



# ASCEND: A Trial of Sertraline vs. CBT for End-stage Renal Disease Patients with Depression

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## Study Protocol

### Treatment Options for Depression in Patients Undergoing Hemodialysis

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## List of Abbreviations

AAKP	American Association of Kidney Patients
BDI-II	Beck Depression Inventory
CATI	Computer Assisted Telephone Interviewing
CBT	Cognitive Behavioral Therapy
DPC	Dialysis Patient Citizens
ESRD	End-Stage Renal Disease
FIBSER	Frequency, Intensity, and Burden of Side Effects Rating
MINI	Mini International Neuropsychiatric Interview
QIDS-C	Quick Inventory of Depressive Symptomatology, Clinician Rating
QIDS-SR	Quick Inventory of Depressive Symptomatology, Self-Report
QOL	Quality of Life
SCID	Structured Clinical Interview for DSM-IV
SF-36	Short-Form 36

## Study Summary

Title	A Trial of Sertraline vs. CBT for End-Stage Renal Disease Patients with Depression (ASCEND)
Short Title	ASCEND Trial
Protocol Number	PCORI CER-1310-07253
Phase	Phase III
Methodology	Randomized, open-label trial
Study Duration	3 years
Clinical Sites	University of New Mexico, Albuquerque, NM University of Texas Southwestern, Dallas, TX University of Washington, Seattle, WA
Data Coordinating Center	Center for Biomedical Statistics, University of Washington, Seattle, WA
Primary Objectives	<ul style="list-style-type: none"> <li>• Compare the efficacy of engagement interview with a control visit in patients undergoing HD with comorbid current major depressive episode or dysthymia in increasing treatment for the condition.</li> <li>• Compare the efficacy of 12-week treatment with sertraline with individual CBT for the treatment of depressive symptoms in patients undergoing HD with comorbid current major depression or dysthymia.</li> </ul>
Secondary Objectives	<ul style="list-style-type: none"> <li>• Compare the efficacy of sertraline with individual CBT in improving patient-reported outcomes and adherence with treatment in patients undergoing HD with comorbid major depression or dysthymia.</li> <li>• Undertake a longitudinal evaluation of depressive symptoms over 12 weeks in patients undergoing HD with comorbid major depression or dysthymia who refuse to accept any treatment.</li> </ul>
Number of Participants	<ul style="list-style-type: none"> <li>• Engagement interview vs. control visit: 200</li> <li>• Sertraline vs. CBT: 120</li> <li>• Cohort study of untreated patients: 40</li> </ul>

Diagnosis and Main Inclusion Criteria	ESRD patients undergoing HD with major depression or dysthymia
Interventions	<ul style="list-style-type: none"> <li>• Engagement Interview</li> <li>• Sertraline drug therapy</li> <li>• Individual CBT</li> </ul>
Duration of study	Up to 16 weeks
Primary Outcomes	<ul style="list-style-type: none"> <li>• Efficacy of Engagement Interview: Initiate treatment for co-morbid depression</li> <li>• Comparative Efficacy of Sertraline vs. CBT: Change in depressive symptoms as per QIDS-C</li> </ul>
Statistical Methodology	<ul style="list-style-type: none"> <li>• Efficacy of Engagement Interview: Fisher's exact test to compare the proportions of patients who initiate treatment for comorbid depression.</li> <li>• Comparative Efficacy of Sertraline and CBT: Longitudinal mixed effects analyses will be applied to QIDS-C to compare means at Weeks 6 and 12 assessments between the CBT and Sertraline groups with the treatment group and clinical center as fixed effects in the model. An unstructured covariance matrix will account for serial correlations in outcome measurements within patients and the model will constrain baseline means of the outcome to be equal in the treatment groups. Linear contrasts will be constructed to estimate for each outcome variable: (a) mean difference in outcome between the treatment groups at Week 12 (primary assessment of treatment effect); (b) mean difference in 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).</li> </ul>

Study Oversight	<ul style="list-style-type: none"> <li>• Local Institutional Review Boards</li> <li>• Data Safety Monitory Board (Chair: Alan Kliger, MD)</li> <li>• Patient Advisory Council (Chair: Lori Hartwell)</li> <li>• Stakeholder Council (Chair: Thomas Parker, MD)</li> </ul>
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Reviewed and approved by:



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Rajnish Mehrotra, Principal Investigator



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Alan Kliger

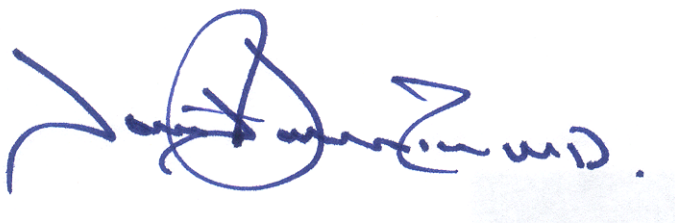
Chair, Data Safety Monitoring Board



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Lori Hartwell

Chair, Patient Council



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Thomas Parker

Chair, Stakeholder Council

## 1. Introduction

The prevalence of comorbid depression is about four-fold higher in patients undergoing maintenance HD than in the general population. A large number of studies have demonstrated that comorbid depression in patients undergoing HD is associated with worse patient-centered outcomes such as lower health-reported quality of life (QOL), greater burden of somatic symptoms, sexual dysfunction, cardiac events, hospitalizations, mortality, and withdrawal from dialysis<sup>[1-17]</sup>. Yet, there is wide variability in the diagnosis and treatment of comorbid depression in HD patients: the condition is not diagnosed in most patients, and when diagnosed, invariably not treated. This may, in part, be because of patients' reluctance to accept the diagnosis and/or therapy and lack of evidence for efficacy of different treatments for depression in patients undergoing HD<sup>[18, 19]</sup>. ASCEND, 'A Trial of Sertraline vs. CBT for End-stage Renal Disease Patients with Depression', is the first multi-center randomized controlled trial that will enroll a racially/ethnically diverse group of English and Spanish-speaking individuals undergoing HD with comorbid major depression or dysthymia in up to 50 dialysis facilities in three metropolitan areas in the United States. The study will (1) compare the efficacy of engagement interview vs. a control visit for patients' probability of starting treatment for comorbid depression; (2) compare the efficacy of sertraline vs. individual CBT for improvement of depressive symptoms in patients undergoing HD with comorbid major depression or dysthymia; and (3) study the evolution of depressive symptoms in a prospective longitudinal cohort of individuals who find all forms of treatment for the condition unacceptable. The results of the study will provide patients and healthcare providers with much needed information when weighing treatment options for comorbid depression.

### 1.1 Background

In the United States, over 400,000 individuals are undergoing HD for the treatment of ESRD in over 5000 dialysis facilities at an annual societal cost of \$50 billion<sup>[20]</sup>. Most ESRD patients have multi-morbidity and report significant impairments in their quality of life (QOL)<sup>[1, 20-25]</sup>. They experience frequent care transitions as they are hospitalized on an average for 12 days every year, and one-third are re-hospitalized within 30 days of discharge<sup>[20]</sup>. In addition to the burden from disease, these individuals have a high burden of treatment. They receive HD treatments at least three times every week and each session is 3-4 hours long. They need to make numerous dietary changes including limiting daily fluid intake, and prescribed 10-12 medications with a median of 17 pills daily<sup>[23, 26]</sup>. With such a high burden of both disease and its treatment, it is imperative to identify effective

interventions to improve patient-centered outcomes for HD patients and to enhance their ability to adhere to complex treatment regimens.

Depression is the most common psychiatric disorder in HD patients. In a recent systematic review of 198 cohorts with 46,505 patients, the summary prevalence of depression using the most stringent criteria for diagnosis, a structured clinical interview, was 23%<sup>[27]</sup>. This prevalence is over four-fold higher than in the general population<sup>[27]</sup>. Several studies have demonstrated a strong association between the severity of depressive symptoms and somatic symptom burden, sexual dysfunction, unemployment, and poor QOL in HD patients<sup>[1-6]</sup>. These outcomes are highly relevant to patients and influence their sense of wellbeing. Numerous studies have also consistently shown an association between the severity of depressive symptoms and cardiac events, hospitalizations, mortality, and withdrawal from dialysis<sup>[7-17]</sup>. Two potential mechanisms may explain these latter associations: First, depression is associated with systemic inflammation, which may be the proximate cause of morbidity and mortality<sup>[28, 29]</sup>. Second, depression makes self-management difficult leading to challenges in adherence with the complex treatment regimens for ESRD<sup>[30]</sup>; depressive symptoms are associated with higher likelihood of patients' shortening the length of and/or skipping dialysis treatments, excessive fluid intake, and lower medication adherence<sup>[31-35]</sup>. Moreover, depression makes navigating care transitions, as frequently experienced by HD patients, difficult.

There is wide variability in the diagnosis and treatment of comorbid depression in HD patients. Even though HD patients have numerous symptoms that affect their well-being (viz., lack of energy, insomnia), physicians often do not recognize them and hence, don't make any attempts to alleviate these symptoms<sup>[36]</sup>. Consistent with this, only 40% of 1089 HD patients with clinically significant depressive symptoms had been diagnosed and/or treated<sup>[10]</sup>. In the USRDS Special Study (ACTIVE-ADIPOSE), 25% of the participants had a CES-D score  $\geq 18$ ; only 5.6% of these individuals were receiving anti-depressants (Kutner, personal communication). While this may suggest the need for systematic screening for depression in the routine care of HD patients, even when implemented, an appropriate intervention is made infrequently<sup>[14, 37]</sup>. In a recent clinical trial, treatment was instituted in only 17% of patients, even though the diagnosis of depression was communicated to physicians directly or through nurses trained to offer treatment recommendations<sup>[38]</sup>. Hence, despite the high prevalence and robust data associating it with poor patient-centered outcomes, comorbid depression is neither diagnosed when present nor treated when identified in HD patients. This is likely due to lack of high-level generalizable evidence for the efficacy of treatment for the condition in this population.

## 1.2 Rationale for Study

### 1.2.1 Engagement Interview

Past studies have also shown that many HD patients with comorbid depression do not wish to receive any form of treatment in part because of the lack of their understanding about depression, and the stigma associated with mental illnesses<sup>[38]</sup>. In a recent cluster randomized controlled clinical trial, 220 HD patients were randomly assigned to provide direct feedback along with evidence-based treatment algorithms, or to specific recommendations from nurses trained in symptom assessment and algorithms to patients. There was no significant difference in the implementation of treatment in the feedback arm (11 of 37) or the nurse recommendation arm (6 of 28). Consistent with this observation, the patients that responded to a survey administered to dialysis patients through our two patient advocacy partners, AAKP and DPC, over 60% ranked “no specific intervention” as their top choice were they to suffer from comorbid depression. Similarly, over 40% of patients approached for participation in a recently completed trial of individual CBT in Brooklyn did not wish to undergo treatment for clinically significant depressive symptoms<sup>[39]</sup>. Hence, it is necessary to determine whether an engagement interview prior to discussing options increases the frequency of treatment for depressive symptoms.

A large number of clinical trials have tested the efficacy of collaborative care for the treatment of depression in primary care in individuals with comorbid illnesses such as diabetes mellitus. An engagement interview, which is based on principles of motivational interviewing, is an integral component of the collaborative care arm of the studies. At least one study was shown to increase acceptance of evidence-based treatment of depression in low-income minority women who are new mothers<sup>[40]</sup>. In another recent study, 925 adult patients treated by 135 primary care clinicians were randomized to watch a depression engagement video, or a tailored interactive multimedia computer program, or a control visit<sup>[41]</sup>. The primary outcome was a composite measure of patient-reported anti-depressant drug recommendation, mental health referral, or both. Individuals randomized to interactive multimedia program were significantly more likely to achieve the primary outcome compared to controls (26% vs. 26.3%); there was no significant difference between the use of depression engagement video and controls (17.5% vs. 16.3%). There are no data on the efficacy of this approach for the increasing the likelihood of treatment for depressive symptoms among patients undergoing HD.

The 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.



### 1.2.2 Comparative Efficacy of individual CBT and anti-depressant drug therapy

There are two distinct approaches to treat depression – cognitive behavioral therapy (CBT, or psychotherapy), and anti-depressant drug therapy. While developing the research plan, responses from 61 ESRD patients indicated that not all treatment options for depression are equally acceptable to every HD patient, since the two approaches for treatment are very different; CBT necessitates multiple encounters with a therapist for patients who already need to go to a healthcare facility for dialysis sessions thrice weekly. Similarly, anti-depressant drug therapy would add 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 insurance coverage and out-of-pocket costs to patients. Hence, the current study will compare two different treatments that, if found to be comparably efficacious, would offer options for treatment that are most acceptable and/or available to them and their providers. There is a paucity of data for the efficacy of either of these approaches for the treatment of comorbid depression in HD patients<sup>[42]</sup>. There is only one clinical trial that has compared the efficacy of citalopram and psychological training for improving depression and anxiety symptoms in patients undergoing hemodialysis<sup>[43]</sup>. In this single-center study, 44 patients undergoing hemodialysis in Iran who scored 8 or more on the Hospital Anxiety and Depression Scale were randomly assigned to either 20 mg/d of citalopram or six one-hour sessions of psychological training. While both treatments resulted in improvement in both anxiety and depressive symptoms, there was no significant difference in the efficacy of these two interventions. This study will compare the efficacy of CBT with anti-depressant drug therapy in a multi-center study in a larger multi-ethnic population to ensure high external validity.

***Cognitive Behavioral Therapy (CBT):*** CBT is a short-term focused psychotherapy for many psychological problems including depression<sup>[44]</sup>. The focus of the therapy is on how the individual is thinking, behaving, and communicating today rather than on their 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<sup>[45]</sup>. Thus, CBT helps the patients learn effective self-help skills that are used in homework assignments that target change in the way they think, feel, and behave now. CBT is action-oriented, practical, rational, and helps the patient gain independence and effectiveness in dealing with real-life issues.

Numerous studies show that CBT is a first-line treatment for depression, is endorsed by clinical practice guidelines from the American Psychiatry Association, and does not have the negative side-effects of medications<sup>[42, 44]</sup>. It would also be expected to reduce relapse because patients may learn self-management techniques during therapy. The efficacy of CBT has been demonstrated in two pilot single-center studies of HD patients with

comorbid depression, setting the stage for a larger-scale testing in a multi-center clinical trial (n=85 and 63) [39, 46]. In the first clinical trial conducted in Brazil, 41 patients in the intervention group received 12 weekly sessions of group CBT by a trained psychologist over three months and 44 patients received the usual treatment [39]. After three months of treatment, there was a significant improvement in depressive symptoms with BDI-II (3 month score,  $14.1 \pm 8.7$  vs.  $21.2 \pm 9.1$ ), major depression module on the MINI (3 month score,  $1.9 \pm 2.8$  vs.  $4.3 \pm 2.9$ ), burden of kidney disease, quality of social interaction, sleep, and mental component summary of health-related quality of life. In the second clinical trial conducted in Brooklyn, New York, 65 patients were randomly assigned to treatment first or wait-list control group [46]. Individual CBT was administered chair side while the patient underwent hemodialysis for three months. The intervention was associated with a significant improvement in depressive symptoms (Beck's Depression II and Hamilton Depression Rating Scale), quality of life (Kidney Disease Quality of Life Short Form), and treatment adherence (inter-dialytic weight gain). This study will test the efficacy of individual CBT, as tested in the latter clinical trial, among patients treated in up to 50 dialysis facilities operated by 7 providers in a geographically, ethnically, and culturally diverse and broader array of patients across a wider age range than done thus far.

**Anti-Depressant Drug Therapy with Sertraline:** Anti-depressant drugs are also a first-line treatment for depression in the general population [42, 47]. The data for anti-depressant drugs are even more limited, as patients with kidney diseases have been excluded from all major clinical trials [18, 19]. The benefits with drug therapy in otherwise healthy individuals cannot be extrapolated to those with chronic medical illnesses as evident from the lack of efficacy of anti-depressant drugs in large clinical trials of patients with asthma and congestive heart failure [48, 49]. Only two randomized trials of drug therapy for the treatment of depression have been reported for HD patients; only one tested the effect on depressive symptoms [48]. In a placebo-controlled trial of 14 patients undergoing hemodialysis, the improvement in depressive symptoms with 8-weeks of treatment with fluoxetine did not reach statistical significance [48]. At least nine non-randomized uncontrolled studies with 7-44 HD patients with comorbid depression each, treated with anti-depressant drugs, have been published, most of which demonstrated improvement in depressive symptoms [49-57]. These limited data allow us to posit a significant improvement in patient-reported outcomes with treatment of comorbid depression in HD patients.

Clinical practice guidelines indicate that only selective serotonin-reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and bupropion meet the balance between efficacy and tolerability [42]. In ESRD patients, loss of renal excretory capacity further complicates drug selection [18]. A recent systematic review of 28 studies for 24 anti-

depressant drugs in patients with kidney disease indicates that both serotonin-norepinephrine reuptake inhibitors and bupropion require dose reduction <sup>[18]</sup>. 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, a selective serotonin reuptake inhibitor, will be used as the anti-depressant for this clinical trial.

The drug is metabolized to an inactive form before being excreted via the kidneys; is safe in patients with heart disease (SADHART trial); and available in generic form <sup>[18, 19]</sup>. In a study of ten HD patients receiving 200 mg sertraline/day for 21 days, the pharmacokinetics were no different than 12 age-matched healthy volunteers <sup>[58]</sup>. At least six studies including 128 dialysis patients treated with sertraline have been published <sup>[50, 56, 57, 59-61]</sup>; three reported improved hemodynamic stability during dialysis, and none reported any intolerability.

### **1.2.3 Evolution of depressive symptoms without any treatment in patients undergoing hemodialysis**

In any individual, a diagnosis of major depression or dysthymia requires treatment. However, some patients are reluctant to either accept a diagnosis or treatment for depression. Over 60% of the patients with kidney disease that we surveyed ranked “no specific intervention” as their top preference for managing clinically significant depressive symptoms. In other patients, the available treatment options may not be feasible or tolerated; this may be from availability and/or insurance coverage for such treatment or unacceptable pill burden and/or adverse effects. As such, there is a need for us to understand the natural course of depressive symptoms in patients undergoing maintenance hemodialysis. Such data are extremely sparse. In a single center observational cohort study, the data on the presence and severity of depressive symptoms using SCID-1 Depression module were available at two different time points, 16-months apart <sup>[62]</sup>. Of the 47 patients with sufficient follow-up data, 12 had a depressive disorder and 2 had dysthymia. Upon follow-up, 7 of the 12 subjects with depressive disorder no longer qualified for a SCID diagnosed depressive disorder while 5 had persistent depression. Of the two patients with dysthymia, they met the SCID criteria for major depression at the second time point. In the SMILE study, 286 subjects completed at least one depression or pain assessment <sup>[63]</sup>. The subjects completed a median of 16 and total of 4452 monthly PHQ-9 assessments; moderate to severe depressive symptoms were reported on 788 (18%). At baseline, 73 patients (26%) reported moderate to severe depressive symptoms, 50% on at least one assessment, and 9% on  $\geq 755$  of assessments

[63]. In this multi-center study, patients that do not find any form of treatment acceptable either within or outside the scope of the clinical trial will be followed for the presence and/or severity of depressive symptoms for up to 12 weeks. This will generate evidence to inform patients on what they should expect if they were to decide not to accept any form of treatment.

## 2. Study Objective and Aims

With the ASCEND study, we seek to test two hypotheses:

- Hypothesis One: In HD patients with comorbid current major depressive episode or dysthymia, an engagement interview significantly increases the frequency of treatment for comorbid depression.
- Hypothesis Two: In HD patients with comorbid current major depressive episode or dysthymia, there is no significant difference in the efficacy of 12-week treatment with individual CBT in a dialysis facility or anti-depressant drug therapy.

### 2.1 Efficacy of the Engagement Interview

The ***primary measure of efficacy*** will be % of patients undergoing hemodialysis with co-morbid depression who initiate treatment for the condition. This will be defined as one of the following:

- Completing at least one psychotherapy session either as a part of the clinical trial or in the community within four weeks of the engagement/control visit.
- Receiving a supply of anti-depressant drug either as a part of the clinical trial or the treating physician within four weeks of the engagement/control visit.

The ***secondary measure*** of efficacy will be the % of patients undergoing hemodialysis with co-morbid depression who are willing to accept treatment. This will be measured by the patient's intent and will be defined as one of the following:

- Signing the informed consent to be randomly assigned to individual CBT or drug therapy.
- Receiving a referral by the research team and/or primary care physician and/or treating nephrologist to a therapist for psychotherapy in the community within two weeks of establishing an engagement/control visit.

