COVER PAGE

1/18/2023

Title: “Interventions Made to Preserve Cognitive Function”

NCT03616535

Date: January 18, 2023

Principal Investigator: Aarti Mathur
Application Number: IRB00152858

JHM IRB - eForm A – Protocol

****

Abstract

End-Stage Renal Disease (ESRD) is a growing public health challenge in the United States. More than 640,000 adults in the US suffer from this devastating chronic condition (1). With a growing prevalence of obesity, hypertension, and diabetes, it is estimated that there will be >1 million ESRD patients by 2025.

Hemodialysis (HD) is the most common form of renal replacement therapy and represents a great burden for ESRD patients. More than 95% of newly diagnosed patients initiate HD, and HD is often their only long-term treatment option (1). The only alternative is kidney transplantation (KT), but with a waiting list of nearly 100,000 patients, a substantial amount of time is spent on HD waiting for KT (1). HD is performed at least 3 times a week for 4-6 hours per session and continues for the patient's lifetime or until successful KT. Using national claims data on 356,668 HD patients, we found that dementia incidence among HD initiates are 10-times that of community-dwelling older adults (2). Even younger HD patients are at elevated risk of dementia, which is unheard of in non-HD patients.

Executive function refers to the ability to flexibly select and inhibit information, understand abstract meaning, innovate ideas, and maintain an active goal. It is essential for complex daily tasks including decision-making, problem solving, and planning. Declines in executive function have important clinical implications including decreased quality of life, personal safety issues, and loss of functional independence. Executive function impairment is an early sign of dementia and Alzheimer's disease (3, 4). Many patients already have partially compromised cognition at HD initiation (6-8), which accelerates while undergoing HD (9, 10). Only 13% of prevalent HD patients have normal cognition (11) and clinicians often fail to recognize declining cognition among patients who are undergoing HD (12). Executive function is the domain of cognition which is most impacted by HD initiation (13). HD patients suffer from a 3-fold higher rate of executive function impairment than general population (14) and 38% of prevalent HD patients have severe impairments in executive function (15). Executive function impairment is not limited to older HD patients; it crosses the age spectrum (15). Severe executive function impairment impedes HD patients' ability to comply with their dialysis schedule, maintain complicated medication regimens for chronic conditions, retain the capacity for independence and self-care (18-20), make informed decisions, and adhere to fluid and dietary restrictions (12), leading to death (14, 21).

Kidney disease and dialysis significantly impact cognitive function; while the only effective interventions for preserving cognitive function among community-dwelling older adults are cognitive training (CT), and/or exercise training (ET), these modalities have not been tested for cognition preservation in hemodialysis patients. We will perform a randomized controlled trial of 200 hemodialysis initiates to test whether CT, ET and combined CT+ET while undergoing hemodialysis preserves executive function compared to standard of care (SC).Participants will undergo assessments for executive function, global cognitive function, physical function, frailty status, quality of life and patient centered outcomes at study entry, 3 months, and 6 months of interventions. Participants randomized to CT will play tablet-based brain-games (Lumosity) and those

randomized to ET will be given a stationary foot peddler. Participants randomized to CT+ET will start with CT (tablet based brain games) followed by ET after a 15 minute break. We will administer the interventions for six months. The primary outcome is change in executive function measured by the Trailmaking Test A and B (TMTA/B) scores between enrollment and 3 months of intervention. Global cognitive function will be a secondary cognitive outcome and will be assessed using the Montreal Cognitive Assessment (MoCA). Changes in secondary cognitive outcomes between baseline and 3 months will be studied. We will also consider the 6-month change in all global cognitive function and executive function as a secondary outcome. The findings from this RCT will provide nephrologists who care for this vulnerable population with the first feasible and effective interventions for their patients who are at risk for experiencing executive function decline.

Objectives

Primary Objective: The primary objective is to determine if receiving CT, ET, or CT+ET preserves executive function relative to those with SC.

Secondary Objectives: The secondary objectives are to compare the rates of secondary cognitive outcomes, ESRD-specific clinical outcomes and patient-centered outcomes among those receiving CT, ET, or CT+ET relative to those in SC.

Background and Significance

Cognitive decline is a growing concern not only in the general population but also among patients undergoing dialysis. The consequences of this cognitive decline are profound and impact morbidity and mortality. Through this study, we hope to identify interventions to preserve cognitive function and develop implementation tools to help disseminate these interventions to dialysis centers nationally.

In a survey we conducted of 101 HD patients, the activities most reported during HD were watching TV (87%), talking (76%), and sleeping (67%). Ninety-five percent participated in passive activities, and <1% reported exercising while on dialysis. The time spent on HD may be a missed opportunity to improve the health of ESRD patients.

In a longitudinal study of 324 HD patients, executive function impairment occurs in 11% of new HD patients during the first year on HD (16). Even though HD patients experience executive function decline due to aging and CVD, HD itself impacts the decline. HD independently leads to poor executive function through the retention of uremic toxins (17) and by inducing recurrent cerebral ischemia (14). Mortality rates for HD patients with poor executive function are comparable to those with diagnosed dementia (22), a highly vulnerable group of HD patients (23).

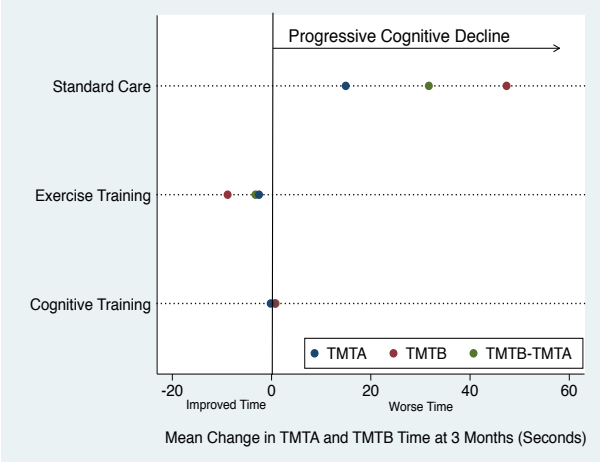
Studies of executive function decline come primarily from gerontology. In older adults, non-pharmacologic interventions like cognitive training (CT) can prevent executive function decline. CT (24, 25) is a promising non-pharmacological intervention to slow executive function decline in otherwise healthy older adults. CT prevents age-related declines in key areas of executive function including abstraction, working memory, verbal reasoning, and inhibition (18, 19, 26-30) by improving the neural structures that mediate executive function (31-33). Multi-domain approaches to CT, rather than memory training alone, have been associated with broad and lasting gains in healthy older adults (30, 34, 35) and benefits of CT are observable up to 10 years post-training (28). CT is an important non-pharmacological intervention that has not been tested in HD patients.

Exercise training (ET), another effective non-pharmacological intervention (25, 36-38), has the greatest impact on executive function in older adults (39-44). Even prior to improving physical function and strength (45), ET in older adults improves executive function (44) through increased: 1) cerebral blood flow (46); 2) brain volume in the prefrontal cortex and hippocampus (47-49); 3) brain-derived neurotrophic factor (50-54); and 4) engagement of neural structures. ET reduces inflammatory markers (C-reactive protein, tumor

necrosis factor alpha, and IL-6) improving brain plasticity and executive function (51, 55). Even a single ET session changes neurophysiology and executive function (56-58). ET has a stronger impact on cognitive function and cortical thickness than it does on aerobic fitness (38).

CT and ET are the only two effective non-pharmacological interventions to impact executive function in older adults. CT+ET over 3 months improved executive function (29, 45, 50, 59) and is more effective than either CT or ET alone (31, 50). CT+ET enhances synaptic connections between brain cells and improves brain plasticity (60, 61). To our knowledge, no studies have tested whether CT+ET impacts executive function among HD patients.

Although all intervention studies designed to preserve executive function have been conducted in older adults, this population has a very different physiology and distinct risk factors for executive function decline. Therefore, these interventions must be tested in HD patients to draw appropriate inferences about their safety and effectiveness.



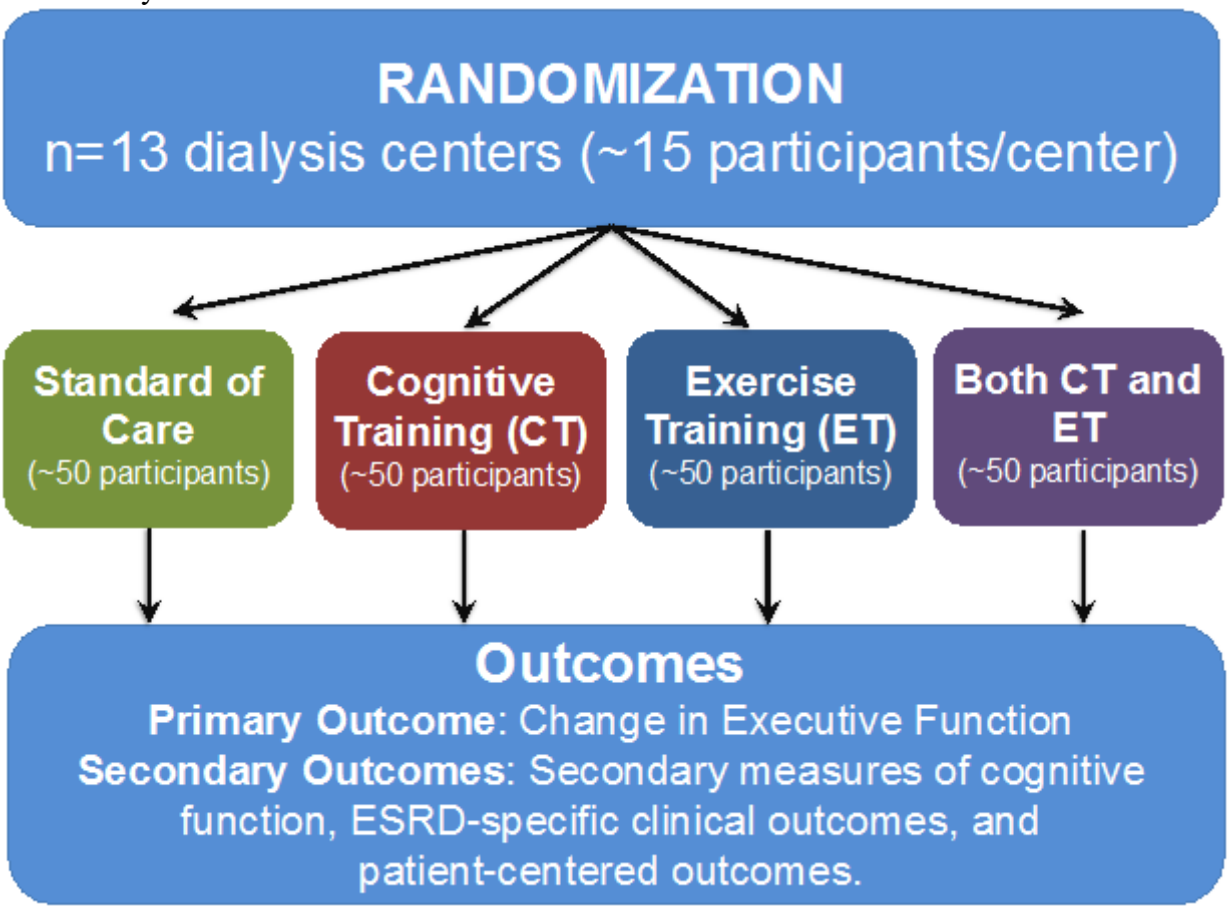
Our pilot RCT of 20 HD patients suggests that intradialytic CT and ET prevent the profound decline in executive function. After 3 months, participants in the intradialytic CT (Lumosity® on a tablet) and ET (foot peddlers) arms had less decline in executive function than those with standard of care (SC), based on the Trail Making Test (TMTA and TMTB) times (Figure) (McAdams-DeMarco, Under Review J Neph). Strikingly, the improvement in TMTB was nearly a minute greater for those in the CT (difference= 47 seconds; P=0.03) and ET arms (difference= 56 seconds; P=0.03), compared with those in the standard of care arm.

Our pilot study of physicians (n=41, 87% response rate) found that 57% believed their ESRD patients could improve cognitive function through intradialytic CT, such as playing tablet-based brain games, and 83% agreed that intradialytic ET, such as using a foot peddler, would improve physical function. They believed their patients would be interested in these interventions (CT: 87%; ET: 83%) and the logistics would be feasible in a dialysis clinic (CT: 93%; ET: 80%). Among HD patients (n=91, 97% response rate), 67% wanted to improve their cognition through intradialytic CT, and 71% wanted to improve their strength and cognition through intradialytic ET.

