agreement between the optimal cutoffs of the BDI and the QIDS-SR-16 and the MINI MDE diagnosis were both moderate, with Kappa coefficients of 0.7, 95% CI (0.6-0.8).

Table 2 Screening Characteristics of Beck Depression Inventory and Quick Inventory of Depressive Symptomatology Scale

Scale Cutoff	Sensitivity	Specificity	PPV	NPV	+ LR	- LR
BDI ≥11	89% (78%-96%)	88% (83%-92%)	67% (55%-77%)	97% (93%-99%)	7.58 (7.35-7.81)	0.12 (0.118-0.125)0
QIDS-SR-16 ≥10	91% (80%-97%)	88% (83%-92%)	67% (55%-77%)	97% (94%-99%)	7.45 (7.23-7.66)	0.10 (0.097-0.103)

Conclusions: Although optimal cutoffs on the BDI and the QIDS-SR-16 have high positive likelihood ratios making them acceptable screening tools, they don't perform well as diagnostic

tools for identifying a MDE given the moderate kappa values. Confirmation of diagnosis by a DSM IV-based interview, i.e. MINI, is needed prior to enrollment into depression treatment trials.

3)Knowledge Gap: Although it is established that depression is associated with poor outcomes in CKD patients on chronic dialysis, there are no published data to demonstrate whether a similar relationship exists in patients with CKD prior to the initiation of chronic dialysis.

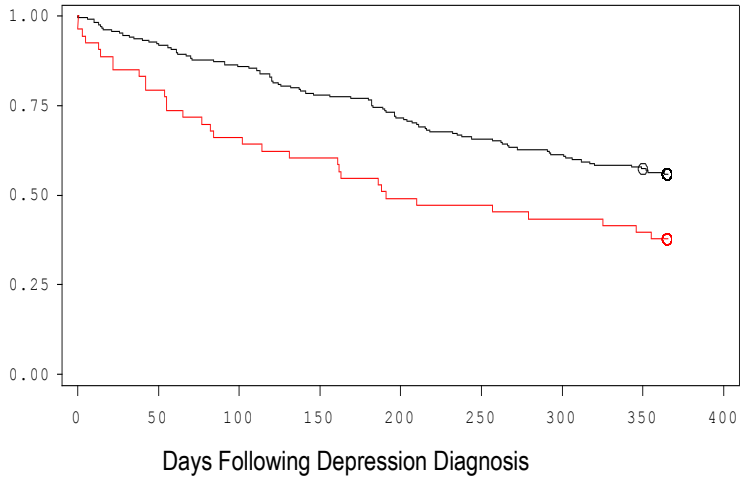


Figure 2 Depressed predialysis CKD patients have worse survival (defined as event-free probability of death, hospitalization or dialysis initiation) than non-depressed CKD patients by Kaplan-Meier survival curve analysis. Red line represents CKD patients with a major depressive episode (MDE) by MINI and black line represents those without a MDE.

Methods: The 272 VA patients with predialysis CKD were prospectively followed for 12 months. Both survival analysis and logistic regression were used to assess the independent association of a MDE with the primary outcome, which was a composite of death, hospitalization or dialysis initiation. Secondary outcomes were each of these outcomes assessed separately.

Results: One-hundred and twenty-seven patients had at least one event (death, hospitalization or dialysis initiation). Percent of composite events was significantly higher among the subjects with a MDE as compared to those without a MDE (63.0% vs. 44.9%, respectively, *P*-value 0.02). Mean survival time based on the composite event was 206.5 days (±19.8 days) for those with a MDE, and 273.3 (±8.5) for those without MDE (Log-rank statistic *P*-value 0.003). **Figure 2** is the Kaplan-Meier survival curve for the primary outcome measure. CKD patients with a MDE had twice the hazard of dying, getting hospitalized or initiating chronic dialysis within a year of depression diagnosis as those without a MDE in both univariate and multivariable Cox Proportional Hazards models (**Table 3**).

Table 3 Depressed CKD patients are twice as likely to die, get hospitalized or start dialysis as those non-depressed.

Variable	Hazard Ratio (95% CI)
Depression Diagnosis	1.85 (1.22, 2.81)
Age, per year increase	0.98 (0.96, 0.99)
White race	1.90 (1.26, 2.89)
CKD Stage 3 vs. 2	3.25 (0.77, 13.73)
CKD Stage 4 vs. 2	3.40 (0.81, 14.35)
CKD Stage 5 vs. 2	8.24 (1.84, 36.84)
Co-morbidity, per number increase	1.22 (1.07, 1.40)
Diabetes mellitus	0.99 (0.66, 1.50)
Albumin, g/dl, per unit decrease	2.04 (1.36, 3.08)
Hemoglobin, g/dl, per unit decrease	1.18 (1.06, 1.33)
Phosphorus, mg/dl, per unit increase	1.08 (0.88, 1.33)

Conclusions: Predialysis CKD patients with a current MDE diagnosed using a gold-standard interview are twice as likely to die, get hospitalized or initiate dialysis as those without a MDE, as well as an increased odd of getting hospitalized approximately by 3-fold and initiating chronic dialysis by 7-fold within 12 months of MDE diagnosis (latter data not shown).

4) Knowledge Gap: Data regarding the efficacy of SSRIs in treating a MDE in CKD is lacking.

Methods: Of our cohort of 57 subjects diagnosed with a current MDE by the gold standard MINI (107-110), 15 participants were prescribed an SSRI at the time of diagnosis. These subjects were those who had an uncomplicated MDE (i.e. no psychosis), did not have suicidal ideation, were not taking any antidepressant medications at enrollment, and agreed to be started on medication for depression. The SSRI used for each subject was chosen as part of their individually-tailored clinical care. Seven subjects were prescribed sertraline 25 mg once daily and were told to increase the dose to 50 mg once daily after 7 days if they were tolerating the medication. Five subjects were prescribed citalopram 20 mg once daily, 2 were prescribed citalopram 10 mg once daily and one subject was started on fluoxetine 20 mg once daily. The QIDS-SR-16 was administered to all subjects at the time of MDE diagnosis and before anti-depressant medication was prescribed and again after 6 months.
Results: The mean QIDS-SR-16 score at baseline was 14.07 (±4.07) and was reduced to 8.47 (±4.47) at 6 mo. The mean difference between baseline and 6-month QIDS-SR-16 score was significant, -5.60 (±4.07), *P*-value 0.0001. None of the subjects reported any adverse events.
Conclusions: Although this pilot is limited by the lack of formal assessment for compliance with SSRIs and by the lack of a placebo control group, the data showed an improvement in depression symptom severity and allows for sample size calculations for our proposed study.

7. <u>Definition of Population to Which the Study is Directed, with Justification</u>: Subjects with moderate to severe CKD Stages 3-5 but not yet initiated on chronic dialysis who meet DSM IV criteria (17, 80) for a Major Depressive Episode (MDE) will be enrolled. We will focus the trial on predialysis CKD and not End-Stage Renal Disease (ESRD) patients already on chronic dialysis because CKD affects a substantially larger proportion of the U.S. population as compared with ESRD, and because it is not known how dialysis initiation may affect the presence of depression. Increased depressive symptoms may occur due to the loss of bodily function, loss of role at work and in family and dependence on the dialysis procedure (28). Although both men and women are affected by CKD and MDE, most patients seen at the Dallas VAMC are men. However, women will not be systematically excluded. The racial and ethnic diversity of patients seen at the Dallas VAMC will ensure inclusion of minorities. Children will not be included. Safety and efficacy of anti-depressants should be established in adults with CKD before testing their use in children with CKD given potential risks.

