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Rationale and Design of A Trial of Sertraline vs. Cognitive Behavioral Therapy for End-stage Renal Disease Patients with Depression (ASCEND)

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Abstract

Major Depressive Disorder (MDD) is highly prevalent in patients with End Stage Renal Disease (ESRD) treated with maintenance hemodialysis (HD). Despite the high prevalence and robust data demonstrating an independent association between depression and poor clinical and patient-reported outcomes, MDD is under-treated when identified in such patients. This may in part be due to the paucity of evidence confirming the safety and efficacy of treatments for depression in this population. It is also unclear whether HD patients are interested in receiving treatment for depression. ASCEND (Clinical Trials Identifier Number NCT02358343), A Trial of Sertraline vs. Cognitive Behavioral Therapy (CBT) for End-stage Renal Disease Patients with Depression, was designed as a multi-center, 12-week, open-label, randomized, controlled trial of prevalent HD patients with comorbid MDD or dysthymia. It will compare (1) a single Engagement Interview *vs.* a control visit for the probability of initiating treatment for comorbid depression in up to 400 patients; and (2) individual chair-side CBT *vs.* flexible-dose treatment with a selective serotonin reuptake inhibitor, sertraline, for improvement of depressive symptoms in 180 of the up to 400 patients. The evolution of depressive symptoms will also be examined in a prospective longitudinal cohort of 90 HD patients who choose not to be treated for depression. We discuss the rationale and design of ASCEND, the first large-scale randomized controlled trial evaluating efficacy of non-pharmacologic *vs.* pharmacologic treatment of depression in HD patients for patient-centered outcomes.

Keywords

End Stage Renal Disease (ESRD); hemodialysis; depression; engagement interview; cognitive behavioral therapy (CBT); sertraline

1. Introduction

In the United States, over 400,000 individuals undergo hemodialysis (HD) for the treatment of End Stage Renal Disease (ESRD) ^[1]. Patients with ESRD have multiple comorbidities, significant impairments in quality of life, and high rates of hospitalization and death ^[1–7]. These patients undergo a complex treatment regimen including numerous dietary restrictions, high pill burdens ^[5, 8], and 3–4 hours of HD generally thrice weekly. Such factors contribute to the significant decrements in physical and psychological well-being experienced by HD patients.

Depression is the most common psychiatric disorder in HD patients, affecting about 25%, a rate that is over four-fold higher than in the general population ^[9]. The presence of depression in HD patients is associated with worse patient-centered outcomes such as lower quality of life, greater burden of somatic symptoms, sexual dysfunction, cardiac events, hospitalizations, mortality, and withdrawal from dialysis ^[2, 10–28]. In a recent meta-analysis of 22 studies, depression was consistently associated with the risk of all-cause death in patients with kidney disease, with a summary risk ratio of 1.59, 95% confidence interval

(1.35–1.87)^[28]. Depression may lead to non-adherence^[29] and is associated with a higher likelihood of shortening the length of and/or skipping dialysis treatments, excessive fluid intake, and lower medication adherence^[30–36].

However, rates of depression diagnosis and treatment are low in this patient population, perhaps due to reluctance of patients to accept diagnosis and/or treatment and lack of robust evidence for the efficacy of depression treatment options in HD patients^[11, 37–39]. Only 54% of HD patients diagnosed with depression using a structured psychiatric interview had a prior history of depression recorded in their medical records, and only 42% of those had anti-depressant medications prescribed^[11]. In a recent trial, treatment for depression was instituted in only 17% of HD patients with depression, even after the diagnosis of depression was communicated to providers^[40]. Knowledge gaps exist regarding whether standard depression treatments used in the general population, such as psychotherapy or anti-depressant medications, are tolerable and efficacious in HD patients. Existing studies of treatment of depression with antidepressant medications are few, and either observational or limited by small sample sizes, an absence of ethnic and racial diversity, lack of controls, non-standard criteria for Major Depression diagnosis, or selection biases^[41–50]. Two single-center studies of Cognitive Behavioral Therapy (CBT) in HD patients reported some efficacy that needs to be confirmed in larger controlled multi-center studies^[51, 52].

ASCEND, A Trial of Sertraline vs. CBT for End-stage Renal Disease Patients with Depression (NCT02358343)^[53], was designed to inform care of patients with a Major Depressive Disorder (MDD) undergoing HD. This will be the first multi-center randomized controlled trial comparing treatments for depression in a racially/ethnically diverse group of prevalent HD patients from three U.S. metropolitan areas, ensuring high external validity. We hypothesize that an Engagement Interview vs. control visit increases the likelihood of initiating treatment for depression in HD patients. We further hypothesize that, in HD patients with a current MDD or dysthymia, there is no meaningful difference in improvement in depressive symptom severity with 12 weeks of individual chair-side CBT or treatment with the selective serotonin reuptake inhibitor (SSRI), sertraline. Finally, we will study the evolution of depressive symptoms in a prospective longitudinal cohort of individuals who choose not to be treated for depression. The results will provide HD patients and providers with much needed information when weighing treatment options for comorbid depression.

2. Methods

2.1 Study sample and setting

Adults ≥ 21 years of age with ESRD receiving thrice-weekly maintenance HD for ≥ 3 months in participating outpatient dialysis facilities who meet Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria for a current episode of MDD (severely depressed mood that persists for at least two weeks) or dysthymia (a depressive disorder characterized by a chronic state of milder depressive symptoms that persists for at least two years) using the Mini International Neuropsychiatric Interview (MINI)^[54] are eligible for participation.