Summary of Significance: There is a high burden of ESRD in the US and most patients undergo time-intensive HD treatment during which interventions could be administered. Replacing passive intradialytic activities with cognitively beneficial activities is a missed opportunity. CT and ET are the only two effective non-pharmacological interventions to preserve executive function, which is supported by our pilot data. The findings from this RCT will provide nephrologists who care for the vulnerable population of HD patients with the first feasible and effective interventions for their patients who are at risk for experiencing executive function decline. Interventions are needed to target the prevention of executive function decline, rather than simply attempting to reverse decline or regain executive function.

Study Procedures

This is a 2 by 2 factorial randomized controlled trial (RCT). We will randomize participants to CT alone, ET alone, both CT+ET, or SC resulting in four arms. Randomization will be achieved through balancing methods over the three stratification factors: study center, sex, and race/ethnicity.



Study Population: Men and women with ESRD and receiving maintenance HD 2-3 times weekly at one of the 13 hemodialysis centers participating in the trial will be eligible. We will only enroll new HD patients, as has been done in other RCTs (89-91) of HD patients. The rationale for enrolling new HD patients are: 1) they will not have already experienced the executive function decline associated with HD; 2) there is a high dementia incidence even within the first year of HD; 3) survival bias is present when studying prevalent HD patients; and 4) we want to intervene before the neurodegenerative process begins.

Inclusion Criteria:
Participants must be:

- Within 3 months to 3 years of initiating HD
- 18 years or older at enrollment
- English-speaking

- Willing to participate in research

Exclusion Criteria:
Patients with the following conditions will not be included in the study:

- Pregnancy
- Angina pectoris
- Chronic lung disease requiring oxygen
- Musculoskeletal conditions that limit mobility
- Upper or lower extremity amputation
- Orthopedic disorders exacerbated by physical activity
- Femoral arteriovenous (AV) access
- Blindness/ Legal blindness
- Hepatitis B infection
- Inability to recognize letters and numbers

In addition to patients with these conditions, patients who are currently incarcerated will be excluded from the study.

All potential female participants of childbearing age will be asked if they are currently pregnant during initial contact by a study team member to introduce the study.

Recruitment/Enrollment: We will recruit approximately 200 adult ESRD patients from Fresenius Kidney Care Hemodialysis Centers and DaVita Dialysis centers located in the greater Baltimore, Maryland area, where we expect 240-250 eligible participants will be receiving HD. The treating provider at the HD center will be required to approve that it is safe for the patient to enroll.

Participating Dialysis Centers:
Fresenius Kidney Care Centers: Fresenius Kidney Care Caroline Street, Fresenius Kidney Care Broadway Street, Fresenius Kidney Care Merritt Boulevard of Dundalk, Fresenius Kidney Care Fleet Street, Fresenius Kidney Care Nashua Court, Fresenius Kidney Care Dundalk, Fresenius Kidney Care Cross Keys, Fresenius Kidney Care White Marsh, Fresenius Kidney Care Anne Arundel, Fresenius Kidney Care Greenspring Drive (Lutherville-Timonium)

DaVita Dialysis Centers: DaVita Downtown Dialysis, DaVita 25th Street Dialysis, DaVita Greenspring Dialysis, and DaVita Good Samaritan Dialysis

Recruitment/Enrollment at Fresenius Kidney Care Centers:
We have obtained a HIPAA waiver to access patient medical records so we may generate a list of potential participants and check for eligibility. The PI/Project Manager/Study Coordinator, or Frenova staff will access the Fresenius Kidney care electronic medical records to identify eligible participants. Additionally, we will provide the clinics with our study brochure for distribution to patients to inform them of the study. If they are interested in hearing more about the study, they may contact us directly. All patients at participating Fresenius dialysis centers who meet eligibility criteria will be contacted either by phone or in person by a research assistant to describe the study. If they are interested in participating in the study and agree to participate, they will provide informed consent and enrolled.

Recruitment/Enrollment at DaVita Dialysis Centers:
The DaVita nephrologist/nurse practitioner will identify potential participants and establish eligibility. All patients who meet the eligibility criteria will be contacted by the DaVita nephrologist/nurse practitioner to

introduce the study and ask if they are interested in learning more. If the patient agrees and would like more information about the study, the nephrologist/nurse practitioner will ask them to sign a DaVita "HIPAA Authorization to Use and Disclose Information for Research Purposes" form so their information may be shared with our study team and we can provide them with more information about the study. DaVita will provide the Program Manager with a list of eligible potential participants with signed DaVita HIPAA authorization forms. Our research team will contact patients on the list either by phone or in-person to discuss the study and if they are interested and agree to participate, they will provide informed consent and enrolled.

Participants will be enrolled at 4 locations in New York City: The Lower Manhattan Dialysis Center 1, The Lower Manhattan Dialysis Center 2, River Renal Services, Inc. and Chinatown Dialysis Center, LLC. The NYU Langone Health study team will analyze and collect data for this study.

Timeline: We will administer the interventions in two waves. In wave 2 (2 years after the start of the study), we will return to the dialysis centers in the first wave and begin enrollment again. This will allow us to identify new HD patients at each center. We will allow 1 month for identification of participants, initial contact by a research assistant, and baseline assessment as described below. Participants will be followed for 1 year after the end of the intervention for mortality and hospitalization.

Randomization:
We will randomize participants after completion of the baseline assessments. Participants will be block randomized (i.e., stratified over time) and stratified by sex, race/ethnicity, and dialysis center. They will be randomly assigned to one of the four study arms using a blind and secure computer based allocation system: a) **6 months of CT alone**, b) **6 months of ET alone**, c) **6 months of CT+ET, d) standard of care**. We will use block sizes of four to ensure desired sizes in each arm. Given the nature of our interventions, it is not possible to blind the participant, treating provider and other HD center staff.

Intradialytic Interventions to Preserve Executive Function:

Cognitive Training: Participants randomized to CT will play "brain games" on a WiFi connected tablet through Lumosity®, a web-based cognitive training program. Lumosity® is available for research purposes and has been used for CT interventions across a variety of research settings (36, 79-81). Lumosity® is available in English, Spanish, French, Portuguese, German, Japanese, and Korean. We chose this intervention because it is well recognized and regarded as a fun activity leading to increased participation and adherence. At each HD session, participants will have 10 different brain games to play and the games will vary for each session. The CT brain games do not teach a specific cognitive domain. We will test whether there is a transfer of training to executive function. This is important to show that we are not just teaching to the test, which can occur when the cognitive exercise is the same as the outcome.

We will configure the tablets to turn off all other features and participants will have access only to the "brain games" feature.

Exercise Training: Participants randomized to the ET arm will be given a stationary foot peddler, which will be placed at a distance from the dialysis chair that is comfortable for the patient. We will adjust the resistance for each participant. The Program manager/Study Coordinator will supervise the first ET sessions and will train research assistants to set up the equipment. To standardize the dose of ET, all ET will start with a 2 minute warm up, then the resistance will be adjusted so that participants are working at perceived exertion of "somewhat strong," using the Borg scale (87) (~50 rpm). Resistance will be increased when the rating falls below "somewhat hard." Blood pressure (SBP/DBP) will be routinely monitored throughout the session and will be kept between 110/50-150/90 mmHg. Heart rate will also be routinely monitored and kept

at <80% of maximum heart rate, which is calculated (220-participant age). This approach is consistent with previous intradialytic ET (75). We will substitute elastic stretch bands if participant becomes unable to use the foot peddlers.

Participants randomized to either CT or ET will engage in the activity for a minimum of 30 minutes during each HD session. After 15 minutes on HD, the research assistant will approach the participant to initiate the intervention. For those in the CT+ET arm, participants will start with 30 minutes of CT, followed by a 15-minute break, and then 30 minutes of ET. Participants will be allowed to continue with their assigned intervention for longer if needed.

A research assistant will be on site throughout the duration of the interventions to set up tablets and foot peddlers, assist participants if needed, monitor safety related to intervention arms, and collect tablets and foot peddlers after participant have completed their assigned intervention for the day. Any safety concerns will be recorded and reported immediately to the Principal Investigator.

Disinfection Protocol:
iPads/Tablets: iPad devices can only be used in the patient treatment area with a protective cover that can be disinfected. IPad devices will be disinfected before leaving the patient's chairside and before being placed back into the storage unit to be recharged. It must be disinfected before being provided to another patient. iPad devices should be cleaned with a soft cloth dampened with an EPA registered tuberculocidal "hospital disinfectant" or a 1:100 dilution of bleach (300-60 mg/L free chlorine). A saturated cloth MUST NOT be used to clean the device; wring out excess solution so the cloth is dampened, not saturated. Any blood or body fluid contamination should be cleaned immediately. The cover should be removed, and both the cover and device cleaned thoroughly. Do not use window cleaners, household cleaners, aerosol sprays, solvents, alcohol, ammonia or abrasives on the iPad device itself. After use, all equipment and supplies must be considered as potentially blood contaminated, and should be separated, handled with caution and either disinfected or discarded.

Alcohol products shall not be used to disinfect large environmental surfaces. When mixing bleach solutions, staff must wear personal protective equipment (PPE), including disposable gloves, face shield or eye protection with full side shields and fluid-resistant gowns.

Exercise Peddlers: Foot peddlers will be disinfected with an EPA registered tuberculocidal "hospital disinfectant" or 1:100 dilution of bleach (300-600 mg/L free chlorine). Foot peddlers will be disinfected following the same protocol outlined for iPads/tablets.

Baseline Assessments: After establishing eligibility, a research assistant will perform a baseline assessment for each participant at each center. Our trained research assistants will assess physical function, Health Related Quality of Life (HRQOL), frailty status, patient-centered outcomes, and executive and global cognitive function at enrollment. These scales have been studied and validated in ESRD (92-97). The baseline assessment consists of 2 parts: a survey/questionnaire and in-person assessments. The survey will take 15-20 minutes to complete and will be done by phone on the participant's non-dialysis day. The in-person assessments will be 30-40 minutes in duration and will allow us to establish a relationship with each participant. We will abstract demographics, health behaviors, medical information, clinical measures, and dialysis factors from each participant's medical record. We will also ask participants about previous cognitive training within the last 6 months. All in-person baseline and follow-up assessments will be administered prior to dialysis initiation as executive function fluctuates during and immediately after HD (11, 98).

Table 2: Assessments Measured at Baseline and at 3- and 6-Month Follow-up (*Only at baseline)			
Assessment	**Collection Method**	**Assessment Tool**	**Timing of Assessment**
Physical function	Direct measurement	IADL/ADL, Short Physical Performance Battery (SPPB): walk speed, chair stands, and balance (99-102)	Baseline and at 3- and 6-month Follow-up
Executive function	Direct measurement	Trail Making Test A and B (TMTA/B) (5), Stroop (103), and Digit Symbol Substitution Tests (104)	Baseline and at 3- and 6-month Follow-up
Global cognitive function	Direct measurement	MoCA (106)	Baseline and at 3- and 6-month Follow-up
Memory	Direct measurement	Auditory/Verbal Learning Test	Baseline, at 3- and at 6-month follow up
Frailty	Direct measurement	Fried Frailty Phenotype (107): low physical activity, unintentional weight loss, poor grip strength, slowed walk speed, exhaustion	Baseline and at 3- and 6-month Follow-up
Quality of life	Validated survey	Kidney Disease Quality of Life (KDQOL) (108-110)	Baseline and at 3- and 6-month Follow-up
Other patient-centered outcomes	Validated self-report instrument	PROMIS-29 short-form profile: anxiety, depression, fatigue, pain, perceived function, sleep disturbance, and participation in social roles/activities, ability to return to work	Baseline and at 3- and 6-month Follow-up
Demographics*	Self-report and abstraction	Age, sex, race/ethnicity, and education	Baseline
Health behaviors	Self-report and abstraction	Smoking status, alcohol intake, illicit drug use	Baseline and at 3- and 6-month follow up
Medical factors	Chart abstraction	History of chronic and infectious diseases	Baseline and at 3- and 6-month follow up
Clinical measures	Chart abstraction	BMI, eGFR, blood pressure, cholesterol	Baseline and at 3- and 6-month Follow-up
Dialysis factors	Chart abstraction	Time on dialysis, access site, schedule, cause of ESRD	Baseline and at 3- and 6-month Follow-up
DSMB Review	Direct observation	Falls during intervention or assessment, hypotension, hypertension, elevated heart rate	At every dialysis session
	Self-report	Cramping and headache	At every dialysis session
	Self-report	Injurious falls	Baseline and at 3- and 6-month Follow-up

All measures of executive function, global cognitive function, frailty, and the SPPB (walk speed, chair stands and balance) will be assessed in-person prior to the start of the dialysis session.