8. <u>Subject Selection, Inclusion and Exclusion Criteria</u>: Waiver of HIPAA authorization will be used to select potential subjects by pre-screening Dallas VAMC outpatient clinic rosters for eligibility criteria. Those eligible will be contacted by phone or a letter and invited to a screening visit to fill out the QIDS-SR-16 depression self-report scale. If they score ≥11, they will be asked to participate in the study or offered alternative management of depression if they refuse.

Inclusion Criteria:

1) Male or female adults 21 years or older. There will be no upper age limit.
2) Presence of stages 3, 4 or 5 CKD based on the National Kidney Foundation definition as an estimated glomerular filtration rate (GFR) of <60 mL/min/1.73 m^2 for a period of at least 3 months (5). Stage 5 patients are eligible only if not initiated on dialysis or recipient of kidney transplantation. The estimated GFR will be determined using the four-variable Modification of Diet for Renal Disease Study formula (82).
3) Presence of a current MDE based on MINI DSM IV-based criteria (72)
4) Quick Inventory of Depressive Symptomatology–Self-report (QID-SR-16) score of ≥11 at enrollment and ≥11 on QIDS-C-16 (QIDS-Clinician rated) at randomization.

5) Able to understand and sign informed consent after the study has been fully explained

Exclusion Criteria: Patients will be excluded if they have co-morbid medical or psychiatric conditions that would put them at risk with the use of sertraline, or if on concomitant medications with potential drug interactions with sertraline (16, 45).

1) No healthcare power of attorney to sign informed consent
2) Unwilling or unable to participate in the protocol or comply with any of its components
3) Kidney transplant recipient
4) Initiated on maintenance dialysis
5) Significant hepatic dysfunction or liver enzyme abnormalities ≥ 3 times the upper limits of normal
6) Terminal chronic obstructive pulmonary disease or cancer
7) Recent history of active bleeding, such as gastrointestinal bleeding requiring hospitalization 3 months prior
8) Current use of class I anti-arrhythmic medications (such as 1C propafenone and flecainide) (45)
9) Use of pimozide, MAO inhibitors, reserpine, guanethidine, cimetidine or methyldopa; tri-cyclic anti-depressants, neuroleptics or anti-convulsants (excluding gabapentin, as it has no significant drug interactions with sertraline and is commonly used in diabetic CKD patients with diabetic neuropathy) (45).
10) Use of other serotonergic drugs or supplements such as triptans, tramadol, linezolid, tryptophan, and St. John's Wort.
11) Ongoing use of anti-depressants
12) Past treatment failure on Sertraline
13) Initiation of psychotherapy for depression in the 3 months prior to study entry
14) Alcohol or substance abuse or dependence that requires acute detoxification at study entry
15) Present or past psychosis or Bipolar I or II disorder
16) Dementia or a Mini-Mental State Examination score of <23
17) Suicidal intent
18) Pregnancy, lactation and women of childbearing potential not using adequate contraception

9. <u>Number of subjects in the Study</u>: Two hundred subjects will be enrolled. Since there are no prior studies on which to base an estimate of effect size, the sample size was selected to detect the smallest clinically meaningful effect size (88). Based on the primary hypothesis, we chose the relevant effect size to be the standardized difference between groups in change from baseline to exit in the QIDS-C-16 and the power to be based on a t-test comparison of this difference. Our preliminary data shows that 15 subjects with CKD and MDE started on a SSRI experienced a mean drop in QIDS-SR-16 of 5.6 with a standard deviation (SD) of 4.1. A difference of 2 points with a SD of 4 points gives an effect size of 0.5, which Cohen classifies as moderate (89). Given this effect size, a t-test will have 80% power to detect a 0.5 effect size with a sample of 128 subjects or 64 per sertraline and placebo groups (Table 1). If the SD should turn out to be larger, for example 5, the effect size would be 0.4 and a sample of 200 or 100 per group would be needed (Table 2). To be conservative, we request 200 subjects.

Table 1: Sample Size to Detect Various Effect Sizes (QIDS-C)

Mean difference between groups	SD of Difference	Effect size	80% Power	90% Power
1.0	4.0	0.25	506	676
2.0	**4.0**	**0.50**	**128**	172
3.0	4.0	0.75	58	78

4.0	4.0	1.00	34	46
5.0	4.0	1.25	24	30

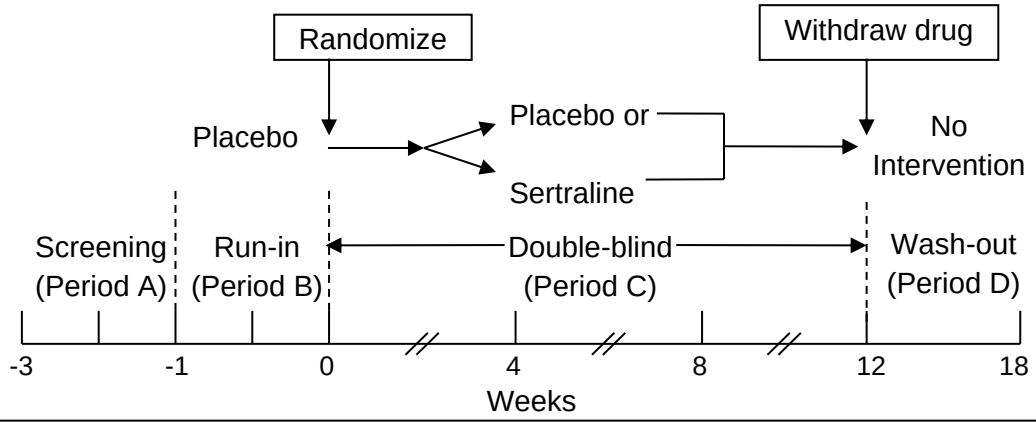
Table 2: Sample Size to Detect Various Effect Sizes (QIDS-C)

Mean difference between groups	SD of Difference	Effect size	80% Power	90% Power
1.0	5.0	0.20	788	1054
2.0	**5.0**	**0.40**	**200**	266
3.0	5.0	0.60	90	120
4.0	5.0	0.80	52	68
5.0	5.0	1.00	34	46

10. Justification for the Use of Vulnerable Populations: N/A

11. Study Design: This is a randomized, double-blinded, placebo-controlled flexible-dose 12-week trial of treatment of MDE with sertraline involving 200 subjects with predialysis stages 3-5 CKD (Figure 1). After signing informed consent, eligibility will be assessed by a structured psychiatric interview using the Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV)-based Mini International Neuropsychiatric Interview (MINI) to determine if a current MDE is present (72, 80). This interview will be administered by a trained person blinded to subject medical history. The subject must also score ≥11 on the 16-item Quick Inventory of Depressive Symptomatology–Self-report (QID-SR-16) scale (76, 77) to be eligible. If eligible, the subject will be invited to enter a single-blinded one-week placebo run-in period (Period B) to monitor compliance prior to randomization. Those who are non-compliant, defined as the ingestion of <65% or >120% of study drug, will be excluded. The subject will then enter the double-blind phase (Period C) and be randomly assigned to receive either sertraline at an initial dose of 50 mg once daily or matching placebo in a 1:1 ratio, stratified by CKD stage. Subjects will be outpatients every 2 weeks for 6 weeks for titration of study drug and monitoring of side effects. The dosage of study drug will be increased at 2-week intervals based on tolerability and response, and can be decreased if intolerable side effects occur. For those specific subjects that do not tolerate the 50 mg/day dose, the dose will be decreased to 25 mg/day, but then uptitration of dose will occur per protocol every 2 weeks (50 mg to 100 mg, etc). The subject will be maintained on a constant dose of drug after the 6 week visit and reassessed for depressive symptoms during visits at weeks 9 and 12. At 12 weeks, tapering of study drug at the rate of 50 mg per week will commence until drug is discontinued, which will take a maximum of 4 weeks (Period D). The subject will return for a final visit 2 weeks after discontinuation of study drug and be reassessed to see if further clinical follow-up is required for depression. See **Figure 1** for design diagram.