Institutional review boards at 3 large metropolitan participating sites, University of Washington in Seattle, University of Texas Southwestern in Dallas, and University of New Mexico in Albuquerque, approved the protocol for patient recruitment. Recruitment of patients from these 3 demographically different urban centers will enrich the study sample with Hispanic and African American (AA) patients who disproportionately suffer from ESRD. The demographics of ESRD patients at each site are as follows: Seattle, 5% Hispanic, 62% White, 17% AA, 15% Asian; Dallas, 43% Hispanic, 41% White, 54% AA, 3% Asian; Albuquerque, 52% Hispanic, 69% White, 3% AA, 1% Asian. The University of Washington functions as both the Clinical Coordinating Center and Data Coordinating Center.

2.1.1 Inclusion and exclusion criteria—Detailed inclusion and exclusion criteria are listed in Table 1. Patients already being treated with anti-depressant medications at very low doses that are generally considered ineffective and can be discontinued without adverse sequelae and need for washout will be eligible to participate (see Appendix). However, the patient should be willing to completely stop the medication prior to entering the Treatment Phase if: 1) the drug is a SSRI or serotonin-norepinephrine reuptake inhibitors (SNRI), regardless of the indication; or 2) the drug is being used to treat depression. Subjects could stay on the allowable drug dose if it is prescribed for a reason other than depression, and the drug is not an SSRI or SSRI/SNRI.

2.2. Study design and procedures

The ASCEND study is an open-label, randomized controlled clinical trial where the participants are potentially involved in three phases – the Pre-screening Phase, the Screening Phase and the Treatment Phase. A schematic of the trial design is presented in Figure 1.

During the Pre-screening Phase, patients are first introduced to the research team by clinical staff at the unit to see if they are interested in completing the Beck Depression Inventory (BDI) II for the presence of depressive symptoms. The BDI II, a 21-item self-report depression questionnaire, was previously validated against DSM IV-based structured interviews for the identification of depression in HD patients [11, 55–57]. An information sheet explaining the purpose of the BDI and affirming voluntary completion of the questionnaire is handed out to the patient. Those willing complete the BDI at the chair-side. Individuals with BDI score ≥ 15 are invited by the research coordinators to provide informed consent to participate in subsequent study-related activities, including review of eligibility with the MINI. The informed consent process is conducted at the chair-side by the research coordinators within 10 days of completing the BDI II. The consent process can occur in a private room before or after HD based on patient preference.

The Screening Phase consists of reviewing the eligibility of patients identified for participation in the clinical trial for treatment. This includes confirming the diagnosis of current MDD or dysthymia by administering the MINI [54], and excluding those with active suicidal intent, present or past psychosis or bipolar I or II disorders, or alcohol and substance abuse. Trained study personnel administer the MINI. Up to four hundred patients who are eligible for participation will be randomly assigned to either a single Engagement Interview

or a Control Visit. Participants who consent to treatment of depression after the Engagement Interview or Control Visit move on to the Treatment Phase within 10 days.

The Treatment Phase is 12 weeks and involves randomization of 180 participants to either individual CBT administered at the HD center or anti-depressant medication treatment with sertraline. Randomized participants undergo blinded serial assessment of depressive symptoms every 6 weeks using the clinician-rated 16-item Quick Inventory of Depression Symptomatology (QIDS-C₁₆)^[58] administered by research personnel blinded to intervention arm, via a Computer Assisted Telephone Interview (CATI). The length of intervention was selected based upon considerable data from the general population indicating that individuals who do not respond to CBT or anti-depressant drug therapy within 12 weeks are highly unlikely to do so with continued treatment ^[59, 60]. In addition, up to 90 patients who refuse to accept treatment either within or outside the clinical trial, will be followed for 12 weeks. These patients will not be a part of the clinical trial, will be offered treatment at each evaluation, and will undergo longitudinal assessment of depressive symptoms at six-week intervals for up to 12 weeks.

2.2.1. Rationale for pre-screening tool—The BDI II was selected as the pre-screening tool to identify patients who may be eligible for participation in the trial because (1) it is easy to administer; (2) it has been commonly used in previous observational studies of depression among ESRD patients; and (3) it has been validated against DSM IV-based structured psychiatric interviews for identifying HD patients at risk for a diagnosis of depression in several studies. The BDI has 21 items, with total scores ranging from 0 to 63, with higher scores indicating more severe depressive symptoms. A cut-off of 15 is used based on these studies to identify clinically significant depressive symptoms in potential HD patients pre-screened for participation ^[11, 55–57].

2.3. Rationale for Engagement Interview

There are data suggesting that many HD patients do not wish to receive any form of treatment for depression, reasons for which are largely unknown, but acceptability of treatment by the patient may be one of the issues ^[40]. Consistent with this finding, >60% of patients that responded to a survey administered during the ASCEND study planning phase through our two patient advocacy partners, American Association of Kidney Patients and Dialysis Patient Citizens, ranked “no specific intervention” as their top choice for treatment of depression. Similarly, >40% of HD patients approached for participation in a recent trial of individual CBT did not wish to undergo treatment for clinically significant depressive symptoms ^[51]. Hence, we plan to determine whether an Engagement Interview prior to the treatment phase increases the frequency of treatment acceptability among patients.

The Engagement Interview delivered by the CBT therapist takes 45–60 minutes and aims to identify treatment ambivalence and resolve practical, psychological, and cultural barriers to receiving treatment for depression. The personalized nature of this session is designed to build trust and promote treatment engagement and is based on principles of motivational interviewing ^[61]. The interviewer adopts a one-down position as learner, tries to understand the patient’s cultural perspectives and values without bias, inquires about the patient’s view

of depression, health-related beliefs, and coping practices, and asks about preferences for depression care. Core features of motivational interviewing are used to problem solve the barriers and to enhance intrinsic motivation for change in a non-confrontational manner. The Engagement Interview consists of five components: 1) eliciting the patient's story about being on dialysis and feeling depressed; 2) obtaining the patient's mental health treatment history and goals for depression treatment; 3) delivering psychoeducation about depression and available treatments; 4) problem-solving practical, psychological and cultural barriers to care; 5) eliciting commitment to treatment or leaving the door open.