Assessment of Executive Function:

- *Trail Making Test A and B (TMTA and TMTB)* scores are validated measures of executive function (i.e., cognitive shifting, cognitive flexibility), attention, concentration, and psychomotor speed (5). These tests measure the time required to connect a series of sequentially numbered (TMTA) and numbered/lettered (TMTB) circles. Needing more time to complete the tests indicates worse executive function; times are capped at 3 minutes for TMTA and 5 minutes for TMTB.
- The *Stroop Test* (reading, color-naming, and interference sub-tasks) (103) evaluates the inhibitory control of executive function and involves reading the name of a color printed in a different color ink: BLUE. The time ratio of color-word interference and color-only tasks will be calculated.
- The *Digit Symbol Substitution Test* (104), which evaluates the speed and working memory components of executive function, consists of 9 number/symbol pairs (for example: 1+, 2X, 3=, etc.) and participants are asked to fill in the corresponding symbol as quickly as possible (for example: 3_,1_, 9_). The correct number of symbols within 90 seconds is measured.

Assessment of Physical Function:

- *Short Physical Performance Battery Lower (SPPB),* a performance-based assessment comprising 3 tasks: 1) repeated chair stands; 2) standing balance; and 3) a 4-meter usual paced walk in those with and without a walk aid (meters/second [m/s]) (101).
- *Instrumental Activities of Daily Living/Activities of Daily Living(IADL/ADL)* have been used by other studies of the aging population to measure disability in the context of restrictions in ability to carry out daily tasks such as bathing and taking medications (99). The IADL/ADL involves a series of questions about ability to perform activities of daily living such as bathing, dressing, and walking.

Assessment of Global Cognitive Function:

- *Montreal Cognitive Assessment (MoCA)* is an alternative to the Modified Mini-Mental State Examination (3MS) and measures global cognitive function across the cognitive impairment continuum and is more sensitive to mild cognitive impairment (106).

- Assessment of Memory: The Auditory/Verbal Learning Test (AVLT) is a screening test for memory impairment. The AVLT measures a patient's immediate recall. A series of unrelated words are presented aloud and participants are asked to recall as many as they can.

Additionally, we will administer the Revised Distrust of the Healthcare System (148) survey to assess individual attitudes of distrust. It assesses the 2 primary domains of distrust: competence and values with the values domain having subthemes of honesty, motives, and equity. The overall 9-item scale has a Cronbach's alpha of 0.83; the values subscale (5-items) had a Cronbach's alpha of 0.73 and the competence subscale (4 items) had a Cronbach's alpha of 0.77, suggesting that the subscales can be used separately or together. Unlike distrust assessment tools prior to it, the revised survey address the multi-dimensional nature of distrust of the healthcare system. The survey will be administered during the baseline assessment.

Follow-up Assessments: We will perform follow-up assessments at 3 months of intervention and 6 months of intervention (measures listed in Table 2) in the dialysis center using a similar approach to the baseline assessment for comparability of the measures. Research assistants blinded to the assigned study arm will perform follow up assessments.

The Principal Investigator/ Program Manager will inform the appropriate dialysis center treating nephrologist/nurse practitioner of any abnormal findings for cognitive function, anxiety, and depression at the 3 month and 6 month assessments.

Data collection for variables needed for DSMB review. Falls during the intervention or assessment will be directly observed by study staff at each intervention session throughout the whole study. Hypotension (SBP<110 mmHg or DBP<50 mmHg) and hypertension (SBP>150 mmHg or DBP>90 mmHg) will be identified during the clinical measurements of blood pressure that occur approximately 10 times throughout the dialysis session. Similarly elevated heart rate (>80% of maximum heart rate calculated as 220-participant age will be identified during the clinical measurements of heart rate that occur approximately 10 times throughout the dialysis session. Cramping and headaches will be noted if a participant tells the study staff that they are experiencing these events. Injurious falls for DSMB review outside of the dialysis session will be self-reported by participants as part of the questionnaire at 3- and 6-months follow-up.

Plan for Fidelity Monitoring**.** In the pilot study, there was a small dropout rate (3/23), which is consistent with other intradialytic exercise interventions at 6 months (86) and there is high compliance (88%) with ET (63). We will allow for temporary noncompliance due to acute illness or travel. We will add additional sessions onto the end of the intervention period (no more than 2 weeks) in any of the study arms, as has previously been proposed in intradialytic intervention trials (86). The Program Manager/Study Coordinator

will visit the dialysis centers administering these arms of the study monthly throughout the course of the intervention to give a refresher on the safe and effective use of the foot peddlers. The PI or project manager will visit each clinic weekly during the administration of the intervention to directly observe compliance and facilitate communication among the HD clinic staff, patients, and study staff. Research assistants will record the:

- Number of sessions with CT, ET, or CT+ET. The number of dialysis sessions during the 6 months of intervention in which a participant engages in CT, ET, or CT+ET will be coded into the ordered categories (0, 1, 2, 3, etc.). We will use fixed effect linear regression models and linear combination methods to test differences in the number of sessions between arms. This is also recorded through Lumosity.
- Duration of CT, ET, or CT+ET during the HD session. We will calculate the mean duration of CT, ET, and CT+ET during each HD session by study arm. We will test whether the mean duration per arm changes over the course of the study (i.e., do participants in certain arms lose interest in participating over time).

We will additionally administer three surveys at follow up to participants to assess their perceptions on the:

- Quality of the interventions on a 5-point scale
- Intervention Carryover outside the HD clinic. We will survey the participants in all study arms to see whether their health behaviors outside the HD sessions have changed since enrolling in the RCT. For example, are they playing other brain games or puzzles at other times or have they changed the physical activity level on their non-dialysis days.
- Cultural Appropriateness of the Intervention. We will assess the appropriateness of CT and ET using a published cultural competency tool for electronic interventions among ESRD patients (85).

Early Termination:

A participant may be removed from the study if:

- Participant violates study procedures
- Staying in the study would be harmful
- Participant develops a medical condition that is not allowed in the study
- Participant is no longer willing to participate in the study
- Participant receives a kidney transplant, or withdrawal of hemodialysis or change in renal replacement therapy
- Participant changes to a dialysis center that does not participate in the study
- There may be other reasons that we do not know at this time

Drugs/ Substances/ Devices: Not applicable

Statistical Methods

Data will be analyzed according to the intention-to-treat principle. We will test the main effect of CT alone (arm 1) and the main effect of ET alone (arm 2) as well as the interaction between CT+ET (arm 3) compared with SC (arm 4). Baseline characteristics will be compared among treatment groups to test adequacy of randomization and identify possible confounders. If there are concerns about imbalances between treatment groups with respect to important risk factors for executive function decline, we will adjust regression-based models as necessary to account for these differences. Competing events (death or KT) will be quantified; if relevant, sensitivity analysis accounting for competing events will be performed.

1.0. Analytic Methods. Effect of CT, ET, and CT+ET on cognitive outcomes:
Change in executive function between baseline and 3 months will be a continuous outcome. Using a linear regression with the cluster option to account for the centers, we will test the null hypothesis (H01) of no difference in the mean change in executive function in CT alone vs. SC against the alternative hypotheses (HA1) that CT alone has a different mean change in executive function than SC. We will then test the null hypothesis (H02) of no difference in the mean change in executive function in ET vs. SC against the alternative hypotheses (HA2) that ET has a different mean change in executive function than SC.

In addition to these two main effects, we will test the effect of CT depends on ET (interaction). The null hypothesis (H03) is that there is no difference in the mean change in executive function for those in the CT, ET, CT+ET or SC arms vs. the alternative hypothesis (HA3) that at least one of the mean changes in executive function differs.

From this model, we will use linear combination methods to test H04 (no difference in mean change in executive function for arm 1 vs. 2) vs. HA4 (arm 1 has a different mean change in executive function than arm 2). We will then test H05 (no difference in mean change in executive function for arm 1 vs. 3) vs. HA5 (arm 1 has a different mean change in executive function than arm 3). We will test H06 (no difference in mean change in executive function for arm 2 vs. 3) vs. HA6 (arm 2 has a different mean change in executive function than arm 3). If H01 is not rejected, we will conclude that there is insufficient evidence that arm 1 is more effective than arm 4 in preserving executive function. If H02 is not rejected, we will conclude that there is insufficient evidence that arm 2 is more effective than arm 4 in preserving executive function. If H03 is not rejected, we will conclude that there is insufficient evidence that arm 3 is more effective than arm 4.

If H01, H02, and H03 are rejected, but H04 is not rejected, we will conclude that arms 1 and 2 are more effective than arm 4, but there is no difference in the effectiveness of arms 1 and 2. Similarly, if H01, H02, and H03 are rejected, but H05 is not rejected, we will conclude that arms 1 and 3 are more effective than arm 4, but there is no difference in the effectiveness of arms 1 and 3. And finally, if H01, H02, and H03 are rejected, but H06 is not rejected, we will conclude that arms 2 and 3 are more effective than arm 4, but there is no difference in the effectiveness of arms 2 and 3.The following table below details the conclusions we will draw based on hypotheses testing if H01 and H02 are rejected:

Table 3: Hypothesis Testing for the Primary Outcome		
	H03 rejected	H03 not rejected
H05 Rejected	Arm 1 is superior to arm 4 and arm 3 is superior to arm 1; i.e., both CT+ET and CT alone are effective strategies compared with SC but CT+ET is more effective.	Arm 3 is superior to arm 1, but there is not sufficient evidence to distinguish arm 3 from arm 4; i.e., CT+ET is not effective compared with SC but better than CT alone.
H05 Not rejected	Arms 1 and 3 are superior to arm 4, but there is not sufficient evidence to distinguish arm 1 from arm 3; i.e., CT+ET is an effective strategy compared with SC, but we cannot tell if the CT+ET is effective beyond that of CT alone.	There is insufficient evidence to distinguish arm 3 from arm 4 and arm 1 from arm 3; i.e., CT+ET is not an effective strategy compared with SC and no better than CT alone.
H06 Rejected	Arm 2 is superior to arm 4 and arm 3 is superior to arm 2; i.e., both CT+ET and ET alone are effective strategies compared with SC but CT+ET is more effective.	Arm 3 is superior to arm 2, but there is not sufficient evidence to distinguish arm 3 from arm 4; i.e., CT+ET is not effective compared with SC but better than ET alone.
H06	Arms 1 and 3 are superior to arm 4, but there is not sufficient evidence to distinguish arm 1 from arm 3;	There is insufficient evidence to distinguish arm 3 from arm 4 and arm 2 from arm 3; i.e., CT+ET is not an effective

Not rejected	i.e., CT+ET is an effective strategy compared with SC, but we cannot tell if CT+ET is effective beyond CT alone.	strategy compared with SC and no better than ET alone.

Power Calculations: We used a Monte-Carlo simulation (1,000 randomly generated datasets) to estimate the power of a 2-by-2 factorial design with linear regression and Huber-White robust standard errors. We powered the RCT to detect a statistically significant difference in the CT+ET group based on a 3-month change in executive function, given the group mean change and SD in the pilot data.

When each arm of the study has 47 participants, we will have 80% power to detect a statistically significant change of 20 seconds between baseline and 3 months comparing the CT+ET arm to the SC arm. We will also have 95% power to detect a statistically significant change of 15 seconds in the CT arm and >99% to detect a statistically significant change of 18 seconds in the ET arm. Therefore, we would need to recruit 200 participants from 16 centers (approximately 13 participants per center). Even if we were to recruit just 22 participants (rather than 47) into each arm of the study, we would still have >80% power to observe statistically significant changes of 15 seconds for the main effects of CT and ET.

Based on the pilot study we assumed an 88% consent rate per arm; this will leave approximately 57-60 participants from which we will need to recruit 50 per arm. We also accounted for 6% attrition in 3 months.

1.1. Change in Secondary Measures of Cognitive Function Over 6 Months. We will use a linear mixed model approach to describe the 3- and 6-month change in secondary cognitive function measures. We will construct a base model by fitting a single slope after enrollment. We will include two random effects: intercept and time relative to enrollment. This will allow for a unique trajectory for each participant, which varies randomly around the trajectory described by the fixed effects. The estimate for the time since enrollment variable will quantify the magnitude of the change in executive and global cognitive function (pre- and post-intervention) associated with CT, ET, and CT+ET. We will explore non-linear functions of time through cubic splines. The model is:

$$(CF_{ij} - CF_{i0}) = \left[\beta_{00} + \beta_{1i}\text{time}_{ij} + \beta_{01}X_i + \beta_{11}X_i(\text{time}_{ij})\right] + \left[b_{0i} + b_{1i}(\text{time}_{ij}) + r_{ij}\right] + \varepsilon_{ij}$$

where time is time since enrollment, and X is the vector of interventions. We recognize that mortality may occur during the study and those who are survivors may be a distinct population and there may be differential mortality by intervention. If we find evidence for this differential survival, we will account for the unobservable executive and global cognitive function after death by 1) creating a composite endpoint that ranks mortality as worse than any change in executive or global cognitive function (composite endpoint), and 2) generate a causal model for change regardless of mortality using a survival-averaged causal effect model. As a sensitivity analysis, we will test that our findings are robust to the analytic approach using global z-scores.