Figure 1 Randomized Double-Blind, Placebo-Controlled Trial of Sertraline Treatment of Depression in Chronic Kidney Disease



12. <u>Detailed Description of Study Procedures by Study Period</u>:

a. Period A - Screening Visit (2 hours): Clinic rosters will be reviewed prior to the clinic date to identify patients for screening. Waiver of HIPAA authorization will be used to select potential subjects by pre-screening Dallas VA outpatient clinic rosters and reviewing CPRS medical records for eligibility criteria, which includes Chronic Kidney Disease with eGFR of <60 but not on chronic dialysis. Those eligible will be asked in person to fill out the QIDS-SR-16 depression self-report scale while they are waiting to be seen in clinic. If they score ≥11 they will be invited to a screening visit to determine eligibility and sign informed consent. If they don't agree to participate, they will be offered alternative options for formal evaluation and treatment of depression. After signing consent, subjects will be administered the Mini-Mental Status Examination and the Mini International Neuropsychiatric Interview (MINI) (72) to identify if a current MDE exists and to exclude past or current psychotic disorder, alcohol or substance abuse, or suicidal ideation. The MINI will be administered by a trained person blinded to subject medical history. Those who score ≥23 on the Mini-Mental and meet MINI criteria for a MDE will participate in the trial and will proceed to the run-in phase. A brief medical history and a physical examination will be performed during the screening visit.
<u>Time Window:</u> A maximum of two weeks will be allowed for the time interval between screening, determining eligibility and entering the run-in period.

b. Period B - Single-Blinded One-Week Placebo Run-In Period:
1) <u>Rationale for run-in phase</u>: A run-in phase, similarly utilized in the SADHART trial (16) is designed for 2 reasons: a) to monitor compliance with study drug and to exclude non-compliant subjects prior to randomization, given that depression has been associated with non-compliance (30-32); b) to ensure that subjects still meet eligibility criteria by QIDS-C-16 score ≥11.
2) <u>Run-in Visit (1 visit, 2 hours)</u>: During the screening visit described above, subjects will be given placebo tablets to take once daily starting the same day as the visit. Subjects will be blinded to study drug and instructed to take the drug once daily in the evening prior to bedtime between the hours of 8-10 pm. The protocol will allow change to morning dosing in cases that

the subject has trouble sleeping. Subjects will return in one week for a second visit (Run-in Visit) at which time they will be administered the 16-item Quick Inventory of Depressive Symptomatology-Clinician Rated (QIDS-C-16) scale (76, 77) QIDS-C-16 to ensure that they meet eligibility criteria defined as a score of ≥11. Compliance to study drug will be ascertained by pill count. Those who are non-compliant, defined as the ingestion of <65% or >120% of study drug, will be excluded. The QIDS-C-16 will be administered by a trained person during this visit. This scale, which assesses the DSM IV-based 9 criterion symptom domains of major depression, will be used to measure the primary outcome. The score on this scale ascertained at the end of the run-in period prior to randomization will serve as the baseline score for comparison of outcome. Blood will be obtained for a complete metabolic panel, parathyroid hormone, complete blood count, prothrombin time, and partial thromboplastin time. Spot urine will be collected for urinalysis and urine protein-to-creatinine ratio, and 24h urine collected for creatinine, protein and urea nitrogen. A blood pregnancy test will be performed in women of childbearing age.

3) Time Window: A maximum of 6 to 12 days will be allowed between starting the run-in period and entering the double-blind phase.

c. Period C - Double-Blind Phase:

1) Randomization and blinding: After the placebo run-in period (and during the Run-In Visit described above) those who qualify will be randomized in a double-blind fashion to receive sertraline or matching placebo in a 1:1 ratio, stratified according to CKD stage (Stage 3, Stage 4, or pre-dialysis Stage 5). To minimize imbalance in treatment allocation and to maximize power for analyses, blocked randomization, using a computerized random number generator, will be used to create a randomization code list for each stage strata. Block size will be determined by the study statistician and will be revealed to the research pharmacist but will not be revealed to participating investigators or research assistants. The statistician will work closely with the research pharmacist who will be responsible for preparing, storing and dispensing study drug to the research assistants. The research assistant will communicate directly with the pharmacist at the time the subjects present for randomization to receive the appropriate randomization code. The assignment sheet will be kept in the office of the research pharmacist until unblinding takes place at the completion of the study.

2) Key Intervention: Subjects will receive 50 mg/d of sertraline or matching placebo for the first 2 weeks of intervention. They will be instructed to take the study medication once a day in the evening prior to bedtime between the hours of 8-10 pm, given that somnolence may occur with sertraline once the dose is escalated. The protocol will allow change to morning dosing in cases that the subject has trouble sleeping (45). Protocol intervention will be based on “measurement-based care” and involve the measurement of depressive symptoms and side effects at each visit (16, 73, 83). Based on clinical response and tolerability, the dosage will be increased to 2 tablets (100 mg/d of sertraline or matching placebo) at week 2, to 3 tablets (150 mg/d or matching placebo) at week 4, and to a maximum dosage of 4 tablets (200 mg/d or placebo) at week 6. If intolerable side effects occur, the dosage will not be increased and will be decreased by 50 mg (1 tablet) at a time. For those specific subjects that do not tolerate the 50 mg/day dose, the dose will be decreased to 25 mg/day, but then uptitration of dose will occur per protocol every 2 weeks (50 mg to 100 mg, etc). Rationale for active drug and dosing: Sertraline

was chosen because it is metabolized extensively by the liver, and its active metabolite, *N*-desmethylsertraline is further metabolized to an inactive form before being renally excreted (45). In addition, the safety and efficacy of sertraline was established among patients with coronary artery disease in the SADHART trial (16). Citalopram, another commonly used SSRI that is formulary at the VA, was rejected because it is not recommended for use in patients with eGFR<20 mL/min (45). Tricyclic anti-depressants were rejected given the risk of QTc prolongation and cardiac arrhythmias (45), which would be particularly dangerous in CKD with a high burden of comorbid CV disease. Initiation of dosing for sertraline is recommended at 50 mg/d as a single dose that may be increased at intervals of at least 1 week to a maximum dosage of 200 mg/d (45).

3) Outpatient Follow-Up Visits (5 visits, 1-2 hours each): Outpatient follow-up visits will be conducted at weeks 2, 4, 6, 9 and 12. Subjects will be asked about their general well-being and a brief physical exam including vital signs will be performed. Pill counts will be performed during each visit to assess adherence to study medication. During the visits at weeks 2, 4 and 6, subjects will be clinically evaluated for dosage escalation of drug using "measurement-based care" based on clinical response and side effect tolerability (83). This technique has been used in both the STAR*D and SADHART trials (16, 73). The QIDS-SR-16 will be administered as the measure for clinical response. Side effect tolerability will be assessed by the self-report Systemic Assessment for Treatment Emergent Effects (SAFTEE) scale (which measures side effect type and severity) (85), and the Frequency, Intensity and Burden of Side Effects Rating (FIBSER) scale (which measures side effect frequency) (86). The QIDS-C-16 will be used as a repeated measure of outcomes and administered by an independent outcomes assessor, Susamei Khamphong, blinded to subjects' responses on the QIDS-SR-16, the SAFTEE, the FIBSER and dose escalation regimen, during visits at weeks 2, 4, 6, 9 and 12. This will be done before the subject is clinically evaluated for dose escalation to ensure blinding for outcomes. Questionnaires for visits can be administered over the phone if on occasion a subject is unable to travel to the study site for a specific visit.

