



SLEEP-HD:

SHORT AND LONG-TERM EFFECTIVENESS OF EXISTING INSOMNIA THERAPIES FOR PATIENTS UNDERGOING HD

Study Protocol

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Study Summary

Title	Short and Long-Term Effectiveness of Existing Insomnia Therapies for Patients Undergoing HD (SLEEP-HD)
Short Title	SLEEP-HD Trial
Protocol Number	RO1 DK 115468
Clinicaltrials.gov Registration	NCT03534284
Phase	Phase III
Methodology	Randomized, open-label trial
Study Duration	5 years
Clinical Sites	University of New Mexico, Albuquerque, NM 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"> Compare the efficacy of six-week treatment with telehealth CBT-I vs. trazodone vs. medication placebo for the treatment of chronic insomnia in patients undergoing HD Compare the sustained efficacy of the 6-week treatment with telehealth CBT-I vs. trazodone vs. medication placebo for the treatment of chronic insomnia in patients undergoing HD by examining outcomes at 25 weeks from randomization
Secondary Objectives	In HD patients with chronic insomnia, compare the efficacy of CBT-I vs. trazodone vs. medication placebo, at 7 and 25 weeks from randomization, for <ul style="list-style-type: none"> Other Patient-Reported Outcomes; Cumulative weekly use of sedatives/hypnotics; and Objective measurement of sleep by actigraphy
Number of Participants	126
Diagnosis and Main Inclusion Criteria	ESRD patients undergoing HD with chronic insomnia
Interventions	<ul style="list-style-type: none"> Telehealth CBT-I Trazodone drug therapy Placebo
Duration of study	Up to 30 weeks
Primary Outcome	<ul style="list-style-type: none"> Insomnia Severity Index

Statistical Methodology	To maximize the use of information and to account for potential loss to follow-up and/or intermittent missing outcome measures, we will use linear mixed models to make inference regarding group differences across time, that includes the baseline, 4, 7, 13 and 25-week ISI measurements
Study Oversight	<ul style="list-style-type: none">• Local Institutional Review Boards• Data Safety Monitor Board (Chair: Vernon Chinchilli)• NIDDK



Reviewed and approved by:

A handwritten signature in black ink, appearing to read "Rajnish Mehrotra".

Rajnish Mehrotra, Principal Investigator

A handwritten signature in black ink, appearing to read "Vernon M. Chinchilli".

Chair, Data Safety Monitoring Board

1. Introduction

1.1 Background

In the United States, 500,000 adults with end-stage renal disease (ESRD) are treated with maintenance dialysis; 88% with in-center hemodialysis (HD) in community-based facilities.[1] Dialysis patients have a short life expectancy, high healthcare utilization, with total annual societal expenses estimated at \$50 billion. [1, 2] Yet, they have poor functional rehabilitation, in part from the high prevalence of many disabling symptoms (median, 9-11); [3] 40-85% has significant sleep disturbances.[4-9] In a nationally representative study of 1643 patients from 335 dialysis facilities in the United States selected using equal probability systematic random sampling, 50% had trouble falling asleep, 59% woke up at night, and 49% had early morning awakening; 53% reported one or more of these symptoms all or most of the time. [8]

At least two factors contribute to the high prevalence of insomnia: First, day/night sleep reversal is a cardinal manifestation of uremia, the symptom complex associated with kidney failure. Animal and human studies indicate that kidney failure is characterized by significant alterations in circadian rhythm and sleep structure and attenuation of nocturnal melatonin surge. [10-17] Studies have also shown that the severity of sleep problems are associated with biochemical measures of kidney failure, suggesting insomnia to be a result of accumulation of various uremic toxins. [18-24] Second, while HD is partially effective in removing many uremic toxins, it introduces countervailing influences that worsen insomnia: several studies have shown that compared with kidney disease patients not treated with dialysis HD patients have a significantly shorter total sleep time and sleep efficiency and greater sleep fragmentation. [25-27] This is a direct result of unpredictable consequences from HD treatment schedules that makes maintaining regular sleep/wake routines challenging. One-third of HD patients are scheduled for the early morning shift, and many of them arrive at the facility at 5:00-6:00 a.m.; these patients have significantly greater insomnia. [25] There is evidence that shows that half of all HD patients nap during dialysis treatments, but this occurs only thrice weekly, further disrupting their sleep routines. [28] Importantly, the higher frequency of sleep disturbances in HD patients is independent of sleep apnea and restless legs syndrome. [8, 12] Given the high frequency and severity of symptoms and the unique disease- and treatment-specific contributors, it is imperative to determine the efficacy of various approaches for treating insomnia in HD patients instead of extrapolating from results of studies in other populations.

In addition to the direct distress, insomnia is an important contributor to other poor health outcomes in HD patients. Insomnia in dialysis patients is strongly associated with daytime sleepiness and worse quality of life. [6, 7, 28, 29] The link is likely causal as successful treatment of insomnia in other populations results in improvements in quality

of life. [30-34] However, this premise has never been tested for HD patients. Fatigue is the most troubling symptom experienced by > 50% of HD patients; studies have shown that poor self-reported sleep quality is associated with worse fatigue. [35-38] There is also accumulating evidence linking insomnia with pain; [39-43] *post-hoc* analyses of two clinical trials has shown that improvement in insomnia is associated with lower long-term pain scores in patients with osteoarthritis. [44, 45] Insomnia is common in HD patients with comorbid depression. [8, 28, 46-48] There is strong evidence that this relationship is bidirectional: the summary data from longitudinal studies indicates that patients with insomnia have a 2-fold higher risk for incident depression 12-48 months later. [49-54] Over 50% of dialysis patients report daytime sleepiness, fatigue, pain, and impaired quality of life, and over 25% have depression.[3, 4, 55] Recent studies have also shown a higher adjusted risk for death in HD patients with poor sleep. [6, 56] In sum, it is evident that insomnia is a contributor to many highly prevalent symptoms and poor health outcomes in HD patients.

Given the wide-ranging effects of insomnia on the health and well-being of HD patients, it is not surprising to note that patients prioritize relieving insomnia highly. Using a nominal group technique to obtain consensus, HD patients and their caregivers ranked sleep, fatigue, and anxiety/stress among the top 10 most important outcomes for clinical trials; mortality ranked only 14th. [57] Yet, no clinical trial has ever been done to determine the efficacy of any treatments for insomnia in HD patients in the United States, and none is presently registered. *Post-hoc* analyses of HEMO and Frequent Hemodialysis Network trials has also shown that improved control of uremia with different dialyzers or by modifying HD frequency and/or treatment time is ineffective in improving insomnia. [58, 59] This indicates that within the constraints imposed by the range of clearances of uremic toxins possible with current dialysis technology, increasing the removal of the dialyzable uremic toxins does not result in meaningful improvement in insomnia. This further argues for testing alternative approaches for treating insomnia as with this clinical trial.

1.2 Rationale for Interventions Being Tested in this Clinical Trial

1.2.1 Comparative Efficacy of telehealth CBT-I and drug therapy

Cognitive Behavioral Therapy for Insomnia (CBT-I) is the first line therapy for insomnia but is largely inaccessible to dialysis patients. A large body of work in other populations has shown that in adults with insomnia, CBT-I improves sleep latency, wake after sleep onset, sleep efficiency, and sleep quality, and can induce insomnia remission. [60-79] Based on this evidence, the American College of Physicians strongly recommends CBT-I as the first-line treatment for insomnia. [80, 81] These studies have limited relevance for HD patients as they have unique challenges to maintaining regular sleep/wake routines; it is not known if CBT-I will be effective in favorably modifying these behaviors to improve sleep. Two clinical trials, one each from Taiwan and China, have demonstrated improvement in sleep quality, assessed with the Pittsburgh Sleep Quality Index, with

group CBT-I. [82, 83] However, these trials also are not useful to inform clinical practice in the United States where patients have to commit 5-6 hours thrice weekly to HD treatments in stand-alone dialysis facilities away from hospitals and medical facilities, making in-person CBT-I inaccessible. Thus, it is imperative to develop innovative solutions to make treatment for insomnia available to HD patients. Some treatment approaches have been tested in other groups such as self-help strategies, internet programs, or over the telephone. [84-87] They introduce newer limitations as they don't involve a face-to-face interaction with a therapist; the effect size for internet-based CBT-I is smaller than when delivered in person. [88] Moreover, they are not useful for patients with limited health literacy or without an internet connection. Telehealth, a two-way video interaction between the patient and the therapist, overcomes the accessibility challenges and has been identified by the American Academy of Sleep Medicine in having the potential to narrow the gap between the availability of sleep providers and the number of patients needing insomnia treatment. [89, 90] To date, only one center has reported a case series of its experience with telehealth CBT-I showing improvement; however, there was no control group to reliably determine efficacy. [91] In this clinical trial, we will use telehealth CBT-I as a comparator and this will serve the dual purpose of testing the efficacy of CBT-I itself for HD patients, and its delivery via telehealth.

As for pharmacotherapy, there is limited evidence to support current practices for insomnia for dialysis patients. Notwithstanding clinical practice guidelines, pharmacotherapy is widely used as a first-line therapy for insomnia including for HD patients; it is also an alternative for patients unwilling to engage with CBT-I or for whom behavioral therapy is unavailable or inaccessible. However, the drugs used widely have either concerns about safety or efficacy, or have been insufficiently studied for patients undergoing HD. Benzodiazepines and non-benzodiazepine benzodiazepine-receptor agonists such as zolpidem are prescribed for 8-26% of HD patients [92, 93] even though two cohort studies have shown that HD patients treated with these drug classes have a significantly higher risk for death. [6, 93] The clinical trials with melatonin in HD patients have been disappointing in demonstrating sustained efficacy. [17, 94, 95] Trazodone is an attractive option as population surveys show it to be the most common or second most common drug prescribed for insomnia in the United States including for HD patients, yet is remarkably understudied. [96-99] This oral triazolopyridine drug, approved by the Food and Drug Administration for treating depression in 1981, is sedating, has no significant anti-cholinergic or cardiotoxic effects, and as it has a short half-life it does not induce daytime sleepiness. [100] It has a low potential for abuse as it does not induce dependence in contrast to benzodiazepines. [101] The drug is metabolized in the liver into inactive metabolites and no dose adjustments are necessary with kidney disease. However, there are very limited data to guide clinical practice. Low-quality evidence suggests its efficacy for treating primary insomnia; in two placebo-controlled trials, treatment with trazodone lasted only 7-14 days, and the only trial testing its efficacy as add-on to CBT-I enrolled just 20 patients. [102-104] Studies have shown the efficacy of trazodone for insomnia in patients with depression, Alzheimer's disease, and alcohol/opiate dependence. [49, 105-111] However, no studies have tested its efficacy and

safety in the setting of partial correction of uremia as with HD and none are underway. Furthermore, HD patients have unique behavioral and scheduling challenges and have greater risk with daytime sleepiness when overlaid upon hemodynamic fluctuations with HD and frailty. This study will generate much-needed evidence to support or refute its widespread use for treating insomnia in HD patients.

