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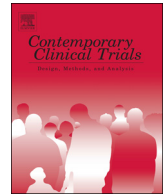
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Rationale and design of technology assisted stepped collaborative care intervention to improve patient-centered outcomes in hemodialysis patients (TĀCcare trial)

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ABSTRACT

Most hemodialysis (HD) patients experience symptoms of depression, pain and fatigue that impair their health-related quality of life (HRQOL) significantly. These symptoms are associated with increased hospitalization and mortality, mediated by behavioral factors (e.g. non-adherence to medication and dialysis) and biological factors (e.g. inflammatory cytokines). Prior interventions to alleviate symptoms and improve HRQOL showed limited effectiveness in HD patients and their effect on bio-behavioral mediators is lacking evidence. It is imperative to improve patient-centered dialysis care and to address call from Kidney Disease Improving Global Outcomes (KDIGO) guidelines for integration of symptom assessment and management in routine HD-care. Technology-Assisted stepped Collaborative Care (TĀCcare) is a multi-center randomized controlled trial (RCT) of 150 diverse HD patients from Pennsylvania and New Mexico, designed to compare the effectiveness of a 12-week stepped collaborative care intervention (cognitive behavioral therapy, CBT) with an attention control arm of technology-delivered health education. Collaborative care provides an integrated multi-disciplinary structured management plan. Furthermore, a stepped approach to pharmacotherapy and/or CBT allows for individualization of treatment according to patients' clinical status, preferences and treatment response. To simplify the delivery of CBT and to minimize patient and provider burden, we will use live video-conferencing with patients in dialysis units. We will examine the effect of these interventions on patient symptoms, HRQOL, treatment adherence and inflammatory biomarkers. This RCT tests a readily implementable intervention that can be integrated in routine HD-care and will generate novel and meaningful insights on strategies to alleviate common symptoms and improve HRQOL in HD.

1. Introduction

Patients with End-Stage Renal Disease (ESRD) on hemodialysis (HD) experience a symptom burden comparable to advanced cancer patients [1–4]. Fatigue, pain and depression are among the most debilitating symptoms, reported by > 60%, 50% and 20% of HD patients, respectively [5–8]. These symptoms often co-exist as "symptom-clusters," can exacerbate one another, and are independently associated with poor health-related quality of life (HRQOL) in HD [2,9–12]. Given their associations with decrements in multiple HRQOL domains, these symptoms are associated with medication and HD sessions non-adherence [13–15]. Non-adherence, as well as biological factors (e.g.
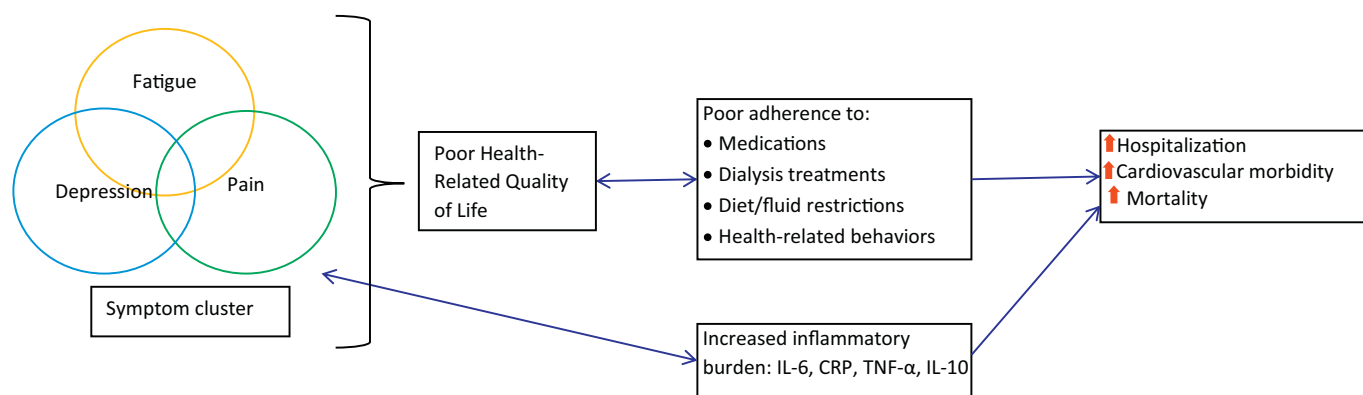
Fig. 1. Symptom burden, inflammation and outcomes in HD patients.

inflammatory cytokines), likely contribute to increased hospitalization and mortality in these patients (Fig. 1) [9,15–18]. Additionally to survival, improvement of these symptoms is extremely important to HD patients and their caregivers [19,20]. Only recently, the Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference on Supportive Care (2015) advocated for integration of symptom assessment and management into routine ESRD care [21]. Additionally, recent Center for Medicare and Medicaid Services (CMS) criteria for ESRD Quality Incentive Program mandate reporting of depression screening and treatment for all patients [22].

Unfortunately, routine treatment approaches for symptoms in HD patients had limited success [5,7,8]. Although promising, studies on the efficacy of pharmacotherapy or psychotherapy [such as cognitive behavioral therapy (CBT)] for depression in HD are methodologically limited (small sample size, observational design, lack of adequate control group, lack of adequate minority racial/ethnic representation) [23–28]. Data also suggest benefits of analgesic medications for pain; and of sleep hygiene, exercise and anemia correction for fatigue [7,29]. No studies have tested the efficacy of CBT for pain or fatigue in ESRD. However, CBT has proven efficacious in similarly symptomatic cancer patients and is based on a conceptual model that highlights the importance of precipitating and perpetuating factors (e.g. poor sleep, physical inactivity, and coping strategies) which exist in ESRD patients [30,31]. Key reasons for poor acceptance and suboptimal results of prior interventions were: failure to target "symptom-clusters", combining pharmacotherapy and behavioral-therapy, incorporating patient treatment preferences, or integrating interventions into existing dialysis-care team-models [8,32,33].