4) Time Window: The total duration of the double-blind phase (Period C) will be 12 weeks.

d. Period D – Wash-out Phase: Withdrawal of Blinded Drug Intervention: At the 12-week visit, tapering of study drug at the rate of 50 mg/week will commence until drug is discontinued. This will take a maximum of 4 weeks since the maximum dose of sertraline will be 200 mg.

1) Rationale for withdrawal of study drug: We considered continuation of sertraline at the end of the double-blind period if the subject was randomized to sertraline (vs. placebo) and was responding to treatment. However, this would not be easily accomplished as unblinding would have to occur for each subject at the end of 12 weeks to find out if the subject was receiving sertraline or placebo, and we intend to keep the trial double-blinded until all subjects complete the study and results are statistically analyzed. Slow tapering of study drug during the withdrawal phase will take place to avoid the occurrence of withdrawal syndrome reported with the abrupt discontinuation of sertraline, which can manifest as dysphoric mood, irritability, agitation, dizziness, sensory disturbances, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures (45, 87).

2) Close-Out Visit (1 hour): A close-out visit will be scheduled 2 weeks after study drug has been discontinued. During this visit, the following procedures will be performed: 1) collection of

any remaining unused study drug; 2) discussion of plans for reporting results of the study to the subject; 3) referral of the subject to their personal physician or Mental Health as appropriate for follow-up if it is determined that there is a need for further depression treatment.

3) Time Window: The maximum duration of the wash-out phase (Period D) will be 6 weeks.

e. DNA Study Procedures: An optional portion of the study will investigate DNA, mRNA, and plasma biomarkers as potential moderators and mediators that are predictive of sertraline (as compared with placebo) treatment response in patients with Major Depressive Episode and CKD. This aim has the potential to produce a clinically useful algorithm to guide treatment, particularly since a large proportion of patients may discontinue SSRI treatment prematurely due to side effect, such as nausea, that is already prevalent among late-stage CKD patients.

Blood samples will be collected at baseline, week 2, and week 12 for future DNA, mRNA and proteomics testing. At each of these time-points, two lavender top EDTA tubes (8 mL each) will be collected, one for direct DNA isolation, and the other for plasma isolation for proteomics. One 2.5-mL PaxGene tube will also be collected at each time-point for direct mRNA isolation. Samples will be de-identified and stored at -80 degrees C for future testing. For plasma collection, blood tubes will be stored at 4 C (after inversion) until centrifugation, which should occur within four hours of blood collection. After centrifugation for 15 minutes at 1200 g at room temperature, the plasma layer will be carefully collected from the top of the tube with a pipette without disturbing the buffy coat. Plasma will be transferred to aliquot vials and capped, and stored upright at -80 degrees. The other two blood tubes, one EDTA and one PaxGene tube, will be also stored at -80 degrees C, until these samples are ready to be processed for DNA and mRNA analyses, respectively.

Genetic testing in Off-Site Location: The samples will be marked with a study unique identifier (NOT name, date of birth or SSN) and stored at University of Texas Southwestern for up to 2 years until the samples are analyzed in batches. The remaining samples will be destroyed after the genetic tests are ran. The investigators may use health information for future genetic research, however any future research project will be receiving appropriate R&D committee approvals, before implementing.

Clinical Measurements:

a. Demographic and Clinical Measurements: Demographic and clinical variables will be collected from the subject and CPRS at screening. A brief physical examination will be performed during each visit where height, weight, waist and hip circumferences and blood pressure (BP) are measured. Two BP, 5 minutes apart, will be taken in the seated position after 5 minutes of rest. Blood will be obtained at screening and 12 weeks by peripheral venipuncture for a complete metabolic panel, parathyroid hormone, complete blood count, prothrombin and partial thromboplastin times. Spot urine will be collected for urinalysis and urine protein-to-creatinine ratio, and 24h urine collected for creatinine, protein and urea nitrogen. A blood pregnancy test will be performed in women of childbearing age.

b. Depression Measures:

Mini International Neuropsychiatric Interview (MINI): The MINI will be administered at the ***screening visit*** and used as the gold standard to determine the presence of a current MDE to determine eligibility, as well as the presence of any psychiatric exclusion criteria. It is a

frequently used semi-structured clinical interview for establishing psychiatric diagnoses based on DSM IV criteria, and has established reliability and validity (72). The feasibility of the use of MINI to identify a MDE was established by the PI in 272 CKD patients enrolled from the VA CKD clinic (*see Work Accomplished*). The MINI will be administered by Susamei Khamphong who was trained and certified in the laboratory of Dr. Trivedi, the senior psychiatry collaborator. Ms. Khamphong has extensive experience with this technique, as well as experience working with CKD patients, having served as the Research Assistant for Dr. Hedayati's pilot study. She will be blinded to patient medical history and scores on self-report questionnaires. Dr. Trivedi has extensive experience and expertise in interpreting the MINI in research conducted in major depression of chronic disease, as well as training personnel in administering this tool to research subjects. He headed the National Coordinating Center for the NIMH multi-site Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial (73), which is the largest clinical trial ever conducted on treatment of depression. The MINI will take 30 to 45 minutes to administer.

Quick Inventory of Depressive Symptomatology-Clinician Rated (QIDS-C-16) Scale: The primary outcome will be assessed using the 16-item QIDS-C-16, which assesses the DSM IV-based 9 criterion symptom domains of major depression (76, 77). This scale was used as an outcome measures in the STAR*D trial (73), and has been validated in outpatients against the Hamilton Rating Scale for Depression (HRSD) (76). It has also been shown to be sensitive to detecting change in the severity of depressive symptoms (77). Scores range from 0 to 27, with higher scores indicating a greater severity of depressive symptoms. This scale will also be administered by Susamei Khamphong who will be blinded to subject treatment assignments and serve as the independent outcomes assessor. It will be administered before randomization (at ***baseline***) and at ***weeks 2, 4, 6, 9, and 12***. This scale will take 5 to 15 minutes to administer.

Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR-16) Scale: A patient self-administered version of the QIDS-C-16, this scale is easy and fast to administer and will be used at 3 points in the study: a) at ***screening*** to identify potential subjects for recruitment; b) at the at ***baseline*** *(end of the run-in period and before randomization)* to determine if subjects are still eligible; c) at ***weeks 2, 4, and 6***to determine clinical response for study drug dose escalation. The QIDS-SR-16was validated against the gold-standard MINI by the PI in her pilot study of predialysis CKD subjects (*see Work Accomplished*). This scale will also take 5 to 15 minutes to complete and will be administered by the research coordinators.

c. Safety and Tolerability Measures:

Systemic Assessment for Treatment Emergent Effects (SAFTEE) scale: A self-administered questionnaire, it lists 55 different types of side effects, the severity of which can be rated by the subject as none, mild, moderate or severe (85). The SAFTEE was used to assess the types and severity of side effects in the STAR*D trial (73). This scale also allows the subjects to rate the burden of side effects as none, mildly, moderately, or markedly in answer to the last item of the questionnaire "how much have all these side effects bothered you/interfered with your daily activities." It will take 5 to 10 minutes to administer and will be given at ***weeks 2, 4, 6, 9, and 12.***

Frequency, Intensity and Burden of Side Effects Rating (FIBSER) scale: A self-administered questionnaire to assess the frequency of side effects on a Likert scale as being present 10%, 25% 50% 75%, 90% or all the time (86). It also assesses the intensity of medication side effects

and the degree to which these side effects have interfered with day to day functions. This questionnaire was also used in the STAR*D trial (73) to assess the frequency, intensity and burden of side effects. It takes 2 to 5 minutes and will be given at ***weeks 2, 4, 6, 9, and 12.***

Serious adverse events: Serious adverse events (SAE) will be collected at ***weeks 2, 4, 6, 9,12 and 16*** and considered the primary outcome for safety. Data on hospitalizations (including date, reason for hospitalization, and length of stay), initiation of renal replacement therapy (including date and modality – hemodialysis, peritoneal dialysis or kidney transplantation) and death will be collected at each visit and confirmed with the subject. These 3 outcomes will also be collected at ***6 and 12 months*** after randomization for power calculations to determine the feasibility of conducting a future large-scale trial designed to investigate whether the treatment of depression improves outcomes in CKD. If the subject is hospitalized at the Dallas VAMC, data will be extracted from CPRS. If the subject is hospitalized elsewhere, a copy of the discharge summary will be requested from the institution where the hospitalization occurred after obtaining a signed release of information from the study subject. Date and cause of death will be confirmed by obtaining a copy of the death certificate.

Platelet aggregation measure: Whole blood will be collected ***at baseline*** (end of run-in and before randomization) and at ***week 12 or exit*** for whole blood aggregation test by ex vivo whole blood impedance platelet aggregometry via a Chrono-log aggregometer, platelet factor 4 and beta-thromboglobulin. This instrument uses electrical impedance in whole blood with simultaneously measuring ATP release by the luminescence method (159). The panel will include thrombin, collagen, ADP, arachidonic acid, and ristocetin. Blood will be tested at Parkland Hospital/University of Texas Southwestern Medical Center, the reference laboratory for this send-out lab at the Dallas VAMC. Use of any anti-platelet agents will be tracked at every visit on all participants, to be included in the analyses of safety as relates to platelet aggregation and bleeding.

Sertraline and *N*-desmethysertraline levels: Plasma sertraline and *N*-desmethysertraline levels will be quantified at week 12 or exit by using high-performance liquid chromatography with fluorescence detection in the reference Mayo Medical Laboratories, Rochester, MN.

d. Overall Function and Quality of Life Measures (obtained at ***baseline, weeks 6 and 12***)**:**

Work and Social Adjustment Scale (WSAS): Overall function will be assessed by the WSAS, a 5-item self-report scale, assessing the subject's view of ability to work, to manage affairs at home and socially, and to form and maintain close relationships (149-150). Each question is rated on a 0 to 8 Likert scale (0 indicating no impairment; 8 indicating severe impairment) with the score ranging from 0-40. A WSAS score above 20 suggests at least moderately severe functional impairment. The WSAS take about 5 to 10 minutes to administer.

Kidney Disease QOL Survey (KDQOL-SF 1.3): This measure was developed by the Kidney Disease QOL Working Group as a kidney disease-specific measure of health-related QOL. It contains 80 items with 8 generic subscales derived from the Medical Outcomes Study SF-36 as well as 12 kidney disease-specific subscales. It takes 15 minutes to administer.

e. Nutritional Status Measures: Nutritional measures will be obtained at ***baseline and week 12 or study exit***. Percent of standard body weight (%SBW) will be calculated as the weight expressed as a percentage of normal body weight for healthy Americans of similar sex, height, age range and skeletal frame size using National Health and Nutrition Evaluation Survey II data

as the reference source (89, 98). Serum prealbumin, albumin and 24h urine for protein and urea nitrogen will be tested in the Dallas VAMC laboratory. Normalized protein nitrogen appearance (nPNA) will be calculated from the 24h urine values using the formula recommended by the National Kidney Foundation guidelines.

f. Medication self-reported adherence: The Morisky Self-Reported Medication-Taking Scale (176) will be used as the measure of medication adherence and will be administered at ***weeks 2, 4, 6, 9 and 12***. It uses a Likert scale ranging from "strongly agree" to "strongly disagree" for 5 items regarding medication-taking behavior and takes 1 to 5 minutes to complete.

g. Cognitive Function Measure: Alternate forms will be used on all tasks when available to control for practice effects. The selected tasks are widely accepted and validated neuropsychological tests and will be administered at ***baseline and week 12 or exit***.

Continuous Performance Test (CPT) (Beck et al 1956): The CPT is a measure of sustained attention during which participants must focus on a continual presentation of stimuli and respond to a target stimulus. Scoring is most frequently based on response time, omission errors (nonresponse to target stimulus), and commission errors (false response to target stimulus) that are then reduced to a single composite discrimination score d'. We are using the CPT-IP version that is available in the MCCB.

Trail Making Test (parts A [TMT-A] and B [TMT-B]) (Reitan 1955; Reitan 1992):The Trail Making Test consists of two parts: part A, which measures psychomotor speed and attention, and part B, which measures both speed and sequencing. The tests involve visual scanning skills and set-shifting ability and assess cognitive flexibility. In the task, participants are presented with numbered circles and asked to connect the numbers (part A). In part B, lettered circles are presented along with the numbers and the subject must connect a series of alternating numbers and letters. Scoring is based on timed correct performance.

Stroop Color and Word Test (Golden 1978; Stroop 1935): The Stroop Color and Word Test is a measure of attention response inhibition. The test consists of three subscales: 1) word – color nouns (e.g., red, blue) printed in black ink are presented and participants must read the word; 2) color – the letter "x" is presented in colored ink and participants are asked to name the color; and 3) color-word – color nouns are presented in discrepantly colored ink and participants are asked to name the color. An Interference score is also calculated to represent a composite of the subscales.

Controlled Oral Word Association Test (COWAT) (Benton et al 1983): The COWAT is a test of verbal fluency that requires participants to generate as many words as possible in three 60 second time periods. Participants are instructed to generate words in a given trial that begin with a particular letter (F, A, S; P, R, W; or C, F, or L) and proper nouns or words with multiple endings are not allowed. Performance is measured by summing the number of acceptable words across all three trials, as well as by the number of errors made.

Rey Auditory Verbal Learning Test (RAVLT) (Lezak 1983; Schmidt 1996.): The RAVLT measures short-term verbal learning and memory, as well as recognition and post-interference recall. The test consists of an auditory presentation of a list of 15 nouns that are read five times, with free recall assessed after each presentation. An interference list is then read to participants followed by recall of the novel list, and another recall evaluation of the original list (i.e., post-

interference recall). Participants are then presented a story containing all of the words from the original list and are asked to identify those words from the story.

h. Markers of Inflammation: C-reactive protein measurements will be performed using a commercially available high-sensitivity assay (Roche diagnostics, Indianapolis, Indiana) (163). Interleukin 6 (IL-6) will be measured by Chemiluminescent Immunoassay as a send-out lab from the Dallas VAMC Specialty Laboratories, Inc., Santa Monica, CA. These labs will be performed at ***baseline and week 12 or exit***.