To summarize, most HD patients have significant impairments in quality of life, largely from the high frequency of disabling symptoms. Insomnia is one of the most frequently reported symptoms and studies of HD patients and/or other populations suggest that it is a significant contributor to other common symptoms and poor health outcomes. There are unique contributors to chronic insomnia in HD patients and these include the biologic effects of residual uremia after partial correction as is achieved with current dialysis technology, maladaptation to treatment schedules, and patients' napping during treatments. There is a compelling need to identify effective treatments for insomnia in HD patients and the interventions being studied in this clinical trial (telehealth CBT-I and trazodone) have a strong scientific premise. If telehealth CBT-I is effective for insomnia in HD patients, it will make a treatment that is presently inaccessible available to patients. Trazodone is widely used but the data on efficacy for insomnia are limited; no such data exist for HD patients.

2. Study Objective and Aims

SLEEP-HD has two specific aims designed to test two hypotheses:

Specific Aim One – To compare the efficacy of six-week treatment with telehealth CBT-I vs. trazodone vs. placebo for the treatment of chronic insomnia in patients undergoing HD.

Hypothesis One - We hypothesize that the efficacy of six-week treatment with both telehealth CBT-I and trazodone will be superior to medication placebo in improving self-reported sleep.

Specific Aim Two – To compare the sustained efficacy of the 6-week treatment with telehealth CBT-I vs. trazodone vs. placebo for the treatment of chronic insomnia in patients undergoing HD by examining outcomes at 25 weeks from randomization.

Hypothesis Two - We hypothesize that telehealth CBT-I will be superior to both trazodone and placebo in improving self-reported sleep at 25 weeks from randomization.

2.1 Comparative Efficacy of individual CBT-I, Trazodone, and Medication Placebo

2.1.1 Primary Measure of Efficacy

The summary score from the Insomnia Severity Index (ISI) at weeks 7 and 25 from randomization will be the primary outcome measures for Aims One and Two, respectively (Appendix One).

2.1.1.1 Rationale for the Primary Measure of Efficacy

The ISI is an instrument that measures insomnia, the condition being treated, in contrast to the Pittsburgh Sleep Quality Index that measures the quality of sleep. This self-report instrument captures both patient perceived severity of insomnia and its effect on daytime function.[112, 113] The 7 items assess severity of sleep onset and maintenance difficulties (both nocturnal and early morning awakenings), satisfaction with current sleep pattern, interference with daily functioning, noticeability of impairment attributed to the sleep problem, and the degree of distress or concern caused by the sleep problem.[112] Each item is rated on a 0-4 scale with a total score range of 0-28. The instrument has been validated using both the classical test and the item response theory.[30, 112, 114-116] The instrument has an excellent internal consistency (Cronbach α , 0.90), and adequate discriminatory capacity with strong correlation with self-reports of sleep onset latency, waking after sleep onset, and early morning awakening.[114] It has strong convergent validity as supported by significant correlations between total ISI score and measures of fatigue, quality of life, anxiety, and depression.[114] ISI is also sensitive to detect changes with treatment and at least two studies have demonstrated that a 6-8 point change in ISI is the minimal clinically important difference that correlates with a significant improvement or worsening in health-related quality of life.[30, 114] These considerations provide a strong rationale for selecting ISI as the primary outcome measure.

2.1.2 Secondary Measure of Efficacy

There are three domains for secondary measure of efficacy

- Patient-Reported Outcomes
- Cumulative Weekly Use of Sedatives and Hypnotics
- Objective Measures of Sleep with Actigraphy

2.1.2.1 Patient-Reported Outcomes

The following seven patient-reported outcomes will be assessed at weeks 7 and 25 from randomization (Appendix One):

- Sleep:
 - Pittsburgh Sleep Quality Index
- Sleepiness
 - Epworth Sleepiness Scale
- Fatigue:
 - Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale

- Pain:
 - Two-Item Graded Chronic Pain Scale
- Depression:
 - Patient Health Questionnaire-9
- Anxiety
 - Generalized Anxiety Disorder-7 Scale
- Quality of Life
 - Short-Form 12

2.1.2.2 Cumulative Weekly use of Sedatives/Hypnotics

This will be defined as the number of days that the patient took a drug to help sleep, and the value of this variable will range from 0 to 7. The drug taken to help sleep will be further categorized as (1) prescription medication; (2) over-the-counter medication; (3) marijuana; or (4) other. A list of potential prescription, over-the-counter, or other sleeping aids is included in Appendix Two.

Even though opiates are sedating, they are rarely primarily used as a sedative. Hence, for purposes of defining this outcome, use of opiates will not be considered when assessing cumulative weekly use of sedatives/hypnotics. Instead, any opiate use in the preceding 7 days will be recorded for descriptive purposes.

2.1.2.3 Objective Measures of Sleep with Actigraphy

Actigraphy data will be collected at three time points – the one-week run-in period (baseline), the sixth week of treatment, and the 25th week from randomization.

The key secondary outcome measure will be the average nighttime sleep efficiency (percent time asleep of time in bed).

The actigraphy data will be used to compute the following variables for additional exploratory analyses:

- Sleep onset latency;
- Total sleep time;
- Wake after sleep onset;
- Daytime inactivity; and
- Light exposure.

3. Study Design and Overview

SLEEP-HD is a *parallel group randomized controlled trial* wherein 126 HD patients treated in community-based dialysis facilities in Seattle and Albuquerque will be randomized 1:1:1 over 31 months to 6-week treatment with telehealth CBT-I, trazodone, or medication placebo (Figure 1). The primary and secondary outcomes for Aims One and Two will be ascertained at weeks 7 and 25 from randomization, respectively. A detailed schedule of study-related procedures is summarized in Appendix Three.

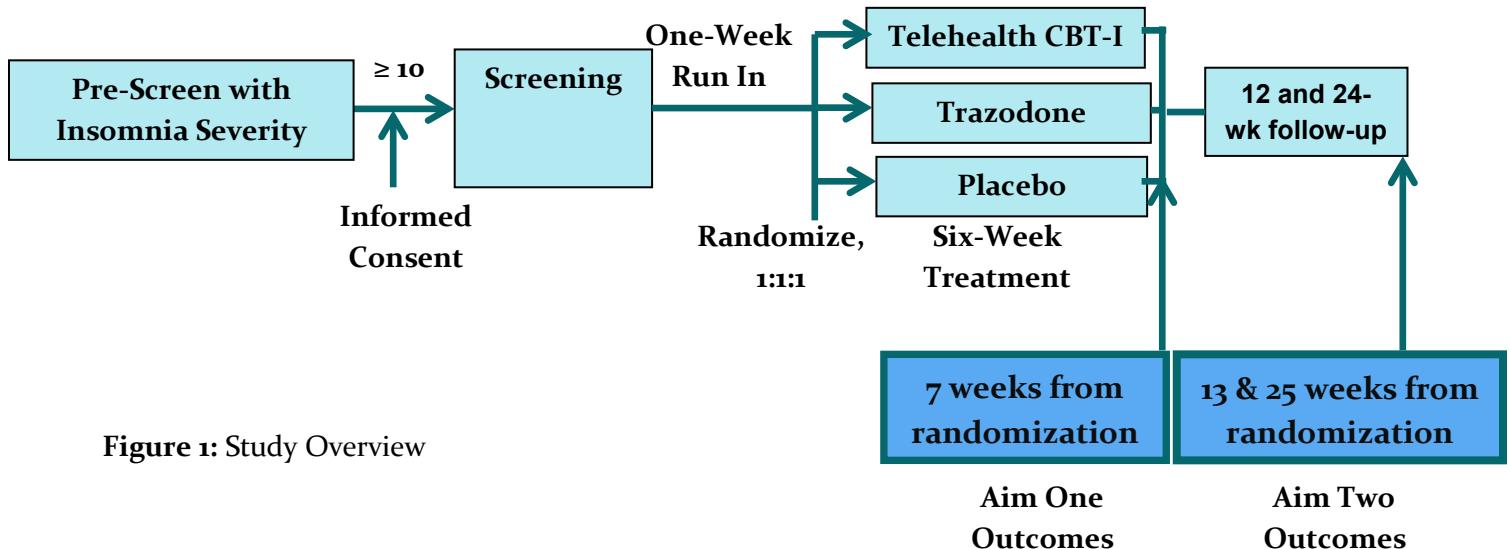


Figure 1: Study Overview

3.1 Rationale for Key Components of the Study Design:

First, patients will be treated with CBT-I and trazodone for 6 weeks. This is the time taken to deliver effective CBT-I and is the period of treatment in previous studies of efficacy of CBT-I. [61, 65, 67, 71-73, 76, 78, 79, 87, 117] Second, while 20% of the patients will be assigned to a medication placebo, none will be assigned to “attention/education control” in order to reduce study complexity. Numerous clinical trials have shown CBT-I to be superior to attention/education control including in patients with coexisting medical conditions making it unnecessary to repeat this comparison.[118] In contrast, despite its widespread use, there is a paucity of placebo-controlled clinical trials testing the efficacy of trazodone for treating insomnia in patients without comorbid depression. [102, 104, 111] Patients randomized to placebo will be able to receive other treatments during these 6 weeks for insomnia other than CBT-I or trazodone from their physicians. Third, the long-term effectiveness will be tested at 25 weeks after randomization, which is a meaningfully long follow-up period for a population with a median life-expectancy of 3 years and will minimize attrition from death or kidney transplantation. Fourth, we considered various treatment options for patients randomized to trazodone or placebo during the 18-week period (weeks 7-24). In the absence of data on short-term efficacy of trazodone for HD patients, it was considered unreasonable to plan to treat patients with the drug for 6 months in a clinical trial. Moreover, the labels for sedatives approved by the Food and Drug Administration for insomnia recommend short-term treatment only: triazolam and temazepam, 7-10 days; and flurazepam, zolpidem, and zaleplon, 4-6 weeks;

studies with only eszopiclone lasted for longer period. We propose that during the 18-week period following the 6-week treatment, all patients will be able to receive and be monitored for any treatments for insomnia prescribed by their physicians, including CBT-I and trazodone.

4. Participant Selection and Withdrawal

4.1 Study Population

4.1.1 Inclusion and Exclusion Criteria:

Inclusion Criteria:

1. Age \geq 18 years;
2. Undergoing thrice-weekly maintenance HD for \geq 3 months;
3. Able to speak English;
4. ISI score \geq 10 at pre-screening with sleep disturbances for \geq 3 nights per week for \geq 3 months.

Exclusion Criteria:

1. Severe depression assessed by Patient Health Questionnaire-2, PHQ-2 and if appropriate, Patient Health Questionnaire-9 [120];
2. Suicidal Ideation;
3. Alcohol abuse on CAGE questionnaire (score \geq 2) or substance abuse on DAST-10 questionnaire (score $>$ 5) [121, 122];
4. Severe restless leg syndrome;
5. Treatment with trazodone in the past one month;
6. Known allergy to trazodone (self-report or by chart review);
7. Current treatment with monoamine oxidase inhibitors or in the preceding 14 days (Appendix Four);
8. Current treatment with linezolid (self-report or by chart review);
9. Current treatment with other drugs that are inhibitors of CYP3A4 (e.g., itraconazole, clarithromycin, voriconazole), or known to prolong QT interval including Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class 3 antiarrhythmics (e.g., amiodarone, sotalol), antipsychotic medications (ziprasidone, chlorpromazine, thioridazine), and quinolone antibiotics (Appendix Four);
10. Pregnancy, or lactation, or women of childbearing potential not willing to use adequate birth control;
11. Life Expectancy $<$ 3 months;
12. Expected to receive a kidney transplant or transition to home dialysis (peritoneal dialysis or home HD) within 6 months;
13. Any other condition including cognitive impairment that, in the opinion of the investigator, should preclude patient participation in the clinical trial.