The TĀCcare trial is based on a Stepped-Collaborative Care Intervention (SCCI) that addresses these barriers to effective treatment implementation and presents an ideal symptom management strategy for HD patients (Fig. 2). SCCI emphasizes a more real-world and flexible intervention that has multiple "active ingredients" (psychotherapy and pharmacotherapy) and includes a care manager actively monitoring treatment response, following an evidence-based protocol to modify treatment content and intensity, and serving as a liaison between the health-care teams to facilitate integration of mental and physical-health treatments [34,35]. In SCCI, patients' adherence, treatment response, preferences and outcomes are monitored actively and treatments are modified as needed to achieve the best possible outcome for each patient. To simplify the delivery of the behavioral therapy component and reduce the patient and provider burden, the current trial will incorporate video-conferencing in dialysis units. This will be the first, multi-center randomized controlled trial (RCT) targeting symptom-clusters and using a SCCI with technology-based delivery of behavioral interventions in HD patients. The results will lead to new approaches for symptom management in HD patients.

2. Methods

2.1. Study overview

This study is a two-site, parallel group, RCT comparing a technology assisted SCCI (TĀCcare) to technology-assisted health education control in improving key patient-centered outcomes in 150 HD patients. After signing informed consent, completing baseline assessments and meeting eligibility criteria, enrolled patients will be randomized 1:1 to TĀCcare or technology-delivered health education and will undergo a 12-week intervention (Fig. 3). The study participants will be recruited using an approach to limit drop-out while enhancing generalizability and the main analysis is intention-to-treat. The main patient-centered outcomes (Aim 1) are: 1) a clinically meaningful change (effect size 0.6) in depression, pain or fatigue *(primary outcome)*; 2) a change in HRQOL and ecological momentarily assessed composite symptom score of fatigue, sleepiness and mood *(secondary outcomes)* after the 12-week intervention. We will also determine the effect of TĀCcare on adherence to medications, diet and HD treatments *(secondary outcomes)* (Aim 2) and we will explore changes in inflammatory biomarker levels (Aim 3) after the 12-week intervention. Since the effect of pharmacotherapy may be delayed, we will measure these outcomes at 6 months and again at 12 months to assess the maintenance of the benefits of our intervention.

2.2. Setting and participants

A total of 150 adult chronic HD patients will be recruited from the two clinical sites at the University of Pittsburgh and the University of New Mexico which collectively have 20 free-standing dialysis clinics that vary in geographic areas, size and population served. These clinics were selected to ensure a diverse HD population with adequate representation of females and minority groups including African Americans, American Indians and Hispanic/Latinos.

2.3. Eligibility criteria

Patient inclusion criteria include: a) 18 years or older; b) undergoing thrice-weekly maintenance HD for over 3 months; c) English or Spanish speaking; d) ability to provide informed signed consent; and e) no evidence of thought disorder, delusions, or active suicidal intent observed or reported. Patient exclusion criteria include: a) evidence of thought disorder, delusions or active suicidal intent – observed or reported; b) active substance abuse; c) too ill or cognitively impaired to participate based on clinicians' judgement; d) anticipated life expectancy of < 1 year; e) unable or unwilling to adhere to study protocol; f) participating in another clinical trial or taking an investigational drug; g) scheduled for living donor kidney transplant within the next 6 months; h) relocating to another dialysis unit within 6 months. We will not exclude patients who are already being treated for pain or
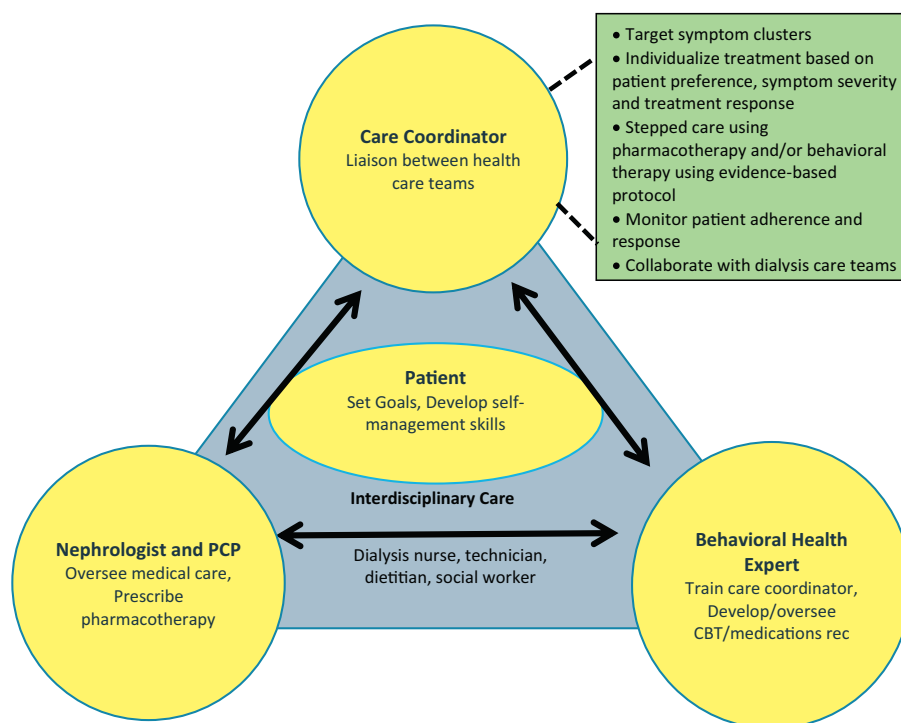
Fig. 2. TACcare model of care.

depression if they screen positive for clinical levels of depression, pain or fatigue as studies suggest that these symptoms are often undertreated in HD patients [36,37].

2.4. Screening

Eligible patients will be screened for:

1) Clinical levels of symptoms: Screening will include 9 questions for depressive symptoms from the Patient Health Questionnaire-9 (PHQ-9), 0–10 point Likert scale of pain (10 = worst pain), and 0–10 point Likert scale of fatigue (10 = worst fatigue) experienced within last 2 weeks [38]. Only symptomatic patients who have clinical levels of at least one of the 3 symptoms (≥ 10 on PHQ-9 and/or ≥ 4 on pain scale and/or ≥ 5 on fatigue scale) will be included in the study. This is important because we are targeting patients with high symptom burden to evaluate the efficacy of TĀCcare.
2) Readiness for Behavior Change: We will use a 5–item Stages of Behavior Change questionnaire to assess patient's readiness for treatment. A clinically significant effect size has been shown for the association between stage of change and psychotherapy outcomes, suggesting that patients who are in the pre-contemplation stage with no intention to change behavior in the foreseeable future are unlikely to actively participate and derive benefit from the treatment [39]. Thus, we will enroll only those patients who are at least in contemplation stage of behavioral change for symptom management ("would be motivated to seek treatment or talk to their doctor about it").