At least one study demonstrated increased acceptance of evidence-based treatment for depression using this technique [61]. The Engagement Interview has also been used more recently as an integral component of the collaborative care arm of several studies for the treatment of depression in the primary care setting [62–64]. Among adolescents with depression, a collaborative care intervention that included an initial in-person engagement session resulted in greater improvement in depressive symptoms as compared with usual care [64].

There are no data on the efficacy of this approach for increasing the likelihood of depression treatment acceptance among patients undergoing HD. The engagement intervention to be tested in this study is the same as the one being used in studies of collaborative care for the treatment of depression, and will include the presentation of a video along with motivational interviewing. To ensure fidelity, following the completion of a one-day engagement training from experts, Nancy Grote, Ph.D., and Yaminette Diaz-Linhart, M.SW., each CBT therapist will be required to complete mock interventions that will be audiotaped and reviewed, using a fidelity adherence form, in order to be certified in the engagement intervention prior to implementation in the clinical trial. During the trial, all sessions of the engagement interview will be audio-taped and a 10% random sample will be periodically reviewed to provide ratings for treatment fidelity using the fidelity adherence form.

Individuals assigned to the *control visit* instead of the Engagement Interview are scheduled for a follow-up discussion with a member of the research team. During this session, they are informed of the diagnosis of MDD or dysthymia, the treatment options available through the clinical trial, and alternatives should they decline participation in the trial. The time spent in providing this information is recorded.

2.4. Treatment Interventions

During the 12-week Treatment Phase, individuals are randomly assigned in a 1:1 ratio to receive either CBT or flexible-dose sertraline. Participants in the CBT arm undergo ten 60-minute individual sessions with a trained therapist in the dialysis facility (8 weekly sessions; then 2 sessions every other week). CBT is administered chair-side while the participant is undergoing HD. A private room is also available at each dialysis center for participants who would prefer to have their session in a totally private setting. For individuals randomized to drug, sertraline is started at an initial dose of 25 mg daily. A “Measurement-Based Care” protocol, based on the presence of patient-reported side effects and response in depressive symptoms, is used to adjust study drug dosing as a model of patient-centered shared-decision making [38, 59, 65, 66]. Dose escalation occurs every 2 weeks to a maximum of 200

mg daily, and the dose is held constant over the last 6 weeks of the Treatment Phase. The dose for each dispensation is determined by assessments made on the first dialysis day of the week, and drug is dispensed on the second dialysis day of the week. At weeks 2, 4, 6, 9, and 12, pill counts are done to monitor adherence, and all unused drug is returned and destroyed.

2.4.1. Rationale for Depression Treatment Options—There are two distinct standard approaches to treatment of depression in the general population: psychotherapy, such as CBT, and anti-depressant drug therapy. During the planning phase of the trial, responses obtained anonymously from 61 patients with kidney disease indicated that the relative acceptability of treatment options for depression varies among patients, a finding that is not surprising since the two approaches have important differences. Psychotherapy entails a time burden and a commitment of energy to treatment. Anti-depressant drug therapy adds to the already high pill burden for HD patients and may result in adverse effects in some patients. Moreover, the availability of each of these treatments varies, in part, by center location, insurance coverage, and out-of-pocket costs to patients. For this reason, both psychotherapy and anti-depressant drug therapy were proposed as treatment options based on patient preferences.

2.4.2. Rationale for Cognitive Behavioral Therapy (CBT)—CBT is a short-term focused psychotherapy for many psychological conditions including depression [67, 68]. The focus of the therapy is on how the individual is thinking, behaving, and communicating in the present rather than on childhood experiences. The therapist assists the patient in identifying specific distortions (cognitive assessment) and biases in thinking and provides guidance on how to change this thinking^[69]. Thus, CBT helps patients learn effective self-help skills that are used in homework assignments that target changes in the way they think, feel, and behave. The homework serves to reinforce the in-session discussion, and provides the participant the opportunity to apply the strategies into their everyday life. As an example, an activities calendar is incorporated into sessions after it is introduced, to emphasize the behavioral activation component of the treatment. CBT is action-oriented, practical, rational, and helps patients gain independence and effectiveness in dealing with real-life issues.

CBT was shown to be efficacious as a first-line treatment for depression in the general population, such that it is currently endorsed by clinical practice guidelines from the American Psychiatry Association as an option for depression treatment. Moreover, it does not cause the potential side-effects associated with common anti-depressant medications [67, 68, 70, 71]. The efficacy of CBT has been demonstrated in two single-center studies of HD patients with depressive symptoms, setting the stage for larger-scale testing in a randomized clinical trial [51, 52]. In the first trial, the efficacy of 12 weekly sessions of group CBT compared with usual treatment was reported for depressed HD patients in Brazil [51]. In the second trial, 65 patients were randomly assigned to individual chair-side CBT first or wait-list control group [52]. CBT was associated with a significant improvement in depressive symptoms by the BDI II. Our present study builds on these single-center experiences by testing the efficacy of individual chair-side CBT among patients treated in up to 50 dialysis facilities in geographically, ethnically, and culturally diverse centers.

The quality and fidelity of the CBT sessions is assured as follows. Therapists at each site undergo rigorous training by the same training team prior to study implementation. All CBT sessions are audio-taped with the permission of patients, and a 10% random sample periodically reviewed by an independent assessor to provide ratings for treatment fidelity using forms that outline the major skills and intervention pieces. Any issues regarding the quality of intervention are addressed with the therapist during their ongoing supervision. This remote oversight is supplemented by six-month in-person monitoring by the trainers.