2.0. Analytic Methods: Effect of CT, ET, and CT+ET on ESRD-specific clinical outcomes.

Staff at NYU Langone Health will help with data analysis. Data will be shared through a HIPAA Compliant Johns Hopkins REDCap database. The NYU Langone Health team will be conducting data analysis for all components of this study and requires all variables to do so.

2.1. Time to Event Outcomes: Mortality. To examine the univariate association between study arm and mortality, separate product-limit estimated cumulative incidence curves will be calculated. Next, we will use a Cox proportional hazards model to estimate the association of study arm with time to the development of mortality. Censoring will occur at loss to follow-up or KT. The hazard function for the Cox model is:

$$\lambda(t|X_i) = \lambda_0(t)\exp(X_i\beta)$$

where xi is the value of the covariate X for the ith participant, and $\lambda 0(t)$ is the baseline hazard function. If the proportional hazards assumption is not met, we will include an interaction with time.

2.2. Dichotomous Outcomes: Poor Lower Extremity Function, poor HRQOL, return to work, and amputation. We will test whether the study arm is associated with poor lower extremity function, poor HRQOL, return to work, and amputation using logistic regression or a modified Poisson regression (145), if the outcome is >10%.

2.3. Count Outcomes: Number of Falls and Hospitalizations. We will use Poisson regression to test whether the study arm is associated with the number of falls and hospitalizations within the 3 months of the intervention.

3.0. Analytic Methods: Effect of CT, ET, and CT+ET on patient-centered outcomes.
Change in Patient-centered Outcome**:** For each patient-centered outcome, we will calculate a score. We will treat each patient-centered outcome as continuous and will estimate the change in these outcomes between baseline and 3 months. We will analyze each patient-centered outcome separately. We will analyze the change in these outcomes using the analytic plan described in 1.0.

3.1. Change in Patient-centered Outcome over 6 Months. Patient-centered outcomes are longitudinal data (3 and 6 months) and analyzed using the analytic plan described in 2.0 for repeated measures of executive function.

4.0. Treatment Effect Heterogeneity. Frailty has been associated with worse trajectories of executive function in older adults (146) and HD patients (16). Therefore, we will explore treatment heterogeneity between those who are frail and nonfrail in all primary and secondary outcomes. We will include an interaction term between frailty status and intervention type (study arm) to assess difference in treatment effect by frailty status. Using a similar approach, we will test for treatment effect heterogeneity by age, sex, and race/ethnicity.

Risks:

Risk from Cognitive Training Intervention:
Participants in the CT arm may feel tired or bored from playing similar cognitive games. They may feel frustrated if they are trying to learn new games and are unsuccessful with the games. Participants may develop a headache due to eyestrain from focusing on the tablet screen. All participants will be encouraged to wear their reading glasses while performing the CT if applicable.

Risk from Exercise Training Intervention:
Participants in the ET arm may experience fatigue, exhaustion, discomfort, muscle soreness, pain or cramping in the legs from using the foot peddler. Participants may experience shortness of breath, a change in heart rate or blood pressure while performing the activity.

Risk from Frailty Measurements and Physical Function Assessments:
Participants may experience fatigue or exhaustion from performing the grip strength, chair stands, balance and walk speed.

Risk from Quality of Life and Health Questionnaires:

Participants may experience fatigue, exhaustion, emotional discomfort or boredom from answering the questionnaires.

Minimization of Risks:
All participants will go through an eligibility screening process. We will enroll only those who meet all of the inclusion criteria and none of the exclusion criteria. The treating nephrologist is required to give permission for a patient to enroll in the study to ensure it is safe for them to participate.

All participants will sign an IRB-approved informed consent. We will inform them that participation is strictly voluntary and that they may decline to continue participation in the study at any time point, discontinue the assessments during the session, or refuse to answer any questions they do not want to. At the start of each session, we will inform the participants in the CT, ET, and CT+ ET arms that they are free to stop the activity at any time if they feel any discomfort or for some other reason cannot continue. Additionally, physicians, nurse practitioners, and dialysis staff will be on staff during the session to help monitor the participants health while undergoing hemodialysis and participating in the study.

The study team will make every effort to protect the participants' privacy by conducting interviews and assessments in an area at the dialysis center that is not within earshot or view of other clinic patients.

Confidentiality and Risk Protection:
We will keep all data collected strictly confidential so there is minimal risk of loss of confidentiality. All participating faculty and staff have received appropriate training in the responsible conduct of research, protection of human subject participants, and HIPAA regulations. All data collection instruments and consent forms will be kept in a locked cabinet. All questionnaires, assessments and cognitive function data will be stored in RedCap, a secured database. To maximize confidentiality, only the study investigators, data manager and key study personnel will have access to the information.

Data Safety Monitoring Board (DSMB) and Adverse Event Reporting*:*
An independent DSMB will be established to oversee the safety and progress of this trial, comprised of five individuals (a patient advocate, an ethicist, a statistician, a nephrologist, and a research nurse) who will serve in this capacity throughout the entirety of the trial. We will ensure that all members of the DSMB disclose of any conflicts of interest. The DSMB will have pertinent experience and review accumulating data from this RCT on a regular basis with the goal of enhancing the safety of the trial participants. A DSMB is warranted in this RCT because the study is being performed in a potentially vulnerable population, namely those with ESRD on HD and this population is at elevated risk of serious outcomes. A medical monitor will be included on the DSMB to review all events and determine whether they classify as AE's/ or SAE's.

We will monitor the number of injurious falls resulting in a medical encounter during the 6 months of interventions. This data will be obtained during the survey portion of our assessments by asking the participant to self-report the number of falls in the last 6 months. Additionally, falls during the intervention or assessment will be directly observed and recorded by study staff. Any falls will be reported to the medical monitor for review and determination whether they classify as an AE or SAE attributable to the interventions.

The DSMB will be identified and managed through the ICTR and will be established and operated using the Guidance put forth by the US Food and Drug Administration "Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees" (*https://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf*). The DSMB will be local and managed by the ICTR to allow for quick convening of meetings in the event of an unexpected result that raises concerns.

None of these individuals will be involved in the design or conduct of the trial. Any unanticipated problem or adverse event will be reported as outlined in JHU IRB policy 103.6(b). When possible the DSMB will be blinded to the study arm.

If any SAEs are more common in one of the three intervention arms compared to the standard of care arm, then the DSMB will consider termination of the study if the risks outweigh the benefits for participants. All SAEs that are deemed to have a causal relationship with the interventions in one of the arms of the study will be reviewed by the DSMB for the consideration of patient safety.

Planned DSMB Reviews:
The Data and Safety Monitoring Board (DSMB) shall review safety data during planned DSMB Data Review Meetings when 10%, 25%, and 50% of enrolled participants have completed 3 months of interventions and to analyze and review the interim analyses of these adverse events during active data collection. Data for the planned safety reviews will include, at a minimum, a listing of all reported AEs and SAEs. The DSMB will be informed of an Expedited Safety Report in a timely manner. The DSMB will have a final meeting at the end of the study.

We have performed a comprehensive literature search of published and unpublished manuscripts to identify possible side effects, adverse events, and serious adverse events of CT and ET interventions. No adverse events were noted in the literature search for side effects, adverse events or serious adverse events for CT. We theorize that the two most common risks associated with CT are the following: 1) boredom 2) frustration and 3) headache.

There are greater risks associated with the ET intervention than with the CT intervention. The main risks associated with ET include: 1) Hypotension or low blood pressure which can cause dizziness and fainting. Hypotension can frequently occur during hemodialysis due to fluid removal. Hypotension is the most common risk of intradialytic ET and can occur in up to 33% of dialysis sessions in which exercise is involved, 2) cramping, muscle soreness, pain and fatigue, and 3) dyspnea or shortness of breath which occurs commonly during exercise. While hypertension and elevated heart rate were not noted as a risk associated with ET, we will also consider hypertension as a possible risk. Blood pressure reading of SBP>150 or DBP>90 mmHg will be considered as hypertension. SBP<110 or DBP<50 mmHg will be considered as hypotension. Heart rate that is consistently >80% of maximum heart rate will be considered as elevated.

Ad Hoc DSMB Reviews
In addition to the pre-scheduled data reviews and planned safety monitoring, the DSMB may be called upon for ad hoc reviews. The DSMB will review any event that potentially impacts safety at the request of the PI or NIDDK representative. In addition, the following events will trigger an ad hoc comprehensive DSMB Safety Review:

- Any death in the study which is considered possibly or definitely related to a study procedure.
- If any of the following adverse events occur at a significant higher rate than expected in the CT, ET, or CT+ET arm: muscle cramping, hypotension, or headache. We have outlined thresholds for pausing rules for rates of cramping, hypotension, hypertension, elevated heart rate, or headache which will trigger a mandatory pause in study enrollment for an unscheduled Data Safety and Monitoring Board review.

Cramping/Muscle Soreness: At the first day of each month, we will perform a Bayesian analysis of the ratio of cramping rates between ET arm (or CT+ET arm) versus the SC group. We will use a prior distribution of beta for each subgroup. We will then analyze the ratio of the distributions using a Monte

Carlo simulation. If there is 75% chance that [rate of cramping in the ET arm or CT+ET arm] divided by [rate of cramping in the SC arm] exceeds 1.10 (10% more in ET arm or CT+ET arm), we will pause the study pending DSMB recommendation.

Hypotension: we will perform a Bayesian analysis of the ratio of hypotension rates between ET arm (or CT+ET arm) versus the SC arm. We will use a prior distribution of beta(0,0)for each subgroup. We will then analyze the ratio of the distributions using a Monte Carlo simulation. If there is an 75% chance that [rate of hypotension in the ET arm or CT+ET arm] divided by [rate of hypotension in the SC arm] exceeds 1.15 (15% more in ET arm or CT+ET arm), we will pause the study pending DSMB recommendation.

Hypertension: At the first day of each month, we will perform a Bayesian analysis of the ratio of hypertension rates between ET arm (or CT+ET arm) versus the SC arm. When calculating hypertension rates, we will exclude dialysis sessions with starting blood pressure being hypertensive. We will use a prior distribution of beta(0,0) for each subgroup. We will then analyze the ratio of the distributions using a Monte Carlo simulation. If there is an 75% chance that [rate of hypertension in the ET arm or CT+ET arm] divided by [rate of hypertension in the SC arm] exceeds 1.15 (15% more in ET arm or CT+ET arm), we will pause the study pending DSMB recommendation.

Elevated Heart Rate (EHR): At the first day of each month, we will perform a Bayesian analysis of the ratio of EHR rates between ET arm (or CT+ET arm) versus the SC arm. We will use a prior distribution of beta (0,0) for each subgroup. We will then analyze the ratio of the distributions using a Monte Carlo simulation. If there is an 75% chance that [rate of EHR in the ET arm or CT+ET arm] divided by [rate of EHR in the SC arm] exceeds 1.08 (8% more in ET arm or CT+ET arm), we will pause the study pending DSMB recommendation.

Headache: At the first day of each month, we will perform a Bayesian analysis of the ratio of headache rates between CT arm (or CT+ET arm) versus the SC arm. We will use a prior distribution of beta(0,0) for each subgroup. We will then analyze the ratio of the distributions using a Monte Carlo simulation. If there is an 75% chance that [rate of headache in the CT arm or CT+ET arm] divided by [rate of headache in the SC arm] exceeds 1.12 (12% more in CT arm or CT+ET arm), we will pause the study pending DSMB recommendation.

After review of the data, the DSMB will make recommendations regarding study conduct and/or continuation.

Temporary Suspension of enrollment for Ad Hoc DSMB Safety Review
A temporary halt in enrollment at all participating centers will be implemented if an ad hoc DSMB safety review is required.

Benefits:

There is no direct benefit to the participants for being in the study. However, there is a possibility of a direct benefit from the participants having access to a cognitive training regime or an exercise training regime. There are no direct benefits to participants randomized to the standard of care arm. All study participants may help providers and other patients in the future by contributing to the knowledge base for performing interventions for patients undergoing hemodialysis.

Payment and Remuneration:

All participants will receive a $10 gift card after completion of study assessments at baseline. Participants in the standard of care arm will receive a $25 gift card after completion of assessments at 3 months, and at 6 months. Participants in the CT, ET, or CT+ET arms will receive a $10 gift card after completion of study assessments at 3 months and at 6 months. Additionally, participants in the intervention arms will receive $5 for each HD session they engage in their assigned intervention. Participants will not receive compensation if they withdraw from the study. Travel or other expenses will not be reimbursed as all the assessments and activities related to the study will be conducted during their regularly scheduled hemodialysis appointment at the dialysis center.