2.5. Randomization

After enrollment and completion of baseline assessments, the Study Coordinating Center at Pittsburgh will assign patients randomly in a 1:1 ratio to either TĀCcare or health education arm, using a computer generated randomization schedule. Randomization will be stratified by the two clinical sites, age (< 60 and ≥ 60 years) and the Charlson

comorbidity index (< 4 and ≥ 4) to minimize the likelihood of group imbalance in these potentially confounding variables. Permuted block design with random block sizes will be used, but the block sizes will not be disclosed to ensure allocation concealment.

2.6. Cross-contamination

Patients in both arms will receive an intervention delivered using video-conferencing. Thus, even though patients at outpatient dialysis clinics are in close proximity to fellow patients, we expect that any chances of cross-contamination between study arms is minimal. Moreover, even if the patients are in different arms at the same unit and interact with each other, these interactions are likely to be brief and unlikely to have any sustained effect on our outcomes of interest. Furthermore, the care coordinator for the intervention and control arm will not be the same person to ensure there is no unintentional contamination from the study staff while delivering the intervention. Lastly, although there is a possibility that the renal providers could start recognizing and recommending symptom management in the control arm patients, this is unlikely given reluctance of patients and providers regarding pharmacotherapy alone, and patient burden associated with in-office CBT.

2.7. Blinding

Neither the patients nor the PI can be blinded due to the nature of the study intervention. However, research staff assessing patient-centered outcomes will be blinded to the group assignment.

3. Treatment intervention study arms

A) Technology Assisted Stepped Collaborative Care Intervention (TĀCcare)

Patients randomized to the intervention arm will receive a stepped-care approach of pharmacotherapy and/or CBT for a 12-week period. The intervention will target one or more symptoms based on patients'
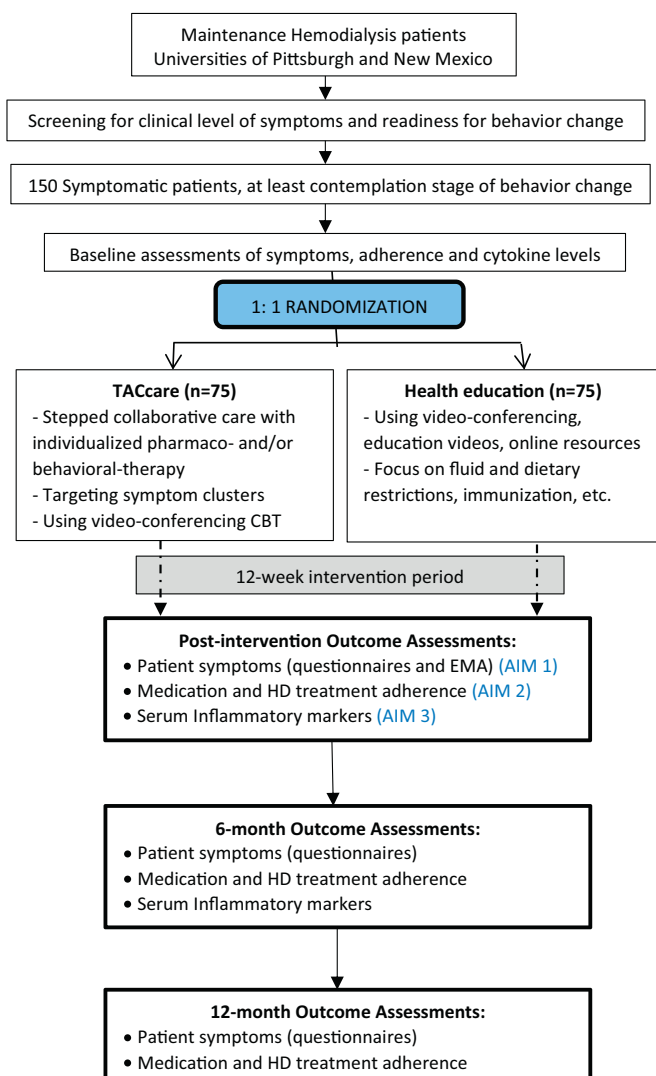
Fig. 3. Overview of TACcare study design.

report of clinical levels of each symptom and patient preference. A local care coordinator at each clinical site will be assigned to each patient. During weekly online video-conferencing sessions, care coordinators will engage the patient actively, encourage and monitor treatment adherence, and assess response and side-effects. Both clinical sites have secure and established telemedicine portals that are routinely used for clinical care and research (Vidyo at University of Pittsburgh and Echo Zoom at University of New Mexico). These live video-based face-to-face sessions will be conducted during one of the thrice weekly HD sessions at the dialysis unit with optional privacy screen. For each dialysis unit, the study will provide iPads, portable secure Wi-fi hotspot, wireless headphones and microphones. Similar to our pilot study (manuscript in preparation), these devices will be pre-programmed to ensure patient's ease and independence of use with minimal training, even among the elderly or those with limited technology experience, thus causing minimal additional burden for the dialysis staff. If there are any medical emergencies during the HD session, the video-based session will be cancelled and rescheduled once the patient is clinically stable. If the patients have the needed technology at home, they will have the option of doing these video-conferencing sessions at home.

B) Stepped Approach to Individualize Treatment

Treatment options include pharmacotherapy or CBT or both, based

on patient's symptom severity and preference. As the causes for fatigue in these patients are multifactorial [7,40], fatigue management algorithm will include assessment of depressive symptoms, sleep quality, pain, physical inactivity and medication side-effects and these contributing factors will be addressed as needed. In addition, we will ensure that dialysis dose and hemoglobin are in target ranges.

At the first weekly video-conferencing session, the care coordinator will identify which symptom/symptoms the patient would like to address, explain the risk and benefits of treatment options in a way that is tailored to the patient's health literacy level, stress the voluntary nature of their treatment preferences, and choose a treatment plan based on shared decision-making. Subsequently, the care coordinators will conduct weekly 45 to 60-min video-conferencing sessions over 12 weeks and will tailor behavioral therapy sessions and/or recommend pharmacotherapy based on an evidence-based protocol. Principles for measurement-based care will be followed every 2 weeks, i.e. changes to treatment will be based on assessment of response to treatment, severity of symptoms and side effects of treatment [41]. Treatment response and patient preferences will inform care coordinator's decision to modify the treatment for which they will follow an evidence-based protocol to add/intensify psychotherapy and/or pharmacotherapy.