13. <u>Anticipated Data and Data Analysis</u>: All models will be checked for the validity of the assumption of normality, and non-normal data will be subjected to appropriate transformation or nonparametric methods will be used. All analyses will include the baseline value of the outcome as a covariate. In addition, baseline demographic and clinical characteristics (e.g., age, gender, length of current MDE, age on onset, etc.) will be considered for inclusion as covariates if they improve the fit of the model. The need for higher order time terms or the transformation log (time+1) to obtain a better fitting model will be considered for the repeated measures analyses. The need for interaction terms will also be considered. All analyses will use all available data from all randomized subjects and utilize "intention-to-treat" analyses. That is, subjects will be analyzed in the treatment group they were randomly assigned to, and analyses will include data on all subjects regardless of adherence to protocol, actual treatment received, or subsequent departure from assessments, treatments or protocol deviation. If the subject withdraws consent, then data collection will stop on that particular subject and their data will be included only up to the point before withdrawal of consent. Sensitivity analyses will also be performed, referred to as "modified intention-to-treat," including all data collected while the subject was receiving study medication, but excluding the data collected after the subject stops taking study drug (i.e., due to intolerable side effects).

All tests will be two-sided with alpha of 0.05 used for significance. A one-sided test was considered as an alternative but rejected because it is possible that we will obtain the result that sertraline is worse than placebo. In that case, a two-sided test will allow for the conclusion that sertraline is significantly worse than placebo but a one-sided test will only allow for the conclusion that sertraline is not significantly better than placebo. We believe that if sertraline were worse than placebo it would be important to be able to make the statement that it was significantly worse.

<u>Aim 1</u>: Determine if treatment with sertraline, as compared with placebo, results in an improvement in depression severity.

<u>Aim 1 Primary Outcome</u>: *The primary outcome is the change from baseline in the QIDS-C-16 score in the sertraline- as compared with the placebo-treated group.* QIDS-C-16 scores will be compared between treatment groups using a random regression model (also known as a mixed effects model) (SAS Proc Mixed) with a random intercept term and time (visit week 2, 4, 6, 9 and 12) as the within-subjects factor and treatment group (sertraline vs. placebo) as the between-subjects factor. The model will contain terms for treatment group, visit week, and treatment group by visit week interaction. The hypothesis will be tested by the significance of the treatment group by time interaction effect or the treatment group main effect. The baseline QIDS-C-16 score will be a covariate in the model. Although every effort will be made to prevent dropouts, this analysis will allow for the inclusion of missing data. A comprehensive sensitivity

analyses will be performed to investigate the consequences of incomplete observations in the analysis of repeated measurement data. Sensitivity analyses will be done using local influence, pattern mixture models, and multiple imputations (90).

Aim 1 Secondary Outcomes: *Secondary outcomes include response to treatment (decline of ≥50% in the baseline QIDS-C-16 score) and remission of depression (QIDS-C-16 score of ≤5).* Each subject will be classified as a responder or non-responder and remitter or non-remitter at each visit using these criteria. A generalized linear mixed model (GLMM) as implemented in the SAS Proc Glimmix program will be employed for the response outcome and the remission outcome. This model adapts the usual continuous-outcome, random regression model for use with a binary outcome. The model will contain terms for treatment group (sertraline vs. placebo) as the between-subjects factor, a random intercept, time (visit week 2, 4, 6, 9 and 12), and treatment group by time interaction as the within subjects factor, and baseline QIDS-C-16 as a covariate. The hypothesis will be tested by the significance of the treatment group by time interaction or the treatment group main effect.

Anticipated Findings: It is anticipated that treatment with sertraline will result in more improvement in depressive symptoms and higher response and remission rates than placebo in Stages 3-5 CKD patients with MDE. Establishing the efficacy of SSRI sertraline for treatment of MDE in patients with CKD will be ground-work for a future larger randomized multi-center trial to investigate whether treatment of depression will improve CKD morbidity and mortality.

Aim 2: Determine if sertraline treatment vs. placebo improves overall function and QOL. Aim 2 outcomes include overall function as assessed by a change in score on the WSAS and QOL as assessed by a change in score on the KDQOL-SF. These are also secondary outcomes. Each of these outcomes will be compared between groups using the random regression analysis as described for Aim 1.

Anticipated Findings: We anticipate that treatment of MDE with sertraline will result in more improvement in QOL than placebo in CKD subjects. Given that poor QOL is associated with mortality in CKD, future large trials can investigate whether this improvement in QOL will translate into better survival for these patients.

Aim 3: Determine if treatment with sertraline, as compared with placebo, is safe and tolerable. This will be assessed by: a. proportion in each group with serious adverse events; b. type, severity and frequency of side effects; c. reduction in platelet aggregation in sertraline vs. placebo group, and whether this reduction correlates with higher plasma sertraline levels. This will be an exploratory outcome.

Aim 3a: The proportion of subjects experiencing a SAE will be the primary safety outcome measure and compared between groups using logistic regression with presence/absence of an SAE as the dependent variable and treatment group along with any other necessary covariates (such as age, eGFR, comorbidities, and depression severity) as the independent variables.

Aim 3b: The outcome measure for *type and severity* of side effects will be assessed by the SAFTEE scale. The proportion of subjects with each type of side effect reported on the SAFTEE

will be compared between treatment groups using the Chi-square test. The maximum SAFTEE global assessment of side effects (first item, 0-4 scale) will be analyzed using an ordinal logistic regression model with maximum SAFTEE global assessment as the dependent variable and treatment group along with any other necessary covariates are the independent variables.

The outcome measure for *frequency of side effects* will be the proportion in each group with side effects reported on the FIBSER scale. For the first item of the FIBSER, a binary outcome will be created with 0 indicating no side effects and 1 indicating side effects present at least some of the time. The binary outcome (side effect presence/absence) will be defined for each subject for each visit and analyzed using a GLMM as described for Aim 1, secondary outcomes. Two additional analyses will be done on the intensity and burden of side effects (items 2 and 3 of the FIBSER, respectively) using only those subjects who experience side effects at some point during the study. The 0 to 6 point scores on items 2 and 3 will be analyzed as continuous outcomes using random regression models as described for Aim 1.

Aim 3c: Paired t-test will be used to test whether platelet aggregability at week 12 or at exit is reduced from baseline. Student's t-test will be used to test whether the change in platelet aggregability from baseline is different in the sertraline-treated as compared with the placebo-treated group. The association of platelet aggregability and sertraline/*N*-desmethylsertraline levels with bleeding episodes requiring blood transfusion or hospitalization will be assessed using both univariate and multivariate logistic regression in separate models, with the presence of such bleeding episodes as the dependent variable and platelet aggregation or sertraline/*N*-desmethysertraline levels as the main independent variables. Independent covariates included in the multivariable logistic model will consist of hemoglobin, platelet count, eGFR, and concomitant therapy with an anti-platelet agent. Linear regression will be used to identify if there is a negative correlation between aggregability and plasma sertraline and *N*-desmethysertraline.

Anticipated Findings: We anticipate that subjects receiving sertraline will have higher rates of minor side effects on SAFTEE and FIBSER but not have higher rates of SAEs than those receiving placebo. We also anticipate that there will be a greater reduction in platelet aggregation in the sertraline-treated as compared with the placebo-treated group, but this reduction will not be associated with increased adverse events such as bleeding episodes requiring blood transfusion or hospitalization. We also anticipate that sertraline and *N*-desmethysertraline levels will inversely correlate with platelet aggregability.