4.1.2 Rationale for key decisions regarding inclusion and exclusion criteria

This study will be limited to patients undergoing in-center HD and patients undergoing home dialysis (peritoneal dialysis, home HD) will not be eligible. The issues challenging patients' ability to maintain regular sleep/wake routines differ by dialysis modality and our approach will limit patient heterogeneity and yield valid estimates.

The other exclusion criteria are likely to make up to 20% of the prevalent population of HD patients ineligible, but this approach will maximize external validity for HD patients with chronic insomnia for whom the two interventions being tested are safe and appropriate. Our approach of allowing patients with sleep apnea to be randomized to a sedative is appropriate as there is evidence that trazodone increases the arousal threshold in patients with sleep apnea without worsening nocturnal hypoxemia.[123-125] To maximize external validity, patients using prescription or over-the-counter sleep medications will be eligible and the usage of such drugs for insomnia will be tracked and will be one of the key secondary outcomes.

4.2 Participant Pre-Screening and Recruitment

4.2.1 Pre-Screening and Enrolling Patients in the Clinical Trial

All patients with ESRD treated in participating dialysis facilities that meet the following three criteria will be eligible to participate in pre- screening: (1) age \geq 18 years; (2) undergoing maintenance HD \geq 3 months; and (3) speak English. These individuals will be invited to complete the 7-item Insomnia Severity Index (ISI) and two questions about the frequency and duration of sleep disturbances. Study personnel will provide all patients with an information sheet that will describe the purpose and nature of pre-screening and provide the patients with an option to opt-out of the pre-screening.

The summary score on ISI will be computed and patients will be managed based on the summary score:

- All patients with an ISI score \geq 10 with symptoms three or more times per week for three months or more will be approached for their willingness to undergo screening activities for participation in the clinical trial within 10 days of pre-screening. Patients that agree to undergo screening will be invited to sign a consent form prior to any further research-related activities. Eligible individuals with a diagnosis of chronic insomnia will undergo a one-week run-in period, at the end of which they will be randomly assigned to (1) telehealth CBT-I, or (2) trazodone, or (3) medication placebo.
- The information on patients with ISI score \geq 10 with symptoms three or more times per week for three months or more who refuse to undergo additional screening

activities will be communicated to the patients' treating nephrologist, with the patient's permission.

- Information on patients with ISI score < 10 or score ≥ 10 with less frequent symptoms and/or for < 3 months, will not be communicated to the patients' treating nephrologist.

4.2.1.1 Re-Administration of Pre-Screening

Some patients may complete the 7-item Insomnia Severity Index (ISI) additional time(s). These include when a patient:

- Scores ≥ 10 and meets the criteria for frequency and duration, but is not consented within 10-days or randomized to treatment within 25-days of pre-screening. Upon expiration of the 10-day or 25-day window, as appropriate, a second ISI will be administered for a valid score to continue screening procedures.
- Score ≥ 10 , meets the criteria for frequency and duration, but has taken trazodone in the preceding 30 days but meets other inclusion and exclusion criteria: If the patient is willing to participate in the clinical trial, s/he will be asked not to take trazodone any further, and an ISI will be re-administered ≥ 30 -days from the last dose of the drug.
- Scores < 10 , 3 months have passed since previous administration.

4.2.2 Diagnosis of Chronic Insomnia

Our approach to pre-screening will help us identify patients with chronic insomnia that meets the Diagnostic and Statistical Manual (DSM-5) criteria for the condition. [126-129] The key elements of the DSM-5 criteria include dissatisfaction with sleep quality or duration with (1) difficulty falling asleep, and/or night-time awakenings, and/or early morning awakening; (2) impact on day-time functioning; and (3) symptoms for ≥ 3 nights/week for ≥ 3 months. [127] This approach will identify patients with persistent symptoms that are highly unlikely to remit spontaneously and hence in the greatest need for treatment. [130-134]

4.3 Early Termination of Study Treatment and Withdrawal of Patients

Active treatment with the study interventions (telehealth CBT-I, or trazodone, or medication placebo) will be terminated if the patient:

- Withdraws informed consent; or
- Asks treatment to be discontinued; or
- Sustains a serious adverse event directly attributable to the study interventions and the treatment cannot be safely reinstated in the opinion of the site investigator;

- In the judgement of the investigator, continued participation of the patient in the clinical trial is a significant risk to the health of the patient;
- Is unable to follow study procedures; or
- Undergoes kidney transplantation; or
- Transfers to home dialysis; or
- Transfers care to a dialysis facility outside the participating metropolitan areas.

If the patient withdraws informed consent, the patient will be withdrawn from the study (“drop-out”). Under all other circumstances all attempts will be made to continue to ascertain primary and secondary outcomes at 7 and 25 weeks from randomization.

5. Study Interventions

5.1 Comparative Efficacy of Telehealth CBT-I vs Trazodone vs. Medication Placebo

The patients will be randomly assigned, 1:1:1 to CBT-I or trazodone or medication placebo using block randomization through the secure study web portal.

5.2 Telehealth CBT-I

5.2.1 Overview of the Intervention

Patients randomized to this arm will receive a treatment session once weekly for six weeks (Table 1 and Appendix Five); [87, 114, 135] each session is anticipated to last about 30 minutes. The content of each of these sessions will be adapted to include changes in behavior during HD treatments (such as napping) and to help patients better adjust to treatment schedules. The CBT-I sessions will be delivered by a therapist face-to-face with the patient via a fully interactive HIPPA-compliant video telehealth platform, Zoom.

Patients will receive CBT-I using a tablet or laptop provided by the study team, or at their home using a personal smart phone, tablet, laptop, or desktop. If the patients use a device provided by the study team, they will receive the telehealth CBT-I sessions in the dialysis facility, while undergoing HD or at another time. If the patients use their personal device, they can receive the telehealth CBT-I sessions at a place of their choosing. The tablets from the study team will be placed in a fresh, transparent plastic bag for each session as recommended to prevent nosocomial transmission of infection in high-risk healthcare setting such as the HD facility. CBT-I therapists will be based in Seattle, WA and New York, NY. Patients will be asked to maintain a **daily sleep diary** throughout the 6-week treatment phase as for the run-in period, and weekly records will be made available to the therapists prior to each session to modify behavioral treatment recommendations, as appropriate.

Table 1: Components of Telehealth CBT-I Intervention

Week	Key Component	Session-Specific
1		Sleep changes with ESRD; rationale for approach; stimulus control instructions
2	Review Diary and Behavioral Sleep Plan	Sleep Scheduling/Bed Restriction
3		Sleep stages and cycles
4		Constructive Worry; Mindfulness/ Relaxation Exercise
5		Changing beliefs, attitudes about sleep/Sleep Hygiene
6		Maintenance/relapse prevention plan

5.2.2 Training and Certification Prior To Implementation in Trial

Each therapist will undergo in-person training by Drs. Cukor and McCurry. 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.

5.2.3 Monitoring the Fidelity of the Intervention

During the conduct of the trial, weekly conference calls will be scheduled with the therapists during which clinical and implementation issues will be discussed, and cases reviewed. All individual CBT sessions will be audio-taped. All CBT-I sessions for the first five patients assigned to each therapist will be reviewed to provide rating for treatment fidelity using forms that outline the major skills and intervention pieces as follows:

- For the first two cases for each therapist, both Drs. McCurry and Cukor will review and score the therapists' fidelity and provide feedback; and
- For the next two cases for each therapist, either Dr. McCurry or Cukor will review all audio recordings, rate fidelity, and provide feedback.

Following the first four patients for each therapist, one sessions from each case will be selected at random and one not at random and be reviewed by either Dr. McCurry or Dr. Cukor. Review of audio recording will be as timely as possible to provide meaningful feedback to therapists and feedback will be provided at the ongoing supervision calls or through email.

This approach will allow therapists to receive support and real-time feedback to ensure the highest standards for delivering the behavioral intervention.

5.2.4 Monitoring Adherence to Intervention

Adherence to CBT-I will be monitored by recording number of completed sessions, duration of each session, nights adhered with recommended sleep window, adherence to recommended sleep/nap routines, and relaxation exercise practice.

5.3 Drug Therapy

5.3.1 Overview of the Intervention

The site investigators will prescribe trazodone (50-100 mg) or corresponding medication placebo to the study participants randomized to the respective arms. The dose range selected for the trial (50-100 mg) is guided by prior studies with trazodone. In a double-blind placebo controlled study in healthy adults, trazodone was effective in inducing deep sleep with this dose range and no further increase was evident at higher doses. [100] In a dose-finding study to improve sleep in patients with major depressive disorder, 31 of the 33 patients treated with trazodone for six weeks with doses up to 100 mg reported improvement in insomnia. [136] Finally, this is the same dose range shown to be effective in improving sleep in several randomized trials in patients with primary insomnia, or sleep disturbances associated with major depression and Alzheimer's. [49, 102-106, 108, 111, 137]

The starting dose for trazodone will be 50 mg, and if after the end of the first or second week of treatment the patients report inadequate improvement in sleep, they will have the option to increase the dose to 100 mg at weeks 2 or 3. The dose achieved by the end of week 3 will be maintained for the remaining three weeks.

To the extent possible, the assessments will be done on the first dialysis day of the week (Monday or Tuesday, respectively, for patients on Monday-Wednesday-Friday or Tuesday-Thursday-Saturday / Sunday-Tuesday-Thursday schedules).

5.3.2 Drug Procurement and Dispensation

Prior to launching the clinical trial, the Investigational Drug Services at Harborview Medical Center, where the PI is based, will procure 50-mg tablets of trazodone from the same manufacturing stock for both clinical sites and prepare matching placebo. A supply of the study medications will be shipped to the Investigational Drug Services at Albuquerque in New Mexico. The medications will be dispensed as per the protocol by the Investigational Drug Services at each site and the study coordinators will hand the study drug to the participants at the dialysis facility when they arrive for their routine HD treatments (during the COVID pandemic, this will be modified to allow coordinators to leave drug with dialysis unit or mail drug via US postal service or inter-office mail); this will occur once during week 1 where a 3-week supply of the drug will be provided (with

capacity to increase the dose to 100 mg starting week 2), and at week 4 where a -week supply of the drug for the dose being taken during week 3.

5.3.3 Monitoring Drug Adherence

The participants will be asked to bring in the medication bottles for study drug at week 4 and week 7, and the coordinators will perform a pill count to assess adherence with the medication. All unused drug will be destroyed by IDS.

6. Ascertainment of Outcomes

6.1 Patient-Reported Outcomes

The primary (ISI) and secondary patient reported outcomes will be ascertained by Computer-Assisted Telephone Interviewing (CATI) at weeks 0, 4, 7, 13, and 25 from randomization by interviewers blinded to the study assignment. The baseline assessment will be performed during the run-in period and prior to randomization. The CATI will run out of Albuquerque, NM under the direction of Mark Unruh who will train the interviewers. CATI operators will conduct the assessments using scripts prepared for the call. The interview is expected to last about 30 minutes.

The order of preference for the day of the week for completing CATI, from optimal to the least preferred, is as follows:

- The day following the first dialysis treatment of the week (Tuesday for patients on a Monday-Wednesday-Friday schedule, and Wednesday for patients on a Tuesday-Thursday- Saturday / Sunday-Tuesday-Thursday schedule);
- The day following the second dialysis treatment of the week – Thursday, or Friday, respectively, for patients on a Monday-Wednesday-Friday or Tuesday-Thursday- Saturday/Sunday schedule;
- Within the first hour of the dialysis session according to the patient's treatment schedule as noted above.