- Receiving a prescription for anti-depressant drug therapy from primary care physician and/or treating nephrologist within two weeks of establishing an engagement/control visit.

## 2.2 Comparative Efficacy of individual CBT and sertraline drug therapy

### 2.2.1 Primary Measure of Efficacy

The primary measure of efficacy will be the mean difference in QIDS-C score at Week 12 between treatment groups.

### 2.2.2 Secondary Measure of Efficacy

Two groups of secondary measures of efficacy will be examined – Patient Reported Outcomes and Treatment Adherence.

#### 2.2.2.1 Patient-Reported Outcomes

The mean difference in the scores for each of the following scales at Week 12 between treatment groups:

- Depressive Symptoms:
  - Global Improvement Scale
  - Beck Depression Inventory-II
- Anxiety Symptoms:
  - Generalized Anxiety Disorder 7- item (GAD-7) 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
- Exercise:
  - Single item Activity Measure

#### 2.2.2.2 Treatment Adherence

This will comprise:

- Non-Adherence with Dialysis as defined by the percentage of all dialysis sessions skipped and/or requested by the patient to be shortened by  $\geq 10$  minutes over the 12-week intervention period. Dialysis sessions missed due to hospitalization will not be included as a skipped treatment.
- Non-Adherence with Fluid Intake as defined by inter-dialytic weight gain (as % of post-dialysis weight) during Week 12 of the study.
- Non-Adherence with Diet and/or Medications as defined by serum phosphorus level measured as a part of routine clinical care during the third month of participation in the study.

### 3. Study Design and Overview

The ASCEND study is an open-label, randomized, controlled clinical trial of HD patients with comorbid depression, with accrual of participants over 24 months, comparing (1) a single engagement interview with a control visit for initiating treatment for comorbid depression in 200 patients; and (2) individual CBT with drug therapy for 12 weeks in 120 HD patients for depressive symptoms at three clinical sites - Seattle, Dallas, and Albuquerque (Figure 1 and Appendix 1). The length of intervention is selected based upon considerable data from the general population that indicate 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. In addition, up to 40 patients who refuse to accept treatment either within or outside the clinical trial, will also 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.

An **Engagement Interview** will comprise a one-on-one session with the patient, during which the health-care provider will use reflective statements and non-judgmental listening techniques, will explore barriers to treatment, and will help the patient articulate ambivalence about engaging in treatment. This session will be enhanced with a 20-minute DVD that the subject will watch with the therapist in the dialysis facility<sup>[64]</sup>. The subject will be encouraged to take the DVD home with them and watch it with their family members as well.

**Cognitive Behavioral Therapy (CBT)** is a short-term psychotherapy that will focus on how the individual is thinking, behaving, and communicating today rather than on their childhood experience. The therapist will assist the patient in identifying specific distortions (cognitive assessment) and biases in thinking and will provide guidance on how to change this thinking<sup>[45]</sup>. Thus, CBT will help the patients to learn effective self-help skills that will target change in the way they think, feel, and behave. CBT will be

administered while the patient is undergoing the HD procedure; however, alternative arrangements will be made for individual patients based upon their preferences.

**Anti-Depressant Drug Therapy** will be delivered with sertraline, a selective serotonin reuptake inhibitor, and the dose will be titrated using the Measurement Based Care Protocol.

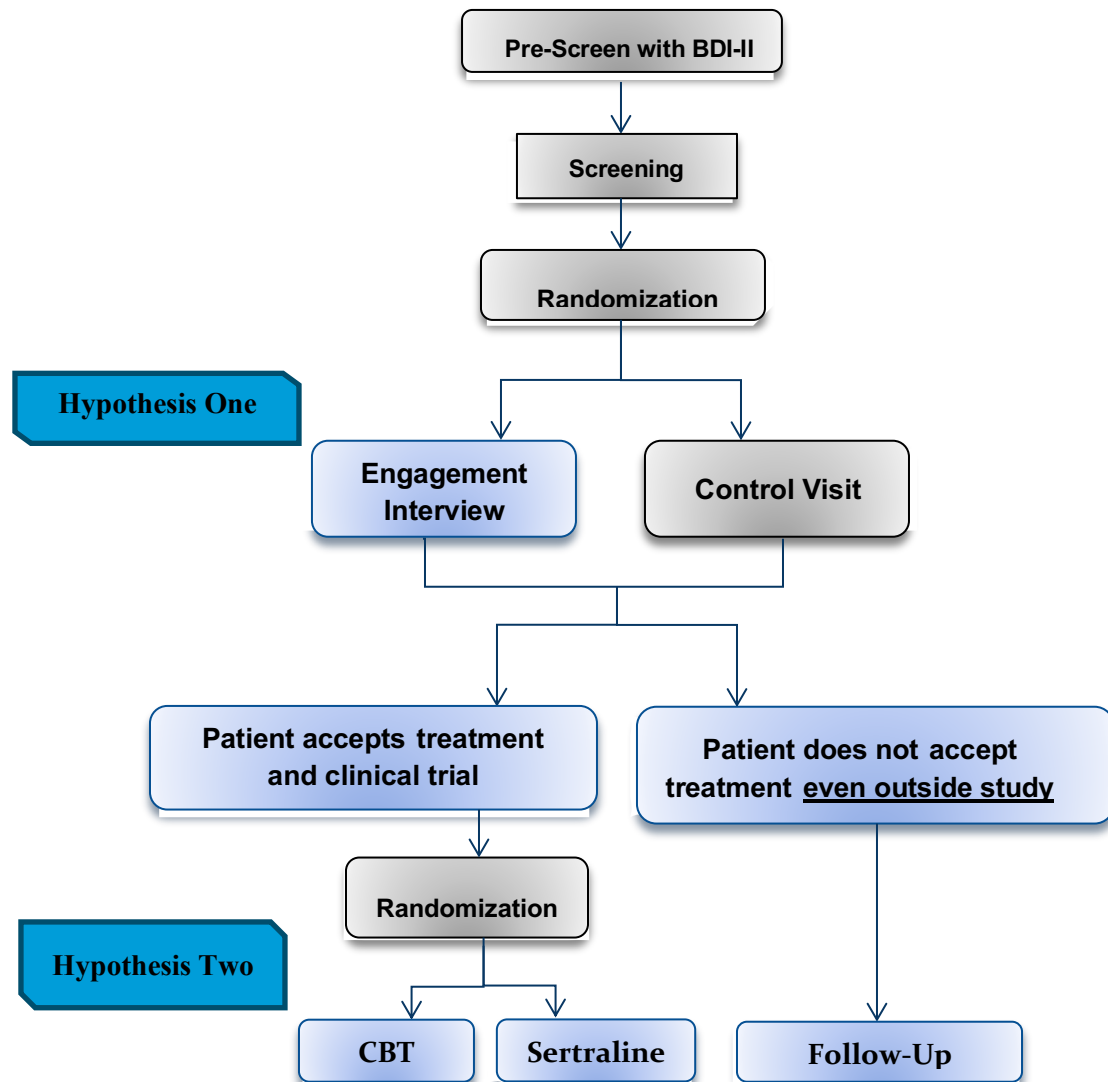


Figure 1 Study Overview



## 4. Participant Selection and Withdrawal

### 4.1 Study Population

#### 4.1.1 Pre-Screening:

All patients with ESRD being treated in participating dialysis facilities that meet the following three criteria, will be eligible to participate in pre- screening: (1) age  $\geq 21$  years; (2) undergoing maintenance HD  $\geq 3$  months; and (3) speak either English or Spanish. These individuals will be invited to complete the 21-item Beck Depression Inventory (BDI). Individuals with BDI score  $\geq 15$  will be invited to participate in subsequent study-related activities.

#### 4.1.2 Subjects for Engagement Interview and Treatment of Comorbid Depression:

Inclusion Criteria:

1. Age  $\geq 21$  years;
2. Undergoing thrice-weekly maintenance HD for  $\geq 3$  months;
3. Able to speak either English or Spanish;
4. BDI-II score  $\geq 15$ ; and
5. Meets diagnostic criteria for either current major depressive episode or dysthymia on the MINI<sup>[65]</sup>.

Exclusion Criteria:

1. Active suicidal intent;
2. Intensive psychotherapy (once weekly) for the treatment of depression;
3. Current drug therapy for the treatment of depression with serotonin receptor uptake inhibitors or serotonin norepinephrine reuptake inhibitors at doses higher than listed in Appendix Two;
4. Evidence of cognitive impairment on Mini-Cog<sup>[66]</sup>;
5. Present or past psychosis or bipolar disorder I or II on the MINI<sup>[65]</sup>;
6. Alcohol or substance abuse diagnosed on the MINI or history of such abuse in the past three months<sup>[65]</sup>;
7. Life expectancy  $< 3$  months, in the judgment of the site principal investigator;
8. Anticipated to receive living related donor kidney transplantation within 3 months;
9. Pregnancy, or lactation, or women of childbearing age not willing to use adequate birth control;
10. Clinical and/or laboratory evidence of chronic liver disease;
11. History of significant active bleeding in the past three months, such as hospitalization for gastrointestinal bleeding;



12. Current use of class I anti-arrhythmic medications (e.g., propafenone, flecanide), pimozone, monoamine oxidase inhibitors, reserpine, guanethidine, cimetidine, tricyclic anti-depressants, triptans, tramadol, linezolid, tryptophan, and St. John's wort; and
13. Known hypersensitivity to sertraline.

## **4.2 Participant Pre-Screening and Recruitment**

### **4.2.1 Pre-Screening and Enrolling Subjects in Engagement Interview Phase**

All eligible patients with ESRD being treated in participating dialysis facilities will be invited to complete the 21-item Beck Depression Inventory (BDI). Study personnel will provide all patients with an information sheet that will describe the purpose and nature of pre-screening and provide patients with an option to opt-out of the pre-screening.

Once the patient completes the BDI-II, it will be reviewed immediately upon receipt for subjects' response to question 9 to determine the presence of suicidal intent; those who answer either "I would like to kill myself" or "I would kill myself if I had the chance" will be emergently triaged.

The summary score on BDI-II will be computed within 48 hours of receipt and subjects will be managed based on the summary score:

- Score  $\geq 15$  will be approached for their willingness to complete the modules of MINI, and undergo other screening activities. Subjects that agree will be invited to sign a consent form (ICF-1) and those individuals with a diagnosis of major depression or dysthymia on the MINI will be randomly assigned to (1) an engagement interview with a trained therapist, or (2) brief discussion with study staff.
- The information on subjects with score  $\geq 15$  who refuse to undergo additional screening activities will be communicated to the patients' treating nephrologist. Subjects will also be presented with a list of mental health care providers and resources in their community. This will include providers who serve safety-net populations like those with Medicaid insurance and those that provide charity care.
- Information on subjects with score  $< 15$  will also be communicated to the patients' treating nephrologist.

### **4.2.2 Re-Administration of Pre-Screening**

Some subjects may complete the 21-item Beck Depression Inventory (BDI) additional time(s). These include when a subject:

- Scores  $\geq 15$ , but is unable to be screened within the 10 day window. A second BDI will be administered for a valid score prior to screening.
- Scores  $< 15$ , 3 months have passed since previous administration.

#### **4.2.3 Enrollment of Subjects in Comparative Efficacy Trial of individual CBT and Anti-Depressant Drug Therapy**

The clinical trial will be limited to patients with major depression or dysthymia, with no additional psychiatric co-morbidity. Subjects with (1) confirmed diagnosis of major depression or dysthymia on the MINI, (2) are willing to receive treatment for comorbid depression, and (3) who meet the inclusion and exclusion criteria, will be approached for their willingness to be randomly assigned to either individual CBT or anti-depressant drug therapy as a part of the clinical trial. All subsequent study-related activities will begin only upon the subjects' signing an informed consent form (ICF-2).

#### **4.2.4 Enrollment of Subjects in Observational Cohort Study with no Active Treatment**

Subjects who (1) are not willing to participate in the clinical trial and (2) do not find any treatment acceptable outside the clinical trial will be invited to participate in the prospective observational cohort for serial assessment of depressive symptoms.

#### **4.2.5 Patients**

#### **4.6 Early Termination of Study Treatment and Withdrawal of Subjects**

Active treatment with the study interventions (individual CBT or sertraline drug therapy) will be terminated if the patient:

- Withdraws informed consent
- Unable to follow study procedures
- Undergoes kidney transplantation
- Transfers to home dialysis
- Transfers care to a dialysis facility outside the participating metropolitan areas.

Under each of these circumstances all attempts will be made to continue to ascertain primary and secondary patient-reported outcomes with computer assisted telephone interviewing (CATI).

## **5. Study Interventions**

### **5.1 Engagement Interview Phase**

Subjects will be randomly assigned to engagement interview or a control visit using block randomization within each site based on variable blocks of size 6 to 10. This will ensure that equal numbers of participants are randomized to each group, and that the two groups are balanced at periodic enrollment intervals. Randomization assignment will be obtained via the secure study web portal hosted at the Data Coordinating Center at the University of Washington.

### 5.1.1 Engagement Interview

#### 5.1.1.1 Overview of the Intervention

Trained CBT therapists at each of the three sites will conduct the engagement interview. The session will be aimed at improving the acceptance of the diagnosis of depression by patients and treatment for the same. The therapist will invite patients to tell their story of recent stress (including medical symptoms) and possible connection to depression. The therapist will use reflective statements and non-judgmental listening techniques so that the patient feels heard. Potential barriers to acceptance of treatment and how to overcome them will be discussed. Motivational interviewing techniques will be used to help the patient articulate potential ambivalence about treatment and therapists will reflect back to the patients their expression of wanting life to be different despite ambivalence about treatment. The session is anticipated to last an hour and maybe supplemented with a 40-minute DVD entitled “Depression Self Care Companion for Better Living” in an effort to improve health literacy regarding depression and its treatment. The subject can watch salient portions of the video along with the therapist, or watch it at home or in the dialysis unit.

#### 5.1.1.2 Training and Certification Prior To Implementation in Trial

Each of the therapists will undergo a **one-day in-person training** to be scheduled in Seattle prior to implementing the intervention. The training will be led by Nancy Grote at the School of Social Work at the University of Washington, supported by Yaminette Diaz Linehart; the latter will focus on adapting the intervention culturally to Latinos.

Following the completion of training, each therapist will be required to complete mock interventions prior to implementation of the intervention in the clinical trial. These mock sessions will be audio recorded and will be reviewed by Drs. Grote and Linehart using a structured fidelity adherence form. Once the therapists are deemed competent in the intervention, they will be ready to implement the intervention in a clinical trial. In the event of staff turnover, any new therapist will need to undergo training procedures prior to start of intervention for the clinical trial.

#### 5.1.1.3 Monitoring the Fidelity of the Intervention

During the conduct of the trial, bi-weekly conference calls will be scheduled with all the therapists during which clinical issues and implementation will be discussed and cases reviewed. All sessions of the engagement interview will also be audio-taped and a 10% random sample will be periodically reviewed to provide rating for treatment fidelity using forms that outline the major skills and intervention pieces.

### 5.1.2 Control Visit

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

## 5.2 Comparative Efficacy of individual CBT vs Anti-Depressant Treatment Drug Therapy

The subjects will be randomly assigned to individual CBT or sertraline drug therapy using block randomization as for the engagement interview. The randomization will occur using the secure study web portal.

### 5.2.1 Individual CBT in Dialysis Facility

#### 5.2.1.1 Overview of the Intervention

Individuals will undergo 10 CBT sessions of 60 minutes each, by a therapist in the dialysis facility (8 weekly sessions; then every other week x 2). The CBT will be administered while the patient is undergoing HD; however, alternative arrangements will be made upon individual patient's preferences. To the extent possible, each session will be scheduled on the same day of the week for any given patient. Standard CBT intervention for depression will be modified for the challenges associated with HD treatment to include psycho-education, adherence with the dialysis prescription, adapting behavioral activation, and identification and challenging ESRD specific cognitive distortions and maladaptive thought patterns (detailed manual in **Appendix Five**).

During the course of intervention, study subjects will undergo assessment of severity of depressive symptoms using Quick Inventory of Depressive Symptoms – Self-Report (QIDS-SR) every two weeks for the first six weeks (weeks 0, 2, 4, and 6) and on weeks 9 and 11. The results of these assessments will be available to the therapist as they will be for titration of the drug therapy.

#### 5.2.1.2 Training and Certification Prior To Implementation in Trial

The training of the therapists in the implementation of the CBT will be held in conjunction with the training for the engagement interview. This training is expected to last two days, will be held **in-person** in Seattle, and led by Daniel Cukor.

Following the completion of training, each therapist will be required to complete mock interventions prior to implementation of the intervention in the clinical trial. These mock sessions will be audio recorded and will be reviewed by Dr. Cukor using a structured fidelity adherence form. Once the therapists are deemed competent in the intervention, they will be ready to implement the intervention in a clinical trial.

**Table 2 Overview of individual CBT for the study**

Sessions 1-2	<p><b>Assessment</b> – Assess patient’s motivation for change, goals for treatment, ‘stage of change’. Evaluate need for patient to modify fluid intake, adherence with medical regimen.</p> <p><b>Psycho-education</b> – highlight similarities/differences between depression and medical illness.</p> <p><b>Behavioral Intervention</b> – Behavioral activation – increase patients’ enjoyable activities.</p>
Sessions 3-6	<p><b>Cognitive Intervention</b> – Train participants in relationship between dysfunctional automatic thoughts and negative perceptions and outcomes; Improve patient’s ability to categorize distorted thoughts and provide rational behavioral responses; Identify recurring patterns of maladaptive thinking and challenge negative schemas.</p>
Sessions 7-8	<p><b>Health Behaviors</b> – Teach and practice healthy living (adherence) skills for HD treatment; Increase positive social contacts – initiating contact, building support network; Teach and practice strategies for managing anxiety</p>
Sessions 9-10	<p><b>Termination</b> – Review newly learned skills and practice eliciting, challenging, and modifying maladaptive thoughts; Plan for termination of therapy – identify which interventions were helpful and which were not, and focus on relapse prevention</p>

### **5.2.1.3 Monitoring the Fidelity of the Intervention**

During the conduct of the trial, bi-weekly conference calls will be scheduled with all the therapists during which clinical issues and implementation will be discussed and cases reviewed. All individual CBT sessions will be audio-taped and a 10% random sample periodically reviewed to provide rating for treatment fidelity using forms that outline the major skills and intervention pieces.

### **5.2.1.4 Monitoring Adherence to Intervention**

A structured form will be developed for therapists to monitor patients’ adherence with health behaviors and/or homework at the start of each session following the first session. This will generate data to describe the association between adherence with skills taught during CBT with observed efficacy with the intervention.

## 5.2.2 Anti-Depressant Drug Therapy

### 5.2.2.1 Overview of the Intervention

The site investigators will prescribe sertraline drug therapy and dose titration will be implemented using “Measurement-Based Care”, a model of patient-centered shared-decision making (Appendix Three). This protocol incorporates standardized assessments of depressive symptoms and drug side effects, and the research team and the patient make joint decisions about the next steps in titration – to maintain, increase, or decrease the dose<sup>[19, 67]</sup>. This will help establish the highest efficacious but tolerable dose tailored for each patient and minimize the risk of under-dosing. The QIDS-SR scale will be used to determine the clinical response for dose titration<sup>[68]</sup>. Side effects 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<sup>[69]</sup>. The assessments will occur every two weeks for the first six weeks (Weeks 0, 2, 4 and 6) and on Weeks 9 and 12 in the dialysis facility while the patient is undergoing HD. To the extent possible, the assessments will be done on the first dialysis day of the week (Monday or Tuesday, respectively, for subjects on Monday-Wednesday-Friday or Tuesday-Thursday-Saturday / Sunday-Tuesday-Thursday schedules). The participant-specific dose at week 6, up to a maximum of 200 mg/d, will be continued for the remaining six weeks.

### 5.2.2.2 Training of Investigators in Measurement Based Care

The investigators, sub-investigators, or any personnel with privileges to prescribe drug therapy at each of the three sites will undergo formal training in the implementation of Measurement Based Care prior to implementation of the study protocol. This training will be led by Drs. Hedayati and Katon.

### 5.2.2.3 Drug Procurement and Dispensation

The drug will be procured as 25 mg, 50 mg, and 100 mg tablets by the Kidney Research Institute at the University of Washington and shipped to each of the three clinical sites. The drug will be stored at the Investigational Drug Services at each of the three sites and will be dispensed for individual patients at two-week periods for the first six weeks and three-week periods for the second six weeks. The dose for each dispensation will be determined by assessments made on the first dialysis day of the week and drugs will be dispensed to the patient on the second dialysis day of the week.