C) Psychotherapy/Cognitive Behavioral Therapy

A short-term focused psychotherapy approach called CBT will be employed to reduce the symptoms of depression, pain and fatigue and will be individualized based on patient's symptom severity, preferences and treatment response. This American Psychiatric Association recommended approach helps patients learn self-help skills to deal with real-life issues [42]. CBT has been shown to be highly efficacious with a moderate effect size in the management of these symptoms [43]. CBT strategies were adapted for HD patients to address challenges and needs in the context of ESRD and HD-dependence and were tested in our pilot study (manuscript under preparation). Specific CBT modifications included: [1] behavioral/psycho-education emphasizing the potential contribution of the diagnosis and treatment of ESRD that contributes to the symptoms burden; [2] identification of negative thought patterns regarding these symptoms and cognitive restructuring; [3] developing pleasant activities and strategies while considering the limitations of individuals with ESRD on HD; [4] identifying and resolving communication difficulties that may exist between the patient and his/her family or medical team that prevents management of symptoms; [5] relaxation and/or guided imagery; and [6] facilitating the understanding of how core beliefs and assumptions, that may be associated with ESRD and/or dialysis, may prevent effective symptom management.

D) Pharmacotherapy

The research team will follow an evidence-based protocol to recommend whether a medication should be initiated, changed or intensified. For pain management we will use the World Health Organization 3-step analgesic ladder modified to adjust medication dosage for HD. Such an approach has also been developed by the Mid-Atlantic Renal and Kidney End-of-Life Coalitions through support by the Center of Medicare and Medicaid Services [44]. This approach has been successfully used in HD patients and has been highly efficacious in controlling pain in over 95% of participants [29]. Pain medication algorithms will be based on whether the patient has neuropathic pain, nociceptive pain or both. Pharmacological treatment of depression will be based on efficacy and safety evidence in HD patients and dose adjustment for HD will be recommended as appropriate [33,45,46]. The research team including nephrologists and internist with symptom management expertise, along with clinical psychologist will make medication recommendations. These providers have training and experience with pharmacotherapy for symptom management. The

recommendations will be conveyed to the patients' primary care provider (PCP) and/or nephrologist by the care coordinator, who will also monitor anti-depressant and analgesic medication adherence and side effects during weekly sessions. Once the patient's PCP and/or nephrologist approve of the medication change, the care coordinator will facilitate implementation of the treatment by communicating and coordinating with the dialysis team and pharmacy if needed, so as to minimize burden on dialysis staff. The research team will not prescribe or provide any medications. To ensure that patient's PCP and/or nephrologist prescribe the recommended by the study medications, we will conduct regular educational and outreach meetings, and will communicate regularly with the physicians throughout the study period.

E) Collaborative Care

An important aspect of TĀCcare is the integration of care provided as part of research with the patient's routine clinical care. The care coordinators will serve as a liaison between the patient and other health care professionals within the patients' medical team. This is important for providing a multi-disciplinary approach to the patient's physical and mental health, for aligning symptom management with the patient's overall plan of care, and for ensuring patient acceptance and adherence to the study team's recommendations. To facilitate such collaboration, the care coordinator will communicate (via email or phone or personal meeting) with the dialysis team at least monthly and whenever medication changes are recommended; participate in monthly dialysis care plan meetings whenever possible, and will discuss any pertinent issues with the dialysis care team (nephrologist, nurses or social worker) at least monthly. We will record the type and frequency of communication with the care team.

The care coordinator will also participate in clinical dialysis care plan meetings and will provide recommendations as appropriate. The care coordinators are Master's level behavioral therapists who received specific training in cultural competence on HD-specific issues and will work closely under the supervision of a local study psychologist.

3.1. Technology assisted health education attention control

Patients randomized to this study group will be provided with iPads during HD (same as the intervention group) and will have weekly sessions to match the frequency of contact in the intervention group. To match the attention and expectations of patients in this group, a care coordinator will use video-conferencing to deliver health education. Although weekly sessions with care coordinator would have been ideal, this is not financially feasible. Thus, these sessions will alternate with sessions in which access to educational videos and online educational material from the National Kidney Foundation (NKF; www.nkf.org) will be provided. Topics relevant to ESRD such as transplantation, heart health, immunizations and age appropriate cancer screening, etc. will be covered.

3.2. Rationale for attention control in study design

It is essential to compare TĀCcare to a control group that receives a treatment that approximates the amount of time and attention received by the treatment group but is unlikely to have a specific effect on the study outcomes. This approach examines the rival hypothesis that improvements in the dependent variable occur because of participant expectancy and the attention received during the course of the treatment rather than from the treatment itself (the so-called Hawthorne effect) [47]. The attention control intervention must be feasible and relevant to the needs and health of the participants and should also be designed to engage participants and to avoid dropouts or selection biases based on the requirements of the experimental intervention [48]. These concerns have factored into our selection of a health education attention control for this study since it is a key issue in patients undergoing maintenance HD, yet it is unlikely to influence our primary outcomes. Comparison to an attention control group will reduce the variability of factors and biases that might influence the outcomes, enhance the interpretability of the study results and enable evaluation of the true effects of our intervention.

3.3. Intervention fidelity and monitoring

To maintain internal validity and enhance intervention fidelity (e.g., consistency across care coordinators and adherence to treatment protocol), care coordinators will follow a study manual specific for the study arm and will receive standardized training in dialysis-specific CBT or health education. Fidelity will be assessed by reviewing 10% of randomly selected audiotaped video-conferencing sessions, and fidelity checklist, and feedback will be provided to the study staff.

3.4. Duration of intervention and follow-up

Each participant will be treated in the assigned group for 12 weeks, death, or loss to follow-up (withdrawal from study, transfer of dialysis clinic, change to peritoneal dialysis or transplantation). The length of intervention was selected based upon national guidelines recommending 8–12 weeks of weekly CBT or initial pharmacological treatment of depression [49,50] as well as our prior results showing successful efficacy of a similar 12-week intervention in cancer patients [51]. If there is any acute change in patient's medical condition/hospitalization during the intervention period, patients will be re-evaluated for their ability and interest to continue participation once medically stable. If needed, the intervention period will be prolonged to complete a total of 12 sessions so that patients have an opportunity to receive adequate treatment and derive cumulative benefit. Outcomes will be assessed again at 6 months to evaluate the intermediate effect of intervention, as it is possible that some patients may not receive intensified interventions (including pharmacotherapy) until late in the window for intervention and will likely not have an immediate effect on the outcomes. A number of studies and meta-analyses evaluating long term effect of 8–12 weeks of CBT or collaborative care on depression, fatigue, or pain show sustained benefit at 12 months [52–56]. Whether such sustained effects are seen in this patient population, remains to be evaluated. Thus, we are evaluating the effects of TACcare at 6 months and 12 months to assess the long-term effect of our intervention.