To the extent possible, the calls for the 4, 7, 13, and 25 weeks will be done on the days as for the baseline call for the patient. If there are individuals that do not have access to a telephone, the study staff will make that available to them to complete the CATI.

If all attempts to complete a follow up CATI call are unsuccessful, the Principal Investigator may authorize the site study coordinator to complete the PROs using paper forms at the bedside. We anticipate this approach to be used only under exceptional circumstances, if at all.

6.2 Cumulative Use of Sedatives and Hypnotics in Prior Week

This secondary outcome measure will be ascertained during the same week as the CATI call is completed, at baseline, and weeks 4, 7, 13, and 25 from randomization. The patients will be asked to report the number of nights during the previous 7 nights that they used a prescription, or over-the-counter, or other sleeping aid(s) (including marijuana, if taken for sleep). This information will be supplemented by a review of the electronic medical records. The study coordinators will be provided with a reference document listing the generic and commercial name of the prescription, over-the-counter, or other sleeping aids as listed in Appendix Two.

The cumulative use of prescription opiates in the previous 7 days will be recorded similarly.

6.3 Actigraphy

Actigraphy will be performed at three time-points: (a) the one-week run-in period; (b) week 7 from randomization; and (c) week 25 from randomization. Each assessment will last 7 days, will be scheduled to start and end with a regularly scheduled dialysis treatment, and the coordinator will meet with the patient in the dialysis facility when the patient reports for treatment. The follow up assessments will be scheduled such that the seven-day period starts the week prior to the CATI and ends the week CATI is performed. It is anticipated that the study coordinators will assess the cumulative weekly use of sedatives and hypnotics (6.2 above) at the same visit as they go to retrieve the actiwatches from the patients.

The actigraphy data will be downloaded and scored using Actiware 6.0.8 software (Phillips Respironics, Bend, OR) to determine wake and sleep based on one-minute epochs. The actigraphy scorers will be blinded to the randomized treatment assignment of the patient. The validity of data from actigraphy will be increased by our approach of asking patients to maintain sleep diaries as this will control for artifacts in data collection, e.g., from removal of the device. [138] Additionally, light sensors, and actigraph event marker data will be used in conjunction to ensure that in-bed and out-of-bed (daytime) periods used for calculating sleep parameters are accurate.

7. Study Procedures and Visits

All study visits will occur in the participating dialysis facility or via a HIPPA-compliant telehealth platform.

7.1 Pre-Screening

- Information sheet will be handed to patients to invite them to complete ISI and two questions on (a) how many days in the week do the patients experience sleep disturbance, and (b) how many months they have been symptomatic;
- Patients who agree will be provided with the questionnaire to complete; the study team will provide assistance for the patients to complete the questionnaire as appropriate.

7.2 Screening

- This will occur in-person, within 10 days of completion of pre-screening;
- Patients with ISI score ≥ 10 will be invited to sign an informed consent form to complete screening activities;
- The demographic information of all patients who consent to participate in the study will be recorded and they will be registered on the online portal;
- The following assessments will be completed (during the COVID pandemic, these may be administered over the telephone):
 - Medication Review to ascertain current use of trazodone or in the preceding one month;
 - Patient Health Questionnaire-2 (PHQ-2); if score on PHQ-2 is ≥ 3 , PHQ-9 will be administered (score for exclusion, ≥ 20). Patients who answer “more than half the days” or “nearly every day” to question 9 of the PHQ-9 will be administered the Columbia Suicide Severity Rating Scale to determine the suicidal intent; those with suicidal ideation will be excluded;
 - CAGE questionnaire for alcohol abuse (score for exclusion ≥ 2) and DAST-10 for substance abuse (score > 5);
 - Cambridge-Hopkins Restless Legs syndrome questionnaire (criteria for exclusion – answer to question 11, moderately or extremely distressing, AND, answer to question 12, 4-5 days per week or every day);
 - Medical history for co-existing illnesses;
 - For women that have had menstrual periods in the last 12 months, will be asked if they are pregnant or currently lactating. Pregnancy will be further excluded by a blood pregnancy test for women randomized to trazodone or medication placebo; and
 - Final review of inclusion and exclusion criteria;
- Eligible participants will be provided with instructions to complete sleep diaries for the run-in period:
 - Patients that choose to complete the sleep diaries online will be provided with log-in details and instructions on how to enter the data in the web-portal;
 - Patients who choose to use the paper-form of sleep diaries will be provided with the sleep diary for the first week along with instructions on how to enter the data;

- The patients' nephrologist will be informed about their enrollment in the clinical trial and if randomized to drug therapy, with a list of medications that could prolong QTc in patients treated with trazodone, as listed in the FDA package insert for the drug;
- The coordinator will place the actiwatch on the patient and provide instructions on wearing the device. The actiwatch will be placed on the arm opposite to the upper extremity with the functional arteriovenous access being used for dialysis. In patients with a lower extremity arteriovenous access or with a central venous catheter, the actiwatch will be placed on the non-dominant arm;
- The 7-day run-in period will start after completion of the screening procedures and placement of the actiwatch; and
- The patients will be scheduled to receive a phone call for the baseline CATI.

7.3 Baseline CATI

- This will occur over the telephone, to the extent possible before the "Baseline Visit";
- A research assistant from Albuquerque, NM, will call the patient to initiate the CATI;
- The following assessments will be completed:
 - Insomnia Severity Index (primary outcome measure); and
 - Seven pre-specified secondary patient-reported outcome measures; and
- A system-configured email will be sent to the site study coordinator upon successful completion of CATI.

7.4 Baseline Visit

- This will occur in-person seven days after the start of the run-in period and to the extent possible, on the first dialysis day of the week (Monday or Tuesday) (during the COVID pandemic, this will be modified to occur over the telephone to the extent possible); and
- The following procedures will be completed at this visit:
 - The patients will return the actiwatches;
 - The online or paper sleep diaries will be reviewed and/or collected;
 - The dialysis days and the start time for the scheduled shift for the preceding seven days; and
 - The case-report form on cumulative weekly use of sedatives/hypnotics and opiates will be completed, assessing the use of sleep aids for the preceding 7 nights.
- The patients will be scheduled to receive a phone call for the baseline CATI.

7.5 Randomization

- This will occur electronically through the web-based portal after CATI is completed, and to the extent possible, the same week as the “Baseline” visit and the baseline CATI, and no more than 25 days after pre-screen with ISI;
- Patients will be randomly assigned to telehealth CBT-I, trazodone, or medication placebo, stratified by site using blocks of varying size to ensure that the three groups are balanced at periodic intervals; and
- The patients should begin treatment within 10 days from the date of randomization (first CBT-I session or provided with the first supply of medication).

7.6 Treatment Visits (Weeks One through 6, through 7 weeks from randomization)

7.6.1 Telehealth CBT-I Visits

- These visits will occur once a week for six weeks via telehealth using the Zoom platform delivered by a therapist based either in New York or Seattle;
- For any given patient, the same therapist will administer each of the six treatments;
- The sessions will be held with the patient either (a) at the dialysis facility (while undergoing HD or at another time), using a personal device or one provided by the research team; (b) or at home using a personal device;
- Prior to each session data from the sleep diaries will be retrieved either from the online portal, or the coordinator collecting it from the patient in-person, or over the telephone by either the coordinator or the therapist; and
- All therapy sessions will be audio-recorded with the permission of the patient.

In the event that the scheduling of six weekly sessions over six weeks becomes impossible, the following priority list should be followed:

1. An extra session (including all assigned homeworks) should be added, so that two sessions are done in the same week (but with maximal time in between them); priority will be given to scheduling sessions 5/6 in the same week.
2. Two sessions can be scheduled back to back with priority given to doubling up sessions 5/6, ¾ (time of treatment should still be ½ hour per session, 1 hour for doubled up sessions).

If a session is started, but could not be completed, providing the remainder of the content should follow the same priority list (extra session is preferred over adding extra time to the next session).

7.6.2 CBT-I Treatment Assessment Visits

7.6.2.1 CBT-I Treatment Assessment Visit One

- This will occur over the telephone about four weeks from the date of randomization;
- The following procedures will be completed at this visit:
 - The online or paper sleep diaries will be reviewed and/or collected;
 - The dialysis days and the start time for the scheduled shift for the preceding seven days will be recorded; and
 - The case-report form on cumulative weekly use of sedatives/hypnotics and opiates will be completed, assessing the use of sleep aids for the preceding 7 nights;
- The patients will be scheduled to receive a phone call for the 4-week CATI.

7.6.2.2 CBT-I Treatment Assessment Visit Two

- This will occur in person about six weeks from the date of randomization;
- The following procedures will be completed at this visit:
 - The online or paper sleep diaries will be reviewed and/or collected; and
 - The coordinator will place the actiwatch on the patient and provide instructions on wearing the device. The actiwatch will be placed on the arm opposite to the upper extremity with the functional arteriovenous access being used for dialysis. In patients with a lower extremity arteriovenous access or with a central venous catheter, the actiwatch will be placed on the non-dominant arm.

7.6.2.3 CBT-I Treatment Assessment Visit Three

- This will occur in person about seven weeks from the date of randomization (during the COVID pandemic, this will be modified to occur over the telephone to the extent possible);
- The following procedures will be completed at this visit:
 - The patients will return the actiwatches;
 - The online or paper sleep diaries will be reviewed and/or collected;
 - The dialysis days and the start time for the scheduled shift for the preceding seven day will be recorded; and
 - The case-report form on cumulative weekly use of sedatives/hypnotics and opiates will be completed, assessing the use of sleep aids for the preceding 7 nights.
- The patients will be scheduled to receive a phone call for the 7-week CATI.

7.6.3 Medication Visits

For patients randomized to trazodone and medication placebo, the visits and related procedures will be identical.

7.6.3.1 Medication Assessment Visit One

- This visit will occur in-person and, to the extent possible, on the day of the first dialysis treatment of the first week following randomization (during the COVID pandemic, this will be modified to occur over the telephone to the extent possible); and
- The patients will be provided with three-week supply of 50-mg trazodone or matching placebo. The patients will be provided with a sufficient supply of drug to increase the dose of the medication to 100 mg starting week 2.

7.6.3.2 Medication Assessment Visit Two

- The visit will occur over the telephone and, to the extent possible, on the day of the first dialysis treatment of the second week following randomization and one week following the “Medication Assessment Visit One”;
- The coordinator will ask the patient if they have been prescribed any new medications since the last visit to screen for contra-indicated drugs to prolong QTc;
- The patients’ response to drug therapy will be assessed and they be advised to:
 - Continue on the 50 mg dose if they are satisfied with their sleep over the previous 7 days; or
 - Increase to 100 mg for patients with persistent problems with sleep in the previous 7 days.

7.6.3.3 Medication Assessment Visit Three

- The visit will occur over the telephone and, to the extent possible, on the day of the first dialysis treatment of the third week following randomization and one week following the “Medication Assessment Visit Two”;
- The coordinator will ask the patient if they have been prescribed any new medications since the last visit to screen for contra-indicated drugs to prolong QTc;
- The patients’ response to drug therapy will be assessed and they be advised to:
 - Patients who have been on 50 mg dose will be assessed and based upon patients’ satisfaction with their sleep will either continue with the 50 mg dose or the dose will be increased to 100 mg;
 - Patients who had been on 100 mg dose will be assessed and based upon patients’ tolerability of the higher dose will either continue with the 100 mg dose or the dose will be decreased to 50 mg.