### 5.2.2.4 Monitoring Drug Adherence

At weeks 2, 4, 6, 9, and 12 subjects will be asked to bring in the bottles that were provided to them at the preceding study visit. Pill count will be done to monitor adherence to drug therapy and all unused drug will be destroyed by IDS.

## 6. Ascertainment of Outcomes

### 6.1 Engagement Interview vs. Control

The **primary outcome** will be assessed six weeks from the time of completion of the engagement interview or control visit. This will be assessed as:

- Subjects enrolled in comparative efficacy trial: Completion of at least one CBT session or receiving at least one dispensation of sertraline.
- Subjects not enrolled in comparative efficacy trial: This will be ascertained with a single telephone call and subjects will be asked if, since the completion of engagement interview or control visit, they have either (1) completed one psychotherapy session, or (2) filled a prescription of anti-depressant drug therapy.

The **secondary outcome** will be ascertained upon completion of the engagement interview or control visit by the therapist or research coordinator, respectively. Patients will be asked to report whether they are willing to (1) enroll in the clinical trial of comparative efficacy of CBT or anti-depressant drug therapy, (2) receive a referral for psychotherapy, or (3) receive a prescription of anti-depressant drug therapy.

### 6.2 Comparative Efficacy of individual CBT and anti-depressant drug therapy

The **primary and secondary patient reported outcomes** will be ascertained by CATI at weeks 0, 6, and 12. If there are individuals that do not have access to a telephone, the study staff will work to make that available to them to complete the CATI. The CATI will run out of Albuquerque, NM under the direction of Mark Unruh who will train the interviewers. All the interviews will be audio recorded and up to 10% of all interviews will be audited to ensure the integrity of the assessment. The CATI interviewers will be blinded to study assignment. Bilingual CATI operators will conduct the assessments using scripts available in both English and Spanish, using the language preferred by the study subject. The interview is expected to last about 30 minutes. The baseline assessment will be performed prior to the first scheduled session of CBT or receiving anti-depressant drug therapy. Each of the three sessions will be scheduled on the day following the first dialysis treatment of the week (Tuesday for subjects on a Monday-Wednesday-Friday schedule, and Wednesday for subjects on a Tuesday-Thursday- Saturday / Sunday-Tuesday-Thursday schedule). If, however, the CATI could not be completed on the designated day, it would be acceptable to complete it during the subsequent non-dialysis days. If the subject is not available for the call on a non-dialysis day, then it is permissible for it to be done within the first hour of the dialysis session according to the subject's treatment schedule as noted above. The calls for the 6 and 12 weeks should be done on a dialysis vs. non-dialysis day based on which was chosen for the baseline call, consistently for each subject.



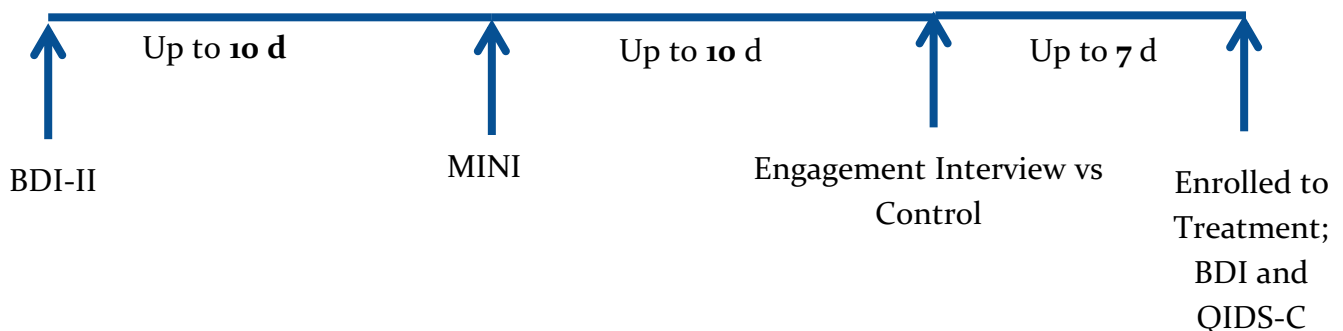
**Measures of adherence** will be ascertained by a structured data extraction from the medical records maintained in the dialysis facility at each site at weeks 0, 6, and 12 of the study. The study staff at each site will be trained in the process prior to the start of the clinical trial. **Adherence with dialysis regimen** will be determined for the preceding six weeks as a composite of % of treatments in which patient requested early termination of HD ( $\geq 10$  minutes) or skipped a session (excluding missed due to hospitalization or changes by dialysis facility). **Adherence with diet and medications** will be determined by (1) weight gain between each of the completed HD treatments over the preceding six weeks; and (2) each measurement of serum phosphorus in the preceding six weeks.

### 6.3 Observational Cohort Study of Patients Who Find Treatment Unacceptable

These subjects will only undergo assessment of severity of depressive symptoms at weeks 0, 6, and 12 using QIDS-C and they will be ascertained using CATI as described above.

## 7. Study Visits

All study visits will occur in the participating dialysis facility and a summary of the screening procedures prior to start of treatment are summarized as:



### 7.1 Pre-Screening

- Information sheet will be handed to patients to invite them to complete BDI-II
- Patients who agree will be invited to complete BDI-II
- Study staff will review response to question 9 of BDI-II and emergently triage patients with suicidal intent
- BDI-II scores will be computed within 48 hours of receipt of surveys

### 7.2 Screening (within 10 days of completion of BDI-II)

- Patients with BDI-II score  $\geq 15$  will be invited to sign consent form to complete screening activities (ICF-1).



- For subjects that consent to participate in the study, the following information will be recorded:
  - Registered on to the online study portal.
  - Demographic Data
  - 7 modules of MINI
  - Mini-COG
  - Health literacy questions:
    - How often do you have someone help you read hospital materials? (Never, Occasionally, Sometimes, Often, Always)
    - How confident are you filling out medical forms by yourself? (Extremely, Quite a bit, Somewhat, Little Bit, Not at all)
    - How often do you have problems learning about your medical condition because of difficulty understanding written information? (Never, Occasionally, Sometimes, Often, Always)
  - Review Inclusion and Exclusion Criteria
- Subjects that meet the inclusion and exclusion criteria will be randomly assigned to engagement interview or control visit through the secure study web portal.

### 7.3 Engagement Interview vs. Control Visit (within 10 days of screening)

- Engagement interview will be conducted by the study therapist and control visit will be delivered by another member of the research team.
- Upon completion of the intervention, subjects will be asked about their preference for treatment :
  - “Both antidepressant medication and a type of counseling called cognitive behavioral therapy can be successful in treating depression. Antidepressant medication involves taking one or more pills once daily which may have only minor side effects. Counseling involves speaking with a therapist once a week during dialysis for approximately 50 minutes to work on patterns of thinking and emotions that are involved in depression. Which of these two treatments would you prefer?
    - Medication
    - Counseling
    - Either
    - Neither”

#### 7.4 Baseline Visit/Week 0

- , Within 7 days of engagement interview or on the day of the control visit, subjects will be approached for their willingness to enroll in the clinical trial of comparative efficacy of treatment options for depression (ICF-2).
- CATI will be scheduled for the non-dialysis day (or the next dialysis session, if the subject is not available on a non-dialysis day) following the day the consent form was signed (within 7 days of signing the consent form).
- Consenting subjects will be randomly assigned to individual CBT or anti-depressant drug therapy at the beginning of the week following the CATI call.
- During **Week 0**, the following data will be recorded for consenting study subjects:
  - Medical History
  - Concomitant Medications
  - QIDS-SR
- Study Intervention will start during the same week:
  - The first session for individual CBT will be scheduled on the second or third dialysis day of the week
  - Patients on sub-therapeutic doses of anti-depressant drugs will be asked to discontinue the drug, in consultation with the physician who initially prescribed the drug (See Appendix Two).
  - Sertraline will be made available on the second dialysis day of the week and the first dose (25 mg) administered under supervision of study staff

#### 7.5 Weeks 2, 4, and 9

- On the first dialysis day of the week, the following will be completed
  - QIDS-SR
  - FIBSER (for subjects in the anti-depressant drug therapy arm)
- On the second dialysis day of the week, subjects in the anti-depressant drug therapy arm will:
  - Return the supply of medications at the prior visit to research staff
  - Receive a new supply of medications from research staff

#### 7.6 Week 6, 11 and 12

- On the first dialysis day of the weeks 6 and 11, the following will be completed
  - QIDS-SR
  - FIBSER (for subjects in the anti-depressant drug therapy arm)
- On the first non-dialysis day (or dialysis day, if subject is not available on a non-dialysis day) of the week 6 and 12:
  - CATI

- On the second dialysis day of Week 6, subjects in the anti-depressant drug therapy arm will:
  - Return the supply of medications at the prior visit from research staff
  - Receive a new supply of medications from research staff

## 7.7 Study Exit

At 12 weeks, study patients will be deemed either to have achieved a response ( $\geq 50\%$  decrease in baseline depressive symptoms) or remission ( $\text{QIDS-C} < 5$ ), or not. The approach to managing participants upon conclusion of the study will depend upon the treatment arm:

- CBT Arm: In individuals with clinically significant depressive symptoms ( $\text{QIDS-C} \geq 11$ ), the 12-week score and its interpretation will be communicated to the patients' treating nephrologist, along with a list of mental health care providers and resources in their community.
- Drug Therapy: Patients that demonstrate either a response or achieve remission will be offered continued treatment in consultation with the treating nephrologist. If patients and/or treating nephrologists do not want continued treatment, sertraline will be gradually tapered by 50 mg/week. In patients that don't achieve a 50% improvement in depressive symptoms, the drug will be gradually tapered to off after 12-weeks. The failure to respond to sertraline will be communicated to the treating nephrologist with information on resources as listed above.

The study team will provide the supply for and oversee the care should the patient and/or treating physician choose to discontinue sertraline. On the other hand, should the treating physician and patient decide to continue with sertraline drug therapy, the study staff will ensure a smooth transition for patients to receive the drug from their pharmacy as a part of their routine clinical care.

## 7.8 Post-Study Follow-up (done on week 12 by CATI)

- Semi-structured interview will be conducted to elicit the experience of patients with the study intervention. This will be included as the last question on the CATI call done on week 12 of the study
- At 30 days from the end of the study, the research staff will ascertain by reviewing the patient's medical records or calling the patient, the occurrence of following events:
  - Death or
  - Hospitalization

## 8. Statistical Analyses

### 8.1 Preliminary 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 evaluation of comparative efficacy of CBT and drug therapy will be compared to assess chance imbalances. If differences are found, these variables will be used as covariates in secondary analyses to evaluate the sensitivity of the primary analysis.

### 8.2 Statistical Analysis for the Engagement Interview Phase

The primary analysis will employ logistic regression adjusting for recruitment site to compare the proportions of patients who initiate treatment for comorbid depression between the engagement interview and control visit groups. The primary analyses will be based on a likelihood ratio test. In secondary analyses, we will compare the proportions of patients who report that they would be willing to initiate treatment for comorbid depression upon completion of engagement interview phase.

#### 8.2.1 Statistical Power for Primary Analysis of the Engagement Interview Phase

Randomized evaluation of an engagement interview will be conducted with 400 patients. In the pilot study by Dr. Cukor, 40% of HD patients accepted treatment for comorbid depression and in studies by Dr. Katon, the engagement interview increases the rate by 10-20% [39]. Based on recent updated assessment of sample size considerations and statistical power, we have updated our target sample size to a total of 120 patients randomized to cognitive behavioral therapy or sertraline drug therapy. Therefore our study design is well powered to detect the anticipated effect of an engagement interview.

### 8.3 Statistical Analysis for the Comparative Evaluation Phase

Longitudinal mixed effects analyses will be applied to the QIDS-C primary outcome and to other continuous secondary outcomes to compare outcome means at the 6 and 12 Week assessments between the CBT and Sertraline groups<sup>[70]</sup>. Treatment group and the Clinical Center will be fixed effects in the model. An unstructured covariance matrix will account for serial correlations in outcome measurements within patients<sup>[71]</sup>. 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).

In addition, we will describe the following proportions for each of the two treatment arms:

- % of patients in each of the two treatment arms that have at least 50% improvement in severity of depressive symptoms from baseline
- % of patients in each of the two treatment that achieve remission at end of follow-up ( $\text{QIDS-C} < 5$ ).

### 8.3.1 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 patients 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<sup>[72]</sup>. Secondary analyses will examine the association between participation in engagement interview prior to randomization, health literacy at baseline, and adherence with the respective intervention on treatment efficacy.

### 8.3.2 Sample size/detectable effect size in the Comparative Evaluation of CBT and Drug Therapy

The sample size for this phase is 120 patients. 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  $0.70$ <sup>[38, 39, 73]</sup>. Assuming a loss- to-follow-up of  $\leq 15\%$ , 120 randomized participants will provide 80% power with 2-sided  $\alpha = 0.05$  to detect a difference in the mean 12-Week QIDS-C between the treatment groups of between 0.40 (if  $R = 0.70$ ) and 0.51 (if  $R = 0.40$ ) of 1 standard deviation in the QIDS-C. 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<sup>[46, 50, 51, 56, 57]</sup>. 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.

### 8.3.3 Overall Approach for Avoidance of bias in the Comparative Efficacy of CBT and drug therapy

Several features of study design will minimize bias. First, a randomized controlled study design will generate the highest level of evidence for treatment efficacy. Second, all HD patients in participating dialysis facilities will be 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 will be measured at two time points after randomization, and hence data on intermediate time points will be available for participants who may drop out. Fourth, computer-assisted telephone interviewing will maximize patient participation and the assessor will be blinded to treatment assignment, both of which will minimize bias in an open-label clinical trial. Fifth, procedures to minimize missing data will be implemented, such as training and certification of study personnel, careful design of data collection forms, documentation of procedures, and implementation of a management system that minimizes data entry errors and patient tracking procedures<sup>[74]</sup>. Should there still be missing data, multiple imputation methods will be utilized as described above<sup>[74]</sup>.

## 8.4 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 patients 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.

## 9. Adverse Events

### 9.1 Potential Adverse Events from Study Interventions

1. **Adverse Effects from CBT:** The risk classification for this arm is “not greater than minimal”. There is risk of experiencing discomfort in exploring psychologically

difficult material. Some people feel temporarily worse when they begin to disclose their intimate feelings, but this is usually mild and transient. Additional potential risks include breach of confidentiality if participants choose CBT to be done while undergoing HD.

**2. Adverse Effects from Sertraline:**

- a. Common side effects (>10%) are transient and include nausea, decrease in appetite, diarrhea, dry mouth, dizziness, headache, insomnia, somnolence, decreased libido, sweating and tremors.
- b. Less common side effects (1-10%) include chest pain, palpitations, agitation, nervousness, pain, rash, impotence, increased appetite, constipation, vomiting, weakness, visual problems, yawning, and tinnitus.
- c. Rare (<1%) potential risks include bleeding, extrapyramidal reactions, neuroleptic malignant syndrome and suicide.
- d. Withdrawal symptoms such as agitation, anxiety, confusion, headache and seizures could occur if sertraline is stopped abruptly.
- e. Use of serotonin reuptake inhibitors has been reported to increase risk for bleeding; this risk may potentially be amplified in the presence of ESRD due to platelet dysfunction with uremia and use of heparin with each HD treatment. However, this adverse event has not been reported in any of the studies with this class of drugs in dialysis patients to date <sup>[48-50, 54-57]</sup>. Nevertheless, participants will be closely monitored for the occurrence of this complication.

**3. Worsening of depressive symptoms.**

**4. Psychological discomfort from completing patient-reported scales**

**5. Loss of patient confidentiality**

## **9.2 Anticipated Adverse Events in the Hemodialysis Population**

Patients undergoing hemodialysis experience a large number of adverse events from their underlying health, co-existing illnesses, and concomitant medications. These adverse events include (1) death, (2) fluid overload, (3) congestive heart failure, (4) vascular access events such as thrombosis or infection or dysfunction, (5) atherosclerotic cardiovascular events, (6) infections such as pneumonia, and (6) laboratory abnormalities such as anemia, hyperphosphatemia, and hyperparathyroidism.

## **9.3 Monitoring for Adverse Events**

The subjects will be monitored for the occurrence of adverse events as:

- The study staff will evaluate the subjects every two weeks for the first six weeks and every three weeks for the next six weeks.



- At these visits, tolerability of sertraline drug therapy will be monitored with the use of FIBSER. Patients 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; (2) the patient has intolerable side effects despite reducing dose to 50 mg/d; or (3) patient becomes pregnant.
- The informed consent document will provide the name of a study staff with a phone number to be contacted in the case of an emergency or if an adverse event occurred outside the time frame of study visits.

## 9.4 Reporting of Adverse Events

All adverse events experienced by study subjects from the time of registration into the study (screening visit for engagement interview phase of study) will be recorded and summarized by random assignment group. The summary will be submitted to oversight groups at periodic intervals.

All serious or unanticipated adverse events will be reported by each of the clinical site to the Data Coordinating Center within 24 hours of becoming aware of these events using a structured reporting form. Each site will also be expected to follow local reporting policies such as to the Institutional Review Board. Serious adverse events are ones that result in death, or are life threatening, or lead to or prolong hospitalization, or result in disability or incapacity. Unanticipated adverse events are unexpected events, which in the opinion of the investigator, could be reasonably be considered to be associated with participation in the research study. The DCC will be responsible for communicating these to the DSMB consistent with the policies agreed upon and outlined in the DSMB charter.

## 9.5 Management of Active Suicidal Intent

The overall incidence of suicide is extremely low. However, since individuals with comorbid depression are at risk for committing suicide and individuals with ESRD are at a higher risk for committing suicide than the general population, care will be exercised to identify and provide help to individuals with suicidal intent.

The suicidal intent could be ascertained by:

- Study Coordinator (initial pre-screen with BDI-II or monitoring with QIDS-SR)
- Therapist (Engagement Interview or CBT sessions)
- CATI (while completing QIDS-C or CATI)

The subjects will be deemed to have active suicidal intent if they answer the following questions:



- BDI-II (question 9): “I will like to kill myself” or “I will like to kill myself if I had the chance”
- QIDS-SR (question 12): “I think of suicide/death several times a week for several minutes” OR “I think of suicide/death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life”.

Each site will be asked to provide three emergency telephone numbers of study personnel; these telephone numbers will be made available to the therapist, CATI operator, and dialysis facility staff. Upon being informed of study subjects with an active suicidal intent, the following process will be followed:

- If the subject is at immediate risk for self-harm, call 911
- If the subject is not at immediate risk for self-harm, site clinician would be immediately contacted by telephone along with an electronic communication to the site study team and DCC.
- The site clinician will assess the suicidal risk using the “Suicidality” module of the MINI, classify the individual’s risk as low, medium, or high, and manage as follows:
  - High ( $\geq 17$  points): Arrange for immediate help
  - Medium (9-16 points): State concern for subject, encourage patient to contact provider, and provide three emergency telephone numbers.
  - Low (1-8 points): Provide three emergency telephone numbers and suggest subject call the numbers if continued symptoms/concerns.

## 10. Data Management

### 10.1 Data Coordinating Center and Data Entry Overview

The DCC will be based at the Center for Biomedical Statistics (CBS) at the University of Washington. Data collection and management of the clinical trial will be web-based and the DCC will support https-secured study-specific ‘.NET’ web page that will provide a centralized location for public information about the project for participants, investigators, and institutional agencies. The web page will contain a link to a study-specific portal. Study personnel will log on to the private portal with individual Shibboleth-based user names and passwords to securely perform data management activities. Shibboleth is a standards-based, open source software package for web single sign-on across organizational boundaries. The web portal will serve as the wrapper for all data management tools and software utilized in the project, including: study ID assignment, screening, randomization, prospective data collection, and study operations reporting.

## 10.2 Computer and Data Security

Access to research data will be restricted to study team members at each site and DCC personnel. The clinical recruitment sites will maintain a secure electronic database that links the study participant ID generated by the portal to participant contact information. Efforts made by clinical sites to contact patients for follow-up visits will be documented in this database. The database will be stored on a secure electronic server with user name and passwords log in for individual users and will be backed up nightly.

## 10.3 Training Procedures

After the planning phase and before the recruitment begins, a training session will be held to train study staff on data collection procedures, including orientation to the Manual of Operations, data entry and management principles, review of study interventions, and quality control procedures.