2.4.3.1. Rationale for Anti-Depressant Drug Sertraline: Anti-depressant medications are also among first-line treatment options for depression in the general population, because they are easily implemented, likely to engender few drug-drug interactions, and are usually the most common form of treatment used in primary care settings [70, 72]. Advantages of anti-depressant medications over psychotherapy include easy prescription and implementation by the dialysis provider, and allowing the patient not to have to spend additional time with the therapist for treatment of another condition, in addition to ESRD. However, data for the safety and efficacy of anti-depressant medications are more limited in HD patients, as those with severe kidney disease have been generally excluded from major clinical trials of anti-depressant drug therapy due to concerns for safety [37, 38]. Potential safety concerns in patients with decreased kidney function include increased bleeding risk, decreased metabolite clearance, and possible drug interactions.

There are only a few trials of anti-depressant drug therapy in HD patients with depression, and most are observational, non-randomized, uncontrolled, or limited by small sample sizes [42–49, 73]. In one small placebo-controlled trial of 14 HD patients, the improvement in depressive symptoms with 8-weeks of treatment with fluoxetine did not reach statistical significance [41]. Furthermore, the efficacy of anti-depressant medications in otherwise healthy individuals cannot be extrapolated to those with chronic medical illnesses, such as ESRD, as evident from the lack of efficacy of anti-depressant drugs in large clinical trials of patients with asthma and congestive heart failure [74, 75].

Clinical practice guidelines indicate that among anti-depressant medications, only SSRIs, SNRIs, and bupropion meet the balance between efficacy and tolerability in the general population [70]. In ESRD patients, loss of renal excretory capacity further complicates drug selection [37]. A recent systematic review of 28 studies for 24 anti-depressant drugs in patients with kidney disease before and after dialysis initiation indicates that both serotonin-norepinephrine reuptake inhibitors and bupropion require dose reduction [37]. However, the magnitude of dose reduction cannot be readily determined, as it is influenced by residual kidney function, which has not been considered in any study. These complicated dosing considerations are likely to make it difficult to balance efficacy and safety for these two drug classes for HD patients, and will likely preclude widespread adoption in clinical practice. Hence, sertraline, an SSRI, will be used as the anti-depressant for this clinical trial.

Sertraline is metabolized to an inactive form by the liver before being excreted via the kidney. It is safe in patients with heart disease, a common comorbidity in HD patients, and is available in generic form [37, 38]. The Chronic Kidney Disease Anti-depressant Sertraline Trial (CAST, Clinical Trials Identifier Number NCT00946998) is the first randomized,

double-blinded, placebo-controlled trial of sertraline in patients with stages 3b-5 non-dialysis CKD, that is currently ongoing [65], but this trial excludes CKD patients who are treated with maintenance dialysis. The experience thus far in the trial indicates good tolerability/safety of sertraline use in patients with reduced kidney function.

2.4.3.2. Rationale for Measurement-Based Care: Dose titration for study drug, sertraline, will be implemented using “Measurement-Based Care,” a model of patient-centered shared-decision making that has been used in previous large clinical trials of anti-depressant medication therapy in non-dialysis populations [38, 59, 65], and is currently being used in the CAST study. This protocol first incorporates standardized assessments of depressive symptoms and drug side effects, followed by decisions made jointly by patient and research team about the next steps in titration of either maintaining, increasing, or decreasing the dose [38, 59, 65, 66]. The Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR₁₆) scale, a self-administered, 16-item questionnaire, will be used to assess the severity of depressive symptoms as the clinical response for dose titration [58]. Side effects, most commonly gastrointestinal and transient, such as nausea and vomiting, will be assessed using the Frequency, Intensity, and Burden of Side Effects Rating (FIBSER) scale, a self-report three-item scale to assess side effects and the degree to which they interfere with day-to-day functions [76]. This will help establish the highest efficacious but tolerable dose tailored for each participant and minimize the risk of under-dosing.

Investigators, sub-investigators, or any personnel with privileges to prescribe drug therapy at each of the three sites undergo formal training in the implementation of Measurement-Based Care protocol. The study nephrologists and psychiatrists are responsible for implementation at their respective sites, while an external investigator provides oversight for dose titration for all 3 sites.

2.5. Outcomes for Efficacy of Engagement Interview

The pre-specified **primary outcome measure** is proportion of participants in the Engagement Interview group vs. the control group for whom treatment for depression is initiated. Treatment initiation is defined as a) completing at least one psychotherapy session, or b) receiving a supply of anti-depressant medication, either as a part of the clinical trial or outside the trial, within four weeks of establishing a diagnosis of MDD and/or dysthymia. This outcome is assessed six weeks from the time of completion of the Engagement Interview or control visit.

The **secondary outcome measure** is proportion of participants in each group willing to accept treatment for depression. This outcome measures the patients’ intent, and is ascertained upon completion of the Engagement Interview or control visit as a) signing informed consent to enter the trial Treatment Phase, or b) receiving a referral for psychotherapy in the community or c) receiving a prescription for anti-depressant medication within two weeks of establishing a diagnosis of MDD or dysthymia.

2.6. Outcomes for Comparative Efficacy of CBT vs. Sertraline

The pre-specified *primary outcome measure* is the change from baseline in the depression symptoms severity score as ascertained blindly by the QIDS-C₁₆ in the CBT group, compared with the sertraline-treated group. Two groups of *secondary outcome measures* are examined as summarized in Table 2: Patient-Reported Outcomes and Treatment Adherence. The primary and secondary patient-reported outcomes are ascertained by CATI at baseline, week 6, and week 12.

2.6.1. Rationale for the Quick Inventory of Depressive Symptomatology-Clinician Rated (QIDS-C₁₆) Scale—QIDS-C₁₆ was chosen as the primary outcome measure as it assesses the 9 criterion symptom domains of Major Depression based on DSM IV, and it has a greater proportion of items core to a diagnosis of MDD compared to other scales. In addition, it provides equivalent weights for each somatic and non-somatic depressive symptom [58, 77]. As a result, QIDS-C is least likely to be biased and inflated by the somatic symptoms of ESRD. Hence, unlike most depression scales, the cutoff score for the diagnosis of depression with QIDS is the same for patients with advanced kidney disease as the general population [78, 79]. Further, the QIDS-C includes clearly stated anchors that estimate the frequency and severity of symptoms and has been validated to track patient ratings of depressive symptoms on the QIDS-SR [58, 77]. It has 16 items. Scores range from 0 to 27, with higher scores indicating greater severity of depressive symptoms.