Costs:

There are no costs to the participant for being in the study.

Coordinating Site Information:

Johns Hopkins will serve as the coordinating center. NYU has an active FWA and OHRP on file that the Johns Hopkins IRB has worked with successfully in the past. The Johns Hopkins PI, Aarti Mathur, and Mara McAdams DeMarco the site lead at NYU will be in frequent contact and address any protocol changes or amendments. All data will be entered into a secure REDCap database and managed by Mara McAdams Demarco at NYU. There will be no changes to data management at Johns Hopkins. The NYU study team will provide the JH study team with any necessary information for annual continuing reviews. The PI will be responsible for education to sites about JHM policies and oversight of protocol events, deviations, and ensuring appropriate reporting. The NYU Langone Health study team will analyze and collect data for this study. To ensure data collection is consistent across sites, that longer term follow-up can be performed, and re-contact for future studies, all data collected over the course of the trial must be shared. All data will be shared over a HIPAA compliant Johns Hopkins secure REDCap data base. We will add NYU study team members to the Johns Hopkins REDCap project in order for them to access any necessary data. Access to the data at NYU will be restricted to only study team members. We will use a Data Access Group created by Johns Hopkins IT to add NYU personnel to the REDCap project. Only authorized personnel will be able to add additional team members to the project after they are added to the IRB.

REFERENCES

1. United States Renal Data System, 2016 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda: National Institute of Diabetes and Digestive and Kidney Diseases, 2016.
2. Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, Au R, Kannel WB, et al. The lifetime risk of stroke: estimates from the Framingham Study. Stroke. 2006;37(2):345-50. doi: 10.1161/01.STR.0000199613.38911.b2. PubMed PMID: 16397184.
3. Albert MS, Moss MB, Tanzi R, Jones K. Preclinical prediction of AD using neuropsychological tests. J Int Neuropsychol Soc. 2001;7(5):631-9. PubMed PMID: 11459114.
4. Kray J, Lindenberger U. Adult age differences in task switching. Psychol Aging. 2000;15(1):126-47. PubMed PMID: 10755295.
5. Spreen O, Spreen E. A compendium of neuropsychological tests: Administration, norms and commentary. 2nd ed. New York: Oxford University Press.

6. Kurella Tamura M, Wadley V, Yaffe K, McClure LA, Howard G, Go R, et al. Kidney function and cognitive impairment in US adults: the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Am J Kidney Dis. 2008;52(2):227-34. doi: 10.1053/j.ajkd.2008.05.004. PubMed PMID: 18585836; PubMed Central PMCID: PMCPMC2593146.
7. Buchman AS, Tanne D, Boyle PA, Shah RC, Leurgans SE, Bennett DA. Kidney function is associated with the rate of cognitive decline in the elderly. Neurology. 2009;73(12):920-7. doi: 10.1212/WNL.0b013e3181b72629. PubMed PMID: 19657107; PubMed Central PMCID: PMCPMC2754333.
8. Elias MF, Elias PK, Seliger SL, Narsipur SS, Dore GA, Robbins MA. Chronic kidney disease, creatinine and cognitive functioning. Nephrol Dial Transplant. 2009;24(8):2446-52. doi: 10.1093/ndt/gfp107. PubMed PMID: 19297357; PubMed Central PMCID: PMCPMC2727297.
9. Harciarek M, Williamson JB, Biedunkiewicz B, Lichodziejewska-Niemierko M, Debska-Slizien A, Rutkowski B. Risk factors for selective cognitive decline in dialyzed patients with end-stage renal disease: evidence from verbal fluency analysis. J Int Neuropsychol Soc. 2012;18(1):162-7. doi: 10.1017/S1355617711001445. PubMed PMID: 22088797.
10. Altmann P, Barnett ME, Finn WF, Group SPDLCS. Cognitive function in Stage 5 chronic kidney disease patients on hemodialysis: no adverse effects of lanthanum carbonate compared with standard phosphate-binder therapy. Kidney international. 2007;71(3):252-9. doi: 10.1038/sj.ki.5001932. PubMed PMID: 17035945.
11. Murray AM. Cognitive impairment in the aging dialysis and chronic kidney disease populations: an occult burden. Adv Chronic Kidney Dis. 2008;15(2):123-32. doi: 10.1053/j.ackd.2008.01.010. PubMed PMID: 18334236; PubMed Central PMCID: PMCPMC2504691.
12. Sehgal AR, Grey SF, DeOreo PB, Whitehouse PJ. Prevalence, recognition, and implications of mental impairment among hemodialysis patients. Am J Kidney Dis. 1997;30(1):41-9. Epub 1997/07/01. PubMed PMID: 9214400.
13. Kurella Tamura M, Vittinghoff E, Hsu CY, Tam K, Seliger SL, Sozio S, et al. Loss of executive function after dialysis initiation in adults with chronic kidney disease. Kidney international. 2017;91(4):948-53. doi: 10.1016/j.kint.2016.11.015. PubMed PMID: 28139292; PubMed Central PMCID: PMCPMC5357463.
14. Murray AM, Tupper DE, Knopman DS, Gilbertson DT, Pederson SL, Li S, et al. Cognitive impairment in hemodialysis patients is common. Neurology. 2006;67(2):216-23. Epub 2006/07/26. doi: 10.1212/01.wnl.0000225182.15532.40. PubMed PMID: 16864811.
15. Kurella M, Chertow GM, Luan J, Yaffe K. Cognitive impairment in chronic kidney disease. Journal of the American Geriatrics Society. 2004;52(11):1863-9. doi: 10.1111/j.1532-5415.2004.52508.x. PubMed PMID: 15507063.
16. McAdams-DeMarco MA, Tan J, Salter ML, Gross A, Meoni LA, Jaar BG, et al. Frailty and Cognitive Function in Incident Hemodialysis Patients. Clin J Am Soc Nephrol. 2015;10(12):2181-9. doi: 10.2215/CJN.01960215. PubMed PMID: 26573615; PubMed Central PMCID: PMCPMC4670760.
17. Griva K, Thompson D, Jayasena D, Davenport A, Harrison M, Newman SP. Cognitive functioning pre- to post-kidney transplantation--a prospective study. Nephrol Dial Transplant. 2006;21(11):3275-82. Epub 2006/07/25. doi: 10.1093/ndt/gfl385. PubMed PMID: 16861731.
18. Levine B, Stuss DT, Winocur G, Binns MA, Fahy L, Mandic M, et al. Cognitive rehabilitation in the elderly: effects on strategic behavior in relation to goal management. J Int Neuropsychol Soc. 2007;13(1):143-52. doi: 10.1017/S1355617707070178. PubMed PMID: 17166313.
19. Mahncke HW, Connor BB, Appelman J, Ahsanuddin ON, Hardy JL, Wood RA, et al. Memory enhancement in healthy older adults using a brain plasticity-based training program: a randomized, controlled study. Proceedings of the National Academy of Sciences of the United States of America. 2006;103(33):12523-8. doi: 10.1073/pnas.0605194103. PubMed PMID: 16888038; PubMed Central PMCID: PMCPMC1526649.
20. Cepeda NJ, Kramer AF, Gonzalez de Sather JC. Changes in executive control across the life span: examination of task-switching performance. Dev Psychol. 2001;37(5):715-30. PubMed PMID: 11552766.
21. Griva K, Stygall J, Hankins M, Davenport A, Harrison M, Newman SP. Cognitive impairment and 7-year mortality in dialysis patients. Am J Kidney Dis. 2010;56(4):693-703. Epub 2010/08/31. doi: 10.1053/j.ajkd.2010.07.003. PubMed PMID: 20800327.

22. Drew DA, Weiner DE, Tighiouart H, Scott T, Lou K, Kantor A, et al. Cognitive function and all-cause mortality in maintenance hemodialysis patients. Am J Kidney Dis. 2015;65(2):303-11. doi: 10.1053/j.ajkd.2014.07.009. PubMed PMID: 25240262; PubMed Central PMCID: PMCPMC4305473.
23. Kurella M, Mapes DL, Port FK, Chertow GM. Correlates and outcomes of dementia among dialysis patients: the Dialysis Outcomes and Practice Patterns Study. Nephrol Dial Transplant. 2006;21(9):2543-8. Epub 2006/06/06. doi: 10.1093/ndt/gfl275. PubMed PMID: 16751655.
24. Gregory SM, Parker B, Thompson PD. Physical activity, cognitive function, and brain health: what is the role of exercise training in the prevention of dementia? Brain sciences. 2012;2(4):684-708. Epub 2012/01/01. doi: 10.3390/brainsci2040684. PubMed PMID: 24961266; PubMed Central PMCID: PMC4061820.
25. Chapman SB, Aslan S, Spence JS, Keebler MW, DeFina LF, Didehbani N, et al. Distinct Brain and Behavioral Benefits from Cognitive vs. Physical Training: A Randomized Trial in Aging Adults. Frontiers in human neuroscience. 2016;10:338. doi: 10.3389/fnhum.2016.00338. PubMed PMID: 27462210; PubMed Central PMCID: PMCPMC4939293.
26. Anand R, Chapman SB, Rackley A, Keebler M, Zientz J, Hart J, Jr. Gist reasoning training in cognitively normal seniors. International journal of geriatric psychiatry. 2011;26(9):961-8. doi: 10.1002/gps.2633. PubMed PMID: 20963768.
27. Karbach J, Kray J. How useful is executive control training? Age differences in near and far transfer of task-switching training. Dev Sci. 2009;12(6):978-90. doi: 10.1111/j.1467-7687.2009.00846.x. PubMed PMID: 19840052.
28. Rebok GW, Ball K, Guey LT, Jones RN, Kim HY, King JW, et al. Ten-year effects of the advanced cognitive training for independent and vital elderly cognitive training trial on cognition and everyday functioning in older adults. Journal of the American Geriatrics Society. 2014;62(1):16-24. doi: 10.1111/jgs.12607. PubMed PMID: 24417410; PubMed Central PMCID: PMCPMC4055506.
29. Shatil E. Does combined cognitive training and physical activity training enhance cognitive abilities more than either alone? A four-condition randomized controlled trial among healthy older adults. Frontiers in aging neuroscience. 2013;5:8. doi: 10.3389/fnagi.2013.00008. PubMed PMID: 23531885; PubMed Central PMCID: PMCPMC3607803.
30. Strenziok M, Parasuraman R, Clarke E, Cisler DS, Thompson JC, Greenwood PM. Neurocognitive enhancement in older adults: comparison of three cognitive training tasks to test a hypothesis of training transfer in brain connectivity. Neuroimage. 2014;85 Pt 3:1027-39. doi: 10.1016/j.neuroimage.2013.07.069. PubMed PMID: 23933474.
31. Fabre C, Chamari K, Mucci P, Masse-Biron J, Prefaut C. Improvement of cognitive function by mental and/or individualized aerobic training in healthy elderly subjects. Int J Sports Med. 2002;23(6):415-21. doi: 10.1055/s-2002-33735. PubMed PMID: 12215960.
32. Maclin EL, Mathewson KE, Low KA, Boot WR, Kramer AF, Fabiani M, et al. Learning to multitask: effects of video game practice on electrophysiological indices of attention and resource allocation. Psychophysiology. 2011;48(9):1173-83. doi: 10.1111/j.1469-8986.2011.01189.x. PubMed PMID: 21388396.
33. Mathewson KE, Basak C, Maclin EL, Low KA, Boot WR, Kramer AF, et al. Different slopes for different folks: alpha and delta EEG power predict subsequent video game learning rate and improvements in cognitive control tasks. Psychophysiology. 2012;49(12):1558-70. doi: 10.1111/j.1469-8986.2012.01474.x. PubMed PMID: 23095124.
34. Chapman SB, Mudar RA. Enhancement of cognitive and neural functions through complex reasoning training: evidence from normal and clinical populations. Front Syst Neurosci. 2014;8:69. doi: 10.3389/fnsys.2014.00069. PubMed PMID: 24808834; PubMed Central PMCID: PMCPMC4009420.
35. McDaniel MA, Binder EF, Bugg JM, Waldum ER, Dufault C, Meyer A, et al. Effects of cognitive training with and without aerobic exercise on cognitively demanding everyday activities. Psychol Aging. 2014;29(3):717-30. doi: 10.1037/a0037363. PubMed PMID: 25244489; PubMed Central PMCID: PMCPMC4634565.
36. Ballesteros S, Prieto A, Mayas J, Toril P, Pita C, Ponce de Leon L, et al. Brain training with non-action video games enhances aspects of cognition in older adults: a randomized controlled trial. Frontiers in aging neuroscience. 2014;6:277. Epub 2014/10/30. doi: 10.3389/fnagi.2014.00277. PubMed PMID: 25352805; PubMed Central PMCID: PMC4196565.