4. Data collection and measures

4.1. Patient-reported outcomes

Instruments with sound psychometric properties in HD patients have been selected to assess a variety of health domains including the outcomes of interest and potential mediators of outcomes such as sleep quality, anxiety and social support (Table 1). These instruments will be administered centrally by blinded interviewers using computer-assisted telephone interviewing (CATI) which provides high rates of data collection, limits selection bias and minimizes study burden [57]. Self-administered questionnaires may be more difficult to complete for the elderly, minority groups, those with high comorbidity and may exclude patients with low literacy, visual problems and diminished dexterity, creating selection bias [58]. The University Center for Social & Urban Research (UCSUR) at the University of Pittsburgh will administer CATI through trained interviewers. This approach was used in the Frequent Hemodialysis Network (FHN) Trial and showed high rate of data capture in HD patients [57]. The anticipated time for the assessment is 20–30 min. To minimize potential confounding from the effects of the HD procedure, the assessments will be performed on a non-dialysis day at the participant's home. Assessments will be done at baseline, after 12 weeks of intervention (primary outcome) and at 6 and 12-month

Table 1
Patient-Reported Outcome (PRO) instruments (Appendix).

Questionnaire	Items	Domains	Psychometric properties
Beck Depression Inventory-II (BDI-II)	21	Depression	Excellent internal consistency, test-retest validity and high sensitivity, specificity and responsiveness to treatment in HD population [46,101]
Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F)	13	Fatigue	Excellent internal consistency, test-retest reliability, responsiveness to interventions and good correlation with SF-36 measured fatigue in HD patients [102,103]
Brief Pain Inventory (BPI) Short form	9	Pain	Extensively used in HD, Excellent construct validity, reliability and responsiveness to treatment [104]
Pittsburgh Sleep Quality Index (PSQI)	19	Sleep quality	Good internal homogeneity, test-retest reliability, discriminant validity, is responsiveness to treatments and has been used in the ESRD population [105,106]
Medical Outcomes Study Short Form-12 (SF-12)	12	Health-related quality of life	The SF-12 scores have excellent intra-class correlation of 0.94 with the SF-36 [107]. SF-36 is commonly used in HD patients, and has been extensively tested for reliability and validity in HD patients, well-accepted, responsive to clinical change [57,108]
Multi-dimensional Scale of Perceived Social Support	12	Perceived social support	Has 3 subscales—family, friends, and significant others, has good internal and test-retest reliability and has been used in ESRD patients [109,110]
Generalized Anxiety Disorder-7 (GAD-7) scale	7	Anxiety	Excellent internal consistency, reliability and validity in the general population [111]
NIH Patient Reported Outcomes Measurement Information System (PROMIS) Adult Global Health questionnaire.	29	Physical function, fatigue, pain, emotional distress, sleep	These domains have excellent internal consistency, convergent validity and significant differences between health and disease [113]
Physical Activity Scale for Elderly (PASE)	10	Physical activity	Measures physical activity over last 7 days and has been shown to correlate with accelerometry data in HD patients [114]

follow-up.

4.2. Measuring symptom severity and variability in real-time using ecological momentary assessment (EMA)

EMA is a tool to evaluate patient symptoms prospectively and repeatedly in real-time, in the patient's natural environment, and while minimizing respondent burden [59]. Whereas conventional, recall-based questionnaires may fail to capture daily and diurnal variation in symptoms seen in HD patients, resulting in misclassification bias, EMA is well suited to ensure high-fidelity ascertainment of symptoms [60]. Because EMA is well suited to identify those who develop symptoms in a particular context, it could prove useful for recognizing patients who develop post-dialysis fatigue, a debilitating, prevalent, but understudied symptom [61,62]. EMA data collection will be operationalized centrally by UCSUR at the University of Pittsburgh. Subjective fatigue/sleepiness, mood, and cognitive alertness will be assessed using a 19-item questionnaire Daytime Insomnia Symptom Scale (DISS) [63], administered via an interactive voice response system using the patient's cellphone (or a study cellphone if the patient does not have one). Responses on a 7-point Likert scale for each question, with higher scores representing greater endorsement of a particular symptom, will be collected and scored to derive a composite symptom severity score of fatigue, sleepiness and mood. Participants will complete the DISS 4 times daily for 7 consecutive days with each assessment generally requiring 2 to 6 min. High patient adherence of over 80% was seen using a similar protocol in our previous study with 55 HD patients completing 1252 of 1540 possible assessments, which did not differ by dialysis day [60]. To minimize patient burden, EMA will be conducted only at baseline and at 12 weeks post intervention.

4.3. Measuring treatment adherence

Treatment adherence will be assessed at baseline, 12-week post intervention and at 6- and 12-month follow-up. *Medication and dietary adherence* will be assessed by using four independent sources: a) self-reported adherence using the 8-item Morisky Medication Adherence Scale (MMAS-8) which also includes items on medication taking behaviors, thus enabling identification of barriers to adherence. This scale is easy to administer, has excellent validity and reliability in patients with chronic conditions, even among those with low literacy [64]. Such self-reported measures have been shown to have moderate to high

concordance with objective measures [65]. This scale will be administered centrally by blinded interviewers using computer-assisted telephone interviewing by UCSUR; b) Medication and/or dietary adherence will also be defined by absolute serum phosphorus level < 6.0 mg/dL or > 1 mg/dL decline in serum phosphorus from preceding month if absolute serum phosphorus level is > 6.0 mg/dL, measured as a part of routine clinical care [66,67]; c) Fluid restriction adherence will be determined by inter-dialytic weight gain percentage (of post dialysis weight over preceding one month). Those with inter-dialytic weight gain over 3.5% will be classified as non-adherent [68]; d) Medication adherence will also be assessed by verifying pharmacy refill rates for antidepressant, analgesic and antihypertensive medications. *Dialysis adherence* data will be obtained by review of dialysis treatment records. Non-adherence with dialysis will be defined by the percentage of all dialysis sessions skipped and/or requested by the patient to be shortened by ≥ 10 min over the 12-week intervention period. Dialysis sessions missed due to hospitalization will not be included as a skipped treatment.