2.6.2. Rationale for Computer Assisted Telephone Interviewing (CATI)—To ensure a high level of fidelity, the Treatment Phase primary and secondary patient-reported outcomes for participants at each of the 3 clinical sites are captured using CATI, administered by research assistants based at one site, the University of New Mexico. These personnel are blinded to patient treatment assignments. This approach was used for the Frequent Hemodialysis Network Trial, which demonstrated that CATI can provide high levels of data capture among the HD population [80]. Previous work demonstrated that providing HD patients with assistance from study staff to complete patient-reported outcomes instruments, as with telephone interviewing, maximizes participation of individuals having problems with vision or manual dexterity or limited literacy, not uncommonly present in HD patients, and minimizes bias [81]. To minimize potential confounding from the effects of the HD procedure, the assessments are performed on the second non-dialysis day of the week with the participant at home.

2.7. Study Exit

At the end of Week 12 of the Treatment Phase, participants will be evaluated and categorized as having 1) achieved a response (≥ 50% decrease in baseline depressive symptoms) or 2) achieved remission (QIDS-C₁₆ score ≤ 5) or 3) failed to respond to treatment (<50% decrease in baseline depressive symptoms). For participants in the CBT arm with clinically significant depressive symptoms (QIDS-C₁₆ ≥ 11), the final QIDS-C₁₆ score and its interpretation is communicated to the treating nephrologist, along with a list of Mental Health care providers and resources in their community for further management of depression. Participants in the sertraline arm who achieve either a response or remission are asked if they would like to continue treatment with sertraline at the current dose. If the

participant or the treating nephrologist does not choose to continue sertraline treatment, study drug is gradually tapered off by 50 mg/week. Such participants, as well as those who fail to respond to study drug, are provided with a list of Mental Health care providers and resources in the community for management of depression.

2.8. Data collection and Measurements

Table 3 summarizes variables collected and time periods for measurements. Demographic and clinical variables, including laboratory data, are collected from electronic medical records and participant self-report during screening, as well as during the trial period. The primary outcome for the Engagement Interview is ascertained by a single phone call 6 weeks from date of the Engagement Interview or control visit. The primary and secondary patient-reported outcomes for treatment are ascertained by CATI at weeks 0, 6, and 12. The assessments for Measurement-Based Care drug dose titration using the QIDS-SR₁₆ and FIBSER occur on Weeks 2, 4, 6, 9 and 12, while the participant is undergoing HD. The QIDS-SR₁₆ is also administered at the same frequency to the patients in the CBT arm, so that both groups are treated similarly. Adverse events are also assessed at each study visit. Adherence to routine treatment regimen, including diet and medication, is ascertained by structured data extraction from the medical records maintained at the dialysis facility at weeks 0, 6, and 12. A pregnancy test is performed before sertraline drug therapy is initiated for female participants of childbearing potential randomized to the drug arm.

2.9. Statistical Analyses

Descriptive statistics will be provided for continuous data and frequency distributions for categorical data. Pre-treatment characteristics of the two randomized groups in both the Engagement Interview Phase and the Treatment Phase will be compared to assess for chance imbalances. If differences are found in pre-specified baseline characteristics, these variables will be used as covariates in secondary analyses to evaluate the sensitivity of the primary analysis.

2.9.1. Statistical Analysis for the Engagement Interview Phase—Logistic regression will be used to compare the proportions of patients who initiate treatment for comorbid depression between the Engagement Interview and control groups. Analyses will be adjusted for recruitment site. The primary analyses will be based on a likelihood ratio test. In secondary analyses, proportions of participants who report willingness to initiate treatment for depression upon completion of the Engagement Interview phase will be compared.

2.9.2. Statistical Analysis for the Treatment Phase—*Intention-to-treat analyses* will be used for assessing all the primary and secondary outcome measures in the Treatment Phase. To compare primary and secondary continuous outcome measures at 6 and 12 weeks between CBT and sertraline intervention groups, longitudinal mixed effects analyses will be used, with treatment group and recruitment center as fixed effects in the model^[82]. An unstructured covariance matrix will be employed to account for serial correlations in outcome measures within participants^[83]. The model will constrain baseline means of the outcome to be equal in the treatment groups based on randomization. Such an analysis is

known to correspond to an ANCOVA when only one follow-up measure is evaluated. Linear contrasts will be constructed to estimate for each outcome variable: (a) the mean difference in the outcome between the treatment groups at Week 12 (primary assessment of treatment effect); (b) the mean difference in the outcome between groups at Week 6 (early treatment effect); (c) the average of the treatment effect estimates from (a) and (b) over Weeks 6 and 12 (persistence of early effect to 12 weeks); and (d) the difference in the estimated treatment effects from (a) and (b) between Week 6 and Week 12 (overall assessment of the treatment effect incorporating both follow-up visits). Finally, the following proportions will be described for each treatment group at end of Week 12: 1) proportion of participants that have *response* to treatment, defined as 50% improvement in severity of depressive symptoms on QIDS-C₁₆ from baseline and 2) proportion that achieve remission (QIDS-C₁₆ ≤ 5).

2.9.2.1. Avoidance of Bias in Treatment Phase: To minimize bias, several features are employed. First, a randomized controlled study design generates the highest level of evidence for comparative efficacy of treatments. Second, all eligible HD patients in participating dialysis facilities are systematically screened, which will assure the selection of a cohort highly representative of the HD patient population with comorbid depression. Third, the primary and secondary outcomes are measured at two time-points after randomization, and hence data on intermediate time-points is captured for participants who may drop out. Fourth, use of CATI to assess outcome measures maximizes patient participation, and the assessors are blinded to treatment assignment, both of which result in minimizing bias in an open-label clinical trial. Fifth, procedures to minimize missing data are implemented, such as standardized training and certification of study personnel, careful design and standardization of data collection forms, documentation of procedures, and implementation of a centralized management system that minimizes data entry errors and features patient tracking procedures^[84].