## 10.4 Responsibilities of the Clinical Sites

Each of the clinical sites will be responsible for maintaining a regulatory binder and maintaining source documents for all data entry. The web portal will generate queries and the sites will be responsible for completing these queries in a timely manner.

## 11. Study Oversight

The research will operate under the oversight provided by:

- Data Safety and Monitoring Board (DSMB);
- Patient Council; and
- Stakeholder Council.

The membership of each of these oversight bodies is listed in **Appendix Four**. Each of the bodies will review and approve the study protocol prior to implementation. Each of the three groups will develop a charter outlining their role in monitoring the progress of the study (The DSMB Charter and the Data Safety Monitoring Plan is available as Appendices Six and Seven, respectively). Each group will convene via a teleconference at least once every six months, or more frequently if deemed necessary.

## References

1. Weisbord, S.D., et al., *Prevalence, severity, and importance of physical and emotional symptoms in chronic hemodialysis patients*. J Am Soc Nephrol, 2005. **16**(8): p. 2487-94.
2. Davison, S.N. and G.S. Jhangri, *The impact of chronic pain on depression, sleep, and the desire to withdraw from dialysis in hemodialysis patients*. J Pain Symptom Manage, 2005. **30**(5): p. 465-73.
3. Drayer, R.A., et al., *Characteristics of depression in hemodialysis patients: symptoms, quality of life and mortality risk*. Gen Hosp Psychiatry, 2006. **28**(4): p. 306-12.
4. Hedayati, S.S., et al., *The predictive value of self-report scales compared with physician diagnosis of depression in hemodialysis patients*. Kidney Int, 2006. **69**(9): p. 1662-8.
5. Peng, Y.S., et al., *Sexual dysfunction in female hemodialysis patients: a multicenter study*. Kidney Int, 2005. **68**(2): p. 760-5.
6. Takaki, J. and E. Yano, *The relationship between coping with stress and employment in patients receiving maintenance hemodialysis*. J Occup Health, 2006. **48**(4): p. 276-83.
7. Kimmel, P.L., et al., *Multiple measurements of depression predict mortality in a longitudinal study of chronic hemodialysis outpatients*. Kidney Int, 2000. **57**(5): p. 2093-8.
8. Chilcot, J., et al., *An association between depressive symptoms and survival in incident dialysis patients*. Nephrol Dial Transplant, 2011. **26**(5): p. 1628-34.
9. Rosenthal Asher, D., N. Ver Halen, and D. Cukor, *Depression and nonadherence predict mortality in hemodialysis treated end-stage renal disease patients*. Hemodial Int, 2012. **16**(3): p. 387-93.
10. Lopes, A.A., et al., *Depression as a predictor of mortality and hospitalization among hemodialysis patients in the United States and Europe*. Kidney Int, 2002. **62**(1): p. 199-207.
11. Edmondson, D., et al., *Association of posttraumatic stress disorder and depression with all-cause and cardiovascular disease mortality and hospitalization among Hurricane Katrina survivors with end-stage renal disease*. Am J Public Health, 2013. **103**(4): p. e130-7.
12. Riezebos, R.K., et al., *The association of depressive symptoms with survival in a Dutch cohort of patients with end-stage renal disease*. Nephrol Dial Transplant, 2010. **25**(1): p. 231-6.
13. Boulware, L.E., et al., *Temporal relation among depression symptoms, cardiovascular disease events, and mortality in end-stage renal disease: contribution of reverse causality*. Clin J Am Soc Nephrol, 2006. **1**(3): p. 496-504.
14. Hedayati, S.S., et al., *Death or hospitalization of patients on chronic hemodialysis is associated with a physician-based diagnosis of depression*. Kidney Int, 2008. **74**(7): p. 930-6.
15. Lacson, E., Jr., et al., *Depressive symptoms associate with high mortality risk and dialysis withdrawal in incident hemodialysis patients*. Nephrol Dial Transplant, 2012. **27**(7): p. 2921-8.
16. Hedayati, S.S., et al., *Physician-diagnosed depression as a correlate of hospitalizations in patients receiving long-term hemodialysis*. Am J Kidney Dis, 2005. **46**(4): p. 642-9.
17. Young, B.A., et al., *Association of major depression and mortality in Stage 5 diabetic chronic kidney disease*. Gen Hosp Psychiatry, 2010. **32**(2): p. 119-24.
18. Nagler, E.V., et al., *Antidepressants for depression in stage 3-5 chronic kidney disease: a systematic review of pharmacokinetics, efficacy and safety with recommendations by European Renal Best Practice (ERBP)*. Nephrol Dial Transplant, 2012. **27**(10): p. 3736-45.
19. Glassman, A.H., et al., *Sertraline treatment of major depression in patients with acute MI or unstable angina*. JAMA, 2002. **288**(6): p. 701-9.
20. System, U.S.R.D., US Department of Public Health and Human Services, Public Health Service, National Institutes of Health, Bethesda, 2012.

21. Fukuhara, S., et al., *Health-related quality of life among dialysis patients on three continents: the Dialysis Outcomes and Practice Patterns Study*. *Kidney Int*, 2003. **64**(5): p. 1903-10.
22. Mapes, D.L., et al., *Health-related quality of life as a predictor of mortality and hospitalization: the Dialysis Outcomes and Practice Patterns Study (DOPPS)*. *Kidney Int*, 2003. **64**(1): p. 339-49.
23. Chiu, Y.W., et al., *Pill burden, adherence, hyperphosphatemia, and quality of life in maintenance dialysis patients*. *Clin J Am Soc Nephrol*, 2009. **4**(6): p. 1089-96.
24. Kalantar-Zadeh, K., et al., *Association among SF36 quality of life measures and nutrition, hospitalization, and mortality in hemodialysis*. *J Am Soc Nephrol*, 2001. **12**(12): p. 2797-806.
25. Kang, E.W., et al., *The association of mental health over time with cardiac outcomes in HEMO study patients*. *Clin J Am Soc Nephrol*, 2012. **7**(6): p. 957-64.
26. Manley, H.J., et al., *Medication prescribing patterns in ambulatory haemodialysis patients: comparisons of USRDS to a large not-for-profit dialysis provider*. *Nephrol Dial Transplant*, 2004. **19**(7): p. 1842-8.
27. Palmer, S., et al., *Prevalence of depression in chronic kidney disease: systematic review and meta-analysis of observational studies*. *Kidney Int*, 2013. **84**(1): p. 179-91.
28. Miller, A.H., V. Maletic, and C.L. Raison, *Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression*. *Biol Psychiatry*, 2009. **65**(9): p. 732-41.
29. Raison, C.L., L. Capuron, and A.H. Miller, *Cytokines sing the blues: inflammation and the pathogenesis of depression*. *Trends Immunol*, 2006. **27**(1): p. 24-31.
30. DiMatteo, M.R., H.S. Lepper, and T.W. Croghan, *Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence*. *Arch Intern Med*, 2000. **160**(14): p. 2101-7.
31. Cukor, D., et al., *Depression is an important contributor to low medication adherence in hemodialyzed patients and transplant recipients*. *Kidney Int*, 2009. **75**(11): p. 1223-9.
32. Everett, K.D., et al., *The relation of stress and depression to interdialytic weight gain in hemodialysis patients*. *Behav Med*, 1995. **21**(1): p. 25-30.
33. Kimmel, P.L., et al., *Psychosocial factors, behavioral compliance and survival in urban hemodialysis patients*. *Kidney Int*, 1998. **54**(1): p. 245-54.
34. Kimmel, P.L., et al., *Behavioral compliance with dialysis prescription in hemodialysis patients*. *J Am Soc Nephrol*, 1995. **5**(10): p. 1826-34.
35. Kutner, N.G., et al., *Psychosocial predictors of non-compliance in haemodialysis and peritoneal dialysis patients*. *Nephrol Dial Transplant*, 2002. **17**(1): p. 93-9.
36. Weisbord, S.D., et al., *Renal provider recognition of symptoms in patients on maintenance hemodialysis*. *Clin J Am Soc Nephrol*, 2007. **2**(5): p. 960-7.
37. Lopes, A.A., et al., *Screening for depression in hemodialysis patients: associations with diagnosis, treatment, and outcomes in the DOPPS*. *Kidney Int*, 2004. **66**(5): p. 2047-53.
38. Weisbord, S.D., et al., *Comparison of symptom management strategies for pain, erectile dysfunction, and depression in patients receiving chronic hemodialysis: a cluster randomized effectiveness trial*. *Clin J Am Soc Nephrol*, 2013. **8**(1): p. 90-9.
39. Cukor, D., et al., *Psychosocial intervention improves depression, quality of life, and fluid adherence in hemodialysis*. *J Am Soc Nephrol*, 2014. **25**(1): p. 196-206.
40. Grote, N.K., et al., *Engaging women who are depressed and economically disadvantaged in mental health treatment*. *Soc Work*, 2007. **52**(4): p. 295-308.
41. Kravitz, R.L., et al., *Patient engagement programs for recognition and initial treatment of depression in primary care: a randomized trial*. *JAMA*, 2013. **310**(17): p. 1818-28.

42. Association, A.P., *Practice Guideline for the Treatment of Patients With Major Depressive Disorder*. 2010.
43. Hosseini, S.H., F. Espahbodi, and S.M. Mirzadeh Goudarzi, *Citalopram versus psychological training for depression and anxiety symptoms in hemodialysis patients*. Iran J Kidney Dis, 2012. **6**(6): p. 446-51.
44. Beck, A., *Depression: Causes and Treatment* 2006, Philadelphia: University of Pennsylvania Press.
45. Beck, J., *Cognitive Therapy: Basics and beyond* 1995, New York: Guilford.
46. Duarte, P.S., et al., *Cognitive-behavioral group therapy is an effective treatment for major depression in hemodialysis patients*. Kidney Int, 2009. **76**(4): p. 414-21.
47. Rayner, L., et al., *Antidepressants for depression in physically ill people*. Cochrane Database Syst Rev, 2010(3): p. Cd007503.
48. Blumenfeld, M., et al., *Fluoxetine in depressed patients on dialysis*. Int J Psychiatry Med, 1997. **27**(1): p. 71-80.
49. Levy, N.B., et al., *Fluoxetine in depressed patients with renal failure and in depressed patients with normal kidney function*. Gen Hosp Psychiatry, 1996. **18**(1): p. 8-13.
50. Atalay, H., et al., *Sertraline treatment is associated with an improvement in depression and health-related quality of life in chronic peritoneal dialysis patients*. Int Urol Nephrol, 2010. **42**(2): p. 527-36.
51. Kalender, B., et al., *Antidepressant treatment increases quality of life in patients with chronic renal failure*. Ren Fail, 2007. **29**(7): p. 817-22.
52. Kamo, T., et al., *Efficacy and pharmacokinetics of fluvoxamine maleate in patients with mild depression undergoing hemodialysis*. Psychiatry Clin Neurosci, 2004. **58**(2): p. 133-7.
53. Kennedy, S.H., J.L. Craven, and G.M. Rodin, *Major depression in renal dialysis patients: an open trial of antidepressant therapy*. J Clin Psychiatry, 1989. **50**(2): p. 60-3.
54. Koo, J.R., et al., *Treatment of depression and effect of antidepressant treatment on nutritional status in chronic hemodialysis patients*. Am J Med Sci, 2005. **329**(1): p. 1-5.
55. Lee, S.K., et al., *The effects of antidepressant treatment on serum cytokines and nutritional status in hemodialysis patients*. J Korean Med Sci, 2004. **19**(3): p. 384-9.
56. Turk, S., et al., *Treatment with antidepressive drugs improved quality of life in chronic hemodialysis patients*. Clin Nephrol, 2006. **65**(2): p. 113-8.
57. Wuerth, D., et al., *Identification and treatment of depression in a cohort of patients maintained on chronic peritoneal dialysis*. Am J Kidney Dis, 2001. **37**(5): p. 1011-7.
58. *FDA Approved Labeling for Zoloft*.
59. Brewster, U.C., et al., *Addition of sertraline to other therapies to reduce dialysis-associated hypotension*. Nephrology (Carlton), 2003. **8**(6): p. 296-301.
60. Dheenan, S., et al., *Effect of sertraline hydrochloride on dialysis hypotension*. Am J Kidney Dis, 1998. **31**(4): p. 624-30.
61. Yalcin, A.U., et al., *Sertraline hydrochloride treatment for patients with hemodialysis hypotension*. Blood Purif, 2002. **20**(2): p. 150-3.
62. Cukor, D., et al., *Course of depression and anxiety diagnosis in patients treated with hemodialysis: a 16-month follow-up*. Clin J Am Soc Nephrol, 2008. **3**(6): p. 1752-8.
63. Weisbord, S.D., et al., *Associations of depressive symptoms and pain with dialysis adherence, health resource utilization, and mortality in patients receiving chronic hemodialysis*. Clin J Am Soc Nephrol, 2014. **9**(9): p. 1594-602.
64. Katon, W.J., et al., *Collaborative care for patients with depression and chronic illnesses*. N Engl J Med, 2010. **363**(27): p. 2611-20.

65. Sheehan, D.V., et al., *The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10*. J Clin Psychiatry, 1998. **59 Suppl 20**: p. 22-33;quiz 34-57.
66. Borson, S., et al., *The mini-cog: a cognitive 'vital signs' measure for dementia screening in multi-lingual elderly*. Int J Geriatr Psychiatry, 2000. **15**(11): p. 1021-7.
67. Trivedi, M.H., et al., *Medication augmentation after the failure of SSRIs for depression*. N Engl J Med, 2006. **354**(12): p. 1243-52.
68. Rush, A.J., et al., *The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression*. Biol Psychiatry, 2003. **54**(5): p. 573-83.
69. Wisniewski, S.R., et al., *Self-rated global measure of the frequency, intensity, and burden of side effects*. J Psychiatr Pract, 2006. **12**(2): p. 71-9.
70. Verbeke, G., Molenberghs, A., *Linear Mixed Models for Longitudinal Data* 2000, New York: Springer.
71. Littell, R.C., J. Pendergast, and R. Natarajan, *Modelling covariance structure in the analysis of repeated measures data*. Stat Med, 2000. **19**(13): p. 1793-819.
72. Schafer, J.L., *Multiple imputation: a primer*. Stat Methods Med Res, 1999. **8**(1): p. 3-15.
73. Hedayati, S.S., et al., *Validation of depression screening scales in patients with CKD*. Am J Kidney Dis, 2009. **54**(3): p. 433-9.
74. Siegel, J., *Innovative Methods in Stakeholder Engagement: An Environmental Scan*. 2012.





## Appendix One: Study Schedule

	Pre-Screen	Engagement		Comparative Effectiveness of Treatment of Depression															Post-Study
		Screen	Interview	Screen	ON STUDY														
WEEK					0	1	2	3	4	5	6	7	8	9	10	11	12		
Eligibility Criteria	X		X																
Information Sheet	X																		
Informed Consent		X		X															
BDI-II	X																		
MINI (7 modules)		X																	
Assess suicidal risk	X	X	X	X	X		X		X		X			X			X		
Cognitive Function		X																	
Health Literacy		X																	
Randomization 1		X																	
Demographic Information		X																	
Engagement Interview/Control Visit			X																
Treatment Preferences			X																
Patient Accepts Study Treatments																			
Randomization 2				X															
Medical History				X															
Concomitant Medications				X	X						X						X		
HD treatment adherence					X						X						X		
Laboratory Test Results					X						X						X		
CBT					X	X	X	X	X	X	X	X		X		X			
Sertraline Dispense					X		X		X		X			X					
Monitor Adherence to Sertraline							X		X		X			X			X		
QIDS-SR					X		X		X		X			X		X			
QIDS-C					X						X						X		
FIBSER					X		X		X		X			X		X			
CATI					X						X						X		
Semi-Structured Interview																	X		
Does Not Accept Treatment					X						X					X			

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## Appendix Two: Highest Dose Level Eligible for Enrollment

Upper limit of doses for anti-depressant drugs for including patients in the clinical trial.

<i>Generic Name</i>	<i>Brand Name</i>	<i>Upper Dose limit for inclusion</i>
<b>Selective Serotonin Reuptake Inhibitors (SSRI)</b>		
sertraline	Zoloft	25 mg daily***
paroxetine	Paxil, Pexeva	10 mg daily***
fluoxetine	Prozac	10 mg daily***
fluvoxamine	Luvox	50 mg daily***
vortioxetine	Brintellix	5 mg daily***
citalopram	Celexa	10 mg daily***
escitalopram	Lexapro	5 mg daily***
<b>Serotonin Norepinephrine Reuptake Inhibitors (SSRI/SNRI)</b>		
duloxetine	Cymbalta	30 mg daily***
reboxetine	Norebox	2 mg daily***
venlafaxine	Effexor or Effexor XR	Extended release 75 mg daily; immediate release 75 mg twice daily***
desvenlafaxine	Khedeza, Pristiq	50 mg daily***
<b>Other Antidepressants</b>		
trazodone	Desyrel, Oleptro	100 mg daily or 50 mg twice daily
nefazodone	Serzone	100 mg daily or 50 mg twice daily
vilazodone	Viibryd	10 mg qd daily
bupropion	Aplenzin, Wellbutrin	100 mg twice daily
mirtazapine	Remeron	15 mg daily
milnacipran	Savella	50 mg daily
levomilnacipran	Fetzima	20 mg daily
buspirone	Buspar	10 mg daily or 5 mg twice daily
imipramine	Tofranil	25 mg daily
clomipramine	Anafranil	25 mg daily
desipramine	Norpramin	25 mg daily
trimipramine	Surmontil	25 mg daily
amoxapine	Aventyl, Asendin	50 mg daily
amitriptyline	Endep, Elavil, Etrafon, Limbitrol, Triavil	50 mg daily
nortriptyline	Asendin HCl, Pamelor	50 mg daily
protriptyline	Vivactil	5 mg daily
doxepin	Adapin, Sinequan	25 mg daily



### Appendix Three: Measurement Based Care Protocol

Week	Clinical Status		Recommended Sertraline Dosing
	QIDS-SR		
0			Initiate sertraline treatment: 25 mg/d x 1 week, then 50 mg/d x 1 week
2	$\leq 5$	Remission (FIBSER <sub>B</sub> , $< 5$ )	Increase dose to 100 mg/d
		Remission (FIBSER <sub>B</sub> , $\geq 5$ )	Continue current dose and address SEs
	6-8	Partial Response (FIBSER <sub>B</sub> , $< 5$ )	Increase dose to 100 mg/d
		Partial Response (FIBSER <sub>B</sub> , $\geq 5$ )	Continue current dose and address SEs
	$\geq 9$	Non-Response (FIBSER <sub>B</sub> , $< 5$ )	Increase dose to 100 mg/d
		Non-Response (FIBSER <sub>B</sub> , $\geq 5$ )	Continue current dose and address SEs
4	$\leq 5$	Remission (FIBSER <sub>B</sub> , $< 5$ )	Increase dose by 50 mg/d since last visit
		Remission (FIBSER <sub>B</sub> , $\geq 5$ )	Continue current dose and address SEs <u>OR</u> Decrease dose by 50 mg
	6-8	Partial Response (FIBSER <sub>B</sub> , $< 5$ )	Increase dose by 50 mg/d since last visit
		Partial Response (FIBSER <sub>B</sub> , $\geq 5$ )	Continue current dose and address SEs <u>OR</u> Decrease dose by 50 mg
	$\geq 9$	Non-Response (FIBSER <sub>B</sub> , $< 5$ )	Increase dose by 50 mg/d since last visit
		Non-Response (FIBSER <sub>B</sub> , $\geq 5$ )	Continue current dose and address SEs <u>OR</u> Decrease dose by 50 mg
6	$\leq 5$	Remission (FIBSER <sub>B</sub> , $< 5$ )	If sertraline dose $< 150$ mg, increase by 50 mg If sertraline dose $\geq 150$ mg, continue current dose
		Remission (FIBSER <sub>B</sub> , $\geq 5$ )	Continue current dose and address SEs <u>OR</u> Decrease dose by 50 mg
	6-8	Partial Response (FIBSER <sub>B</sub> , $< 5$ )	Increase dose by mg (max. 200 mg/d)

		Partial Response (FIBSER <sub>B</sub> , $\geq 5$ )	Continue current dose and address SEs <u>OR</u> Decrease dose by 50 mg
	$\geq 9$	Non-Response (FIBSER <sub>B</sub> , $< 5$ )	Increase dose by mg (max. 200 mg/d)
		Non-Response (FIBSER <sub>B</sub> , $\geq 5$ )	Continue current dose and address SEs <u>OR</u> Decrease dose by 50 mg
9	$\leq 5$	Remission (FIBSER <sub>B</sub> , $< 5$ )	Continue current dose
		Remission (FIBSER <sub>B</sub> , $\geq 5$ )	Continue current dose and address SEs <u>OR</u> Decrease dose by 50 mg
	6-8	Partial Response (FIBSER <sub>B</sub> , $< 5$ )	Continue current dose
		Partial Response (FIBSER <sub>B</sub> , $\geq 5$ )	Continue current dose and address SEs <u>OR</u> Decrease dose by 50 mg
	$\geq 9$	Non-Response (FIBSER <sub>B</sub> , $< 5$ )	Continue current dose
		Non-Response (FIBSER <sub>B</sub> , $\geq 5$ )	Continue current dose and address SEs <u>OR</u> Decrease dose by 50 mg
12			Begin drug taper at rate of 50 mg/week until discontinued

## Appendix Four: Membership of Oversight Groups

### **Data Safety Monitoring Board (DSMB)**

Alan Kliger (Chair), Yale University, New Haven, CT

Michael Hollifield, VA Long Beach Health Care System, Long Beach, CA

J Richard Landis, University of Pennsylvania, Philadelphia, PA

Michael Rocco, Wake Forest University, Winston-Salem, NC

Suzanne Watnick, Oregon Health Sciences Center, Portland, OR

### **Patient Council**

Lori Hartwell (Chair)

Monica Alfonzo

Richard Blaine

Diana Headlee

Linda Oakford

Heather Powell

Glenda Roberts

Nancy Spaeth

Cal Sturdivant

## **Stakeholder Council**

	<b>Organization</b>	<b>Representative</b>
Patient Organizations	American Association of Kidney Patients	Gary Green Diana Clynes
	Dialysis Patient Citizens	Hrant Jamgochian Nancy L Scott
Dialysis Providers	DaVita	Allen Nissenson
	Fresenius Medical Care	Ravi Thadhani Ann Mooney
	Northwest Kidney Centers	Leanna B. Tyshler
	Renal Ventures	Tom Parker (Chair)
Research	National Institutes of Health	Robert Star
Clinical Professionals' Representatives	American Nephrology Nurses Association	Leslie Dork
	Council for Nephrology Social Workers	Leanne Peace
	National Renal Administrators' Association	Debbie Cote Helen Currier
	Nephrologists	Greg Braden Arti Gupta Fred Finkelstein
	Psychiatrist	Lewis Cohen

## Appendix Five CBT manual Pages 1-4



Daniel Cukor, PhD  
Nisha Ver Halen, PhD.