37. Lautenschlager NT, Cox KL, Flicker L, Foster JK, van Bockxmeer FM, Xiao J, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. JAMA : the journal of the American Medical Association. 2008;300(9):1027-37. doi: 10.1001/jama.300.9.1027. PubMed PMID: 18768414.
38. Jonasson LS, Nyberg L, Kramer AF, Lundquist A, Riklund K, Boraxbekk CJ. Aerobic Exercise Intervention, Cognitive Performance, and Brain Structure: Results from the Physical Influences on Brain in Aging (PHIBRA) Study. Frontiers in aging neuroscience. 2016;8:336. doi: 10.3389/fnagi.2016.00336. PubMed PMID: 28149277; PubMed Central PMCID: PMCPMC5241294.
39. Anderson-Hanley C, Nimon JP, Westen SC. Cognitive health benefits of strengthening exercise for community-dwelling older adults. Journal of clinical and experimental neuropsychology. 2010;32(9):996-1001. doi: 10.1080/13803391003662702. PubMed PMID: 20408001.
40. Best JR, Nagamatsu LS, Liu-Ambrose T. Improvements to executive function during exercise training predict maintenance of physical activity over the following year. Frontiers in human neuroscience. 2014;8:353. doi: 10.3389/fnhum.2014.00353. PubMed PMID: 24904387; PubMed Central PMCID: PMCPMC4034407.
41. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol Sci. 2003;14(2):125-30. doi: 10.1111/1467-9280.t01-1-01430. PubMed PMID: 12661673.
42. Etnier JL, Chang YK. The effect of physical activity on executive function: a brief commentary on definitions, measurement issues, and the current state of the literature. J Sport Exerc Psychol. 2009;31(4):469-83. PubMed PMID: 19842543.
43. Hillman CH, Belopolsky AV, Snook EM, Kramer AF, McAuley E. Physical activity and executive control: implications for increased cognitive health during older adulthood. Res Q Exerc Sport. 2004;75(2):176-85. doi: 10.1080/02701367.2004.10609149. PubMed PMID: 15209336.
44. Erickson KI, Kramer AF. Aerobic exercise effects on cognitive and neural plasticity in older adults. Br J Sports Med. 2009;43(1):22-4. doi: 10.1136/bjsm.2008.052498. PubMed PMID: 18927158; PubMed Central PMCID: PMCPMC2853472.
45. Barcelos N, Shah N, Cohen K, Hogan MJ, Mulkerrin E, Arciero PJ, et al. Aerobic and Cognitive Exercise (ACE) Pilot Study for Older Adults: Executive Function Improves with Cognitive Challenge While Exergaming. J Int Neuropsychol Soc. 2015;21(10):768-79. doi: 10.1017/S1355617715001083. PubMed PMID: 26581789.
46. Guiney H, Lucas SJ, Cotter JD, Machado L. Evidence cerebral blood-flow regulation mediates exercise-cognition links in healthy young adults. Neuropsychology. 2015;29(1):1-9. doi: 10.1037/neu0000124. PubMed PMID: 25068671.
47. Colcombe SJ, Erickson KI, Scalf PE, Kim JS, Prakash R, McAuley E, et al. Aerobic exercise training increases brain volume in aging humans. J Gerontol A Biol Sci Med Sci. 2006;61(11):1166-70. PubMed PMID: 17167157.
48. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, et al. Exercise training increases size of hippocampus and improves memory. Proceedings of the National Academy of Sciences of the United States of America. 2011;108(7):3017-22. doi: 10.1073/pnas.1015950108. PubMed PMID: 21282661; PubMed Central PMCID: PMCPMC3041121.
49. Voss MW, Prakash RS, Erickson KI, Basak C, Chaddock L, Kim JS, et al. Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. Frontiers in aging neuroscience. 2010;2. doi: 10.3389/fnagi.2010.00032. PubMed PMID: 20890449; PubMed Central PMCID: PMCPMC2947936.
50. Anderson-Hanley C, Arciero PJ, Brickman AM, Nimon JP, Okuma N, Westen SC, et al. Exergaming and older adult cognition: a cluster randomized clinical trial. Am J Prev Med. 2012;42(2):109-19. doi: 10.1016/j.amepre.2011.10.016. PubMed PMID: 22261206.
51. Nascimento CM, Pereira JR, Pires de Andrade L, Garuffi M, Ayan C, Kerr DS, et al. Physical exercise improves peripheral BDNF levels and cognitive functions in mild cognitive impairment elderly with different bdnf Val66Met genotypes. J Alzheimers Dis. 2015;43(1):81-91. doi: 10.3233/JAD-140576. PubMed PMID: 25062900.
52. Hotting K, Roder B. Beneficial effects of physical exercise on neuroplasticity and cognition. Neurosci Biobehav Rev. 2013;37(9 Pt B):2243-57. doi: 10.1016/j.neubiorev.2013.04.005. PubMed PMID: 23623982.

53. Knaepen K, Goekint M, Heyman EM, Meeusen R. Neuroplasticity - exercise-induced response of peripheral brain-derived neurotrophic factor: a systematic review of experimental studies in human subjects. Sports Med. 2010;40(9):765-801. doi: 10.2165/11534530-000000000-00000. PubMed PMID: 20726622.
54. Leckie RL, Oberlin LE, Voss MW, Prakash RS, Szabo-Reed A, Chaddock-Heyman L, et al. BDNF mediates improvements in executive function following a 1-year exercise intervention. Frontiers in human neuroscience. 2014;8:985. doi: 10.3389/fnhum.2014.00985. PubMed PMID: 25566019; PubMed Central PMCID: PMCPMC4263078.
55. Loprinzi PD, Herod SM, Cardinal BJ, Noakes TD. Physical activity and the brain: a review of this dynamic, bi-directional relationship. Brain Res. 2013;1539:95-104. doi: 10.1016/j.brainres.2013.10.004. PubMed PMID: 24120986.
56. O'Leary KC, Pontifex MB, Scudder MR, Brown ML, Hillman CH. The effects of single bouts of aerobic exercise, exergaming, and videogame play on cognitive control. Clin Neurophysiol. 2011;122(8):1518-25. doi: 10.1016/j.clinph.2011.01.049. PubMed PMID: 21353635.
57. Roig M, Skriver K, Lundbye-Jensen J, Kiens B, Nielsen JB. A single bout of exercise improves motor memory. PloS one. 2012;7(9):e44594. doi: 10.1371/journal.pone.0044594. PubMed PMID: 22973462; PubMed Central PMCID: PMCPMC3433433.
58. Statton MA, Encarnacion M, Celnik P, Bastian AJ. A Single Bout of Moderate Aerobic Exercise Improves Motor Skill Acquisition. PloS one. 2015;10(10):e0141393. doi: 10.1371/journal.pone.0141393. PubMed PMID: 26506413; PubMed Central PMCID: PMCPMC4624775.
59. Maillot P, Perrot A, Hartley A. Effects of interactive physical-activity video-game training on physical and cognitive function in older adults. Psychol Aging. 2012;27(3):589-600. doi: 10.1037/a0026268. PubMed PMID: 22122605.
60. Bennett EL, Diamond MC, Krech D, Rosenzweig MR. Chemical and Anatomical Plasticity Brain. Science. 1964;146(3644):610-9. PubMed PMID: 14191699.
61. Spatz HC. Hebb's concept of synaptic plasticity and neuronal cell assemblies. Behav Brain Res. 1996;78(1):3-7. PubMed PMID: 8793031.
62. Sungkarat S, Boripuntakul S, Chattipakorn N, Watcharasaksilp K, Lord SR. Effects of Tai Chi on Cognition and Fall Risk in Older Adults with Mild Cognitive Impairment: A Randomized Controlled Trial. Journal of the American Geriatrics Society. 2016. doi: 10.1111/jgs.14594. PubMed PMID: 27874176.
63. Kouidi EJ, Grekas DM, Deligiannis AP. Effects of exercise training on noninvasive cardiac measures in patients undergoing long-term hemodialysis: a randomized controlled trial. Am J Kidney Dis. 2009;54(3):511-21. doi: 10.1053/j.ajkd.2009.03.009. PubMed PMID: 19646801.
64. Desideri G, Kwik-Uribe C, Grassi D, Necozione S, Ghiadoni L, Mastroiacovo D, et al. Benefits in cognitive function, blood pressure, and insulin resistance through cocoa flavanol consumption in elderly subjects with mild cognitive impairment: the Cocoa, Cognition, and Aging (CoCoA) study. Hypertension. 2012;60(3):794-801. doi: 10.1161/HYPERTENSIONAHA.112.193060. PubMed PMID: 22892813.
65. Cheema BS, Singh MA. Exercise training in patients receiving maintenance hemodialysis: a systematic review of clinical trials. American journal of nephrology. 2005;25(4):352-64. doi: 10.1159/000087184. PubMed PMID: 16088076.
66. Liao MT, Liu WC, Lin FH, Huang CF, Chen SY, Liu CC, et al. Intradialytic aerobic cycling exercise alleviates inflammation and improves endothelial progenitor cell count and bone density in hemodialysis patients. Medicine (Baltimore). 2016;95(27):e4134. doi: 10.1097/MD.0000000000004134. PubMed PMID: 27399127; PubMed Central PMCID: PMCPMC5058856.
67. Bennett PN, Fraser S, Barnard R, Haines T, Ockerby C, Street M, et al. Effects of an intradialytic resistance training programme on physical function: a prospective stepped-wedge randomized controlled trial. Nephrol Dial Transplant. 2015. doi: 10.1093/ndt/gfv416. PubMed PMID: 26715763.
68. Giannaki CD, Hadjigeorgiou GM, Karatzaferi C, Maridaki MD, Koutedakis Y, Founta P, et al. A single-blind randomized controlled trial to evaluate the effect of 6 months of progressive aerobic exercise training in patients with uraemic restless legs syndrome. Nephrol Dial Transplant. 2013;28(11):2834-40. doi: 10.1093/ndt/gft288. PubMed PMID: 23929523.
69. Parsons TL, Toffelmire EB, King-VanVlack CE. The effect of an exercise program during hemodialysis on dialysis efficacy, blood pressure and quality of life in end-stage renal disease (ESRD) patients. Clin Nephrol. 2004;61(4):261-74. PubMed PMID: 15125032.