7.6.3.4 Medication Assessment Visit Four

- The visit will occur in-person and, to the extent possible, on the day of the first dialysis treatment of the fourth week following randomization and one week following the “Medication Assessment Visit Three” (during the COVID pandemic, this will be modified to occur over the telephone to the extent possible);
- The coordinator will ask the patient if they have been prescribed any new medications since the last visit to screen for contra-indicated drugs to prolong QTc;
- The medication bottle provided to the patient on the prior visit will be collected;
- The coordinators will perform a pill count to assess adherence for the preceding 7 days;
- The dialysis days and the start time for the scheduled shift for the preceding seven days will be recorded;
- The patients will be provided with a three-week supply of trazodone or medication placebo at the same dose that they were on the prior week;
- The case-report form on cumulative weekly use of sedatives/hypnotics and opiates will be completed, assessing the use of sleep aids for the preceding 7 nights; and
- The patients will be scheduled to receive a phone call for the 4-week CATI.

7.6.3.5 Medication Assessment Visit Five

- The visit will occur in-person and, to the extent possible, on the day of the first dialysis treatment of the sixth week following randomization and two weeks following the “Medication Assessment Visit Four”;
- The coordinator will ask the patient if they have been prescribed any new medications since the last visit to screen for contra-indicated drugs to prolong QTc;
- The patients will be reminded to start maintaining online or paper sleep diaries; and
- The coordinator will place the actiwatch on the patient and provide instructions on wearing the device. The actiwatch will be placed on the arm opposite to the upper extremity with the functional arteriovenous access being used for dialysis. In patients with a lower extremity arteriovenous access or with a central venous catheter, the actiwatch will be placed on the non-dominant arm.

7.6.3.6 Medication Assessment Visit Six

- The visit will occur in-person and, to the extent possible, on the day of the first dialysis treatment of the seventh week following randomization and one week following the “Medication Assessment Visit Five” (during the COVID pandemic, this will be modified to occur over the telephone to the extent possible);
- The medication bottle provided to the patient on the prior visit will be collected;

- The coordinators will perform a pill count to assess adherence for the preceding 14 days;
- The online or paper sleep diaries will be reviewed and/or collected;
- The dialysis days and the start time for the scheduled shift for the preceding seven days will be recorded;
- The patients will return the actiwatches;
- The case-report form on cumulative weekly use of sedatives/hypnotics and opiates will be completed, assessing the use of sleep aids for the preceding 7 nights;
- The patients will be scheduled to receive a phone-call for the 7-week CATI; and.
- If the patient wants to continue trazodone past the six-week treatment period, the site investigator will facilitate the treatment plan in partnership with the primary nephrologist and/or the primary care physician.

7.6.4 CATI Visits in Treatment Phase

7.6.4.1 Four Week CATI

- This will occur over the telephone at four weeks from the date of randomization;
- A research assistant from Albuquerque, NM, will call the patient to initiate the CATI;
- The following assessments will be completed:
 - Insomnia Severity Index (primary outcome measure); and
 - Seven pre-specified secondary patient-reported outcome measures; and
- A system-configured email will be sent to the site study coordinator upon successful completion of CATI.

7.6.4.2 Seven Week CATI

- This will occur over the telephone at seven weeks from the date of randomization;
- A research assistant from Albuquerque, NM will call the patient to initiate the CATI;
- The following assessments will be completed:
 - Insomnia Severity Index (primary outcome measure); and
 - Seven pre-specified secondary patient-reported outcome measures; and
- A system-configured email will be sent to the site study coordinator upon successful completion of CATI.

7.7 Long-Term Follow-Up Visits

7.7.1 Long-Term Follow-Up Visit 0

- This will occur over the telephone, and to the extent possible on the day of the first dialysis treatment of the 12th week following randomization; and
- The patients will be scheduled to receive the 13-week CATI.

7.7.2 Long-Term Follow-Up Visit 1

- This visit will occur over the telephone, and to the extent possible on the day of the first dialysis treatment 13 weeks following randomization;
- The dialysis days and the start time for the scheduled shift for the preceding seven days will be recorded;
- The case-report form on cumulative weekly use of sedatives/hypnotics and opiates will be completed, assessing the use of sleep aids for the preceding 7 nights; and
- Patients will be asked if they have received CBT-I or trazodone since the completion of the treatment phase of the clinical trial.

7.7.3 Long-Term Follow-Up Visit 2

- The visit will occur in-person and, to the extent possible, on the day of the first dialysis treatment 24 weeks following randomization;
- The patients will either be provided with paper sleep diaries or be reminded to enter the sleep diaries online;
- The coordinator will place the actiwatch on the patient and provide instructions on wearing the device. The actiwatch will be placed on the arm opposite to the upper extremity with the functional arteriovenous access being used for dialysis. In patients with a lower extremity arteriovenous access or with a central venous catheter, the actiwatch will be placed on the non-dominant arm; and
- The patients will be scheduled to receive a phone call for the 25-week CATI

7.7.4 Long-Term Follow-Up Visit 3

- This visit will occur in-person and, to the extent possible, on the day of the first dialysis treatment 25 weeks following randomization (during the COVID pandemic, this will be modified to occur over the telephone to the extent possible);
- The online or paper sleep diaries will be reviewed and/or collected;
- The dialysis days and the start time for the scheduled shift for the preceding seven days will be recorded;
- The patients will return the actiwatches;
- The case-report form on cumulative weekly use of sedatives/hypnotics and opiates will be completed, assessing the use of sleep aids for the preceding 7 nights; and
- Patients will be asked if they have received CBT-I or trazodone since the completion of the treatment phase of the clinical trial.

7.7.5 Long-Term CATI Visits

7.7.5.1 Thirteen Week CATI

- This will occur over the telephone about 13 weeks from the date of randomization;
- A research assistant from Albuquerque, NM, will call the patient to initiate the CATI;
- The following assessments will be completed:
 - Insomnia Severity Index (primary outcome measure); and
 - Seven pre-specified secondary patient-reported outcome measures; and
- A system-configured email will be sent to the site study coordinator upon successful completion of CATI.

7.7.5.2 Twenty-Five Week CATI

- This will occur over the telephone about 25 weeks from the date of randomization;
- A research assistant from Albuquerque, NM will call the patient to initiate the CATI;
- The following assessments will be completed:
 - Insomnia Severity Index (primary outcome measure); and
 - Seven pre-specified secondary patient-reported outcome measures; and
- A system-configured email will be sent to the site study coordinator upon successful completion of CATI.

7.8 Early Closeout

For patients that choose to terminate participation in the study, all efforts will be made to collect the following information:

- Cumulative use of sedatives and hypnotics and opiates in the previous 7 days; and
- Schedule an early closeout CATI for collecting data on primary and secondary patient-reported outcome measures.

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 three randomized groups will be compared to assess chance imbalances.

8.2 Statistical Analysis for Aim One

The primary outcome for Aim 1 is the ISI measured at 6 weeks after initiation of treatment. Given that we have three arms, a simple analysis for this aim would be an ANOVA analysis of the outcome Y_7 , adjusted site (Seattle or Albuquerque) and the baseline measure Y_0 . However, to maximize the use of information and to account for potential loss to follow-up and/or intermittent missing outcome measures, we will use a

comprehensive longitudinal analysis to make inference regarding group differences across time. Specifically, we will use linear mixed models for the analysis of all outcomes including the baseline, 4, 7, 13 and 25-week ISI measurements. [146] For longitudinal models we will use indicator variables to model the 4, 7, 13, and 25-week changes from baseline (control group temporal trend) and then use two sets of treatment-by-time interactions to characterize the difference in the change over time for the CBT-I group compared to placebo, and the trazodone group relative to placebo. Our primary analysis will use linear mixed model estimation assuming an unstructured outcome covariance matrix in order to minimize model assumptions. Given randomization, we know the baseline group mean difference are zero and therefore, an appropriate longitudinal model imposes this known baseline constraint. The primary test for Aim 1 is a longitudinal variation on ANOVA that would simultaneously test that both the CBT-I treatment by 7-week interaction, and the trazodone by 7-week interaction are zero. This null hypothesis assumes that the change from baseline to 7-weeks is the same for each of the three treatment groups. Secondary analysis will estimate the confidence interval for the pairwise comparisons of each of the three groups from the longitudinal model. A similar analytic approach will be taken for analyses of data for each of the nine pre-specified secondary outcomes. Exploratory analyses will be undertaken to determine if there is preliminary evidence for effect modification by gender, race/ethnicity, restless legs syndrome, cumulative use of sedatives/hypnotics or opiates, dialysis shift, and treatment adherence to CBT-I or trazodone.

8.2.1 Statistical Power for Aim One

A power analysis using a simple pre-post analysis for 7-week outcomes controlling for baseline is a conservative estimate of the power for the longitudinal model since the simple analysis would only use 7-week complete cases. In order to determine an appropriate sample size we focused on the literature that informs the variance in the primary outcome measure, and the literature that identifies individual-level clinically meaningful differences. The standard deviation for ISI in large clinical trials in other patient populations has ranged from 3.8-5.6; [77, 139-144] based on these studies, we assume that the standard deviation of the 6-week ISI will be between 4.0 and 6.0 and we conservatively use 6.0 as the basis of sample size estimation. Moreover, the minimal clinically important difference for this scale is between 6 and 8 for indication of an individual successful response to treatment, and in order to test for meaningful group differences we seek to have adequate power to detect a meaningful group difference. [30, 114] For patient-reported outcome measures “moderate” effect sizes have been characterized as those with a standardized difference (Cohen’s) of between 0.50 and 0.80. [145] Therefore, with a standard deviation of 6.0 we would seek to power our study to detect a group difference of 3.0-4.8 points on the ISI using this criterion. Given that two studies have suggested that the minimal clinically important difference for ISI is between 6 and 8 points we ultimately targeted a group difference of 4.0 as the alternative that we would power our study to detect. [30, 114] This difference is smaller than the reported minimal clinically important difference and is in the moderate range of effect sizes based

on Cohen's classification. Using simulation methods and assuming a correlation of 0.50 for baseline and follow-up measures we determined that 110 patients evaluated at 6 weeks is sufficient to obtain >90% power to detect the ANOVA alternative consistent with our hypothesis. Specifically, we assume that relative to placebo, CBT-I and trazodone groups differ by < 4.0 points (and hence are equally effective). In order to have 110 evaluated patients we would need to inflate the enrolled sample size to account for an anticipated 10% loss to follow-up and arrive at our final sample size of n=126 (note: the loss to follow-up of 16/126 = 13%).

8.3 Statistical Analysis for Aim Two

The primary outcome for Aim 2 is the ISI measured 25 weeks from randomization. The analysis will leverage the same longitudinal model fit for aim 1, with a parallel primary hypothesis test and confidence interval estimation at 25-weeks as at 7-weeks. Secondary analysis will estimate the full trajectory over time for each treatment group and allow comparison of the group longitudinal profiles. A similar analytic approach will be taken for analyses of data for each of the 9 pre-specified secondary outcomes. Exploratory analyses will be undertaken to determine if there is evidence for effect modification by gender, race/ethnicity, restless legs syndrome, concomitant medications, and treatment adherence.