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### Session 1: The patient's narrative, assessment and psychoeducation

#### What is cognitive behavioral therapy (CBT)?

Cognitive behavioral therapy, or CBT, is the most studied effective psychotherapy treatment for moderate depression. CBT is a relatively short-term, focused psychotherapy for a wide range of psychological problems including depression. The focus of CBT is on how one is thinking, behaving, and communicating today rather than on early childhood experiences, in contrast to traditional psychotherapy. The therapist assists the patient in identifying specific distortions (cognitive assessment) and biases in thinking and provides guidance on how to change this thinking. CBT teaches the patient to learn effective self-help skills that are used in homework assignments that help change the way the person currently thinks, feels and behaves. CBT is action-oriented, practical, rational, and helps the patient gain independence and mastery in dealing with practical issues.

**Purpose of CBT of Depression in ESRD:** To explore the thoughts and feelings associated with dialysis treatment in the ESRD patient and to modify distorted thoughts and maladaptive beliefs that contribute to depressed affect in the ESRD patient. The therapy also aims to examine and modify behaviors that contribute to depressed affect

#### Overall Goals:

- 1) Provide education about depression in the ESRD patient
- 2) Improve strategies for coping with side effects of hemodialysis
- 3) Help patient to modify behavior schedule to include more pleasurable activities
- 4) Provide support and guidance for improving health-related behaviors

#### Goals for session 1:

- Learn about patient's condition
- Develop rapport with patient
- Assess cognitive, behavioral and interpersonal deficits
- Assess patient's motivation for change
- Educate patient about depression
- Inform patient about purpose of therapy
- Develop goals for therapy

#### Narrative – The patient tells their story

Ask the patient to tell their personal story about how they came to be on dialysis. Give the patient the opportunity to process the sequence of events that led to the initiation of dialysis. Although it may have occurred several years prior, often times the patient has not had the opportunity to tell their story in an organized and comprehensive way. The narrative will provide you with information about the patient's beliefs and behaviors and will serve as an opportunity to develop rapport with the patient.

#### Pay attention to:

- 1) The affective tone of the story: Is the patient angry? Regretful? Sad? Or calm?
- 2) The characters: Who are the people involved in the patient's care?
- 3) Attitudes: How does the patient recall her initial interactions with doctors and dialysis staff

#### Assessment - Assess for Cognitive, Behavioral and Interpersonal Deficits

Using the "Cognitive Assessment" worksheet, explore the patient's depressive thoughts. Identify thoughts that are associated with feelings of sadness, anger or anxiety. Possible thoughts may include:

"I feel angry when I have to wake up early to take the access-a-ride van to dialysis 3 times/week."

"I feel sad when I think about all the friends I used to have at my old job who I don't get to see anymore."

"I feel nervous because I want to go to a bbq this weekend but I worry that I won't be able to say no to all the food"

Assess the patient's behavior profile. Are there specific behaviors that are contributing to the patient's depressed mood? Are there specific behaviors that are interfering with the patient's adherence to the dialysis prescription? For example:

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Is the patient maintaining a healthy diet?

Is the patient exercising?

Is the patient engaging in social activities with others?

**Assess for suicidality** - Patients will routinely be screened for changes in depression and suicidality. If a subject scores >30 on the BDI, scores a 2 or greater on question 9 of the BDI or indicates any active suicidal ideation then the attending physician, the PI, and the charge nurse will be immediately notified and a full suicide evaluation will take place. If it is determined to be a true suicidal risk then immediate steps will be taken to guarantee the subject's safety. Depending on the nature of the situation and the extent of the crisis, the investigator has the capability of calling a consulting psychiatrist to come to the dialysis center or to having the mobile crisis unit respond.

### Psychoeducation – Socialize the patient to the treatment

Provide the patient with the "Information about Depression" handout. Discuss the similarities/differences between symptoms of depression and ESRD. Explain the rationale and purpose of cognitive behavioral therapy. Be sure to use language that the patient can identify with. Briefly outline the plan for the therapy and introduce the concept of homework. Offer the patient an opportunity to ask questions about the process of therapy.

"The patient may have some questions about your role in their dialysis treatment. Be sure to provide clear information about how you will interact with their physicians and about the limitations of your involvement in their care. Provide detailed information about confidentiality and it's limits.

### Interventions

#### – Promote "Buy In"

Using motivational interviewing skills, have subject begin to identify reasons they would like to see their depression improve. Give patient "Identifying your Motivation" worksheet and instruct patient on how to complete the worksheet. It is helpful to start the worksheet in session and allow the patient to complete the assignment at home. This reduces anxiety about the homework and helps to ensure that the patient completes the homework as intended.

#### - Improve Sleep Hygiene

Introduce initial goal of improving sleep hygiene. Provide the patient with the "Better Sleeping with hemodialysis handout." Discuss the handout with the patient and encourage he/she to share their own difficulties with sleep. This serves as an entrée into the process of therapy. It is minimally invasive and offers a directive strategy for improving sleep.

### Homework

Complete the MI Worksheet - "Identifying Your Motivation"

Prochaska, J and Di Clemente, C (1983) Stages and Processes of self-change of smoking; towards an integrative model of change. Journal of Consulting and Clinical Psychology, 51: pp390-395.

### Functional Impairments

**Social Functioning** - Depression can affect the degree to which dialysis patients engage in social interactions. Discuss with the patient the ways in which their social functioning has changed since being on dialysis.

### SOME PATIENT EXAMPLES...

- 1) Decreased energy level and fatigue can affect motivation to go out or interact with others
  - a. "Dialysis makes me too tired to talk to anyone"
- 2) Shame or embarrassment about illness and treatment can cause patients to avoid social interaction
  - a. "I'll be embarrassed when I have to turn down drinks and food at a party"
  - b. "I didn't go to the family reunion because I didn't want to be a burden on anyone."
  - c. "I don't want people to see the bump/scars from my fistula/graft. I don't want to have to explain what it is, but if I don't people will wonder what's wrong with me."
- 3) Feelings of worthlessness and decreased libido can have a significant impact on romantic relationships
  - a. How do I explain ESRD and dialysis to someone I'm interested in dating?
  - b. Nobody's going to want to date a sick person
  - c. I just don't have any sexual motivation anymore
- 4) The dialysis regimen can reduce the amount of time a patient has to interact with others
  - a. "I feel lonely because I'm not working anymore and I have no social life"
  - b. "After working a full day and coming to dialysis at night, I don't have the time or energy to go out with my friends."

### Educational and Occupational Functioning

Treatment for ESRD including dialysis sessions, doctor visits and occasional hospitalizations can have a significant impact on the patient's ability to pursue educational and career goals. Furthermore, the overlapping symptoms of depression and ESRD such as fatigue, low energy, decreased motivation, and poor concentration can limit one's ability to function effectively in a school or work environment. Discuss with the patient the ways in which symptoms have impacted his/her ability to function at school, work, or home.

### SOME PATIENT EXAMPLES...

- Treatment for ESRD can feel like a burden and can interfere with work or school schedules

## Session 2: Motivation and Behavioral Activation

Goals for session 2:

- 1) Review homework: "Identifying Your Motivation" worksheet
- 2) Assess impairment in social, educational and occupational functioning

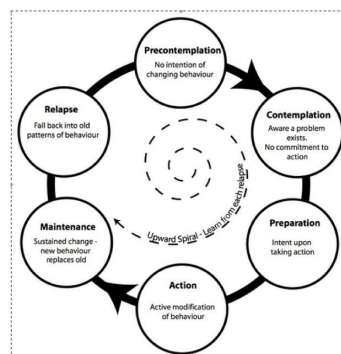
### Identify Motivation

Review the patient's motivations for becoming "less depressed." Discuss with the patient what it was like to complete the worksheet.

Sample questions include:

- "Was it difficult to imagine ways in which your life would be better if you were less depressed?"
- "How will changing particular beliefs and behaviors improve your life?"
- "Are there any drawbacks to changing these beliefs or behaviors?"

Identify what stage of change the patient is in.



- a. "I have to take off of work for doctor's appointments and when I'm not feeling well."
- b. "Everytime I try to get my life back on track I end up in the hospital."
- c. "It's hard to find a part-time job that will work with my dialysis schedule"
- 2) Having a chronic illness like ESRD can affect self esteem and confidence.
  - a. "This shut down career opportunities. I don't feel as confident in my skills and abilities"
- 3) Low energy, fatigue and low motivation can make it difficult to pursue career or educational goals
  - a. "After coming home from dialysis I just don't have the energy to start looking for a job."
  - b. "Why bother finishing school when I know no one will hire me because I'm sick."

### Intervention

#### Behavioral Activation:

- 4) Identify behavioral targets with a special emphasis on addressing fatigue.

Suggestions for the patient...

- a. Sometimes you may feel too tired or not motivated to do anything. This is part of the cycle of depression. When your energy and motivation are low you engage in fewer activities that give you pleasure or make you feel accomplished. You then end up feeling bad about yourself for not doing anything and your energy and motivation remain low. The very act of scheduling an activity in a calendar will increase the likelihood that you will follow through with the activity. If you push yourself to start the activity you will likely find that as you engage in the activity you will feel more energized and it is likely that at the end you will feel pleasure and pride for having completed the activity.
- 5) Instruct the patient in reward planning and activity scheduling.

Suggestions for the patient...

- a. Think about the activities or hobbies that used to give you pleasure. If you're having trouble coming up with some activities, try to think back to earlier times in your life when you had more fun, maybe as a young adult or adolescent or even as a child. What kinds of activities were fun for you back then? Maybe we can modify some of these past hobbies to make them fit into your current life
- b. Although watching TV can bring you some relaxation and pleasure, too much of it can lead to boredom or exacerbate fatigue. Try to limit TV watching to specific programs or time slots of the day.



## Suggested Activities

- |                           |   |
|---------------------------|---|
| 1) Going for a walk       | 9) Spending time with kids or grandchildren |
| 2) Learning to Cook       | 10) Going fishing                           |
| 3) Reading                | 11) Attend religious services               |
| 4) Listening to music     | 12) Play games/cards/dominoes               |
| 5) Going out with friends |   |
| 6) Taking a class         |   |
| 7) Knitting               |   |
| 8) Word games/puzzles     |   |

### Homework

Complete the "Weekly Activity Schedule" – pleasant events scheduling. Fill in activities for the first day in session with the patient so that they will know how to complete it.

## Session 3: Automatic Thoughts

Goals for session 3:

- 1) Review homework: "Weekly Activity Schedule"
- 2) Train patient in relationship between automatic thoughts and feelings
- 3) Review "Levels of Cognition" diagram
- 4) Elicit automatic thoughts in session
- 5) Evaluate reasons for and challenge hopelessness
- 6) Provide Handout "The depressed dialysis patient"

### Review the Weekly Activity Schedule

Review the patient's activity schedule. Discuss with the patient what it was like to complete the schedule.

Sample questions include:

- "Did you feel any different after completing the activities?"
- "What got in the way of completing activities?"
- "Which activities do you think you would like to make part of your regular schedule?"

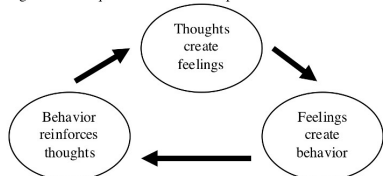
Spend some time exploring barriers to engaging in pleasurable activities. With a focus on specific barriers, try to identify some strategies for overcoming obstacles. Explain to the patient that it is normal to encounter obstacles when trying to change behavior and review the patient's motivations for change.

### The relationship between automatic thoughts and feelings

Often patients are unaware that their thoughts produce their feelings. They may confuse thoughts and feelings as being one in the same, or they may believe that feeling states occur spontaneously in response to external events. Use the "Levels of Cognition" handout to explain the relationship between thoughts, feelings and behavior. In your explanation be sure to address the following points:

- "Thoughts create feelings" – our interpretation of a situation determines how we will feel and behave in response to the situation.
- Automatic Thoughts – some thoughts occur more readily than others. Automatic thoughts are our "go-to" thoughts and they tend to arise spontaneously in varying situations. They are a quick and dirty perception and are often distorted and dysfunctional.
- "Core beliefs affect automatic thoughts" – Past experiences, culture and relationships shape our core beliefs and these beliefs influence the content of our automatic thoughts.
- 1) "Core beliefs produce rigid assumptions and rules" – people use "if-then" statements, "shoulds", "musts" and "have to's" and if they find that they are not meeting these assumptions they are vulnerable to depression or anxiety

- 1) "Thoughts do not equal facts" – Our interpretations of a situation are not always accurate.



### Elicit an Automatic Thought

Elicit the patient's automatic thought by first asking the patient to label their feelings. If the patient is having difficulty articulating their feelings offer common words that people use to describe their feeling state such as angry, calm, annoyed, sad, down, lonely, hopeless, frustrated...etc. After the patient has labeled their feeling use follow up questions to explore the automatic thought that is creating the feeling. For example:

- |            |  |
|------------|--|
| Patient:   | I feel depressed.  |
| Therapist: | Can you tell me why you feel depressed?  |
| Patient:   | OK. I feel depressed because my doctor told me that my phosphorous levels are high, but I know I'm doing everything I'm supposed to do.  |
| Therapist: | Now let's try to take it a step further. Sometimes you have to tune into your own thoughts to figure out which thoughts are creating your feelings. Take a minute to listen to the thoughts going through your mind. Now try completing this sentence. Getting the news about your phosphorous levels depresses you because... |
| Patient:   | Because no matter what I do I can't get my levels right and it just keeps going on and on. I don't think I'll ever get this under control.   |

Notice how the patient has arrived at a hopeless automatic thought, "I don't think I'll ever get this under control." This thought includes both a helpless attribution – *I can't control this* – and a prediction about the future – *this will never change*.

Use the handout "The Depressed Dialysis Patient" to review the process of identifying automatic thoughts with the patient.

### Homework

- 1) Complete Thought log 1 – Train the patient on how to complete the thought log and complete a practice "situation-feeling-thought" sequence in session.
- 2) Complete Weekly Activity Schedule

## Session 4: Categorizing Distorted Thoughts

Goals for session 4:

- 1) Review homework: "Weekly Activity Schedule"
- 2) Review homework: "Thought Log"
- 3) Identify cognitive distortions from thought log
- 4) Train patient in categorizing distorted automatic thoughts
- 5) Elicit and challenge automatic thoughts in session
- 6) Provide Handout "Challenging the depressed dialysis patient"

### Review Weekly Activity Schedule

Review the patient's activity schedule. Discuss with the patient what it was like to complete the schedule.

### Review Thought Log 1

Review the thought log and identify cognitive distortions. Look for thoughts that include global statements about the self, others or the future. Pay attention to key words such as "should," "must," "never," or "always."

### Categorizing Distorted Automatic Thoughts

Review with the patient the concept of distorted thoughts. Discuss how our perceptions of events can be skewed by core beliefs about our self, the world and others. Review the "Categories of Automatic Thoughts" handout with the patient. Go through each category and review an example. While going through the list, ask the patient to consider if he or she relates to any of the categories. After you have reviewed each category, return to the patient's thought log and have the patient identify which types of distortion are evident in his or her automatic thoughts. Below are some examples of cognitive distortions that you may hear from a dialysis patient.

### Cognitive Distortions of the Dialysis Patient

Automatic Thought	Distortion
"He'll think I'm sick and not attractive because of my graft site"	Mind Reading
"I'll never get my lab levels right"	Fortune Telling
"It will be unbearable if I can never eat that again."	Catastrophizing
"I'm a burden"	Labeling
"Nothing ever goes right for me."	Overgeneralizing
"Dialysis takes up all of my time. I never have time to do anything else"	Negative Filter
"I should be providing for my family"	Shoulds
"This all happened because I didn't take care of myself."	Personalizing

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<b>"This all happened because I didn't take care of myself."</b>	<b>Personalizing</b>
<b>"The doctors run my life. I can't make any decisions for myself anymore."</b>	<b>Dichotomous Thinking</b>

### Challenging Distorted Thoughts

Once the type of distortion has been identified, you must first help the patient distinguish thoughts from facts. Encourage the patient to assume the role of an investigator looking for evidence. Some sample questions include:

- "What is the evidence that this thought is true?"
- "Have you ever tested this belief?"
- "Can you think of any evidence that contradicts this belief?"
- "Have there been other times when you believed a situation was hopeless but it turned out ok?"

You can also encourage the patient to do a cost-benefit analysis of the thought. Some sample questions include

- 1) "What are the costs and benefits of thinking that you'll never get your levels right?"
- 2) "How does thinking this way help you?"
- 3) "How does thinking this way hurt you?"

Other techniques that can be helpful in challenging distorted thoughts include:

- Defining the Terms – define the meaning of the terms you are using
  - How would you define "being a burden?"
  - What makes a "sick person?"
- Role Playing - Both the therapist and the patient role play both sides of the thought
- Examining Variations in Behavior in Various Situations – challenge the tendency to generalize from a single behavior to a label of the entire person.
  - Can you think of times or situations when the label "burden" doesn't suit you?
  - Are there some situations in which you are less "lazy?"
  - Are there times when you are not seen as a "sick" person?

Using the handout "Challenging the Depressed Dialysis Patient" practice with the patient identifying categories of cognitive distortion.

### Homework

- 1) Complete Thought log 2 – Train the patient to identify the type of cognitive distortion and challenge the distortion by providing a rational response.
- 2) Complete Weekly Activity Schedule

### Homework

- 1) Complete Weekly Activity Schedule – continue self-directed reward planning and activity scheduling
- 2) Complete Thought Log 3 – Have patient record thoughts and moods, identify distortions and generate alternative responses on thought log.

## Session 5: Cognitive Restructuring

Goals for session 5:

- 1) Review homework: "Weekly Activity Schedule"
- 2) Review homework: "Thought Log 2"
- 3) Train patient in developing rational responses to distorted automatic thoughts
- 4) Provide handout "Cognitive Restructuring – Fluid Intake"

### Review Weekly Activity Schedule

Review the patient's activity schedule. Is the patient continuing to add new activities that are rewarding and pleasurable? Address any barriers to behavioral activation that have arisen.