70. Marinho SM, C M, Jesm B, Eduardo Jc C, D F, S P, et al. Exercise training alters the bone mineral density of hemodialysis patients. J Strength Cond Res. 2016. doi: 10.1519/JSC.0000000000001374. PubMed PMID: 26863587.
71. Kolewaski CD, Mullally MC, Parsons TL, Paterson ML, Toffelmire EB, King-VanVlack CE. Quality of life and exercise rehabilitation in end stage renal disease. CANNT J. 2005;15(4):22-9. PubMed PMID: 16491995.
72. Painter PL, Nelson-Worel JN, Hill MM, Thornbery DR, Shelp WR, Harrington AR, et al. Effects of exercise training during hemodialysis. Nephron. 1986;43(2):87-92. PubMed PMID: 3713951.
73. Painter P, Moore G, Carlson L, Paul S, Myll J, Phillips W, et al. Effects of exercise training plus normalization of hematocrit on exercise capacity and health-related quality of life. Am J Kidney Dis. 2002;39(2):257-65. doi: 10.1053/ajkd.2002.30544. PubMed PMID: 11840365.
74. Moug SJ, Grant S, Creed G, Boulton Jones M. Exercise during haemodialysis: West of Scotland pilot study. Scottish medical journal. 2004;49(1):14-7. doi: 10.1177/003693300404900104. PubMed PMID: 15012046.
75. DePaul V, Moreland J, Eager T, Clase CM. The effectiveness of aerobic and muscle strength training in patients receiving hemodialysis and EPO: a randomized controlled trial. Am J Kidney Dis. 2002;40(6):1219-29. doi: 10.1053/ajkd.2002.36887. PubMed PMID: 12460041.
76. Johansen KL. Exercise in the end-stage renal disease population. J Am Soc Nephrol. 2007;18(6):1845-54. doi: 10.1681/ASN.2007010009. PubMed PMID: 17442789.
77. Sheng K, Zhang P, Chen L, Cheng J, Wu C, Chen J. Intradialytic exercise in hemodialysis patients: a systematic review and meta-analysis. American journal of nephrology. 2014;40(5):478-90. doi: 10.1159/000368722. PubMed PMID: 25504020.
78. Tong A, Winkelmayer WC, Wheeler DC, van Biesen W, Tugwell P, Manns B, et al. Nephrologists' Perspectives on Defining and Applying Patient-Centered Outcomes in Hemodialysis. Clin J Am Soc Nephrol. 2017;12(3):454-66. doi: 10.2215/CJN.08370816. PubMed PMID: 28223290.
79. Zickefoose S, Hux K, Brown J, Wulf K. Let the games begin: a preliminary study using attention process training-3 and Lumosity brain games to remediate attention deficits following traumatic brain injury. Brain injury. 2013;27(6):707-16. Epub 2013/05/16. doi: 10.3109/02699052.2013.775484. PubMed PMID: 23672446.
80. Sternberg DA, Ballard K, Hardy JL, Katz B, Doraiswamy PM, Scanlon M. The largest human cognitive performance dataset reveals insights into the effects of lifestyle factors and aging. Frontiers in human neuroscience. 2013;7:292. Epub 2013/06/27. doi: 10.3389/fnhum.2013.00292. PubMed PMID: 23801955; PubMed Central PMCID: PMC3687527.
81. Mayas J, Parmentier FB, Andres P, Ballesteros S. Plasticity of attentional functions in older adults after non-action video game training: a randomized controlled trial. PloS one. 2014;9(3):e92269. doi: 10.1371/journal.pone.0092269. PubMed PMID: 24647551; PubMed Central PMCID: PMCPMC3960226.
82. Kesler SR, Lacayo NJ, Jo B. A pilot study of an online cognitive rehabilitation program for executive function skills in children with cancer-related brain injury. Brain injury. 2011;25(1):101-12. doi: 10.3109/02699052.2010.536194. PubMed PMID: 21142826; PubMed Central PMCID: PMCPMC3050575.
83. Morrison GE, Simone CM, Ng NF, Hardy JL. Reliability and validity of the NeuroCognitive Performance Test, a web-based neuropsychological assessment. Front Psychol. 2015;6:1652. doi: 10.3389/fpsyg.2015.01652. PubMed PMID: 26579035; PubMed Central PMCID: PMCPMC4630791.
84. Tartaglione EV, Derleth M, Yu L, Ioannou GN. Can computerized brain training games be used to identify early cognitive impairment in cirrhosis? Am J Gastroenterol. 2014;109(3):316-23. doi: 10.1038/ajg.2013.306. PubMed PMID: 24594947.
85. Axelrod DA, Kynard-Amerson CS, Wojciechowski D, Jacobs M, Lentine KL, Schnitzler M, et al. Cultural Competency of a Mobile, Customized Patient Education Tool for Improving Potential Kidney Transplant Recipients' Knowledge and Decision-Making. Clin Transplant. 2017. doi: 10.1111/ctr.12944. PubMed PMID: 28263408.
86. Graham-Brown MP, March DS, Churchward DR, Young HM, Dungey M, Lloyd S, et al. Design and methods of CYCLE-HD: improving cardiovascular health in patients with end stage renal disease using a structured programme of exercise: a randomised control trial. BMC nephrology. 2016;17(1):69. doi: 10.1186/s12882-016-0294-7. PubMed PMID: 27391774; PubMed Central PMCID: PMCPMC4938939.

87. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc. 1982;14(5):377-81. PubMed PMID: 7154893.
88. Kurella Tamura M, Yaffe K. Dementia and cognitive impairment in ESRD: diagnostic and therapeutic strategies. Kidney international. 2011;79(1):14-22. Epub 2010/09/24. doi: 10.1038/ki.2010.336. PubMed PMID: 20861818; PubMed Central PMCID: PMC3107192.
89. Bhan I, Dobens D, Tamez H, Deferio JJ, Li YC, Warren HS, et al. Nutritional vitamin D supplementation in dialysis: a randomized trial. Clin J Am Soc Nephrol. 2015;10(4):611-9. doi: 10.2215/CJN.06910714. PubMed PMID: 25770176; PubMed Central PMCID: PMCPMC4386253.
90. Urena-Torres P, Bridges I, Christiano C, Cournoyer SH, Cooper K, Farouk M, et al. Efficacy of cinacalcet with low-dose vitamin D in incident haemodialysis subjects with secondary hyperparathyroidism. Nephrol Dial Transplant. 2013;28(5):1241-54. doi: 10.1093/ndt/gfs568. PubMed PMID: 23328710.
91. Delmez JA, Kelber J, Norwood KY, Giles KS, Slatopolsky E. A controlled trial of the early treatment of secondary hyperparathyroidism with calcitriol in hemodialysis patients. Clin Nephrol. 2000;54(4):301-8. PubMed PMID: 11076106.
92. McAdams-Demarco MA, Law A, Garonzik-Wang JM, Gimenez L, Jaar BG, Walston JD, et al. Activity of daily living disability and dialysis mortality: better prediction using metrics of aging. Journal of the American Geriatrics Society. 2012;60(10):1981-2. Epub 2012/10/13. doi: 10.1111/j.1532-5415.2012.04161.x. PubMed PMID: 23057455.
93. McAdams-DeMarco MA, Law A, King E, Orandi B, Salter M, Gupta N, et al. Frailty and mortality in kidney transplant recipients. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2015;15(1):149-54. Epub 2014/11/02. doi: 10.1111/ajt.12992. PubMed PMID: 25359393.
94. McAdams-DeMarco MA, Law A, Salter ML, Boyarsky B, Gimenez L, Jaar BG, et al. Frailty as a novel predictor of mortality and hospitalization in individuals of all ages undergoing hemodialysis. Journal of the American Geriatrics Society. 2013;61(6):896-901. Epub 2013/05/29. doi: 10.1111/jgs.12266. PubMed PMID: 23711111; PubMed Central PMCID: PMC3938084.
95. McAdams-DeMarco MA, Law A, Salter ML, Chow E, Grams M, Walston J, et al. Frailty and early hospital readmission after kidney transplantation. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2013;13(8):2091-5. Epub 2013/06/05. doi: 10.1111/ajt.12300. PubMed PMID: 23731461.
96. McAdams-DeMarco MA, Law A, Tan J, Delp C, King EA, Orandi B, et al. Frailty, Mycophenolate Reduction, and Graft Loss in Kidney Transplant Recipients. Transplantation. 2014. Epub 2014/11/14. doi: 10.1097/TP.0000000000000444. PubMed PMID: 25393156.
97. McAdams-DeMarco MA, Suresh S, Law A, Salter ML, Gimenez LF, Jaar BG, et al. Frailty and falls among adult patients undergoing chronic hemodialysis: a prospective cohort study. BMC nephrology. 2013;14:224. Epub 2013/10/18. doi: 10.1186/1471-2369-14-224. PubMed PMID: 24131569; PubMed Central PMCID: PMC3852906.
98. Costa AS, Tiffin-Richards FE, Holschbach B, Frank RD, Vassiliadou A, Kruger T, et al. Clinical predictors of individual cognitive fluctuations in patients undergoing hemodialysis. Am J Kidney Dis. 2014;64(3):434-42. doi: 10.1053/j.ajkd.2014.02.012. PubMed PMID: 24679895.
99. Katz S, Akpom CA. A measure of primary sociobiological functions. International journal of health services : planning, administration, evaluation. 1976;6(3):493-508. Epub 1976/01/01. PubMed PMID: 133997.
100. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. The Gerontologist. 1969;9(3):179-86. Epub 1969/01/01. PubMed PMID: 5349366.
101. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol. 1994;49(2):M85-94. PubMed PMID: 8126356.
102. Hartmann EL, Kitzman D, Rocco M, Leng X, Klepin H, Gordon M, et al. Physical function in older candidates for renal transplantation: an impaired population. Clin J Am Soc Nephrol. 2009;4(3):588-94. Epub 2009/03/06. doi: 10.2215/cjn.03860808. PubMed PMID: 19261824; PubMed Central PMCID: PMC2653669.

103. MacLeod CM. Half a century of research on the Stroop effect: an integrative review. Psychol Bull. 1991;109(2):163-203. PubMed PMID: 2034749.
104. Wechsler D. Wechsler Memory Scale, revised. San Antonio: Psychological Corporation, 1987.
105. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. J Clin Psychiatry. 1987;48(8):314-8. Epub 1987/08/01. PubMed PMID: 3611032.
106. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. Journal of the American Geriatrics Society. 2005;53(4):695-9. doi: 10.1111/j.1532-5415.2005.53221.x. PubMed PMID: 15817019.
107. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146-56. Epub 2001/03/17. PubMed PMID: 11253156.
108. DiMatteo MR, Hays R. The significance of patients' perceptions of physician conduct: a study of patient satisfaction in a family practice center. J Community Health. 1980;6(1):18-34. Epub 1980/01/01. PubMed PMID: 7430419.
109. Hays RD KJ, Mapes DL, Coons SJ, Amin N, Carter WB. KDQOL-SF version 1.2: A Manual for Use and Scoring. Santa Monica: Rand; 1995.
110. Patel SS, Shah VS, Peterson RA, Kimmel PL. Psychosocial variables, quality of life, and religious beliefs in ESRD patients treated with hemodialysis. Am J Kidney Dis. 2002;40(5):1013-22. Epub 2002/10/31. doi: 10.1053/ajkd.2002.36336
S0272638602001592 [pii]. PubMed PMID: 12407647.
111. Dong J, Pi HC, Xiong ZY, Liao JL, Hao L, Liu GL, et al. Depression and Cognitive Impairment in Peritoneal Dialysis: A Multicenter Cross-sectional Study. Am J Kidney Dis. 2016;67(1):111-8. doi: 10.1053/j.ajkd.2015.06.025. PubMed PMID: 26255306.
112. Kurella M, Luan J, Yaffe K, Chertow GM. Validation of the Kidney Disease Quality of Life (KDQOL) cognitive function subscale. Kidney international. 2004;66(6):2361-7. doi: 10.1111/j.1523-1755.2004.66024.x. PubMed PMID: 15569327.
113. Hain DJ. Cognitive function and adherence of older adults undergoing hemodialysis. Nephrol Nurs J. 2008;35(1):23-9. PubMed PMID: 18372760.
114. Xu R, Pi HC, Xiong ZY, Liao JL, Hao L, Liu GL, et al. Hyponatremia and Cognitive Impairment in Patients Treated with Peritoneal Dialysis. Clin J Am Soc Nephrol. 2015;10(10):1806-13. doi: 10.2215/CJN.02240215. PubMed PMID: 26231192; PubMed Central PMCID: PMCPMC4594065.
115. Liu GL, Pi HC, Hao L, Li DD, Wu YG, Dong J. Vitamin D Status Is an Independent Risk Factor for Global Cognitive Impairment in Peritoneal Dialysis Patients. PloS one. 2015;10(12):e0143782. doi: 10.1371/journal.pone.0143782. PubMed PMID: 26630385; PubMed Central PMCID: PMCPMC4668056.
116. Wang Q, Yang ZK, Sun XM, Du Y, Song YF, Ren YP, et al. Association of Social Support and Family Environment with Cognitive Function in Peritoneal Dialysis Patients. Perit Dial Int. 2017;37(1):14-20. doi: 10.3747/pdi.2016.00084. PubMed PMID: 28153965.
117. Atkinson HH, Rosano C, Simonsick EM, Williamson JD, Davis C, Ambrosius WT, et al. Cognitive function, gait speed decline, and comorbidities: the health, aging and body composition study. J Gerontol A Biol Sci Med Sci. 2007;62(8):844-50. PubMed PMID: 17702875.
118. LeBlanc ES, Wang PY, Janowsky JS, Neiss MB, Fink HA, Yaffe K, et al. Association between sex steroids and cognition in elderly men. Clin Endocrinol (Oxf). 2010;72(3):393-403. doi: 10.1111/j.1365-2265.2009.03692.x. PubMed PMID: 19744108; PubMed Central PMCID: PMCPMC2852485.
119. Atkinson HH, Rapp SR, Williamson JD, Lovato J, Absher JR, Gass M, et al. The relationship between cognitive function and physical performance in older women: results from the women's health initiative memory study. J Gerontol A Biol Sci Med Sci. 2010;65(3):300-6. doi: 10.1093/gerona/glp149. PubMed PMID: 19789197; PubMed Central PMCID: PMCPMC2822281.
120. Klepin HD, Geiger AM, Bandos H, Costantino JP, Rapp SR, Sink KM, et al. Cognitive factors associated with adherence to oral antiestrogen therapy: results from the cognition in the study of tamoxifen and raloxifene (Co-STAR) study. Cancer Prev Res (Phila). 2014;7(1):161-8. doi: 10.1158/1940-6207.CAPR-13-0165. PubMed PMID: 24253314; PubMed Central PMCID: PMCPMC3924583.
121. Wilson VK, Houston DK, Kilpatrick L, Lovato J, Yaffe K, Cauley JA, et al. Relationship between 25-hydroxyvitamin D and cognitive function in older adults: the Health, Aging and Body Composition Study.