2.9.2.2. Plan for Handling Missing Data: The potential for bias due to loss-to-follow-up is a concern as poor adherers who discontinue either intervention are at risk both for loss to follow-up and poor outcomes. The mixed effects modeling approach will mitigate the effects of loss-to-follow-up after the Week 6 visit by incorporating information from baseline and the Week 6 measurements for participants who subsequently drop out of the study when estimating treatment effects at Week 12. Multiple imputations will be used to further limit the effects of missing outcome measurements. Baseline and follow-up factors beyond the analyzed outcome can be incorporated into the imputation model to account for dependence of the missing data mechanism on other measured factors, including measures of patient adherence to the intervention. Data augmentation using Markov Chain Monte Carlo (MCMC) simulation will be applied to generate imputed values^[85]. Secondary analyses will examine the association between participation in the Engagement Interview prior to randomization and adherence with the respective intervention on treatment efficacy.

2.9.3. Statistical analysis of data from observational cohort of patients who refuse to accept any treatment for comorbid depression—Longitudinal mixed effects analyses will be performed to describe the change in depressive symptoms for this cohort; no comparisons will be made with data from the clinical trial. The proportion of

participants who begin treatment during follow-up will be described as well. If sufficient numbers of patients initiate CBT or treatment with sertraline, then we will generate propensity scores for treatment and use these to conduct observational data-based estimates of treatment effects, and compare these estimates with those obtained from the randomized trial.

2.10. Protection of Human Participants

Institutional review boards at each of the 3 clinical sites approved the protocol before implementation, and all participants sign informed consent prior to the screening phase and research procedures. Multiple layers of oversight to ensure the safety of study participants have been put into place, including monitoring for adverse events. A central and independent Data Safety and Monitoring Board oversees study conduct at least twice yearly or more often as indicated. In addition, a nationally representative Patient Council (comprised of 8 patients with kidney disease) and Stakeholder Council (includes representatives from 2 patient advocacy organizations, 5 dialysis providers, the National Institute of Diabetes and Digestive and Kidney Diseases, American Nephrology Nurses Association, Council of Nephrology Social Workers of the National Kidney Foundation, and National Renal Administrators Association) provide advice and oversight for the conduct of the clinical trial.

Tolerability of sertraline within the trial is monitored by the use of the FIBSER. In addition, participants are asked at visits 2, 4, 6, 9 and 12 if they have experienced any side effects or adverse events, which are captured on the adverse event case report form and entered into the study portal. Information regarding severity, time of onset and resolution, whether the event was related to the research study, and action taken by the research team is also captured and recorded. Treatment for participants assigned to the sertraline arm will be withdrawn if (1) they experience a serious adverse event attributable to the study drug and in the judgment of the site PI, the medication cannot be safely reinstituted (e.g., clinically significant bleeding), (2) the subject has intolerable side effects despite reducing dose to 50 mg/d, or (3) the participant becomes pregnant. However, patients will continue to be followed for ascertainment of primary and secondary outcomes as scheduled.

Women of childbearing potential are screened for pregnancy and women who are not pregnant or lactating are advised to use an effective method of preventing pregnancy during the study. Participants will be withdrawn from the study, irrespective of treatment arm, if (1) one withdraws consent, (2) is unable to follow study procedures, (3) develops active suicidal intent, or (4) as decided by the Data Safety and Monitoring Board. If an individual reports active suicidal ideation or intent at any point during the trial, each of the three clinical sites follows a site-specific protocol to explore the risk of - and protect the subject from - self-harm, which includes assessment by the suicidality module within the MINI and specific referral actions.

2.11. Estimation of Power and Sample Size

The sample size for randomized evaluation of the Engagement Interview will be up to 400. In a pilot study, 40% of HD patients accepted treatment for comorbid depression, and

experience in other medical settings suggests that the engagement interview increases the rate by 10–20% [51]. In order to have 80% power to detect a difference in proportions of 40 vs. 55% (a 15% absolute increase), 186 participants would need to be enrolled per arm, for a total of 372 participants. Therefore, this design is well-powered to detect the anticipated effect of an Engagement Interview.

The sample size for the comparative evaluation between CBT and sertraline is 180. The serial correlation in self-reported depression scales in data from published and unpublished studies in HD patients or those with advanced kidney disease by members of this consortium, over approximately 12 weeks, typically ranges between $R = 0.40$ and 0.70 [40, 51, 78]. Assuming a loss-to-follow-up of 15%, 180 randomized participants will provide 80% power with 2-sided α of 0.05 to detect a difference in the mean 12-Week QIDS-C₁₆ between the treatment groups of between 0.327 (if $R = 0.70$) and 0.419 (if $R = 0.40$) of 1 standard deviation in the QIDS-C₁₆. This range of detectable effect sizes is well within the range of differences observed in the randomized and non-randomized trials of CBT or anti-depressant drug therapy for comorbid depression in HD patients [43, 44, 48, 49, 52]. Moreover, the magnitude of effect size that is detectable is in the range of what is considered to be a clinically meaningful improvement in depressive symptoms. Smaller effect sizes may exist that may be statistically significant in larger studies. However, they are unlikely to be clinically meaningful or relevant to patients in the selection of treatment options.

3. Discussion

Depression is a prevalent comorbidity in patients with ESRD treated with maintenance dialysis that is independently associated with poor clinical and patient-reported outcomes, but has been previously under-recognized and under-treated. The ASCEND study is the first large-scale multi-center randomized controlled trial to evaluate the efficacy of non-pharmacologic vs. pharmacologic treatment of depression in HD patients. This trial is especially important because (1) it will evaluate several patient-centered outcomes, (2) the interventions in this trial can be readily implemented as part of standard clinical care if found to be beneficial, (3) comorbid depression has become increasingly important to dialysis payers, and (4) the study engages multiple stake holders which will ensure the feasibility of the study, as well as future implementation and generalizability of results.