### Review Thought Log 2

Now that the patient has learned to categorize and challenge distorted thoughts, it is time to teach the patient how to generate an alternative rational response to the automatic thought. The thought challenging techniques described in session 4 will generate significant evidence that opposes the automatic thought. Using this evidence, help the patient to consider more positive alternative interpretations of the situation.

### Cognitive Restructuring

Now that the patient has learned to categorize and challenge distorted thoughts, it is time to teach the patient how to generate an alternative rational response to the automatic thought. The thought challenging techniques described in session 4 will generate significant evidence that opposes the automatic thought. Using this evidence, help the patient to consider more positive alternative interpretations of the situation.

At first, it may be useful to have the patient adopt an alternative perspective to approach the situation. For example, you can ask the patient to imagine what she might tell a friend who was having some of these negative thoughts.

Use the "Cognitive Restructuring – Fluid Intake" handout to illustrate an example of cognitive restructuring for the dialysis patient. Fluid and diet restriction is commonly identified as a significant source of stress for dialysis patients. Patients often worry about how they will be perceived by others if they have to turn down food or drink at a social gathering, and they often feel that the diet and fluid restrictions are an unfair burden on their daily life. The handout provides an example of how the patient's automatic thoughts about fluid intake can be reframed to be more rational.

Remind the patient that these automatic thoughts have been around for a long time and they've been strengthened by frequent use. Therefore, the goal is not to rid your mind completely of these automatic thoughts, but to instead be able to argue the thoughts when they arise. With practice over time the frequency and intensity of the thoughts will likely diminish.

## Session 6: Patterns of Maladaptive Thinking

Goals for session 6:

- 1) Review homework: "Weekly Activity Schedule"
- 2) Review homework: "Thought Log 3"
- 3) Help patient identify recurring patterns of maladaptive thinking
- 4) Identify and challenge maladaptive assumptions
- 5) Begin to identify and challenge negative schemas

### Review Weekly Activity Schedule

Review the patient's activity schedule. Is the patient continuing to add new activities that are rewarding and pleasurable? Address any barriers to behavioral activation that have arisen.

Often patients will be hesitant to schedule activities for the days on which they get dialysis. Encourage the patient to consider brief, mildly taxing activities that he or she can do on dialysis days. For example, the patient can plan to call a friend, rent a movie, or complete a word puzzle.

### Review Thought Log 3

Review Thought log 3. Address any questions the patient may have about categorizing distorted thoughts and generating alternative responses. Discuss with the patient how the process of monitoring thoughts has affected his or her thoughts, feelings and/or behavior.

### Patterns of Maladaptive Thinking

While reviewing and discussing the patient's completed thought logs listen for recurrent themes or patterns of thought. Reflect these themes and patterns back to the patient and explore how these patterns repeatedly affect the patient's mood and behavior. A discussion of past episodes of depression or conflict may help to reveal the repetition of these themes. Below is a list of maladaptive themes that you might hear from a dialysis patient.





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### Session 7: Healthy Living

Goals for session 7:

- 1) Review homework: "Weekly Activity Schedule"
- 2) Review homework: "Thought Log 3"
- 3) Evaluate Depression (BDI) and Anxiety (BAI)
- 4) Explore links between mood and healthy living.
- 5) Use MI techniques to identify areas of potential health improvement.
- 6) Develop behavioral plan with "Better Living" handout

#### Review Weekly Activity Schedule

Review the patient's activity schedule. Is the patient continuing to add new activities that are rewarding and pleasurable? Address any barriers to behavioral activation that have arisen.

#### Review Thought Log 3

Review Thought log 3. Address any difficulties with generating alternative responses. What does it feel like to adopt a new perspective? How have your alternative responses impacted your relationships and experiences?

#### The Link between Mood and Healthy Living

Illness can have a significant impact on mood, as we see in many patients with ESRD, but it is also true that our mood can affect our health. A patient's mood state can alter behaviors that are essential to healthy living. In patients with ESRD depressive symptoms such as low motivation, low energy, withdrawal, and anhedonia can interfere with the patient's adherence to medication prescriptions, and diet and recommendations. Failure to adhere to these prescriptions can negatively impact the patient's overall health.

Explore with the patient the ways in which their depressed, anxious or angry mood affects their ability to adhere to medication, exercise, follow their diet, or attend doctor's appointments and dialysis sessions. The link between mood and these health-specific behaviors may not be obvious to the patient. It is helpful for the therapist to use the vertical descent technique to explore the association between mood and non-adherence. For example:

Therapist: It seems like you've been putting on a significant amount of weight in between sessions.  
Patient: It's just hard to stick to the diet. I like to eat certain foods that make me feel good.  
Therapist: Why do you think it feels good to eat those foods?  
Patient: Because it makes me feel like nothing has changed in my life.  
Therapist: And what would it mean to you if things were how they used to be.  
Patient: It would mean I was in control of my life again.  
Therapist: And being out of control makes you feel...  
Patient: It makes me feel angry.  
Therapist: So it seems that your anger is really affecting your ability to take care of yourself by sticking to your diet.

#### Motivation for Healthy Living

Review with the patient their motivation for adhering to prescriptions for managing their ESRD and for maintaining an overall healthy lifestyle. If the patient is having difficulty identifying specific motivators the therapist can offer suggestions. Some possible motivators might include:

- 1) "To be there for my children"
- 2) "To be there for my spouse"
- 3) "I want to return to work"
- 4) "I want to achieve my career goals"
- 5) "I want to feel good"
- 6) "I want to be able to return to some of my old hobbies/activities"

Once the motivation has been determined, help the patient identify areas of potential health improvement. Use the handout "A Plan for Better Living" to explore the benefits and drawbacks to changing health behaviors. After selecting targeted behaviors brainstorm with the patient to generate strategies for modifying the health behaviors.

Below are some useful tips for improving adherence to diet, exercise and medication.

#### Strategies for Improving Adherence

Diet	Exercise	Medication
Review lists of approved foods with the dietitian	Put out sneakers and exercise clothes	Set the alarm on your cell phone or clock as a reminder to take medication
Use smaller cups/glasses to reduce liquid intake	Select exercise activities that are fun as well as healthy	Pair your medication taking behavior with another daily habit, such as a meal or brushing your teeth
Find specific ingredients that are approved and that you enjoy and try to experiment with new recipes that incorporate the ingredients	Find an exercise partner and plan to exercise together on a regularly scheduled basis.	Always keep spare medication in your purse or wallet

#### Homework

- Complete Weekly Activity Schedule – continue self-directed reward planning and activity scheduling. Include health-related behaviors on schedule.
- Complete Thought Log 3 – Have patient record thoughts and moods, identify distortions and generate alternative responses on thought log.

### Session 8: Anxiety Management

Goals for session 8:

- 1) Review homework: "Weekly Activity Schedule"
- 2) Review homework: "Thought Log 3"
- 3) Explore anxious thoughts and consequent behaviors
- 4) Discuss healthy strategies for coping with anxiety
- 5) Train patient in diaphragmatic breathing

#### Review Weekly Activity Schedule

Review the patient's activity schedule. Was the patient able to introduce or modify any health behaviors?

#### Review Thought Log 3

Review Thought log 3. Are there persistent maladaptive thoughts that are resistant to change? Does the patient need to utilize problem-solving skills to modify challenges in his or her environment?

#### Managing Anxiety

Using the techniques already discussed work with the patient to elicit anxious thoughts associated with dialysis and ESRD. Categorize, challenge and modify the irrational worried thoughts with the patient.

It also important to explore behavioral strategies for managing anxiety. Many of the challenges faced by the ESRD patient can lead to worry about quality of life, pain and mortality. It is helpful for the patient to have to multiple resources in order to manage their anxiety regarding these issues. Sample worries and corresponding coping skills are listed below:

Anxiety about medical procedures or fistula/graft surgeries:

- 6) Encourage the patient to gain information about the procedure from valid sources such as the doctor, nurses or a trusted fellow patient.

Worries about mortality

- 7) Share concerns with social support network
- 8) Use religious coping strategies such as talking with religious leaders, prayer, attending services
- 9) Seek therapy from a trained professional

Concerns about pain management

- 10) Discuss relaxation techniques: diaphragmatic breathing, visualization, distraction

#### Diaphragmatic Breathing

Often patients are used to breathing air into the upper portion of their chest. When anxious this breathing may become more rapid and shallow, causing greater anxiety and

#### Maladaptive Assumptions and the Vertical Descent Technique

Once themes have been identified the therapist can use the *Vertical Descent* technique to evaluate the underlying assumption behind the maladaptive thought. Vertical descent is a line of questioning that begins by assuming that the maladaptive thought is true and examining the implications of this belief. For example:

Therapist: You said that you don't want to go to the family reunion. Why is that?  
Patient: I don't want to have to ask anyone for help getting there and getting around.  
Therapist: What would it mean if you did have to ask for help.  
Patient: That I'm a burden.  
Therapist: Why would it bother you if you were a burden to family members?  
Patient: Because it means I'm useless and that I'm a loser.

Below is a list of thoughts and assumptions that you may hear from a dialysis patient:

I hate asking for help	If I ask for help I am a burden.
I'm not working and I'm not bringing in any money	If I can't provide for my family then I am not a real man
No one's going to want to date me	I'll be alone forever
I worry if I can trust my doctors	I'm going to end up sick in a bed, unable to take care of myself
I have no control over my own life.	I'm helpless

#### Identifying Negative Schemas

After examining the patient's maladaptive thoughts and assumptions you begin to develop a sense of his core beliefs, or *negative schemas*, about his self and others. Schemas are the lens through which the patient sees the world and this lens is colored by past experiences, relationships and events. Depressive schemas may include beliefs about vulnerability competence, weakness, helplessness, failure, rejection, and humiliation. The schemas of depressed dialysis patients often reflect concerns about disconnection (e.g. I don't know what my role is in my family anymore) and loss of personal autonomy (e.g. I have no control over my life). The therapist can identify schemas by paying attention to repeated thought patterns and by using vertical descent to access underlying beliefs.

#### Homework

- 1) Complete Weekly Activity Schedule – continue self-directed reward planning and activity scheduling
- 2) Complete Thought Log 3 – Have patient record thoughts and moods, identify distortions and generate alternative responses on thought log.

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potentially leading to hyperventilation. In diaphragmatic breathing, the diaphragm is contracted which pushes the abdomen out and draws air into the lower lungs. Diaphragmatic breathing can help to “turn on” the parasympathetic nervous system, restoring the body to a state of rest. The therapist should first model diaphragmatic breathing for the patient and then practice the technique in session.

A common diaphragmatic breathing exercise is as follows:

- 1) Sit or lie comfortably, with loose garments.
- 2) Put one hand on your chest and one on your stomach.
- 3) Slowly inhale through your nose or through pursed lips (to slow down the intake of breath).
- 4) As you inhale, push your belly/ stomach out and feel your stomach expand with your hand.

### Homework

- Complete Weekly Activity Schedule – continue self-directed reward planning and activity scheduling. Include health-related behaviors on schedule.
- Complete Thought Log 3 – Have patient record thoughts and moods, identify distortions and generate alternative responses on thought log.

## Session 9: Highlights

Goals for session 9:

- 1) Review homework: “Weekly Activity Schedule”
- 2) Review homework: “Thought Log 3”
- 3) Review of all sessions using “highlights” form
- 4) Identify areas of continued emphasis

### Review Weekly Activity Schedule

Review the patient’s activity schedule. Discuss with the patient how the process of scheduling activities and self-rewards has affected their daily mood.

### Review Thought Log 3

Review Thought log 3. Discuss with the patient how the process of monitoring and challenging automatic thoughts has affected their daily mood.

### Review of Highlights from the Therapy

Using the “Highlights” worksheet have the patient recall the important components of the therapy. Begin with a review of the patient’s initial motivation for changing his or her mood. How have things changed for the patient as they approached their goal? Continue with a discussion of the ways in which adding pleasurable activities has impacted both daily and overall mood. Next, have the patient practice eliciting, challenging and modifying a repeated automatic thought. Support the progress they have made in developing these techniques and remind the patient that as with any newly learned skill, this requires frequent practice. Conclude with a review of the health behaviors that the patient wishes to adopt in order to live a more healthy life.

### Prepare for Termination

Have the patient explore his or her feelings about completing the therapy. Let the patient know that it is normal to experience some feelings of sadness, anxiety or anger as the relationship between the two of you is coming to an end. Give the patient an opportunity to share his or her feelings about the relationship.

### Homework

- Complete Weekly Activity Schedule – continue self-directed reward planning and activity scheduling. Include health-related behaviors on schedule.
- 1. Ask the patient to take some time to think about what he or she liked or disliked during the therapy.

## Session 10: Plan of Action

Goals for session 10:

- 1) Develop plan for after end of therapy
- 2) Identify helpful and non-helpful interventions
- 3) Discuss past episodes of depression and plan for management of future episodes
- 4) Complete “My Plan of Action”

### What Happens Next?

In the final session the therapist should focus on helping the patient consolidate the gains made during the therapy, and developing a long term plan for handling future stress and episodes of depression. Begin by asking the patient to discuss which interventions he or she found to be helpful and which were not helpful. Have the patient explore how they have benefitted from the helpful interventions and how they plan to continue to use these skills or techniques in the future. With regard to the non-helpful interventions, ask the patient why it was not helpful and what, if anything, could have been done differently to make it more useful. The therapist should also inquire as to whether or not there were areas or topics omitted that the patient would have liked to address.

In order to prepare for managing future episodes of depression it is important to have the patient recall past episodes of depression. In this discussion the therapist should inquire about:

- Specific stressors that may have contributed to the onset of the episode
- Early warning signs or symptoms
- Helpful coping strategies that were used in the past
- Support Network

This information will be useful for the patient in early detection and possible prevention of depressive episodes in the future. It is important for the therapist to inform the patient that some people experience recurrent episodes of depression and that the techniques they have learned will be valuable tools for handling depression in the future. It may be a helpful practice to have the patient imagine a future scenario in which they effectively manage depressive thoughts and feelings.

For some patients, continued therapy may be warranted and the therapist should provide referrals for appropriate psychological care.

### My Plan of Action

Have the patient complete a “Plan of Action.” This is an opportunity for the patient to write a prescription for future episodes of depression. The therapist should instruct the patient to outline a plan of action in which they detail which interventions they will use to treat their symptoms of depression. Within the plan the patient can also specify behaviors and activities that he or she will do in order to prevent future episodes of depression.

Session 1  
Cognitive Assessment sheet  
Information About Depression  
Better sleeping with hemodialysis  
Identifying your motivation

Session 2  
Weekly Activity Schedule

Session 3  
Levels of Cognition  
The depressed dialysis patient  
Thought log I (3.3)  
Weekly Activity Schedule

Session 4  
Categories of Automatic thoughts  
Challenging The depressed dialysis patient  
thought log II (4.4)  
Weekly Activity Schedule

Session 5  
Thought Log III (5.1)  
Cognitive restructuring – Fluid intake  
Weekly Activity Schedule

Thought Log III  
Weekly Activity Schedule

Session 7  
Thought Log III  
A Plan for Better Living  
Weekly Activity Schedule

Session 8  
Varies  
Weekly Activity Schedule

Session 9  
Highlights  
Weekly Activity Schedule

Session 10  
My plan of ACTION

Session 6



## CBT manual Pages 25-28

### Forms

Patient ID \_\_\_\_\_

#### Cognitive Assessment

Describe a situation in which you feel sad or depressed:

---

---

Complete the following sentence: "I would feel sad because I am thinking . . .":

---

---

"And this would bother me, because it would mean . . .":

---

---

"I would feel less depressed if . . .":

---

---

Substance use :

Current use of psychiatric medications (include dosage) \_\_\_\_\_

Who prescribes? \_\_\_\_\_

Use of alcohol/other drugs (kind and amount) \_\_\_\_\_

Previous episodes of depression:

Onset

Duration

Precipitating events

Treatment

Previous manic/hypomanic episodes (if any):

Onset Duration

Precipitating events

Treatment

Suicidal intent: None Weak Moderate Strong

#### Better Sleeping with Hemodialysis

One of the more troubling experiences for medically ill or depressed patients is insomnia. Some people experience difficulty falling asleep, while others wake several times during the early morning hours. Even though sleep difficulties are often part of your body's changes due to kidney failure and hemodialysis, a number of cognitive-behavioral interventions may help you sleep more and more restfully.

Before you attempt any interventions, you should note the number of hours per night that you sleep and the number of times that you wake. You can then compare improvements in your sleep.

-- Develop regular sleep times. Go to bed and get out of bed at about the same time, regardless of how tired you are. Also avoid naps.

-- Use your bed only for sleep and sex. Insomnia is often the result of increased arousal preceding bedtime and while lying awake in bed. If you use the bed for reading, talking on the phone, and worrying, the bed is associated with arousal (anxiety). Read or talk on the phone in another room.

-- Sleep is often disturbed by urinary urgency. Reduce or eliminate liquid intake several hours before bedtime. Avoid all caffeine products, heavy foods, and liquor.

-- Do not try to fall asleep—this will only increase your frustration and anxiety. Paradoxically, a very effective way of increasing sleep is to practice giving up trying to fall asleep. You can say to yourself, "I'll give up trying to get to sleep and just concentrate on the relaxing feelings in my body."

-- If you are lying awake at night for more than 15 minutes, get up and go in the other room. Typical automatic thoughts are "I'll never get to sleep," "I need to get to sleep immediately," and "I'll get sick from not getting enough sleep." The most likely consequence of not getting enough sleep is that you will feel tired and irritable. Although these are uncomfortable inconveniences, they are not catastrophic.

-- Your therapist can teach techniques that will enhance your restfulness. Try to make your mind go blank. Count backward by threes from 100 or 1,000, as slowly as possible. Visualize a relaxing scene— for example, snow falling on a house in the woods at night.

#### Information about Depression

What Is Depression?

Depression has a variety of symptoms, such as loss of energy, loss of interest in activities and in life, sadness, loss of appetite and weight, difficulty concentrating, self-criticism, feelings of hopelessness, physical complaints, withdrawal from other people, irritability, difficulty making decisions, and suicidal thinking. Many depressed people feel anxious as well. Feelings of tiredness, low energy, and lack of interest are normal during a medical illness.

Clinical depression differs from being "sick", in that the low mood lasts longer and includes feelings of self-criticism, hopelessness, and despair.

Who Gets Depressed?

Depression is not something that happens to people who are "unusual" or "crazy." It is everywhere. About 20- 30% of ESRD patients could be diagnosed with depression. There is no one cause of depression. These factors can be related to your illness, your social relationships, your thoughts or your behavior. (It is most likely related to all of these areas, at least somewhat.)

Although each of the factors of stress and loss may make you prone to depression, they do not necessarily have to result in depression. Certain ways of thinking can increase your chances of becoming depressed, however. You are more likely to become depressed if you think that you are entirely to blame, that nothing can change, and that you should be perfect at everything. These interpretations of stress and loss are the "cognitions" or thoughts that you have about yourself and your environment.

What Is Cognitive-Behavioral Treatment of Depression?

The cognitive-behavioral treatment of depression works by identifying and addressing the behaviors and thinking patterns that cause and maintain depression. This therapy focuses on your present, here-and-now thoughts and behaviors.

What Is Expected of You as a Patient?

Cognitive-behavioral treatment of depression requires your active participation.. Your therapist will give you homework exercises to assist you in modifying your behavior, your thoughts, and your relationships. Although many patients suffering from depression feel hopeless about improvement, there is an excellent chance that your depression may be substantially reduced with this treatment.