4.4. Measuring selected pro/anti-inflammatory cytokines

Selected cytokines *(high sensitivity C - reactive protein; hs-CRP, Interleukin; IL-6, IL-10 and Tumor Necrosis Factor; TNF-α)* were chosen based on their reported associations with the outcomes of interest [9,16,18,69]. All blood samples will be shipped at regular intervals and cytokine measurements will be performed centrally at the University of Pittsburgh. We will collect 10 mL of blood drawn pre-dialysis at baseline, post 12-week intervention and at 6-month follow-up. Serum will be aliquoted within 4 h of the blood draw, shipped on dry ice and stored at −80 °C for batch analysis. Cytokine levels will be measuring using Luminex™ bead-set (Millipore Corporation, Billerica MA and Luminex™ 100 IS apparatus, Austin TX) in accordance with the manufacturer's instructions using standardized validated assays and operating procedures.

4.5. Descriptors and potential covariates

Baseline patient data collection will include socio-demographic data such as age, gender, race, ethnicity, education, marital and employment status, household income, etc. The patient's clinical characteristic such as years on dialysis, comorbid conditions, concomitant medications, etc. along with data on hospitalizations, mortality and transplantation

will be obtained from patient interviews and medical chart abstraction. Routine monthly laboratory assessment done by the dialysis clinics will be extracted.

5. Adverse events and serious adverse events

Adverse events (AEs) and serious adverse events (SAEs) will be collected every 2 weeks and whenever the study team learns of an event between the biweekly assessments during the intervention period. These will also be collected at 6- and 12-month follow-up, during which patients will be asked to report all SAE/AEs since the last assessment. The pre-specified serious adverse events include – death, hospitalization/ER visit, bleeding requiring transfusion or hospitalization (due to possible selective serotonin reuptake inhibitor mediated reduction in platelet aggregation), medication overdose requiring ER visit/hospitalization (as determined by review of medical records) and acute suicidal intent. Relatedness of AE/SAEs with study interventions, especially with medications prescribed for symptom management, will be reviewed by external Adverse Events committee and reported.

6. Side effects and tolerability data

The side effects and tolerability data will be collected every 2 weeks in both study arms. The side effects will be collected using the modified Patient Related Inventory of Side Effects (PRISE) questionnaire [70]. This 20-item questionnaire asks about occurrence and tolerability of 20 common side effects. We will also add an open-ended question to record any other symptoms that patients might have. Although this questionnaire was developed and used to assess side effects of antidepressant medications, we will use the same questionnaire for assessing side effects and tolerability of pain medications because of significant overlap in the commonly reported side effects of these medications.

7. Outcomes

The primary outcome of the trial is clinically meaningful change (effect size 0.6) in depression, pain or fatigue as ascertained blindly by the *Beck Depression Inventory-II (BDI-II), Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F)* and *Brief Pain Inventory (BPI) Short form* questionnaires respectively, after a 12-week intervention as compared to control arm. We used effect size (ES) i.e. standardized mean difference instead of raw mean difference as our outcome as this places the emphasis on the most important aspect of an intervention - the size of the effect - rather than its statistical significance. Moreover, in our study the 3 symptoms will be measured using different instruments with varying scales, and ES facilitates standardizing the observed changes in these symptoms. By quantifying the magnitude of the difference between the two study groups, ES gives a more complete and clinically relevant picture of health status change. Cohen's d effect size of 0.6 is considered moderate size and is likely to translate into clinically meaningful improvements in the symptoms [71]. Secondary patient-reported outcomes include change in HRQOL and EMA-measured composite score of fatigue, sleepiness and mood after 12-week intervention. Additional secondary outcomes include adherence to medications, diet and HD treatments; as well as changes in levels of biomarkers of inflammation.

7.1. Statistical analysis

Distributions of baseline characteristics will be compared between the groups to assess effectiveness of randomization, and statistical differences will be accounted for as covariate in secondary adjusted analyses. All primary analyses will be adjusted for the variables used in stratified randomization (site, age, and comorbidity) and unadjusted analyses will also be reported per CONSORT recommendations [72,73].

The stratification variables are potentially prognostic of the outcomes, which likely will make the adjusted analyses more efficient than unadjusted [74,75]. The primary analyses will use the 'intent-to-treat' approach in which subjects are analyzed in their assigned group, regardless of treatment adherence, withdrawal or deviation from protocol. We will also perform per-protocol analysis of patients with > 75% and > 50% average adherence based on medication and/or CBT adherence to examine the impact of adherence and protocol deviations. General linear mixed models (GLMMs) will be used for inferential analyses of primary and secondary outcomes. Unless otherwise specified, all tests will be conducted using two-sided 5% level of significance. We will report our findings according to the CONSORT guidelines [76].

7.2. Primary outcomes

The three primary patient-reported outcome measures are changes in depression, pain or fatigue as ascertained blindly by the BDI-II, FACIT-F and BPI questionnaires respectively, after a 12-week intervention. Changes in all symptom levels will be assessed and analyzed for each patient. For example, if a patient enters the study because of significant depressive symptoms, we will also assess changes in their levels of fatigue and pain, in addition to changes in depressive symptoms. The rationale for this is that many of these symptoms co-exist, and treatment of one symptom may affect other symptom levels. Also, it may be that patients may not self-perceive some symptoms. For example, if during the course of the intervention, it becomes apparent that patient's fatigue is more likely a manifestation of underlying depressive symptoms, then they will be offered CBT/medications for depression, in addition to CBT for fatigue. We will use Benjamini-Hochberg correction to maintain a false-discovery-rate of 5% when testing each of the three primary symptom outcomes [77]. Analyses will use GLMM for each outcome with fixed treatment group (TĀCcare or health education), time (baseline, 3, 6, and 12 months), and group by time interaction, adjusting for variables used in the stratified randomization. The inclusion of the random patient intercepts will account for the within-patient correlation due to repeated measures. The group by time interaction captures the treatment effect. This model will be used to test our primary hypothesis of treatment effect after 12 weeks of intervention (immediate effect). In a secondary analysis, we will also test intermediate (6 months) and sustained (12 months) improvements in outcomes. Although we expect patient characteristics to be balanced between groups due to randomization, we will add baseline factors found to be different between groups in secondary adjusted analyses.