The trial is designed to not only gauge the effect of the two treatment arms on depressive symptoms, but also to assess how changes in depression may be correlated with patient-reported measures of health and well-being and with changes in essential indicators of treatment adherence. While some evidence suggests that depression can be successfully treated in ESRD, few well-controlled, randomized data are available regarding the potentially greater impact of improved psychological functioning on these secondary outcomes [39]. Poor sleep quality and fatigue are cardinal symptoms of depression, and depression may influence the patient's level of anxiety and assessment of quality of life [39]. Social support indices were shown to correlate with level of depressive symptoms, as well as satisfaction with life, [32] but the impact of improved psychological functioning on intimate relationships is largely unexplored. There is a need for research on the role that physical activity/exercise may play in modulating depression in dialysis patients [26], as in the general

population, bidirectional associations between activity and depressive symptoms may be evident. Finally, it is important to continue to assess potential associations between depression and indicators of nonadherence to recommended dietary and fluid intake, as well as decreased time adherence with the dialysis treatment prescription^[32–34]. These parameters may significantly impact patient success in navigating care transitions and avoiding costly hospitalization/re-hospitalization.

Demonstrable efficacy of CBT and/or anti-depressant drug therapy in improving depressive symptoms and other meaningful patient outcomes is expected to be highly relevant to both HD patients and caregivers. In addition, results of this study will potentially change clinical practice by informing regulators, policy makers, and dialysis organizations on how to restructure the delivery of healthcare to provide meaningful improvement in health of HD patients. For example, the results of the study could serve as an impetus for incorporating individual CBT delivered in the dialysis facility and/or drug therapy in the care of patients identified to be depressed. The ASCEND study has the potential to transform the clinical paradigm, as each of the two interventions can be readily integrated into the care of HD patients. First, Federal regulations mandate that each dialysis facility be staffed with a medical social worker who is charged with performing “psychosocial evaluations... providing casework and group work services to patients and their families in dealing with the special problems associated with ESRD...”^[86]. If the ASCEND trial demonstrates that CBT is effective in improving outcomes relevant to dialysis patients, a cadre of qualified professionals already exists within the current staffing structure of dialysis facilities to implement the intervention. Social workers are supported by the payments for dialysis treatments to facility providers. Second, Sertraline is an anti-depressant drug that is available in a generic form and easily prescribed. Hence, if it demonstrated to be both safe and effective, it can also be readily adapted into clinical practice.

Dialysis regulators and providers are increasingly recognizing the clinical problem of comorbid depression and its consequences. Most patients undergoing HD in the United States are Medicare beneficiaries, and the Quality Incentive Program (QIP) is a pay-for-performance program developed by the Centers for Medicare and Medicaid Services for dialysis facilities. Under this program, up to 2% of payments for all Medicare beneficiaries for an entire year are withheld should the dialysis facilities fail to meet the minimum threshold for quality standards. Starting January 1, 2016, one of the quality metrics includes certification by dialysis facilities that all patients are screened for and referred for appropriate management of depression.

One of the major strengths of this study is that it has engaged a broad group of stakeholders including patients and caregivers, patient advocacy organizations, National Institutes of Health, dialysis facility providers, and societies for nephrology social workers, nurses, and administrators. To this end, we have established a nationally representative Patient Council and a Stakeholder Council that guide us in the design and implementation of the study. The Patient Council incorporates the ‘patient voice’ and ensures that our study addresses issues that are meaningful to our hemodialysis patients. The Stakeholder Council for the ASCEND Study is composed representatives from ten organizations, including partnerships with 5 dialysis providers that operate dialysis facilities in 50 states and cumulatively provide care to

80% of hemodialysis patients in the country. This extensive engagement has allowed us to consider and develop plans to overcome potential barriers to the conduct of the study.

Despite these strengths, a few limitations of the study also deserve mention. First, a “no treatment” comparator control group (a group that is not receiving treatment for depression) is lacking, which could make the interpretation of success of either intervention (sertraline or CBT) less clear. This issue posed an ethical dilemma of knowingly assigning patients with major depression to no treatment under the auspices of a clinical trial and hence, this arm was not included in the final study design. Nonetheless, the study is designed to longitudinally follow patients who choose not to receive any treatment for depression. Analyses will be performed to describe the change in depressive symptoms for this cohort, although no comparisons will be made with data from the randomized clinical trial. Another potential limitation is introduction of bias due to loss-to-follow-up, as poor adherers who discontinue either intervention are at risk both for loss to follow-up and poor outcomes. However, the analysis plan allows a mixed effects modeling approach to mitigate the effects of loss-to-follow-up by incorporating information from baseline and the Week 6 measurements for participants who subsequently drop out of the study before Week 12.

4. Conclusion

The ASCEND clinical trial will be the first large-scale randomized controlled trial to evaluate the comparative efficacy of non-pharmacologic and pharmacologic treatments of depression in HD patients, and will provide the first evidence regarding whether an engagement interview increases acceptability of treatment for comorbid depression. Successful completion of this clinical trial will bridge a large knowledge gap in the management of psychosocial health of maintenance dialysis patients for practicing nephrologists and, most importantly, generate data to help inform decisions for maintenance dialysis patients faced with a diagnosis of major depression or dysthymia. Depression represents a potentially modifiable risk factor for poor outcomes, such as hospitalization and death, in this patient population. Therefore, the ASCEND study results can be used to design and power a much larger future trial evaluating the effects of depression treatment on hard outcomes such as cardiovascular events and death.