8.3.2 Statistical Power for Aim Two

We have based our sample size on Aim 1 yet we retain strong power to detect long-term treatment effects. A power analysis using a simple pre-post analysis for 25-week outcomes controlling for baseline is a conservative estimate of the power for the longitudinal model since the simple analysis would only use 25-week complete cases. If we assume 20% loss to follow-up through 24 weeks then we would have 100 evaluated patients. For this Aim we would have 90% power to detect a CBT-I treatment effect of 4.0 points relative to trazodone and placebo and within the range of moderate treatment effects defined by standardized group differences of 3.0-4.8 points.

8.4. Plan for Handling Missing Data

The potential for bias due to loss-to-follow-up is a concern. The mixed effects modeling approach will mitigate the effects of loss-to-follow-up after the Week 4 visit by incorporating information from baseline and the Week 4 measurements for patients who subsequently drop out of the study when estimating treatment effects at Week 7.

8.5 Overall Approach for Avoidance of bias

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 chronic insomnia. Third, the primary and secondary outcomes will be measured at four 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.

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”. The greatest risk with CBT is discomfort/fatigue associated with restricting time in bed (including reducing daytime napping); these symptoms are usually temporary but will be monitored closely given their overlap with post-dialysis symptoms. Additional potential risks include breach of confidentiality if participants choose CBT to be done while undergoing HD.
2. **Adverse Effects from Trazodone:**
 - a. Side effects (>5%) reported more frequently than with placebo are (i) drowsiness; (ii) nervousness; (iii) dizziness; (iv) fatigue; (v) dry mouth; (vi) nausea; and (vii) vomiting.
 - b. The most significant adverse event is priapism but is extremely rare.
 - c. Anti-depressant drugs can increase suicidal thoughts in young adults
3. **Psychological discomfort from completing patient-reported scales**
4. **Loss of patient confidentiality**

9.2 Anticipated Adverse Events in the Hemodialysis Population

Patients undergoing HD 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 patients will be monitored for the occurrence of adverse events as:

- 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;
- The study staff will evaluate the patients 5-6 times during the six week treatment period either via tele-health or in-person, depending on the randomized arm; and
- Patients will be withdrawn from treatment if they experience a serious adverse event directly attributable to the study intervention and in the opinion of the site investigator, the treatment cannot be safely reinstated.

9.4 Reporting of Adverse Events

All adverse events experienced by study patients from the time of registration into the study (randomization) 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 sites 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 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

It is possible that some patients who are administered the PHQ-9, may report an active suicidal intent. We anticipate this to be a rare but significant event. However, since individuals with ESRD are at a higher risk for committing suicide than the general population, care will be exercised to identify and provide appropriate help to individuals with suicidal intent. The suicidal intent could be ascertained by:

- Study Coordinator (initial pre-screen with PHQ-9); or
- CATI (while completing PHQ-9).

The patients will be deemed to have active suicidal intent if they respond to question 9, “thoughts that you would be better off dead or of hurting yourself in some way” as “more than half the days” or “nearly every day”.

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

- If the patient is at immediate risk for self-harm, call 911;
- If the patient is not at immediate risk for self-harm, the clinical care team and the site investigator will be immediately contacted by telephone to collectively develop a plan for further care. In addition, an electronic communication will be sent to the site study team and DCC.

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 the:

- Data Safety and Monitoring Board (DSMB);
- Institutional Review Boards of each participating site; and
- NIDDK.

The DSMB Charter and the Data Safety Monitoring Plan is available as Appendices Five and Six, respectively and will be convened via a teleconference at least once every six months, or more frequently if deemed necessary.

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Appendix One: Patient Reported Outcome Instruments

1. Insomnia Severity Index (ISI)
2. Pittsburgh Sleep Quality Index (PSQI)
3. Epworth Sleepiness Scale
4. FACIT Fatigue Scale
5. Graded Chronic Pain Scale (GCPS)
6. Patient Health Questionnaire-2 (PHQ 2)
7. Patient Health Questionnaire-9 (PHQ-9)
8. Generalized Anxiety (GAD-7);
9. Short Form 12 (SF-12)
10. CAGE Questionnaire
11. Drug Abuse Screening Test (DAST-10)
12. Cambridge-Hopkins Restless Legs Syndrome (RLS-SFDQ13)

Appendix Two: List of Drugs Used as Sedatives/Hypnotics

Brand Name	Generic Name
PRESCRIPTION MEDICATIONS	
Ambien	Zolpidem
Amytal Sodium	Amorbarbital sodium
Ativan	Lorazepam
Belsomra	Suvorexant
Butisol	Butabarbital sodium
Dalmane	Flurazepam
Desyrel	Trazodone
Doral	Quazepam
Edluar	Zolpidem
Elavil	Amitriptyline
Gabitril	Tiagabine
Halcion	Triazolam
Hetiloz	Tasimelteon
Intermezzo	Zolpidem
Klonopin	Clonazepam
Librium	Chlordiazepoxide
Lunesta	Eszopiclone
Lyrica	Pregabalin
Mebaral	Mephobarbital
Minipress	Prazosin
Nembutal	Pentobarbital
Neurontin	Gabapentin
Notec	Chloral hydrate
Oleptro	Trazodone
Phenobarbital	Phenobarbital
Precedex	Dexmedetomidine hydrochloride
Prosom	Estazolam
Pulvules	Secobarbital
Quetiapine	Quetiapine
Remeron	Mirtazapine
Restoril	Temazepam
Risperdal	Risperidone
Rozerem	Ramelteon
Seconal	Secobarbital

Brand Name	Generic Name
Serax	Oxazepam
Serzone	Nefazodone
Seroquel	Quetiapine
Silenor	Doxepin
Sinequan	Doxepin
Sonata	Zaleplon
Tasimelteon	Tasimelteon
Valium	Diazepam
Xanax	Alprazolam
Zolpimist	Zolpidem
Zyprexa	Olanzapine

OVER THE COUNTER MEDICATIONS

Aceta-Gesic	Acetaminophen / diphenhydramine
Advil PM	Diphenhydramine / ibuprofen
Aleve PM	Diphenhydramine / naproxen
Alluna	Valerian-Hops
Bayer PM	Aspirin / diphenhydramine
Care One Sleep Aid	Doxylamine
Compoz Nighttime Sleep Aid	Diphenhydramine
dimenhydrinate	Dimenhydrinate
Doans PM	Diphenhydramine / magnesium salicylate
Dormin	Diphenhydramine
Doxytex	Doxylamine
Equaline Sleep Aid	Doxylamine
Equate Sleep Aid	Doxylamine
Excedrin PM	Acetaminophen / diphenhydramine
Headache Relief PM	Acetaminophen / diphenhydramine
Ibuprofen PM	Diphenhydramine / ibuprofen
Legatrin PM	Acetaminophen / diphenhydramine
Mapap PM	Acetaminophen / diphenhydramine
Midol PM	Acetaminophen / diphenhydramine
Motrin PM	diphenhydramine / ibuprofen
Night Time Pain	Acetaminophen / diphenhydramine
Nighttime Sleepaid	Doxylamine
Nytol	Diphenhydramine
Nytol QuickCaps	Diphenhydramine
Pain Relief PM Extra Strength	Acetaminophen / diphenhydramine
Percogesic Extra Strength	Acetaminophen / diphenhydramine

Brand Name	Generic Name
Simply Sleep	Diphenhydramine
Sleep Aid	Doxylamine
Sleepinal	Diphenhydramine
Sominex	Diphenhydramine
Tranquil Nighttime Sleep Aid	Diphenhydramine
Tylenol PM	Acetaminophen / diphenhydramine
Tylenol Sore Throat Nighttime	Acetaminophen / diphenhydramine
Twilite	Diphenhydramine
Unisom Sleeptabs	Doxylamine
Unisom SleepTabs	Doxylamine
Unisom PM Pain	Acetaminophen / diphenhydramine
Unisom SleepGels	Diphenhydramine
Unisom SleepMelts	Diphenhydramine
ZzzQuil	Diphenhydramine
Z-Sleep	Diphenhydramine
OTHERS	
5-hydroxytryptophane	5-HTP
Chamomile	
Kava	
Lemom Balm	Melissa Officinalis
L-tryptophan	
Marijuana	
Melatonin	
Passion flower	Passiflora Incarnata
St. John Wort	
Valerian	



Appendix Three: Study Schedule

	Pre-Screen	Screen	Run-In		Treatment						Follow-up from Randomization		
WEEK			-1	0	1	2	3	4	5	6	7	13	25
Insomnia Severity Index	x			x				x			x	x	x
Structured Interview, Inclusion/Exclusion Criteria		x											
Randomization				x									
CBT-I Telehealth Visits*					x	x	x	x	x	x			
CBT-I Visits (coordinator)							x			x			
Trazodone/Placebo In-Person Visits					x			x		x			
Trazodone/Placebo Telephone Visits						x	x						
Treatment Adherence Assessment							x		x		x	x	
CATI				x			x				x	x	x
Actigraphy with sleep diary			x						x				x
Concomitant Sedatives/Hypnotics				x			x				x	x	x

*Patient randomized to CBT-I will maintain sleep diaries for each of the six-week treatment period

Appendix Four: List of Concomitant Medications that are an Exclusion Criteria

Brand Name	Generic Name
Anti-Microbials	
Avelon	Moxifloxacin
Avelox	Moxifloxacin
Biaxin	Clarithromycin
Cipro	Ciprofloxacin
Diflucan	Fluconazole
Levaquin	Levofloxacin
Neofloxin	Ciprofloxacin
Onmel	Itraconazole
Prevpac	Clarithromycin
Sporanox	Itraconazole
Trican	Fluconazole
Vfend	Voriconazole
Zithromax	Azithromycin
Zyvox	Linezolid
Other Medications	
Almarytm	Flecainide
Apocard	Flecainide
Azilect	Rasagiline
Betapace	Sotalol
Cin-Quin	Quinidine
Cordarone	Amiodorane
Convert	Ibutilide
Dridol	Droperidol
Droleptan	Droperidol
Duraquin	Quinidine
Ecrinal	Flecainide
Eldepryl	Selegiline
Emsam	Selegiline
Flecaine	Flecainide
Geodon	Ziprasidone
Haldol	Haloperidol
Inapsine	Droperidol

Brand Name	Generic Name
Marplan	Isocarboxazid
Mellaril	Thioridazine
Nardil	Phenelzine
Nexterone	Amiodorane
Novoridazine	Thioridazine
Orap	Pimozide
Ormazine	Chlorpromazine
Pacerone	Amiodorane
Parnate	Tranylcypromine
Procan	Procainamide
Pronestyl	Procainamide
Quinact	Quinidine
Quinaglute	Quinidine
Quinidex	Quinidine
Quinora	Quinidine
Sotacor	Sotalol
Sotalex	Sotalol
Tambocor	Flecainide
Thioril	Thioridazine
Thorazine	Chlorpromazine
Xomolix	Droperidol
Zelapar	Selegiline