#### Weekly Activity Schedule

Date: \_\_\_\_\_

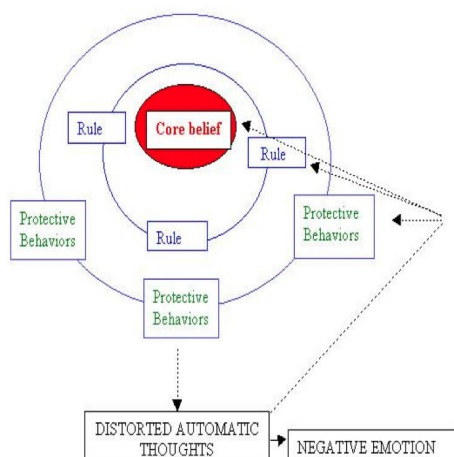
Name: \_\_\_\_\_

Instructions: Select \_ pleasurable activities and schedule them throughout the week. Rate how much you expect to enjoy them. Once you've done them, go back and rate how much you actually enjoyed the activity. Rate the amount of pleasure from 0 (no pleasure) to 10 (most pleasurable)

Time	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
7AM							
8AM							
9AM							
10 AM							
11 AM							
Noon							
1 PM							
2 PM							
3PM							
4 PM							
5 PM							
6 PM							
7 PM							
8 PM							
9PM							
10 PM							
11PM							
midnight							
1-3 AM							
3-6AM							



## Levels of Cognition

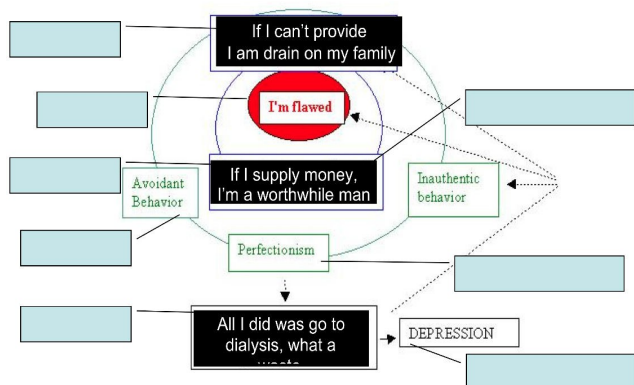


## Daily Record of Automatic Thoughts

Date:

Time	Situation: What happened, where, and who was involved.	Emotions: Specify emotion and rate its intensity (0–100%).	Automatic thoughts: Write thoughts that preceded emotions; rate each for confidence in accuracy (0–100%).

## Challenging the Depressed Dialysis Patient



## Categories of Distorted Automatic Thoughts

**Mind reading/ Fortunetelling:** You assume that you know what people think without having sufficient evidence of their thoughts. "He thinks I'm a loser." You predict the future negatively.

**Catastrophizing:** You believe that what has happened or will happen will be so awful and unbearable that you won't be able to stand it. "It would be terrible if I failed."

**Discounting positives:** You claim that the positive things you or others do are trivial. "That's what wives are supposed to do—so it doesn't count when she's nice to me," or "Those successes were easy, so they don't matter."

**Overgeneralizing:** You perceive a global pattern of negatives on the basis of a single incident. "This generally happens to me. I seem to fail at a lot of things."

**Dichotomous thinking:** You view events or people in all-or-nothing terms. "I get rejected by everyone," or "It was a complete waste of time."

**Shoulds:** You interpret events in terms of how things should be, rather than simply focusing on what is. "I should do well. If I don't, then I'm a failure."

**Personalizing:** You attribute a disproportionate amount of the blame to yourself for negative events, and you fail to see that certain events are also caused by others. "The marriage ended because I failed."

**Regret orientation:** You focus on the idea that you could have done better in the past, rather on what you can do better now. "I could have had a better job if I had tried," or "I shouldn't have said that."

**Emotional reasoning:** You let your feelings guide your interpretation of reality. "I feel depressed; therefore, my marriage is not working out."

**Judgment focus:** You view yourself, others, and events in terms of evaluations as good–bad or superior–inferior, rather than simply describing, accepting, or understanding. You are continually measuring yourself and others according to arbitrary standards, and finding that you and others fall short. You are focused on the judgments of others as well as your own judgments of yourself. "I didn't perform well in college," or "If I try to cook, I won't do well," or "Look how successful she is. I'm not successful."

## CBT manual Pages 33-37

### Daily Record of Automatic Thoughts II

Date:

Name:

Time	Situation: What happened, where, and who was involved.	Emotions: Rate intensity (0–100%).	Automatic thoughts: Write thoughts that preceded emotions; rate each for confidence in accuracy (0–100%).	Cognitive Distortion Identify the specific distortion being used from the list on 'distortions' handout	Rational Response Write possible responses to each automatic thought; rate each for confidence in accuracy (0–100%).

### Daily Record of Automatic Thoughts III

Date:

Name:

Situation: What happened, where, and who was involved.	Emotions: Rate intensity (0–100%).	Automatic thoughts: Write thoughts that preceded emotions; rate each for confidence in accuracy (0–100%).	Cognitive Distortion	Rational Response Write possible responses to each automatic thought; rate each for confidence in accuracy (0–100%).	Alternate Response How would you have reacted differently/the situation turned out, if you believed the rational response.

### Daily Record of Automatic Thoughts

Date:

Fluid Example

Situation: What happened, where, and who was involved.	Emotions: Rate intensity (0–100%).	Automatic thoughts: Write thoughts that preceded emotions; rate each for confidence in accuracy (0–100%).	Cognitive Distortion	Rational Response Write possible responses to each automatic thought; rate each for confidence in accuracy (0–100%).	Alternate Response How would you have reacted differently/the situation turned out, if you believed the rational response.
At Jim's house, he offered me a glass of water in front of everyone.	Embarrassed 80% Angry 30%	It would be so embarrassing to not take the drink. I don't think I could stand it. 80%  I shouldn't have to watch what I drink.	Catastrophizing  Shoulds	He'll understand that it's part of my staying healthy 80%  Everyone has something annoying to do to keep healthy 100%	I would have just said No thanks Jim, I have to watch how much I drink because of my kidneys and then I wouldn't have had the drink and felt good about it.

### Highlights

In session 1 I identified the following as my primary motivation for taking control of my mood.

Since then I realized that the closer I got to this goal \_\_\_\_\_

In session 2 I listed \_\_\_\_\_ and \_\_\_\_\_

as my most pleasurable activities. I have/have not been successful at incorporating them into my life.

In session 3 we reviewed automatic thoughts. The most common thought I have is \_\_\_\_\_

This is an example of the \_\_\_\_\_ distortion. I know it's not true because \_\_\_\_\_

If there is one thought that I could convince myself is not true it would be \_\_\_\_\_

The things that I can do to help myself live a more healthy life are \_\_\_\_\_

The things that I can do to start living healthier are \_\_\_\_\_



## Appendix Six: DSMB Charter

### Data and Safety Monitoring Board (DSMB) Charter

#### Title: A Trial of Sertraline and CBT in End-stage Renal Disease Patients with Depression (ASCEND) Randomized Controlled Trial

**Funder Name:** Patient Centered Outcomes Research Institute (PCORI)

**Principal Investigator:** Rajnish Mehrotra, MD MS

**Date of Document:** 03/29/2017

**Version:** 1.1

#### Reviewed and Accepted by DSMB Members:

Alan Kliger, MD (Chair)	Date
Michael Hollifield, MD	Date
J Richard Landis, PhD (Biostatistician)	Date
Michael Rocco, MD	Date
Suzanne Watnick, MD	Date

#### Reviewed and Accepted by Funder by:

Julie McCormack, MA, Project Officer	Date
--------------------------------------	------

**Prepared and Accepted by:**

Rajnish Mehrotra, MD MS, Principal Investigator for the ASCEND Trial      Date

Patrick Heagerty, PhD, Coordinating Center Statistical Advisor      Date

Tessa Rue, MS, Unblinded Coordinating Center Statistician      Date

<b>Terms used in this document related to the Data Safety Monitoring Board activities</b>	
<b><u>Term</u></b>	<b><u>Definition</u></b>
<b>Blinding Status</b>	
Blinded	Access to aggregate (i.e., total) results only.
Semi-Blinded	Access to results split by randomized treatment arm, but without knowledge of the actual treatment assignment (i.e., Treatment A versus Treatment B)
Unblinded	Access to the decode information for A and B as described in the Semi-Blinded definition
<b>Individuals and Groups</b>	
Data Safety Monitoring Board (DSMB)	<i>Unblinded</i> An independent group charged with monitoring the safety of patients in the ASCEND trial, and the scientific integrity of the trial
Funder	<i>Initially Blinded</i> The Funder is the organization that provides funding and other support, and oversees trial implementation.
Principal Investigator	<i>Initially Blinded</i>

	The Principal Investigator is the physician who serves as the scientific leader of the trial
Coordinating Center / Study Management Team	<i>Initially Blinded</i> The Coordinating Center and Study Management Teams are responsible for trial logistics, including interaction with sites, data collection and cleaning, supply of study materials and updates to the Funder.
Unblinded Coordinating Center Statistician*	<i>Initially Unblinded</i> The unblinded statistician who prepared the Closed Report
Coordinating Center Statistical Advisor**	<i>Initially Semi-Blinded</i> The semi-blinded statistician who will assist with the interpretation of the Closed Report.
<b>Open and Closed Report, Session, Minutes</b>	
Open	The Open Session may be attended by all groups described above. The Open Report will be discussed, and Open Minutes will be recorded.
Closed	The Closed session may be attended by semi-blinded and unblinded persons only. The (Semi-Blinded) Closed Report will be discussed, and Closed Minutes will be recorded.

\* The Unblinded Coordinating Center Statistician is unblinded, but has no contact with patients or the day-to-day study activities.

\*\* The Coordinating Center Statistical Advisor is semi-blinded, but has no contact with patients or the day-to-day study activities.



# **A Trial of Sertraline and CBT in End-stage Renal Disease Patients with Depression (ASCEND)**

## **Data and Safety Monitoring Board (DSMB) Charter**

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## **Part 1: Introduction**

The Data and Safety Monitoring Board (DSMB) will be responsible for assessing safety and efficacy during conduct of the ASCEND trial, as well as ensuring the validity and scientific merit of the trial. This charter describes the roles and responsibilities of the DSMB for this trial. The DSMB will meet on a regular basis, and will provide recommendations to the Principal Investigator for the ASCEND study on whether to continue, modify, or terminate the study.

### ***1.1 Charge to the DSMB***

The DSMB will monitor the conduct of the study and review interim results for the purpose of recommending whether or not to continue the trial as designed. The fundamental responsibilities of the DSMB are to assure:

- The ongoing safety of study participants, and
- The scientific integrity of the trial.

In addition, the DSMB will use established guidelines to monitor the study for important safety variables suggesting harm.

The DSMB is also charged to recommend whether to continue the study, terminate the study, continue the study with major or minor modifications (such as modifications to inclusion/exclusion criteria or criteria to determine eligibility for cross-over), or temporarily suspend enrollment and/or treatment in the study until uncertainty is resolved.

### ***1.2 Protocol Summary***

The ASCEND study is a two phase randomized, controlled trial randomizing 200 depressed patients undergoing hemodialysis to receive either engagement interview or control visit, and the second phase randomizing 120 patients accepting intervention, to

either CBT or drug therapy. Those who do not accept treatment are followed observationally. The goals of this study are to 1) evaluate the impact of an engagement interview on receiving treatment; and 2) compare the effectiveness of treatments for depression in patients undergoing hemodialysis. The primary outcome for the first randomization will be at 6 weeks post-randomization assessing treatment (either psychotherapy or drug therapy) uptake. The primary outcome for the second randomization will be at 12 weeks post-randomization assessing depressive symptoms.

With N=200 patients, the ASCEND study will have 80% power to detect a 15% difference in uptake between the engagement interview group (55%) and the control visit group (40%). The primary analysis will employ logistic regression adjusting for recruitment site to compare the proportions of patients who initiate treatment for depression between the engagement interview and control visit groups.

For the second phase of the trial (N=120), the study is powered on the Quick Inventory of Depressive Symptomatology-Clinician rated (QIDS-C) score, as measured at the primary study endpoint of 12 weeks. The QIDS-C is a 16-item questionnaire used to assess depressive symptoms. The primary analysis will utilize analysis of covariance (ANCOVA) to compare CBT to Sertraline with the following analysis parameters: 85% follow-up at 12 weeks; two-sided Type 1 error rate of  $\alpha=0.05$ ; adjustment for recruitment site, first randomization, and the QIDS-C baseline score. Depending on the within-person correlation from baseline to 12 weeks (estimated range .4-.7), the study will have 80% power to detect an effect size of  $0.40(r=0.7) - 0.51(R=0.4)$ .

### **1.3 DSMB Membership and Responsibilities**

The DSMB is an independent multidisciplinary group consisting of four clinicians in the fields of nephrology and psychiatry and one biostatistician who collectively have experience in the treatment of subjects with depression, and/or experience with care for patients with end stage renal disease, and/or in the conduct and monitoring of randomized clinical trials. The duration of membership will span until six months after the end of patient recruitment.

All DSMB Members have agreed by contract that proceedings from DSMB meetings and related activities are confidential. DSMB Members will not act as investigators or sub-investigators for these trials and will have no trial involvement outside their role on the DSMB.

No Member of the DSMB will be an employee of PCORI. DSMB Members must disclose all active agreements (direct or indirect) with pharmaceutical companies, biotechnology

companies, or contract research organizations. Members of the DSMB will be responsible for advising the Board of any changes in their financial interests in the aforementioned companies.

The DSMB membership has been restricted to individuals free of apparent significant conflict of interest. The source of conflict may be financial, scientific and/or regulatory in nature. Thus, neither study investigators nor individuals employed by the funder or regulatory agencies are to be Members of the DSMB.

The DSMB will be responsible for deciding whether consultant agreements or financial interests of the members have the potential for conflict of interest. Members of the DSMB who develop significant potential or perceived conflicts of interest will be asked to resign from the committee.

The DSMB Members and Chair are listed in Appendix 1.

As part of this study, the DSMB is established to provide an independent review and assessment of the accumulating safety and efficacy data, and to further safeguard the interests and safety of the participating subjects. The primary role of the DSMB is to make a recommendation to the Principal Investigator based on analysis of available data.

The objective of the DSMB is to independently monitor and assess the study. At each interim meeting, the DSMB will undertake a comprehensive review and assessment of the cumulative study safety data. The DSMB will determine if safety of sertraline is sufficient to allow the trial to continue. The DSMB will use *a priori* defined, and, where appropriate, *ad hoc* analyses to assess safety. The DSMB will utilize all available trial data when forming any recommendation to discontinue the study or unblind the results. The Study Management Team will consult with the DSMB as needed on substantive changes to the protocol or study conduct once the trial begins.

The DSMB will be responsible for ensuring the timely review of the accumulated safety data. Based on the reviews and assessments of the data, the DSMB will inform the Principal Investigator of any safety concerns and will provide recommendations for appropriate actions.

### **1.3.1 DSMB Chair**

The DSMB Chair will have the following additional responsibilities: chair the meeting, confirm quorum, summarize recommendations, set an agenda for the Closed Session of the meeting, and record Open and Closed Minutes of the DSMB meetings. If a DSMB

member can no longer continue, the Chair is responsible for selecting his or her replacement.

### **1.3.2 DSMB Statistician**

The DSMB statistician will provide guidance to the voting Members of the DSMB on issues of a statistical nature.

## **1.4 *Responsibilities of the Study Management Team and Coordinating Center***

The Coordinating Center and Study Management Team work in tandem but are distinct entities. Representatives from the Study Management Team are charged with the day-to-day management of the trial; the Unblinded Coordinating Center Statistician and Coordinating Center Statistical Advisor are not involved in these activities and have no contact with sites or patients. The Study Management team and their roles are listed in Appendix.

The Study Management Team is responsible for providing timely and accurate data to the Unblinded Coordinating Center Statistician for inclusion in reports to the DSMB. In addition, the Study Management Team will review the Open Report and may present information about the status of the trial and any issues related to study execution during the Open Session. The Study Management Team must maintain an up-to-date, accurate study database by such processes as retrieving CRFs promptly, entering and validating the data, querying suspicious data, and coding adverse events.

### **1.4.1 Principal Investigator**

The Principal Investigator for the ASCEND study will be the physician leading the conduct of the clinical trial, and will oversee activities of the Study Management Team.

The Principal Investigator must set an agenda for the Open portion of the meeting, and will receive the recommendations of the DSMB. The Principal Investigator will distribute the recommendations to the Study Management Team, Internal Review Boards, and others as appropriate.

### **1.4.2 Unblinded Coordinating Center Statistician**

The Unblinded Coordinating Center Statistician must produce and validate the DSMB report, keeping any potentially unblinding information confidential and out of reach of other members of the coordinating center (with the exception of unblinded programmers). This individual will also be responsible for delivering the Open and Closed Reports to the DSMB.

The Unblinded Coordinating Center Statistician will be responsible for getting approval from the DSMB in the event that personnel directly associated with the study must be given information that could potentially unblind them.

#### **1.4.3 Coordinating Center Statistical Advisor**

The Coordinating Center Statistical Advisor must review and present the Closed Report during the Closed Session and answer questions from the DSMB that are of a statistical nature, or other questions as deemed appropriate by the DSMB.

Due to potential for bias, the Coordinating Center Statistical Advisor should not make study design decisions after viewing the semi-blinded results; after the first data review, such decisions should be made by a blinded person as appointed by the Principal Investigator.

### **Part 2: Procedures of the DSMB**

#### **2.1 *Blinding***

The DSMB will be unblinded in its assessment of safety data. The DSMB will have full access to all data as needed for safety assessment and will have access to comparative results of safety data, aggregated by treatment arm.

To maintain the integrity of the trial, the Funder, Principal Investigator and the study investigators will not have access to any unblinded or semi-blinded summaries of interim data prior to the conclusion of the trial and the final database lock. Access to semi-blinded information will be restricted to the DSMB and Unblinded Coordinating Center Statistician and Coordinating Center Statistical Advisor. The Unblinded Coordinating Center Statistician will generate an Open Report that includes aggregate information and a Closed Report that includes unblinded information by randomized treatment assignment.

The DSMB may direct questions and request further data from the Unblinded Coordinating Center Statistician, Coordinating Center Statistical Advisor or Study Management Team directly. The DSMB will determine what is communicated to blinded persons regarding additional requests.

#### **2.2 *DSMB Report***

The DSMB Report should provide information that is accurate to the extent possible, although all data will not be clean. Follow-up should be complete, if possible, to within three months of the date of the DSMB meeting, and the data snapshot should occur

approximately one month in advance of the meeting. Some "last-minute" data (e.g., Serious Adverse Events, Enrollment, and Follow-up Rates) will be even more current. The reports should be sent to the DSMB Members at least eleven days prior to the date of the meeting. Based upon the enrollment rate, the Study Management team will determine target dates for the DSMB meetings. The report will be based mainly on monitored data, but will include all safety data available at the time the report is prepared. If major changes occur due to data corrections, those changes will be highlighted in future DSMB Reports.

Each DSMB Report will have two main sections: an Open Section (blinded information) that contains information on recruitment, eligibility violations, baseline characteristics, data on completeness of follow-up and compliance, and other study management issues; and a Closed Section (unblinded information) which contains safety information displayed by treatment arm, analyses of Adverse Events, and efficacy data based on intent-to-treat analyses of primary endpoints. The details of these reports can be found in the Data Safety Management Plan (DSMP). DSMB Members will receive both the Open and Closed Sections of the Report. The Principal Investigator may communicate information from the Open Section of the DSMB Report to the Study Management Team.

This DSMB Report will be assembled by Unblinded Coordinating Center Statistician in consultation with the Coordinating Center Statistical Advisor.

DSMB Members will return their Closed Reports to the Coordinating Center Statistical Advisor at the conclusion of each DSMB meeting. The DSMB may retain their copies of the Open Report. Open and Closed Minutes are recorded by the Chair of the DSMB. Copies of the Open Minutes are distributed to the Principal Investigator and DSMB. Copies of the Closed Minutes are distributed only to the DSMB, and are archived by the chair until after the study database has been locked and treatment results unblinded.

The DSMB may wish to request clarification on existing reports or additional information. The Unblinded Coordinating Center Statistician will create ad hoc reports to address these questions. The Study Management Team and other persons may be informed about these ad hoc requests at the discretion of the DSMB.

### **2.3     *Scheduled DSMB Meetings***

The following table depicts a proposed meeting schedule for the DSMB. This schedule can be altered as necessary by the Principal Investigator or DSMB. Alterations will be attached in Appendix 2 and will not require amendment to this charter.

<b>Proposed Meeting Date</b>	<b>Function</b>	<b>Estimated Number of Subjects in Study</b>
Jul 2015	Safety Looks	50/22
Jan 2016	Safety Looks	150/67
Jul 2016	Safety Looks	250/112
Jan 2017	Safety Looks	350/157

Unscheduled DSMB meetings can be called as necessary by the DSMB. To call an unscheduled meeting, the DSMB Chair will contact the Coordinating Center Statistical Advisor. Typically, the Principal Investigator will not be told the reason for the meeting. Information to be communicated to the Principal Investigator regarding the meeting is determined by the DSMB.

#### **2.4 DSMB Meeting Structure**

The meetings will typically begin with an Open Session, followed by a Closed Session. All Closed Sessions will also include an Executive Session. There may also be a final open session where the DSMB may verbally give recommendations and answers questions from the Principal Investigator and Study Management Team.