Aim 4: Investigate mechanisms by which sertraline may affect outcomes. We will determine if sertraline treatment vs. placebo will improve: a. nutritional status; b. adherence to prescribed medications; c. cognitive functioning; and d. markers of inflammation. These will be exploratory outcomes.

Aim 4a: The percent of standard body weight (%SBW) will be calculated as the weight expressed as a percentage of normal body weight for healthy Americans of similar sex, height, age range and skeletal frame size using National Health and Nutrition Evaluation Survey II data as the reference source (89, 98). Paired t-test will be used for normally distributed variables and Wilcoxon signed rank sum for variables non-normally distributed to test whether %SBW, nPNA, prealbumin and albumin at week 12 or exit are reduced in subjects from baseline. Student's t-

test or Wilcoxon rank sum will be used to test whether the changes from baseline are different in the sertraline vs. placebo groups. Linear regression models (or non-parametric regression if the variable not normally distributed) will be constructed with %SBW, nPNA, prealbumin or albumin as the dependent variables and treatment group as the main independent variable. Independent covariates will include age, eGFR, presence of edema, and albuminuria.

Aim 4b: The Morisky Self-Reported Medication-Taking Scale (176) will be used as the measure of medication adherence. The Likert point scores on items 1 thru 5 will be analyzed as continuous outcomes using random regression models as described for Aim 1.

Aim 4c:

1) Participants treated with sertraline will have significantly greater improvements in cognitive functioning versus those receiving placebo. The *primary outcome* measure will be the composite score derived from the Trail Making Test parts A and B, Continuous Performance Test, Stroop, Controlled Oral Word Association Test, and Rey Auditory Verbal Learning Test. The composite measure at week 12 will each be compared between groups using analysis of covariance (ANCOVA) with the baseline value of the composite as a covariate in the model. If a participant is missing more than two cognitive tests, their data will not be used. If one cognitive test is missing at a visit then the missing test will be imputed using multiple imputation techniques. Please note that missing data (particularly in the form of missing one of the tests in the battery) are highly unlikely, and every effort will be made to perform all tests at all visits.

2) Participants treated with sertraline will have significantly greater improvements in each cognitive functioning domain (attention, executive function, and verbal learning and memory) versus those receiving placebo. The cognitive tests that measure attention (Trails A and Continuous Performance Test) will be analyzed together using multivariate analysis of covariance (MANCOVA) at week 12. The treatment group main effect will be tested and baseline values will be included as covariates. The tests that measure executive function (Trails B, Stroop, and COWAT) will be similarly analyzed by MANCOVA. The between groups comparison of the Rey Auditory Verbal Learning Test at 12 will be made using ANCOVA with the baseline value as a covariate.

The family-wise correction will be used to address concerns of multiple comparisons since 3 tests are to be conducted (Ilsley et al 1995). If a subject is missing an entire cognitive domain battery at a visit (e.g., the attention battery at week 12) then the subject cannot be used in the analysis of that cognitive battery, but if the subject has data for other cognitive batteries at that visit (e.g., executive function at week 12), then those data would be used. If a subject is missing one component of a cognitive battery (for example, the subject has Trails A data but is missing the Continuous Performance Test at week 12), then the missing test will be imputed using multiple imputation techniques and the cognitive battery used in the analysis.

Aim 4d: *Sertraline treatment vs. placebo will decrease levels of markers of inflammation, C-reactive protein (CRP) and IL-6, from baseline.* Wilcoxon signed rank sum for paired groups and nonparametric regression will be used for comparisons, given that CRP and IL-6 are not normally distributed.

Anticipated Findings: We anticipate that subjects treated with sertraline will have more improvement from baseline in measures of nutritional status, adherence to prescribed medications, cognitive function and inflammation than those treated with placebo.

Aim 5: Collect data on death, hospitalizations, and dialysis initiation at 6 and 12 months after randomization for power calculations to determine the feasibility of conducting a large-scale trial designed to investigate whether the treatment of depression improves outcomes in CKD. This aim is exploratory and there may not be enough events to show a statistically significant difference in outcomes between the sertraline-treated and placebo-treated groups. Nevertheless, the following statistical analysis is anticipated.

Percent of patients with composite events (death, hospitalization or dialysis initiation) at 6 and 12 months will be compared between groups (sertraline vs. placebo) using Chi-square test. Mean survival time will be compared among groups using Log-rank statistic. Kaplan Meyer survival curves and Cox Proportional Hazards models will be used to evaluate the independent association of treatment with sertraline with the primary composite outcome. Secondary outcomes will be each of these 3 events assessed separately. Multivariable models will be adjusted for clinically relevant covariates such as age, gender, race, comorbidities, eGFR, etc.

Anticipate Findings: It is anticipated that there will be enough preliminary data to conduct sample size calculations for a large multi-center trial, such as a VA Cooperative study, aimed to investigate whether treatment of major depressive episode with sertraline vs. placebo will improve outcomes in patients with moderate to advanced chronic kidney disease.

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14. Provisions for Managing Adverse Events: Adverse Events (AEs) and Serious Adverse Events (SAEs) will be defined per the *VHA Handbook 1058.01*, 2/27/09, and VA/ICH/FDA regulation-compliant version:

Adverse Event (AE) is defined as any unfavorable and unintended change in the structure (signs), function (symptoms), or chemistry (laboratory data) of the body temporally associated with any use of a clinical trial intervention. An AE does not have necessarily have to have a causal relationship with the treatment.

Serious Adverse Event (SAE) is any medical occurrence that:

1) Results in death
2) Is life threatening
3) Requires inpatient hospitalization or prolongs existing hospitalization
4) Results in a significant, persistent or permanent disability or incapacity
5) Is a congenital anomaly
6) Requires intervention (medical or surgical) to prevent permanent impairment or damage
7)

Unanticipated Problem (UP) are events involving any aspect of the research study and anyone including participants, research staff, or others not directly involved in the research. They are always *unanticipated* by definition.

Given the comorbidity associated with CKD and MDE, it is expected that a large number of AEs will be observed, most of which will not be related to the study intervention. For this reason, only SAEs will be reported, and AEs will be reported as listed below in ***Stopping Points***. Realistic

SAEs for CKD patients include 1) *death*, 2) *hospitalization* and 3) *dialysis initiation*. Realistic SAEs for patients with MDE also include *suicide*. *The VA CSR&D Centralized Data Monitoring Committee (DMC)* will provide study oversight to ensure the safety of subjects (see below). *The PI will report any SAEs to the Dallas VA IRB and the DMC not more than 2 working days after the time the PI or study staff become aware of the event, and UPs will be reported not more than 5 working days after becoming aware of the problem.*

SAEs Unique to This Study

All study team members will complete the "Suicide Prevention" training modules on the VA website: VA employees will use the LMS system and WOCs will use the EES system. In addition, all study team members will be trained prior to study initiation in the identification and assessment of suicidal risk based on both participant responses to study instruments as well as in-depth questioning of participants about their current suicidality. Training will include case scenarios, and will be administered by a trained specialist in Dr. Trivedi's group.

An additional objective scale to measure suicidal ideation will be administered to subjects at each visit that formally assesses suicide risk. This questionnaire, the "Concise Health Tracking – Self-Rated Scale" or CHRT, has been previously used by Dr. Trivedi's group in other studies of depression and is attached. Any subject that states "neither agree nor disagree", "agree", or "strongly agree" to items 5, 6, or 7 will be identified at that visit and further queried.