Appendix Five: Cognitive Behavioral Therapy for Insomnia Session Outlines

Session 1	<ul style="list-style-type: none"> ▪ Treatment overview ▪ Information on insomnia in ESRD patients and sleep 1 ▪ Behavioral/sleep scheduling strategies 1
Session 2	<ul style="list-style-type: none"> ▪ Follow-up on goal setting, 3Ps, behavioral/scheduling strategies 1 ▪ Behavioral/scheduling strategies 2
Session 3	<ul style="list-style-type: none"> ▪ Follow-up on behavioral/scheduling strategies 1 and 2 ▪ Information on insomnia, sleep, and ESRD
Session 4	<ul style="list-style-type: none"> ▪ Follow-up on behavioral/scheduling strategies ▪ Constructive worry ▪ Relaxation/mindfulness
Session 5	<ul style="list-style-type: none"> ▪ Follow-up on behavioral/scheduling, constructive worry techniques, and relaxation practice ▪ Sleep hygiene recommendations ▪ Adopting beliefs and attitudes that contribute to good sleep
Session 6	<ul style="list-style-type: none"> ▪ Review of all behavioral and cognitive strategies ▪ Evaluate progress and review goal attainment ▪ Maintenance of treatment gains and relapse prevention

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SESSION 1/6

1. Introduction (1 min)
2. Treatment overview and agenda (3 min)
3. **Insomnia and living your life on hemodialysis (7 min)**
 - 3.1. What is important in your life and how is insomnia impacting that?
 - 3.2. Futility of trying to “control” sleep
 - 3.3. Treatment will teach you skills that will prepare you to sleep (“surfing the sleep wave”) *and* to keep moving towards your valued goals even when you have a bad night
4. **Information on sleep and insomnia 1/2 (5 min)**
 - 4.1. General information on the definition, prevalence, impact, and risk factors of insomnia
 - 4.2. Spielman’s “3P” model with predisposing, precipitating, and perpetuating factors
 - 4.3. Information on how kidney disease and dialysis treatment precipitate and perpetuate insomnia symptoms
5. **Behavioral/scheduling strategies 1/2: Reinforcing the associations between bed/bedroom, bedtime, and sleep (10 min)**
 - 5.1. Present rationale
 - 5.2. Discuss each recommendation:
 - Do not use the bed/bedroom for non-sleeping activities
 - Allow at least one hour to unwind before bedtime
 - Go to bed only when sleepy
 - Get out of bed at the same time every morning
 - Avoid prolonged daytime naps or napping after 3:00 pm
 - Get out of bed when unable to sleep within 15-20 min
 - How to account for an early morning or late night dialysis shift
6. **Self-monitoring: The sleep diary (3 min)**
 - 6.1. Rationale for good record keeping
 - 6.2. Review baseline sleep diaries for adherence, missing or unclear data
7. **Homework assignment (1 min)**
 - 7.1. Apply first behavioral/scheduling strategy (stimulus control)
 - 7.2. Set treatment goals
 - 7.3. Identify predisposing, precipitating, and perpetuating factors
 - 7.4. Review handouts

SESSION 2/6

1. Set agenda (1 min)
2. Review sleep diary of the past week (2 min)
3. Review treatment goals and identification of predisposing, precipitating, and perpetuating factors (1 min)
4. **Review application of stimulus control strategies (10 min)**
 - 4.1. Review rationale
 - 4.2. Evaluate adherence
 - 4.3. Identify methods to enhance adherence
5. **Behavioral/sleep scheduling strategies 2/2: Limiting time spent in bed to actual sleep time (15) min**
 - 5.1. Introduce rationale
 - 5.2. Set initial sleep window based on non-dialysis days
 - 5.3. Explain the procedure to readjust the sleep window on a weekly basis
 - 5.4. Explain accommodations if dialysis treatment begins or ends during the sleep window
6. **Homework assignment (1 min)**
 - 6.1. Apply behavioral/scheduling strategies
 - 6.2. Review handouts

SESSION 3/6

1. Set agenda (1 min)
2. **Review sleep diary of the past week (3 min)**
 - 2.1. Set new sleep window based on non-dialysis days
3. **Review application of behavioral/scheduling strategies (15 min)**
 - 3.1. Review rationale
 - 3.2. Evaluate adherence
 - 3.3. Identify methods to enhance adherence
4. **Information on sleep and insomnia 2/2 (10 min)**
 - 4.1. Present sleep stages and cycles
 - 4.2. Review changes in sleep patterns over the lifespan
 - 4.3. Sleep and ESRD
5. **Homework assignment (1 min)**
 - 5.1. Apply behavioral/scheduling strategies
 - 5.2. Review handouts

SESSION 4/6

1. Set agenda (1 min)
2. **Review sleep diary of the past week (2 min)**
 - 2.1. Set new sleep window based on non-dialysis days
3. **Review application of behavioral/scheduling strategies (5 min)**
 - 3.1. Evaluate adherence
 - 3.2. Identify methods to enhance adherence
 - 3.3. Set new sleep window
4. **Constructive worry (10 min)**
 - 4.1. Present rationale
 - 4.2. Discuss types of thoughts for which constructive worry can be helpful/unhelpful
 - 4.3. Plan application of constructive worry strategy
5. **Relaxation/mindfulness (10 min)**
 - 5.1. Present rationale
 - 5.2. Practice
6. **Homework assignment (2 min)**
 - 6.1. Apply behavioral/scheduling strategies
 - 6.2. Complete constructive worry sheet as needed
 - 6.3. Practice relaxation during day and night
 - 6.4. Review handouts

SESSION 5/6

1. Set agenda (1 min)
2. **Review sleep diary of the past two weeks (2 min)**
 - 2.1. Set new sleep window
3. Review homework and use of constructive worry and relaxation techniques (1 min)
4. **Review application of behavioral/scheduling strategies (5 min)**
 - 4.1. Review rationale
 - 4.2. Evaluate adherence
 - 4.3. Identify methods to enhance adherence
 - 4.4. Set new sleep window
5. **Sleep hygiene recommendations (5 min)**
6. **Changing beliefs and attitudes about sleep and insomnia (15 min)**
 - 6.1. Keep realistic expectations
 - 6.2. Avoid blaming insomnia for all daytime misfortunes
 - 6.3. Revise misconceptions about the causes of insomnia
 - 6.4. Do not catastrophize after a poor night's sleep
 - 6.5. Avoid placing too much emphasis on sleep
 - 6.6. Develop tolerance to the effects of sleep loss
7. **Homework assignment (1 min)**
 - 7.1. Apply behavioral/scheduling strategies
 - 7.2. Complete treatment summary and relapse prevention booklet
 - 7.3. Review handouts

SESSION 6/6

1. Set agenda (1 min)
2. Review sleep diary of the past two weeks (2 min)
3. **Review treatment components (5 min)**
 - 3.1. Behavioral/scheduling strategies
 - 3.2. Sleep hygiene and information on sleep and insomnia
 - 3.3. Beliefs and attitudes about sleep and insomnia
 - 3.4. Values review
 - 3.5. Constructive worry
 - 3.6. Relaxation
4. **Evaluate progress and goal attainment (10 min)**
 - 4.1. Chart progress
 - 4.2. Review valued areas of life and any changes that have occurred in how much insomnia interferes
 - 4.3. Check goal attainment and provide feedback on progress and adherence
 - 4.4. Emphasize areas needing more attention
5. **Relapse prevention (10 min)**
 - 5.1. Make distinction between lapse and relapse
 - 5.2. Discuss the inevitability of occasional poor nights
 - 5.3. Identify high risk situations/circumstances
 - 5.4. Devise action plan for insomnia lapses
6. Closure (2 min)

Appendix Six: Data Safety Monitoring Board Charter

Reviewed and Accepted by DSMB Members:

Vernon Chinchilli, PhD (Chair and Biostatistician)

Deidra Crews , MD

Jennifer Flythe, MD

Prepared and Accepted by:

Rajnish Mehrotra, MD MS, Principal Investigator

Patrick Heagerty, PhD, Data Coordinating Center Statistical Advisor

Tessa Rue, MD, Unblinded Data Coordinating Center Biostatistician

Terms used in this document related to the Data Safety Monitoring Board activities	
<u>Term</u>	<u>Definition</u>
Blinding Status	
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 versus Treatment C)
Unblinded	Access to the decode information for A, B, and C as described in the Semi-Blinded definition
Individuals and Groups	
Data Safety Monitoring Board (DSMB)	<p><i>Unblinded</i></p> <p>An independent group charged with monitoring the safety of patients in the SLEEP-HD trial, and the scientific integrity of the trial</p>
Funder	<p><i>Initially Blinded</i></p> <p>The Funder is the organization that provides funding and other support and oversees trial implementation.</p>
Principal Investigator	<p><i>Initially Blinded</i></p> <p>The Principal Investigator is the physician who serves as the scientific leader of the trial</p>
Clinical Coordinating Center / Study Management Team	<p><i>Initially Blinded</i></p> <p>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.</p>
Unblinded Data Coordinating Center Statistician*	<p><i>Initially Unblinded</i></p> <p>The unblinded statistician who prepared the Closed Report</p>

Data Coordinating Center Statistical Advisor ^{**}	<i>Initially Semi-Blinded</i> The semi-blinded statistician who will assist with the interpretation of the Closed Report.
Open and Closed Report, Session, Minutes	
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 Data Coordinating Center Statistician is unblinded, but has no contact with patients or the day-to-day study activities.

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

Part 1: Introduction

The Data and Safety Monitoring Board (DSMB) will be responsible for assessing safety and efficacy during conduct of the SLEEP-HD 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 SLEEP-HD 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 DSMB Membership and Responsibilities

The DSMB is an independent multidisciplinary group consisting of two nephrologists and one biostatistician who collectively have experience in the treatment of patients undergoing maintenance hemodialysis, and/or in the conduct and monitoring of randomized clinical trials in nephrology. The duration of membership will span until six months after the end of patient recruitment.

All DSMB Members have agreed 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 NIH/NIDDK. 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.

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 patients. 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 trazodone 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.

1.2.1 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.

1.2.2 DSMB Biostatistician

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

1.3 Responsibilities of the Study Management Team and Data Coordinating Center

The Study Management Team and Data Coordinating Center 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 Data Coordinating Center Statistician

and Semi-blinded Data Coordinating Center Statistical Advisor are not involved in these activities and have no contact with sites or patients.

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 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.

1.3.1 Principal Investigator

The Principal Investigator for the SLEEP-HD 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, Institutional Review Boards, and others as appropriate.

1.3.2 Data Coordinating Center Statistical Advisor

The Data 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 Data 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.

1.3.3 Unblinded Data Coordinating Center Statistician

The Unblinded Data 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 data 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 Data 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.

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, Data Coordinating Center Statistician, and the Unblinded Data Coordinating Center Statistician. The Unblinded Data 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 Data Coordinating Center Statistician, Data 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 weeks of the date of the DSMB meeting, and the data snapshot should occur approximately 10 days 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 ten 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: Open Section (blinded information) that contains information on recruitment, eligibility violations, baseline characteristics, data on completeness of follow-up and adherence, 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 Data Coordinating Center Statistician in consultation with the Data Coordinating Center Statistical Advisor.

Open and Closed Minutes will be recorded by the Chair of the DSMB. Copies of the Open Minutes will be distributed to the Principal Investigator and DSMB. Copies of the Closed Minutes will be distributed only to the DSMB and will be 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 Data 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 DSMB will plan on meeting via teleconference every six months; the first meeting will be scheduled about six months from the start of recruitment but no later than December 2018. The DSMB may request interim meetings in between the six-month periods.

Unscheduled DSMB meetings can be called as necessary by the DSMB. To call an unscheduled meeting, the DSMB Chair will contact the Data 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 answer 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. The Principal Investigator will present the results of the Open Report and will be available to answer any questions from the members of the DSMB.