7.3. Secondary outcomes

Our secondary patient-reported outcomes are changes in HRQOL (SF-12 mental and physical component score) in TĀCcare versus control arm after a 12-week intervention. EMA-measured composite symptom severity score will be evaluated at baseline and post-intervention (12 weeks). Adherence outcomes include adherence to medications, diet and dialysis treatments (all continuous variables) measured at 12-weeks, and at 6- and 12-months follow-up. Biomarkers of inflammation include hs-CRP, IL-6, IL-10, and TNF-α measured at baseline, 12-week, and 6-months follow-up. GLMM will also be used to analyze these outcomes. Benjamini-Hochberg correction will be applied to the biomarker analyses. We will also assess the bi-directional association and calculate correlations between the biomarkers and symptoms. Moreover, we will examine how adjusting for the biomarkers influences the TĀCcare effect on the symptoms, and how adjusting for the symptoms influences the effect on the biomarkers.

7.4. Subgroups

The response to treatment interventions may differ among certain patient subgroups. Thus, to explore heterogeneity of intervention

effects, we will examine pre-specified subgroups including age – age ≤65, age > 65; sex – male, female; race – white, black, others; Charlson comorbidity index – < 4, 4 or more; and dialysis vintage ≤1 year, vintage > 1 year.

7.5. Missing data

The extent, reasons, randomness of missing data will be examined to identify possible covert missing data mechanisms. Baseline characteristics and intermediate outcomes among those who do or do not complete the study will be compared. The primary analytical approaches (GLMMs) can manage data that are missing (i.e., either missing completely at random or missing at random).

7.6. Sample size and power

We powered our study to detect a clinically meaningful difference in our primary outcomes – depression, pain, or fatigue – after 12 weeks of intervention while considering feasibility of subject recruitment. Since there is no validated composite endpoint consisting of the 3 outcomes, we will test the effect of TĀCcare on each of the outcomes. In order to address the issue of multiple testing of our primary outcome, we calculated power controlling for False Discovery Rate (FDR) of 5% using the Benjamini-Hochberg correction [77]. To be more conservative, [1] we used a two-sided two-sample *t*-test in the calculations and [2] assumed that the intervention has a true effect on exactly one endpoint.

Our primary analysis will compare groups after 12 weeks intervention using contrast from a mixed model that includes all time points (baseline, 12 weeks, 6 months, and 12 months). By using all available longitudinal data, our primary analytical approach would be more efficient than t-test and would provide greater power to detect differences. We will also have increased power if the intervention has real effect on more than one endpoint. The projected total sample size is 150, or 75 per randomization group. After accounting for the estimated 10% lost-to-follow-up, the effective total sample size is 136. Our sample size provides 88% power to detect an effect size of 0.6 controlling for 5% FDR for 3 endpoints assuming a true difference exists in 1 out of 3 endpoints. If differences exist on 2 of 3 endpoints, we will have 89% power to detect an effect size of 0.5. The detectable effect size is consistent with what we observed in our study of SCCI in cancer patients (effect size was 0.7 for depression, 0.6 for pain and 0.3 for fatigue, respectively) [51]. From prior studies, the range of estimated standard deviation for BDI score (depression) was 7.5–9.8, for FACIT-F (fatigue) was 10.9–15.0, for BPI (pain) was 1.2–2.6 (for BPI, 1-point change is considered clinically important) [51,78,79]. The effect size of 0.6 is equivalent to a mean difference of 4.5–5.9 in BDI score, 6.5–9.0 for FACIT-F, and 0.7–1.6 for BPI. These effect magnitudes are well within the range of differences observed in symptom treatment trials and are considered to be clinically meaningful [51,78,79].

Our sample size is also sufficient to detect effect sizes observed in the literature for our secondary outcomes (HRQOL; composite score of fatigue, sleepiness, and mood measured by EMA) [51,60]. For the biomarker analyses, we have 81% power to detect an effect size of 0.5 if a difference exists in 2 of 4 biomarkers to be tested.

8. Protection of human subjects

The study protocol has been approved by the Institutional Review Board (IRB) at the Universities of Pittsburgh and New Mexico. Although this trial involves minimal risk, we will implement a data and safety monitoring plan at multiple levels to ensure the safety of participants and the validity and integrity of the data. An independent Data Safety and Monitoring Board will oversee the conduct of the study. Safety and tolerability will be monitored in the study as outlined before. If a patient reports suicidal or homicidal ideation or abuse to another individual, the study psychologist will evaluate and facilitate appropriate

treatment, referral and notification of authorities as needed. For chronic pain management, opioid management strategies have been adapted from the Center for Medicaid and Medicare's Opioid Misuse Strategy 2016 guidelines. If recommendation for opioid use is made, patients will be informed of the risks, benefits and limitations of therapy. Opioid use will be monitored rigorously using the Pennsylvania and New Mexico Prescription Drug Monitoring Program System and the patient's physicians will be informed. Use of opioid contract will be recommended and the lowest possible dose will be used. Dose adjustments will be recommended cautiously. Screening and identification of patients who may be at high risk for aberrant behaviors will occur at the initiation or dose escalation of opioid therapy using the validated Opioid Risk Tool [80]. In patients identified as high risk for opioid misuse, referral to a pain management specialist will be recommended. For all patients on opioids, the study team will administer the Current Opioid Misuse Measure (COMM) every month to monitor opioid use/misuse. For patients with score ≥9 (positive score) on COMM, indicating current opioid misuse, referral to a specialized pain management service such as pain clinic will be considered. Opioid use and dosage in both arms will be reported at the end of the study.

9. Discussion

There is an urgent need to test newer approaches for symptom management in HD patients, given the high symptom burden, its negative health consequences and lack of optimal treatment options. Since depression, pain and fatigue often co-exist as "symptom clusters" and may exacerbate each other, an intervention targeting multiple symptoms simultaneously is warranted. TĀCcare is the first intervention of any kind to target three of the most debilitating ESRD-related symptoms, rather than individual symptoms of fatigue, pain and depression. This randomized controlled trial will build on a stepped-approach for pharmacotherapy and/or behavioral-therapy and will allow for individualization of treatment according to patient's clinical status, preferences and treatment response. Additionally, using a collaborative multi-disciplinary approach, the patients' symptom management will be integrated with overall model of dialysis care, thus increasing patient acceptability and adherence. TĀCcare addresses the KDIGO call in 2015 for integration of symptom assessment and management in routine ESRD care [21].