If a subject is discovered to have ***acute suicidal intent*** (that is, has a stated plan or needs inpatient care), the following *referral actions* will be followed:

a) If the patient is thought to be an immediate threat to themselves or others, they will be escorted to the Emergency Department for further evaluation by the Mental Health consult team and possible admission.

b) If the patient is not thought to be an immediate threat to themselves or others, they will be escorted to the Mental Health Clinic for triage.

c) In addition, the Research Pharmacist will unblind the subject to the Mental Clinic MD, who will decide what drug treatment to offer the patient after assessment. The Mental Health MD will be advised to slowly titrate down the dose if the patient was on sertraline (in order to avoid withdrawal symptoms) and if the MD decides to discontinue this medication.

2) Bleeding requiring hospitalization: Bleeding has been reported with SSRI use and CKD patients may be at increased risk of bleeding due to platelet dysfunction secondary to uremia.

Stopping Points:

Withdrawal from drug: Study drug will be terminated if the subject encounters the following. However, unless the subject chooses to withdraw consent, study assessments will continue as per protocol.

1) Any *adverse event* attributed to blinded study drug that in the opinion of the PI would obviate the reinstitution of drug, such as bleeding requiring hospitalization.
2) Intolerable side effects despite a decrease in the dose of study drug to a minimum of 50 mg per day and subject decides to stop study drug.

3) Worsening of depressive symptoms that in the opinion of the PI would obviate continuation of study drug or presence of acute suicidal intent as defined above.
4) Pregnancy.
5) Recommendation by the DMC.

Withdrawal from study: The subject will be withdrawn from the study if the subject decides to withdraw informed consent. All the assessments and data collected to that point will be used but no additional data will be collected.

The PI will document that a stopping point has occurred and notify the subject to discontinue and return study drug. The subject will be scheduled for a close-out visit to arrange follow-up with their personal physician or Mental Health as indicated. *A stopping point will be reported to the DMC and the IRB not more than 5 working days after becoming aware of the problem. If the stopping point is an SAE, it will be reported not more than 2 working days.*

15. Risk/Benefit Assessment: The overall risk classification for the research is greater than minimal. Minimal potential risks to subjects include 1) breach of confidentiality; 2) physical risks such as discomfort, bleeding, or bruising from venipuncture; and 3) side effects of sertraline. Common side effects of sertraline (affecting >10% of individuals) may be temporary and include nausea, decrease in appetite, diarrhea, dry mouth, dizziness, headache, insomnia, somnolence, decreased libido, sweating and tremors. Less common side effects of sertraline (1-10%) include chest pain, palpitations, agitation, nervousness, pain, rash, impotence, increased appetite, constipation, vomiting, weakness, visual problems, yawning, and tinnitus. Rare (<1%) but greater than minimal potential risks such as bleeding, extrapyramidal reactions, neuroleptic malignant syndrome and suicide have been much less commonly reported with sertraline use (45-47). Abnormal bleeding, serious allergic reactions, liver damage, kidney damage, psychosis, worsening depression, arrhythmias, and SIADH have been reported. Withdrawal symptoms such as agitation, anxiety, confusion, headache and seizures could occur if sertraline is stopped abruptly.

To minimize potential risks, subjects will be seen frequently (every 2-3 weeks) to monitor for any study drug side effects or adverse events. The SAE monitoring period will be from initiation of study drug to at least 30 days beyond the end of treatment. The PI will continually reassess risks vs. benefits to subjects throughout the study period and at any time an unexpected or serious adverse event occurs. The PI will report any SAEs to DMC and IRB (see below for DMC). Please see *section 20* for provisions for *subject confidentiality*.

This study could have potential benefits for both study subjects and others; therefore, the risks to subjects are reasonable in relation to the anticipated benefits to research subjects and others. The benefits include the knowledge that may be gained. If the results of this study are positive, it could lead to improved outcomes (improvement in depression and quality of life) of study subjects with CKD and MDE and non-study patients with similar diseases.

16. Data Safety and Monitoring Plan: *The VA CSR&D Centralized Data Monitoring Committee (DMC) at Hines* will provide independent study oversight to ensure the safety of subjects and

the validity and integrity of the data. The DMC will perform an initial review of the protocol with regards to recruitment/retention strategies, safety plan, monitoring of adverse events, and analysis plans. Routine progress reports will be provided by the PI to the DMC as requested annually and non-routine data reports will be provided as needed and include data on serious adverse events and stop points. The CSR&D DMC will review the study data every 6 months for adverse event occurrence, safety monitoring, overall performance and data generation and assess risk-to-benefit ratio. The DMC will generate non-routine reports to the PI and IRB in the event of any unexpected findings that would jeopardize subject safety.

17. Process for Obtaining Informed Consent and Protecting Patient Privacy: Written informed consent will be witnessed and obtained prior to enrollment by the study coordinator and the PI in accordance with OHRP guidelines and the Dallas VA IRB. Consent will be obtained in CKD clinic or CRU private rooms for protection of patient privacy. Potential subjects will be provided with information detailing the purpose of the study, procedures involved, that participation is voluntary, risks and possible benefits, alternatives to participation and the option to withdraw. Questions by subjects will be encouraged and answered.

18. Documentation of Informed Consent: The individuals obtaining consent will enter the appropriate research enrollment accept or decline note into the CPRS. A copy of the signed consent form will be given to the subject, a copy retained for the research files and another copy scanned into CPRS. The research enrollment note placed in CPRS will follow the structure in Chapter 8 of the PPHRS. Patients with reduced decision-making capacity requiring a legal authorized representative will not be included in the study.

19. Payment to Subjects for Their Participation: Many of patients travel over 50 miles to come to the Dallas VA and will need to do so for 8 outpatient visits during the course of the study. We plan to reimburse patients $50.00 each for visit 1 and for visit 6 (week 12), which are study visits with blood draws, and $25.00 for each of the other 6 study visits to cover travel and parking expenses. An additional $50.00 will be given to subjects who agree to the optional genetic testing part of the study.

20. Provisions for Data Storage and Confidentiality: All efforts will be utilized to ensure subject confidentiality and all data will be held confidentially. HIPAA regulations will be discussed with all subjects and HIPAA consent will be obtained with the study consent. Subjects will be identified using unique identifiers and will not be referred to by name or social security number on research documents. All paper records will be maintained in a locked cabinet in the research team's locked office. Computerized data will be de-identified, stored separately from the key code, and stored on the VA-secured network that is accessible from a password protected computer in a locked office of the research team. In accordance with VA guidelines, all records of this research study will continue to be securely maintained for a minimum of six years from the date of completion of the study. The records will be kept in a locked file cabinet or locked room with limited access or stored at a VA-approved storage facility. If the PI leaves the VA facility, the research records will be retained by the institution. Only members of the research team, VA DMC and the Dallas VA IRB will have access to subject individually identifiable private information. A de-identified limited dataset will be transported and stored

offsite at UT Southwestern Medical Center North Campus located at 6363 Forest Park Road for statistical analysis by biostatistician Dr. Thomas Carmody, after permission to transport and store data offsite has been approved by the Dallas VAMC.

21. Provisions for Storage/Analysis of Research Specimens: N/A

22. Dissemination of Research Results: We expect to generate data regarding the safety and efficacy of sertraline used for treatment of major depressive episode in patients with CKD. We will also generate estimates of treatment effect size for power analysis for a future multicenter trial in this population of patients. The proposed mechanism for data sharing will be via publication in discipline specific journals and through presentation of the preliminary findings at annual national and specialty meetings for kidney disease. We will adhere to the NIH policies on sharing of research resources, as outlined in “Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources” (NIH Office of Technology Transfer, December 1999).

23. Multi-Center Research: N/A