2.4.2 Closed Session

Closed DSMB Sessions involving only DSMB Members and the Data 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 patient 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 2 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 two 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 Data 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.

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 SLEEP-HD trial's study performance and safety outcomes will be conducted by the Data Safety and Monitoring Board (DSMB). The DSMB consists of 3 members, (Chair: **Dr. Vernon Chinchilli**, PhD, Dr. Deidra Crews MD, and **Dr. Jennifer Flythe**, 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

A total of 126 patients will be recruited into this clinical trial, with 75 patients anticipated to be enrolled in Seattle and 50 in Albuquerque. The randomization will be block randomized on site, with random size block assignment within site to maintain balance between treatment groups.

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 patients, extending the trial in time, increasing the trial sample). Decision guidelines in the SLEEP-HD 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 adherence with respect to patient recruitment and eligibility, retention and follow-up, randomization and blinding, and quality of data will be conducted and monthly reports generated.

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 by more than 50%; and
- (2) the response rate for the ISI by CATI will be no less than 85% at the 7-week time-point among those randomized to CBT-I, trazodone, or placebo;

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). Adherence 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 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.

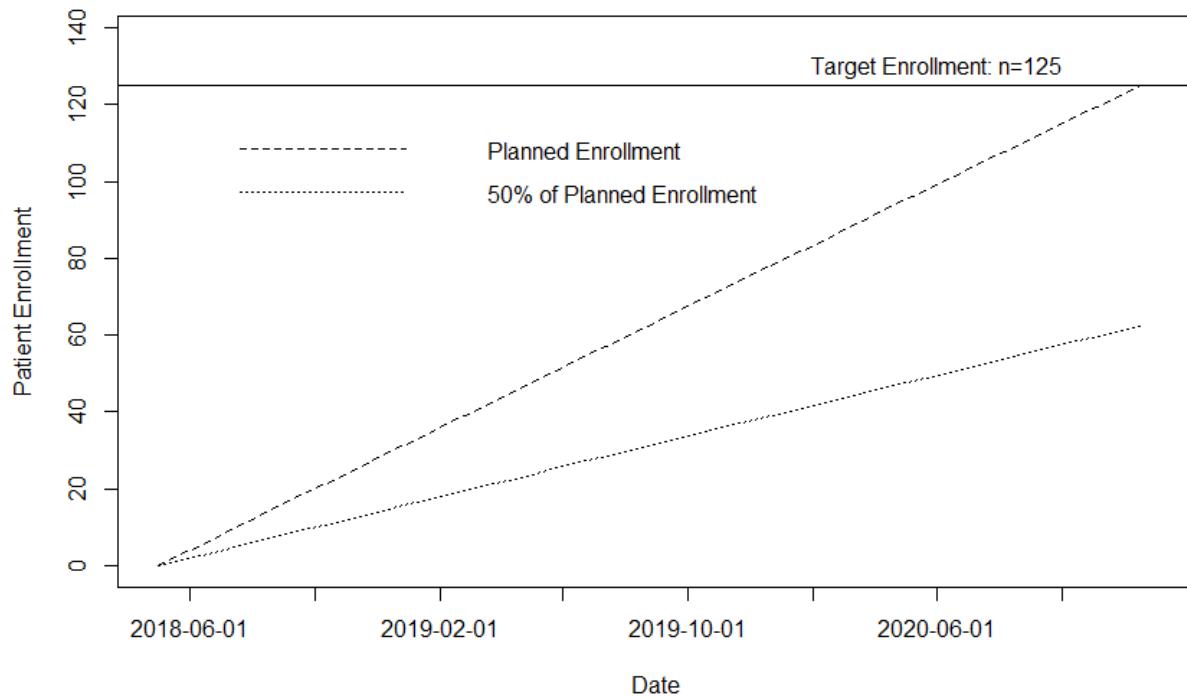
The SLEEP-HD study aims to enroll up to 126 patients with the following distribution among the sites: 76 patients at Seattle and 50 patients at Albuquerque. Tables 1 and 2 and Figure 1 are performance monitoring examples that will be included in future Open DSMB Reports.

Table 1. Cumulative and Current Report Period Study Recruitment

Site	Current Report Period			Cumulative		
	Seattle	Albuquerque	Total	Seattle	Albuquerque	Total
Screened						
Eligible						
Enrolled						
Randomized to CBT-I, trazodone, or placebo						

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

	Seattle	Albuquerque	Total
Randomized to CBT-I, trazodone, or placebo			
CATI assessment completed at 7 weeks			
CATI assessment completed at 25 weeks			

Figure 1. Cumulative Enrollment.


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 or prolongs 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 trazodone include drowsiness, nervousness, dizziness, fatigue, dry mouth, nausea, vomiting, or priapism. CBT is considered minimal risk to a patient, although there is a potential for a loss of patient confidentiality since CBT-I may be done while patient is undergoing HD. Among patients randomized to CBT-I or trazodone or medication placebo, all adverse events possibly associated with trazodone or medication placebo will be reported in Table 4. All serious adverse events regardless of possible association to intervention will be reported in Table 4. 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.

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

Event	Group A'	Group B'	Group C'	Expected* (over 6-month period)	Threshold For Action	p-value**
Adverse Event						
Priapism				1%	5%	
Serious Adverse Event						
Death				8%	12%	
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 to Group C

Rates of death and hospitalization were estimated from annual rates reported in the USRDS Annual Data Report and projected for the 6-month study period

Patient ID	SAE Description	System Organ Class ¹	Treatment Group	Age	Sex	Enrollment Date	SAE Date	Date of PI review	Relationship to Study ²	Action Taken ³	Outcome ⁴
Ex1	Death	2	A	70	F	22Jul2018	23Jul2018	25Jul2018	1	1	5
Ex2	Hospitalization-CHF	2	B	70	M	30Oct2018	30Nov2018	4Dec2018	2	4	2

Table 5. Detailed tabulation of (Closed Report) Serious Adverse Events that have occurred during the SLEEP-HD study.

¹System Organ Class: 1. Blood and Lymphatic System Disorders
 2. Cardiac Disorders
 ...
 26. Vascular Disorders

²Relationship: 1. Unrelated
 2. Unlikely related
 3. Possibly related
 4. Related

³Action Taken: 1. None
 2. Study Rx dosage reduced
 3. Study Rx interrupted
 4. Study Rx discontinued permanently

⁴Outcome: 1. Resolved, no follow-up needed
 2. Ongoing/treatment continued
 3. ER visit/Prolongation of hospitalization
 4. Patient died

4.3 Treatment Efficacy Monitoring

We will report aggregate 7-week and 25-week ISI 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 7- and 25-weeks. However, the DSMB is charged not to make a recommendation to terminate the study based on interim efficacy estimates. CBT-I and trazodone are accepted standard of care treatments for insomnia. 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 patients are built into the study protocol. CBT-I and trazodone 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 patients. Patients will also be monitored more frequently than in usual clinical practice and at all follow up time points, patients will be asked about adverse events and unanticipated health events that may or may not be related to the study procedures.

The study protocol is designed to allow close monitoring of patients randomized to either of the three arms with a total of five visits during the six-week treatment period for patients randomized to trazodone or medication placebo.

5. Scheduled Reporting

Three weeks prior to each DSMB review, the Data Coordinating Center (DCC) will summarize administrative reports that describe study progress including patient 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.

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 related or possibly related to the study will be reported to the DSMB chair, as they occur. The DSMB may call an emergency meeting, if necessary.

Appendix Eight: COVID Risk Mitigation Plan for SLEEP-HD

Pre-screening (ISI)	<u>In person</u> (need <5 minutes which are very important to build up the rapport with the patient)
Consent & Screening	<u>In person</u> - Consent process Screening questionnaire packet (as much as possible in person) <u>On phone/online</u> Any screening questions not completed in person Review of EMR for inclusion/exclusion determination
Run-In visits	<u>In person</u> <ol style="list-style-type: none"> 1) Actiwatch placement & instruction, sleep diary delivery & instruction, CBT Manual delivery <u>On phone/online</u> <ol style="list-style-type: none"> 2) randomization, CATI, sedative/hypnotics <p>*Participants can return Actiwatches and completed diaries to unit where RC's will pick up, OR mail back to RC's. Watches and diaries will be placed in sealed ziplock bag and kept untouched for 3-4 days.</p>
Treatment visits	<u>In person</u> <ol style="list-style-type: none"> 3) Actiwatch placement & instruction, sleep diary delivery & instruction <u>Mail</u> <ol style="list-style-type: none"> 4) Drug delivery/collection (can be done the inter-office mail or US Postal Service with return label directly to the patient; follow-up with a phone call) <u>On Phone/online</u> <ol style="list-style-type: none"> 5) Study Medication Follow-Up Visits (all via phone). 6) Visit Assessments and sedative/hypnotics can be done via phone/online. 7) CATI calls over the phone/online. <p>*Participants can return Actiwatches and completed diaries to unit where RC's will pick up, OR mail back to RC's. Watches and diaries will be placed in sealed ziplock bag and be kept untouched for 3-4 days.</p>
Drug collection	<u>Collection process</u>

	<ol style="list-style-type: none"> 1) Patient brings bottle to dialysis unit, to hold at unit for coordinator or to be sent to research team through inter-office mail 2) Keep it untouched in zip lock bags for 3-4 days 3) Use mask and gloves during accountability and sanitize the bag 4) Drop off at pharmacy in zip lock bag (UNM) or store in research office (UW).
CBT-I Telehealth Visits	<p><u>Process</u></p> <ol style="list-style-type: none"> 1) Participants can use their own device or a device provided by the study 2) If participants using their own device, coordinator may need to help participant set up zoom and use a laminated card with step-by-step instructions 3) If participants use study device, one device and one earbud/headphone set will be left at the study unit for the six-week duration of treatment 4) Either dialysis unit staff or coordinator will bring tablet and headphones to patients at each CBT-I visit 5) Coordinator visits at weeks 4 and 6 can be done online/over the phone or in person
Follow-up visits	<p><u>In person</u></p> <ol style="list-style-type: none"> 6) Actiwatch placement & instruction, sleep diary delivery & instruction <p><u>On phone/online</u></p> <ol style="list-style-type: none"> 7) Treatment Adherence Assessment, ISI and sedative/hypnotics can be done via phone/online. <p><u>Mail</u></p> <ol style="list-style-type: none"> 8) Gift cards can be sent by inter-office mail or US postal service, or can be delivered at the time of Actiwatch & diary collection; 9) Signed gift card receipt can be left at the unit, scanned and sent or inter office back to research staff.
Key Touchpoints	<ol style="list-style-type: none"> 1) Initial survey/ISI 2) Consent form & Screening 3) Drug delivery/collection 4) Watch/sleep diary set-up 5) Tablet for CBT-I set-up
Actiwatch cleaning/sanitizing	<ol style="list-style-type: none"> 1) Follow current manual of procedure with updated cleaning protocol provided by vendor 2) Keep watch sealed in zip lock bags for 3-4 days after each use

	<ul style="list-style-type: none">3) Watches and wristbands will be removed from zip locks and cleaned per vendor instructions between wearings.4) Use mask, gloves during this process5) Each participant will be provided with a new, disposable wristband and will use it for all 3 Actigraphy collection time points. It will be disposed of once Actigraphy collection is complete.
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