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Figure 1.
Schematic of A Trial of Sertraline vs. CBT for End-stage Renal Disease Patients with Depression (or ASCEND) design

Table 1**Inclusion and Exclusion Criteria**

Inclusion Criteria
Age ≥ 21 years
Undergoing thrice-weekly maintenance HD for ≥ 3 months
Able to speak English
Beck Depression Inventory II score ≥ 15
Current Major Depressive Disorder or Dysthymia on the MINI ^[54] ^a
Able to understand and sign informed consent.
Exclusion Criteria
Unwilling or unable to participate;
Active suicidal intent;
Cognitive behavioral therapy within 3 months prior for depression; or ongoing intensive psychotherapy (once weekly) for depression
Current drug therapy with SSRI ^b or SNRI ^c at doses higher than listed in <i>Appendix</i>
Evidence of cognitive impairment on Mini-Cog ^d ^[87]
Present or past psychosis or bipolar disorder I or II on the MINI ^[54]
Alcohol or substance abuse diagnosed on the MINI or history of such abuse in the past three months ^[54]
Life expectancy < 3 months, in the judgment of the site principal investigator
Anticipated to receive living related donor kidney transplantation within 3 months
Pregnancy, or lactation, or women of childbearing age not willing to use adequate birth control
Clinical and/or laboratory evidence of chronic liver disease
History of significant active bleeding in the past three months, such as hospitalization for gastrointestinal bleeding
Ongoing use of class I anti-arrhythmic medications (e.g., propafenone, flecainide), pimozide, monoamine oxidase inhibitors, reserpine, guanethidine, cimetidine, tri-cyclic anti-depressants, triptans, tramadol, linezolid, tryptophan, and St. John's wort;
Known hypersensitivity to sertraline

^aMINI: Mini International Neuropsychiatric Interview

^bSSRI: selective serotonin reuptake inhibitor

^cSNRI: serotonin norepinephrine reuptake inhibitor

^dMini-Cog: Mini cognitive assessment instrument

Table 2

Secondary Outcome Measures for Treatment Phase

Category	Outcome Variable	Measurement Tool
Patient-Reported Outcomes	Depressive symptoms	Patient Global Improvement Scale Beck Depression Inventory II
	Anxiety	Generalized Anxiety Disorder 7-item scale
	Effect of disease on well-being	Sheehan Disability Scale
	Fatigue	Short-Form 36 Energy/Vitality Sub-scale
	Health-related quality of life	One-Item Global Quality of Life Scale Satisfaction with Life Scale
	Perceived social support	Multi-Dimensional Scale of Perceived Social Support
	Sleep	Pittsburgh Sleep Quality Index
	Physical activity	Single-item Activity Measure
Adherence	Dialysis non-adherence	% treatments skipped or shortened by 10 minutes over 12-week intervention
	Dietary non-adherence	Inter-dialytic weight gain as % of post-dialysis weight over the preceding six weeks Serum phosphorus during 3 rd month

Table 3**Variables and Measurements**

Measurement	Time Period
<i>Depressive symptoms measures</i>	
Beck Depression Inventory-II	Pre-screening, Weeks 0, 6 and 12.
Mini International Neuropsychiatric Interview	Screening, (suicidality module administered throughout the study)
QIDS-C ₁₆ (blind assessor) ^a	Weeks 0, 6 and 12
QIDS-SR ₁₆ (self-report) ^b	Weeks 0, 2, 4, 6, 9 and 12
Global Improvement Scale	Weeks 0, 6 and 12
<i>Cognitive function measure</i>	
Mini-Cog ^c	Screening
<i>Health Literacy measure</i>	
STOFHLA ^d (3 items)	Screening
<i>Safety and tolerability measure</i>	
FIBSER ^e	Weeks 2, 4, 6, 9, and 12
<i>Health-related quality of life measure</i>	
One-item global quality of life scale	Weeks 0, 6 and 12
Satisfaction with Life Scale	Weeks 0, 6 and 12
<i>Anxiety symptoms measure</i>	
GAD-7 scale ^f	Weeks 0, 6 and 12
<i>Fatigue measure</i>	
SF-36 Energy/Vitality Sub-scale	Weeks 0, 6 and 12
<i>Perceived Social Support measure</i>	
Multi-Dimensional Scale of Perceived Social Support	Weeks 0, 6 and 12
<i>Sleep measure</i>	
Pittsburgh Sleep Quality Index	Weeks 0, 6 and 12
<i>Exercise measure</i>	
Single item Activity Measure	Weeks 0, 6 and 12
<i>Adherence measures</i>	
Inter-dialytic weight gain	Values for 6 weeks prior to baseline visit, Weeks 0–12

Measurement	Time Period
Shortened treatments, missed dialysis appointments and hospitalizations	For 6 weeks prior to baseline visit, Weeks 0–12
Pill count	Weeks 2, 4, 6, 9, and 12
<i>Demographic and comorbidity measures</i>	
Demographics, past	Screening
Medical history, list of comorbidities	Screening
Hemodialysis summary	Screening
Concomitant medications	Screening, Weeks 0, 6 and 12
<i>Blood tests</i>	
Hemoglobin	Screening; all results from the 12-week study period
Serum potassium	Screening; all results from the 12-week study period
Serum phosphorus	Screening; all results from the 12-week study period
Serum albumin	Screening; all results from the 12-week study period
Serum parathyroid hormone	Screening; all results from the 12-week study period
Kt/V urea	Screening; all results from the 12-week study period

Note: Week 0 denotes baseline assessment.

^{a, b} QIDS-C₁₆ and QIDS-SR₁₆: Quick Inventory of Depressive Symptomatology-Clinician Rated and Self-Report scales

^c Mini-Cog: Mini cognitive assessment instrument

^d STOFHLA: Short Test of Functional Health Literacy

^e FIBSER: Frequency, Intensity and Burden of Side Effects Rating Scale

^f GAD-7 scale: Generalized Anxiety Disorder 7-item scale