The high symptom burden in this population is associated not only with poor HRQOL but also with increased mortality. In fact, depression has been associated with a 45% increased risk of death, based on a meta-analysis of over 67,000 ESRD patients [81]. Similarly pain frequency and intensity have been significantly associated with increased mortality [32]. In addition, a 10-point increase in fatigue score on the SF-36 vitality subscale is associated with a 10% increase in mortality (p < 0.001) in this population [9,10]. Unfortunately, health care providers are largely unaware, untrained and often under-recognize patient symptoms. We have demonstrated that the sensitivity of renal providers' recognition of HD patients' depression and pain was < 20% and was 50% for fatigue [82]. Given the focus on biochemical and dialysis-related targets in the current model of dialysis care, it is not surprising that providers and patients have divergent clinical and research priorities [82,83]. As a result, many patient symptoms go untreated despite available treatment options. For example, in a study of ESRD patients starting dialysis, only 16% of the depressed patients were receiving any depression treatment [37]. Similarly, 75% of the 200 HD patients with reported pain were found to have ineffective pain management [36].

TĀCcare intervention design takes into account several important considerations for symptom management in HD. Firstly, it offers a choice of pharmacotherapy and behavioral therapy in a stepped-care approach, thus providing a real-world intervention allowing for incorporation of patient preferences. A stepped care intervention may be defined as "the least costly, least intensive, and least restrictive

treatment judged sufficient to meet the person's needs and goals and should be attempted initially before more costly and restrictive treatments are attempted" [84,85]. Many of the HD patients are reluctant to accept pharmacotherapy alone for symptoms, and it may even impair their HRQOL due to additional pill burden or side-effects from medication interactions [86,87]. In the *Symptom Management Involving End-Stage Renal Disease (SMILE) trial*, < 30% of the depressed patients accepted anti-depressant medication recommendations [87,88]. In these patients, uptake of CBT may be greater than that of medications – in a 3-month trial of chairside CBT for depression in HD patients, recruitment rate was over 95%, and patients' volitional drop-out rate was less than1% despite a high prevalence of personality disorders in the sample [25]. This high adherence to behavioral therapy is in stark contrast to the rates of medication non-adherence in these patients, which are estimated to be over 90% in some studies [14]. Thus, by offering patients a choice of treatment options, and involving them in shared decision-making, TĀCcare provides an individualized real-world approach, which is likely to have high patient acceptance and adherence. Moreover, by incorporating patient voice, it gives patients more control over their treatment, and is likely to have higher patient engagement.

Secondly, by using technology to deliver CBT via video-conferencing, TĀCcare overcomes patient related barriers of face-to-face CBT such as additional doctors' appointments, transportation, costs, etc. Furthermore, technology-delivered CBT allows for more efficient use of therapist time as compared to chair side CBT in dialysis units by saving travel time for the therapist. Moreover, since self-guided computerized CBT programs are unlikely to be successful in these patients due to the high prevalence of poor health literacy, visual impairment, and limited use/accessibility of technology-based health resources, especially in the minority groups; TĀCcare provides a novel way to leverage technology and deliver CBT in these patients [89]. There is growing evidence from randomized controlled trials that behavioral interventions delivered via interactive video-conferencing are as efficacious as face-to-face interventions [90,91]. By utilizing minimal additional clinical resources, this intervention can be scaled quickly, even to areas where trained therapists may not be readily available. Additionally, by testing the intervention in a diverse ethnic and racial cohort, our findings will be readily generalizable across cultural/racial backgrounds and can be readily adopted and widely disseminated in routine dialysis care.

This study will also reveal novel insights on the effect of decreased symptom burden on levels of inflammatory cytokines, which may have huge implications for preventing cardiovascular morbidity and mortality in HD patients [92,93]. There is also growing evidence on the strong association of depressive symptoms, fatigue and chronic pain with several inflammatory cytokines (IL-6, IL-10, TNF-α, and hs-CRP) in HD patients and in the general population [9,16,18,69]. In cancer patients, a theoretical framework of immune dysregulation causing patient symptoms has been proposed through activation of the Hypothalamic-Pituitary Adrenal (HPA) axis [94]. It is quite plausible that a similar bidirectional relationship exists between immune system dysfunction and symptom burden in HD patients as well. In HD patients, an association of inflammation and mortality is well-established – a recent meta-analysis of over 100 studies concluded that high levels of inflammatory cytokines (CRP and IL-6) are independent predictors of increased all-cause and cardiovascular mortality [93,95]. Thus, systemic inflammation may be a mechanistic link between these patient symptoms and adverse outcomes including mortality in HD patients (Fig. 1). Treatment of these symptoms in other chronic disease states has been shown to decrease inflammatory burden, but evidence for such improvements in bio-behavioral mediators in ESRD patients is limited [25,69,96–99].

Despite these strengths, there are some limitations of the study to be considered. Firstly, the intervention cannot be blinded. Thus, we have employed several features to minimize bias including – a) randomized controlled study design which generates the highest level of evidence for comparative effectiveness of treatments; and b) use of centralized

computer-assisted telephone interviewing for outcome measures which maximizes patient participation, and ensures the assessors are blinded, both of which minimize bias in an open-label clinical trial. Secondly, there is a possibility that there may be increased symptom recognition and management in the control arm by the renal providers. However, this is unlikely given reluctance of patients and providers regarding pharmacotherapy alone, and patient burden associated with in-office CBT. However, we will monitor use of CBT and medications for symptom management in the controls. Lastly, renal providers may be reluctant to prescribe pharmacotherapy for symptom management. However, the study will conduct renal provider education, offer multidisciplinary approaches for symptom management, and provide a framework for collaborative care to facilitate integration of symptom management in the dialysis treatment plan [100].

10. Conclusion

TĀCcare is the first, large multi-center randomized controlled trial to test the efficacy of a stepped-collaborative care intervention targeting symptom clusters of depression, pain, and fatigue in HD patients. It leverages novel technology-based tools and resources to potentially alleviate these common symptoms and to improve HRQOL in a scalable, resource-efficient manner, while advancing mechanistic insights into the underlying inflammatory process.

Conflicts of interest

None.

Disclosures

None.

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