Journal of the American Geriatrics Society. 2014;62(4):636-41. doi: 10.1111/jgs.12765. PubMed PMID: 24635412; PubMed Central PMCID: PMCPMC3989387.
122. Yaffe K, Barnes D, Lindquist K, Cauley J, Simonsick EM, Penninx B, et al. Endogenous sex hormone levels and risk of cognitive decline in an older biracial cohort. Neurobiol Aging. 2007;28(2):171-8. doi: 10.1016/j.neurobiolaging.2006.10.004. PubMed PMID: 17097195.
123. Espeland MA, Shumaker SA, Limacher M, Rapp SR, Bevers TB, Barad DH, et al. Relative effects of tamoxifen, raloxifene, and conjugated equine estrogens on cognition. Journal of women's health. 2010;19(3):371-9. doi: 10.1089/jwh.2009.1605. PubMed PMID: 20136553; PubMed Central PMCID: PMCPMC2867626.
124. Saliba D, Buchanan J, Edelen MO, Streim J, Ouslander J, Berlowitz D, et al. MDS 3.0: brief interview for mental status. Journal of the American Medical Directors Association. 2012;13(7):611-7. doi: 10.1016/j.jamda.2012.06.004. PubMed PMID: 22796362.
125. Flythe JE, Xue H, Lynch KE, Curhan GC, Brunelli SM. Association of mortality risk with various definitions of intradialytic hypotension. J Am Soc Nephrol. 2015;26(3):724-34. doi: 10.1681/ASN.2014020222. PubMed PMID: 25270068; PubMed Central PMCID: PMCPMC4341481.
126. Bennett PN, Fraser S, Barnard R, Haines T, Ockerby C, Street M, et al. Effects of an intradialytic resistance training programme on physical function: a prospective stepped-wedge randomized controlled trial. Nephrol Dial Transplant. 2016;31(8):1302-9. doi: 10.1093/ndt/gfv416. PubMed PMID: 26715763.
127. Marinho SM, Moraes C, Barbosa JE, Carraro Eduardo JC, Fouque D, Pelletier S, et al. Exercise Training Alters the Bone Mineral Density of Hemodialysis Patients. J Strength Cond Res. 2016;30(10):2918-23. doi: 10.1519/JSC.0000000000001374. PubMed PMID: 26863587.
128. Wong J, Davis P, Patidar A, Zhang Y, Vilar E, Finkelman M, et al. The Effect of Intra-Dialytic Exercise on Inflammation and Blood Endotoxin Levels. Blood Purif. 2017;44(1):51-9. doi: 10.1159/000455059. PubMed PMID: 28241125.
129. Chigira Y, Oda T, Izumi M, Yoshimura T. Effects of exercise therapy during dialysis for elderly patients undergoing maintenance dialysis. J Phys Ther Sci. 2017;29(1):20-3. doi: 10.1589/jpts.29.20. PubMed PMID: 28210031; PubMed Central PMCID: PMCPMC5300797.
130. Manfredini F, Mallamaci F, D'Arrigo G, Baggetta R, Bolignano D, Torino C, et al. Exercise in Patients on Dialysis: A Multicenter, Randomized Clinical Trial. J Am Soc Nephrol. 2016. doi: 10.1681/ASN.2016030378. PubMed PMID: 27909047.
131. Dannhauser TM, Cleverley M, Whitfield TJ, Fletcher BC, Stevens T, Walker Z. A complex multimodal activity intervention to reduce the risk of dementia in mild cognitive impairment--ThinkingFit: pilot and feasibility study for a randomized controlled trial. BMC Psychiatry. 2014;14:129. doi: 10.1186/1471-244X-14-129. PubMed PMID: 24886353; PubMed Central PMCID: PMCPMC4037760.
132. Donner Y, Hardy JL. Piecewise power laws in individual learning curves. Psychon Bull Rev. 2015;22(5):1308-19. doi: 10.3758/s13423-015-0811-x. PubMed PMID: 25711183; PubMed Central PMCID: PMCPMC4577530.
133. Geyer J, Insel P, Farzin F, Sternberg D, Hardy JL, Scanlon M, et al. Evidence for age-associated cognitive decline from Internet game scores. Alzheimers Dement (Amst). 2015;1(2):260-7. doi: 10.1016/j.dadm.2015.04.002. PubMed PMID: 27239508; PubMed Central PMCID: PMCPMC4876906.
134. Hardy JL, Nelson RA, Thomason ME, Sternberg DA, Katovich K, Farzin F, et al. Enhancing Cognitive Abilities with Comprehensive Training: A Large, Online, Randomized, Active-Controlled Trial. PloS one. 2015;10(9):e0134467. doi: 10.1371/journal.pone.0134467. PubMed PMID: 26333022; PubMed Central PMCID: PMCPMC4557999.
135. Hooker CI, Carol EE, Eisenstein TJ, Yin H, Lincoln SH, Tully LM, et al. A pilot study of cognitive training in clinical high risk for psychosis: initial evidence of cognitive benefit. Schizophr Res. 2014;157(1-3):314-6. doi: 10.1016/j.schres.2014.05.034. PubMed PMID: 24954429; PubMed Central PMCID: PMCPMC4384393.
136. Kesler SR, Sheau K, Koovakkattu D, Reiss AL. Changes in frontal-parietal activation and math skills performance following adaptive number sense training: preliminary results from a pilot study. Neuropsychol Rehabil. 2011;21(4):433-54. doi: 10.1080/09602011.2011.578446. PubMed PMID: 21714745; PubMed Central PMCID: PMCPMC3152634.
137. Kesler S, Hadi Hosseini SM, Heckler C, Janelsins M, Palesh O, Mustian K, et al. Cognitive training for improving executive function in chemotherapy-treated breast cancer survivors. Clin Breast Cancer.

2013;13(4):299-306. doi: 10.1016/j.clbc.2013.02.004. PubMed PMID: 23647804; PubMed Central PMCID: PMCPMC3726272.
138. Rattray B, Smee D. Exercise improves reaction time without compromising accuracy in a novel easy-to-administer tablet-based cognitive task. J Sci Med Sport. 2013;16(6):567-70. doi: 10.1016/j.jsams.2012.12.007. PubMed PMID: 23337198.
139. Schneider S, Abeln V, Popova J, Fomina E, Jacubowski A, Meeusen R, et al. The influence of exercise on prefrontal cortex activity and cognitive performance during a simulated space flight to Mars (MARS500). Behav Brain Res. 2013;236(1):1-7. doi: 10.1016/j.bbr.2012.08.022. PubMed PMID: 22944515.
140. Barnes DE, Yaffe K, Belfor N, Jagust WJ, DeCarli C, Reed BR, et al. Computer-based cognitive training for mild cognitive impairment: results from a pilot randomized, controlled trial. Alzheimer Dis Assoc Disord. 2009;23(3):205-10. doi: 10.1097/WAD.0b013e31819c6137. PubMed PMID: 19812460; PubMed Central PMCID: PMCPMC2760033.
141. Orandi BJ, Luo X, Massie AB, Garonzik-Wang JM, Lonze BE, Ahmed R, et al. Survival Benefit with Kidney Transplants from HLA-Incompatible Live Donors. The New England journal of medicine. 2016;374(10):940-50. doi: 10.1056/NEJMoa1508380. PubMed PMID: 26962729; PubMed Central PMCID: PMCPMC4841939.
142. Kucirka LM, Grams ME, Lessler J, Hall EC, James N, Massie AB, et al. Association of race and age with survival among patients undergoing dialysis. JAMA : the journal of the American Medical Association. 2011;306(6):620-6. doi: 10.1001/jama.2011.1127. PubMed PMID: 21828325; PubMed Central PMCID: PMCPMC3938098.
143. Muzaale AD, Massie AB, Wang MC, Montgomery RA, McBride MA, Wainright JL, et al. Risk of end-stage renal disease following live kidney donation. JAMA : the journal of the American Medical Association. 2014;311(6):579-86. doi: 10.1001/jama.2013.285141. PubMed PMID: 24519297; PubMed Central PMCID: PMCPMC4411956.
144. Boyarsky BJ, Massie AB, Alejo JL, Van Arendonk KJ, Wildonger S, Garonzik-Wang JM, et al. Experiences obtaining insurance after live kidney donation. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2014;14(9):2168-72. doi: 10.1111/ajt.12819. PubMed PMID: 25041695; PubMed Central PMCID: PMCPMC4194161.
145. Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol. 2004;159(7):702-6. Epub 2004/03/23. PubMed PMID: 15033648.
146. Mitnitski A, Fallah N, Rockwood MR, Rockwood K. Transitions in cognitive status in relation to frailty in older adults: a comparison of three frailty measures. The journal of nutrition, health & aging. 2011;15(10):863-7. PubMed PMID: 22159774.
147. Ghosh D, Elliott MR, Taylor JM. Links between analysis of surrogate endpoints and endogeneity. Statistics in medicine. 2010;29(28):2869-79. doi: 10.1002/sim.4027. PubMed PMID: 20803482; PubMed Central PMCID: PMCPMC2997195.
148. Shea, J.A., et al., Development of a Revised Health Care System Distrust Scale. Journal of General Internal Medicine, 2008. 23(6): p. 727--732.

COVER PAGE

1/18/2023

Title: “Interventions Made to Preserve Cognitive Function”

NCT03616535

The statistical methods were updated to account for COVID-19 shutdowns as described below.

Study Design

IMPCT was a randomized controlled trial (RCT) of CT, ET, and combined CT+ET interventions in a 2×2 factorial design, as previously reported. The study team performing assessments was not the same as those providing the interventions and was masked to the intervention. Participants were enrolled, and baseline assessments were conducted (09/2018-02/2023). Primary and secondary outcomes were measured at 3 months. Those collecting primary and secondary outcomes were masked to the intervention assignment. Due to COVID-19 shutdowns, 9 baseline assessments (not included in the trial) and 25 follow-ups at 3 months were interrupted.

All participants provided written informed consent and were compensated with $10 (funding from NIDDK R01DK114074). This trial was approved by the Johns Hopkins Institutional Review Board (IRB00152858) and sIRB with NYU, and reviewed by the Fresenius Medical Care Holdings, Inc. Investigator Initiated Trials Review Committee and DaVita Clinical Research. COVID-19 restrictions in dialysis facilities between 2020-2022 affected recruitment and study operations, leading to the Data and Safety Monitoring Board (DSMB) recommendation of trial termination. Therefore, this trial was terminated on 12/08/2023. The study was registered at clinicaltrials.gov (NCT03616535).

Eligibility

We recruited English-speaking adult (≥18 years) patients with ESKD who had initiated thrice weekly hemodialysis within 3 months to 3 years (09/2018-06/2022) at 14 dialysis centers in the Baltimore, Maryland area and 1 dialysis center in New York City, New York. We limited the study to participants with 3 months-3 years of hemodialysis to capture a population that had potentially reversible cognitive impairment. Exclusion criteria were: 1) inability to participate in ET without assistance; 2) conditions limiting participation (pregnancy, angina pectoris, chronic lung disease requiring oxygen, musculoskeletal conditions, lower- or upper-extremity amputation, orthopedic disorders exacerbated by physical activity, femoral vascular access, legally blind, inability to recognize numbers and letters as well as hepatitis B infection requiring medical isolation); and 3) incarceration.

Randomization

After the baseline assessment, 121 participants were block-randomized (based on sex, race, and dialysis center, factors chosen to remove their effects on cognition) into 4 arms using a secure computer-based allocation system (R).

Statistical Analysis

Baseline characteristics of participants were presented by arm and compared using ANOVA test for normally distributed continuous variables, Kruskal-Wallis test for nonnormally distributed continuous variables, and Chi-squared test for categorical variables. Differences in the primary and secondary outcomes were tested using these methods as well.

For CT, ET and CT+ET arms, we evaluated each participant's adherence to the assigned intervention as: the number of dialysis sessions that the participant attended and participated in the intervention/the number of dialysis sessions that the participant attended)*100%.

The effect of interventions was analyzed according to the intention-to-treat principle. Changes in executive function, global cognitive function, ESKD-specific clinical outcomes, and patient-centered outcomes between baseline and 3 months were handled as continuous outcomes. After visually verifying the linearity, normality, and equal variance assumption, we used linear regression to test the main effect of CT alone and the main effect of ET alone as well as the interaction between CT+ET compared with SC; we also tested these effects with an ANCOVA analysis. In addition, we tested whether the impact of CT, ET, and CT+ET differed from each other. The main comparison used models adjusted for age at enrollment, education, and baseline measures of outcomes, which were adapted to account for imbalances between groups with respect to important risk factors for the outcomes.

All analyses were performed using Stata 16.1 (StataCorp, College Station, TX). Statistical significance was defined as a two-sided p-value <0.05. There was no missingness in adjusted covariates.