##### **2.4.1 Open Session**

In order to allow the DSMB to have adequate access to insights from the Study Management Team, an Open Session of the DSMB meeting will be held during each DSMB meeting. Members of the Study Management Team, and other persons as needed, may be present during the Open Sessions (either in person or by telephone). The blinded information covered in the Open Session will be contained in the Open Report.

##### **2.4.2 Closed Session**

Closed DSMB Sessions involving only DSMB Members and the Coordinating Center Statistical Advisor will be held after the Open Session to allow discussion of unblinded data from the Closed Report. The information covered in the Closed Session will be contained in the Closed Report.

##### **2.4.3 Executive Session**



Executive DSMB Sessions involving only DSMB Members will be held to allow discussion of study data without the members of the study team present.

A representative of the Funder may be present at DSMB open sessions unless the DSMB Chair decides that the presence will inhibit free and open discussion or appear to compromise the DSMB's independence. The Funder may be permitted to attend Closed and Executive Sessions at the discretion of the DSMB Chair.

## **2.5 DSMB Recommendations**

During the DSMB meetings, issues relating to subject safety and scientific integrity of the trial will be reviewed and discussed. Afterward, the DSMB may hold a brief meeting with the Principal Investigator to review the status of the study and make its recommendations. These recommendations will primarily use the guidelines defined in this Charter or the DSMP. The DSMB will also make recommendations, as appropriate, regarding the conduct and management of the trial.

A quorum, defined as 3 DSMB Members including the Chair, must be present or available by teleconference in order for the DSMB to make any formal recommendations. Further, a recommendation to stop the trial must be made by a majority vote of the DSMB (i.e., either unanimously or four to one in favor of the recommendation). Other recommendations may be made by simple majority.

Any recommendations which could compromise the blind will be communicated in writing to the Principal Investigator within 5 business days of the meeting.

In the event that the study is recommended to be terminated, the Coordinating Center Statistical Advisor and the Principal Investigator will meet with the DSMB to review the semi-blinded report and discuss the reasons for this recommendation. At this time the Principal Investigator may become semi-blinded before deciding whether to accept the recommendation to terminate the study.

## **2.6 Meeting Minutes**

### **2.6.1 Open Minutes**

The Open Session Minutes will be recorded by the DSMB Chair and will summarize the DSMB's findings during the Open Session in addition to the overall recommendation from the Closed Session discussions as to whether the trial should continue, continue with modifications or be terminated. A copy of the Open Minutes will be sent to the

Principal Investigator, who will disseminate the recommendations to the Study Management Team as appropriate.

These Open Session Minutes must be devoid of any statements having the potential to compromise the blinding of the study, since these minutes will be distributed to the Principal Investigator.

At a minimum, the following question should be addressed by the DSMB:

- Does the DSMB feel that it is ethical to continue the trial as presently designed?

The results of deliberations should be communicated to the Principal Investigator in writing following the meeting.

### **2.6.2 Closed Minutes**

The Closed Session Minutes will be recorded by the DSMB Chair and will summarize the discussion of the semi-blinded data and other issues the DSMB wishes to document but keep in confidence.

### **Part 3: Appendices to Charter**

#### **Appendix 1: Rosters and Contact Information**

<b>DSMB</b>		
<b>Name</b>	<b>Address</b>	<b>E-mail address</b>
Alan Kliger, MD (Chair)	Yale University New Haven, CT	alan.kliger@ynhh.org
Michael Hollifield, MD	VA Long Beach Health Care System Long Beach, CA	Michael.Hollifield@va. gov
J Richard Landis, PhD	University of Pennsylvania Philadelphia, PA	landisjr@mail.med.upe nn.edu
Michael Rocco, MD	Wake Forest University Winston-Salem, NC	mrocco@wakehealth.e du
Suzanne Watnick, MD	Oregon Health Sciences Center, Portland, OR	watnicks@ohsu.edu

<b>Funder</b>		
<b>Funder Project Officer</b>		
<b>Name</b>	<b>Address</b>	<b>E-mail address</b>
Julie McCormack, MA	PCORI Washington, DC	jmccormack@pcori.org

Study Management Team and Coordinating Center			
Name	Address	E-mail address	Phone & fax
<b>Principal Investigator for the ACEND Trial</b>			
Rajnish Mehrotra, MD MS	University of Washington  Seattle, WA 98195- 6490	mehrotr@uw.edu	P: 206-744- 4933  F: 206-744- 2252
<b>Unblinded Coordinating Center Statistician</b>			
Tessa Rue, MS	University of Washington  Seattle, WA 98195- 9461	ruet@uw.edu	P: 206-543- 4246  F: 206-543-5881
<b>Semi-blinded Coordinating Center Statistical Advisor</b>			
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## Appendix Seven: Data Safety and Monitoring Plan

### 1. Overview

This Data Safety and Monitoring Plan (DSMP) defines the oversight and monitoring activities that will ensure and maintain both the safety of participants and the scientific integrity and validity of the trial data. The plan also describes the procedures for adverse event reporting and details guidelines for recommendations related to trial continuance.

### 2. Data and Safety Monitoring Board

Review of the ASCEND trial's study performance and safety outcomes will be conducted by the Data Safety and Monitoring Board (DSMB). The DSMB consists of 5 members, (Chair: Dr. **Alan Kliger** MD, Dr. **Michael Hollifield** MD, Dr. **J Richard Landis**, PhD, Dr. **Michael Rocco**, MD, Dr. **Suzanne Watnick**, MD). The DSMB is expected to meet twice annually (every 6 months) to review study performance and safety outcomes in Open and Closed Reports, and to review study enrollment reports quarterly. *Ad hoc* sessions may be scheduled as required should a serious adverse event need to be reviewed as a group.

Aggregate study performance and safety data will be presented during the open sessions of DSMB meetings. Safety and efficacy data will be presented by treatment arm during the closed sessions. Review by the DSMB provides assurances that the trial can continue, without jeopardizing patient safety. The DSMB is also responsible for protecting the confidentiality of the trial data and for monitoring the quality of both the data and study implementation procedures.

### 3. Study Sample Size and Design

Each recruitment site will enroll approximately 133 patients. The first randomization is block randomized on site, with random size block assignment within site to maintain balance between treatment groups. The second randomization is blocked on site and on treatment arm (engagement interview or control visit).

Randomized evaluation of an engagement interview will be conducted with up to 400 patients. In the pilot studies, 40% of HD patients accepted treatment for comorbid depression and the engagement interview increases the rate by 10-20. In order to have 80% power to detect a difference in proportions of 40% versus 55% (a 15% increase) we would need to enroll 100 patients per arm, or a total of 200 participants. Therefore our study design is well powered to detect the anticipated effect of an engagement interview.

The sample size for the randomized comparison of Sertraline to CBT is 120 patients. 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  $0.70$ . Assuming a loss- to-follow-up of  $\leq 15\%$ , 120 randomized participants will provide 80% power with 2-sided  $\alpha = 0.05$  to detect a difference in the mean 12-Week QIDS-C between the treatment groups of between 0.40 (if  $R = 0.70$ ) and 0.51 (if  $R = 0.40$ ) of 1 standard deviation in the QIDS-C. 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. 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.

#### **4. Monitoring Guidelines**

Based on findings following review of study data by the DSMB, the Board may recommend: continuation of the trial, termination of the trial, or modifications to the protocol (e.g. adding new measurements for safety monitoring, discontinuing high risk subjects, extending the trial in time, increasing the trial sample). Decision guidelines in the ASCEND trial are based on group differences in adverse event rates as explained below.

##### *4.1 Performance Monitoring*

Performance monitoring will be an ongoing activity performed by the study principal investigator and statistician, and status reports will be reviewed by the DSMB during their regular meetings. Procedural reviews to address protocol compliance with respect to subject recruitment and eligibility, retention and follow-up, randomization and blinding, and quality of data will be conducted and monthly reports generated. Any protocol violation that affects patient safety will be reported to the DSMB immediately.

Performance data will be reviewed in aggregate and by site. It is expected that:

- (1) the overall enrollment rate will not drop below the expected rate (15 patients per month for 24 months) by more than 50%.
- (2) missing treatment uptake will be no greater than 15% at the six-week follow-up;
- (3) the response rate for the QIDS-C will be no less than 85% at the 12-week time-point among those randomized to Sertraline or CBT;

Data will be entered on-line into a REDCap database hosted at the Data Coordinating Center (DCC). Data will be entered into fields with automated validation and logical checks built in. Outcome measures will be collected by Computer Assisted Telephone Interview (CATI). Compliance will be assessed based on the weekly conference calls and data submitted to the DCC on a weekly basis. If it is determined by the study PI that either study protocol is not being followed or that reporting is inadequate at any site, further action will be taken to address these issues. These actions may include additional in-person site visits if appropriate or additional educational/problem-solving sessions by phone or in person regarding the study protocol. Compliance rates and any concerns regarding deviation from study protocol will be reported to the DSMB on a quarterly basis for review and determination if additional measures need to be employed such as protocol changes or discontinuing enrollment at that site.

The ASCEND study aims to enroll up to 400 subjects with the following distribution among the sites: 167 subjects each at Seattle and Dallas and 66 subjects at Albuquerque. We plan to start screening subjects on March 17, 2015 and stop recruitment on March 16, 2017. Tables 1 and 2 and Figure 1 are performance monitoring examples that will be included in future Open DSMB Reports.

**Table 1. Cumulative and Current Report Period Study Recruitment**

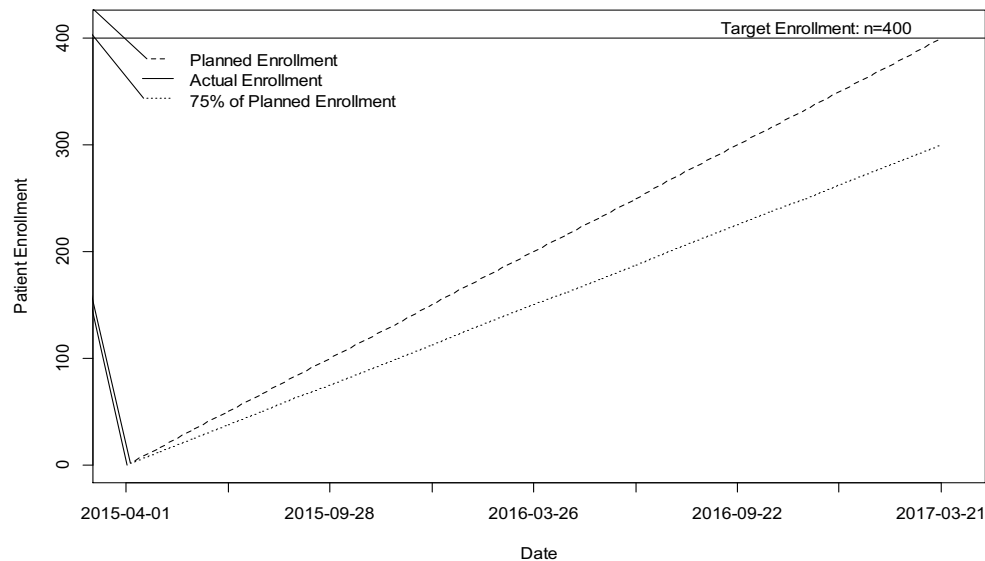
Site	Current Report Period				Cumulative			
	Seattle	Dallas	Albuquerque	Total	Seattle	Dallas	Albuquerque	Total
Screened								
Eligible								
Enrolled								
Accepted treatment, randomized to CBT or Sertraline								
Not accepting treatment								

**Table 2. Follow-up rates by site, n / N (%).**

	Seattle	Dallas	Albuquerque	Total
Treatment uptake assessed at 6 weeks				
Accepted treatment, randomized to CBT or Sertraline				
CATI assessment completed at 12 weeks				
Not accepting treatment				
CATI assessment completed at 12 weeks				



**Figure 1.** Cumulative Enrollment.



Follow up rates will be further tabulated by treatment arm in the Closed DSMB report.

**Table 3.** Follow-up rates by group, n / N (%)(closed report).

12 week CATI assessment completed	A	B	Total
Randomized to A'			
Randomized to B'			
Not accepting treatment			
<b>Total</b>			

A/B blinding designations for engagement interview or control

A'/B' blinding designations for CBT or Sertraline

#### 4.2 Safety Monitoring:

Safety reports will summarize adverse and serious adverse event data and will be reviewed at regular and *ad hoc* DSMB meetings. A serious adverse event is defined as any experience that is fatal or life-threatening, is permanently disabling, or requires inpatient hospitalization.

Patients undergoing hemodialysis experience a large number of adverse events from their underlying health, co-existing illnesses, and concomitant medications. These adverse events include death, fluid overload, congestive heart failure, vascular access events such as thrombosis or infection or dysfunction, atherosclerotic cardiovascular events, infections such as pneumonia, and laboratory abnormalities such as anemia, hyperphosphatemia, and hyperparathyroidism. Adverse events possibly associated with use of Sertraline include suicide ideation and suicide attempts and bleeding. CBT is considered minimal risk to a patient, although there is a potential for a loss of patient

confidentiality since CBT will be done while patient is undergoing HD. Among patients randomized to CBT or Sertraline, all adverse events possibly associated with Sertraline will be reported in Table 4. All serious adverse events regardless of possible association to intervention will be reported in Table 4. The research team will follow the participants for a period of 30 days from the end of 12 weeks of participation for the occurrence of death or hospitalization. Detailed reporting of serious adverse events will be given in Table 5, by treatment group sorted chronologically. If adverse or serious adverse events occur in different proportion in the study groups and there are concerns regarding the negative effects of either intervention, then the research team in consultation with both the study statistician and the DSMB may make protocol changes or discontinue the study.

Any suicide attempt (occurring within six weeks of the study procedures) will be immediately reported by the PI to the DSMB chair. These events will prompt a review if the event rate in either study arm exceeds the indicated threshold.

**Table 4. Adverse event incidence rate (number of events / number at risk) and threshold for action (Closed Report)**

Event	Group A'	Group B'	Expected* (over 4- month period of participation)	Threshold For Action	p-value**
<b>Adverse Event</b>					
Suicide Ideation <sup>1</sup>			10%	20%	
<b>Serious Adverse Event</b>					
Major bleeding <sup>2</sup>			2%	5%	
Suicide Attempt			<1%	3%	
Death			5%	10%	
Any Hospitalization			25%	40%	

\* Expected rates calculated based on expected number of events in a population

\*\* P-value calculated for the rate ratio comparing treatment Group A to Group B.

<sup>1</sup> Suicidal ideation is defined as scoring moderate (9-16 points) or high ( $\geq 17$  points) risk on the MINI suicidality module. Estimates obtained from *Chen et al*, *Psychosomatics* 2010;51: 528-528e6 (prevalence of suicide plan or suicide attempt),

<sup>2</sup> Hospitalization or death for hemorrhage from any site, including gastrointestinal, vascular access, and central nervous system. The estimates are based on several published estimates of populations of patients undergoing hemodialysis such as from the DOPPS (*Sood et al*, *Kidney Int* 2013; 84: 600-608)

Rates of death and hospitalization were estimated from annual rates reported in the USRDS Annual Data Report and projected for the 4-month study period



**Table 5.** Detailed tabulation of (Closed Report) Serious Adverse Events that have occurred during the ASCEND study.

Ex2	Hospitalization-CHF	B'	70	M	30Oct2011	30Nov2011	1	2	4	3
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<sup>1</sup>Frequency: 1. Single Episode  
2. Intermittent  
3. Continuous

<sup>2</sup>Relationship: 1. Unrelated  
2. Unlikely  
3. Possibly related  
4. Probably related  
5. Definitely related

<sup>3</sup>Action Taken: 1. None  
2. Conservative action  
3. Concomitant Medication  
4. Operative action

<sup>4</sup>Outcome: 1. Resolved, no residual effects  
2. Resolved, residual effects  
3. Continuing  
4. Subject lost to follow-up. No data available  
5. Subject died



#### *4.3 Treatment Efficacy Monitoring*

We will report aggregate 12-week QIDS-C scores by blinded treatment group for monitoring by the DSMB. We will also provide a z-score assessment of the evidence for the difference between treatment arms at 12 weeks. However, the DSMB is charged not to make a recommendation to terminate the study based on interim efficacy estimates. CBT and Sertraline are accepted standard of care treatments for depression. The study aims to provide valid estimates of treatment efficacy and early stopping for efficacy would jeopardize the primary analysis. Efficacy data is provided only to inform any safety or performance concerns that may arise.

#### *4.4 Procedures for minimizing research-associated risk*

A number of strategies for minimizing research-associated risk to subjects are built into the study protocol. CBT and Sertraline are standard treatments frequently used in clinical practice. This protocol only randomizes the choice of treatment. The doses being used are also standard doses without any additional risks posed to subjects. Subjects will also be monitored more frequently than in usual clinical practice and at all follow up time points, subjects will be asked about adverse events and unanticipated health events that may or may not be related to the study procedures.

In this study, we have developed safety plans for addressing suicide ideation. We are also employing additional procedures for patients randomized to Sertraline to ensure safety for these patients. These procedures are described below.

##### *4.4.1 Patients who endorse suicide ideation*

Since we will ask patients about suicide ideation (SI) during the screening phase as well as during the study, there is a high likelihood of identifying patients experiencing SI. If a patient endorses an SI item during screening or at the baseline visit, the site investigator will be notified. These patients will not be randomized to either CBT or Sertraline and will be referred to their primary care provider. If an individual reports active suicidal ideation or intent at any point during the trial, a cascade of events will be triggered to explore the risk of-and protect the subject from-self-harm. The site clinician will be immediately contacted who will in turn assess risk using the suicidality module of the MINI.

##### *4.4.5 Patients randomized to Sertraline*

Tolerability of Sertraline will be monitored every two weeks for the first six weeks and every three weeks for the second six weeks with the use of FIBSER. Treatment for subjects

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; (2) the subject has intolerable side effects despite reducing dose to 50 mg/d; or (3) subject becomes pregnant.

## **5. Scheduled Reporting**

One month prior to each DSMB review, the Data Coordinating Center (DCC) will summarize monthly administrative reports that describe study progress including subject accrual by site, demographics, and the sites' adherence to inclusion/exclusion criteria and other protocol requirements, including retention rates at each follow up point. These reports are prepared monthly and reviewed internally by the study research team for ongoing quality control. The DCC will also produce safety reports that list adverse events, serious adverse events, deaths, and in aggregate to the DSMB.

With each review the DSMB will decide to approve the study and protocol as is, recommend protocol changes in the interest of patient safety, or stop the study based on overwhelming evidence of safety concerns. The DSMB will provide the recommendation in a written letter to the principal investigator. In addition the DSMB will inform the investigator of any changes in the proposed timing of future DSMB reviews. The review may result in an amendment to the protocol, which must be approved by the IRB.

The DSMB report will begin with a brief narrative section that describes the status of the study, progress or findings to-date, issues, and the procedures that produced the report (e.g., data obtained by a specific date). The report will provide a study description along with a current organization chart, current timetable and study schedule as well as a list of study clinical and administrative centers. Data will be presented that describe the administrative status of the study including recruitment and forms handling. Study data reports describe demographic and baseline clinical characteristics and provide a safety assessment. Tables will be provided by site as well as for the whole study population. AE/SAE rates for each group will be presented in the closed report. Finally, the report will include a brief evaluation by the DSMB, with recommendations as to whether or not the trial will continue.

The DSMB will transmit a copy of their recommendations to the Principal Investigator who will disseminate to the clinical investigators at each recruitment site. The clinical investigators are responsible for forwarding the information to their local IRB.

### ***5.1 Serious Adverse Event Reporting***

Since reporting rules vary by institution, the following statements are a conservative guide to reporting adverse events for this trial and may be further amplified with DSMB guidance.

Any suicide attempt that occurs during a subject's window of study participation in the CBT vs Sertraline trial is reportable to the principal investigator and DSMB within 24 hours of the site investigator learning of the event. The notification to the DSMB and the IRB, will include a determination from the study Principal Investigator as to likelihood of relation to the study procedure. Every site IRB shall receive notification from the Principal Investigator, of any suicide attempt regardless of where the attempt occurred.

Unexpected adverse events which are serious, but not life threatening, and have a causal relation to the research, (unexpected in this context means not mentioned in the informed consent) must be reported to the DSMB within 7 days and to the local IRB within two weeks of the event. Serious adverse events will be reported to the DSMB chair, as they occur. The DSMB may call an emergency meeting, if necessary.