Exercise Training and Cognitive Function in Kidney Disease

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MRI collection site

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LIST OF ABBREVIATIONS

COI	Conflict of Interest
DHHS	Department of Health and Human Services
DMC	Data Monitoring Committee
DSMB	Data and Safety Monitoring Board
DSMP	Data and Safety Monitoring Plan
FERPA	Family Educational Rights and Privacy Act
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IBC	Institutional Biosafety Committee
ICD	Informed Consent Document
ICH	International Conference of Harmonization
IDE	Investigational Device Exemption
IDS	Investigational Drug Service
IND	Investigational New Drug
IRB	Institutional Review Board
LAR	Legally Authorized Representative
OHRP	Office of Human Research Protections
OPRS	Office for the Protection of Research Subjects
PHI	Protected Health Information
PI	Principal Investigator
PPRA	Protection of Pupil Rights Amendment
QA/QI	Quality Assurance/Quality Improvement
SAE	Serious Adverse Event
SOP	Standard Operating Procedure

1.0 Project Summary/Abstract

Chronic kidney disease (CKD), affects over 45% of all individuals over 70 years of age. Patients with moderate CKD have more than a two-fold increased risk of cognitive impairment than those without CKD; furthermore, as many as 20-70% of patients with CKD have established cognitive impairment and overt dementia. The burden of cognitive impairment and dementia leads to functional decline and accelerated loss of independence, contributing to the tremendous individual, societal, and economic burden of CKD (i.e., 20% of Medicare expenditures in adults >65 years of age). There is no recommended treatment to prevent cognitive decline in CKD patients, and the few medications available for cognitive impairment have only short term modest effects. There is a critical need to evaluate therapies to forestall cognitive impairment, and maintain or improve cognitive functioning in older patients with CKD. To address this need, we will test the hypothesis that older patients with moderate/severe CKD and pre-clinical cognitive impairment randomized to a 6-month home-based exercise program will improve cognitive function and MRI measured brain structure, compared to a usual care control group. We are focusing on patients with pre-clinical cognitive impairment in order to capture a therapeutic window in the disease process, which will allow us to possibly prevent dementia before brain atrophy becomes irreversible. **This is a pilot study for feasibility.** Our central hypothesis is that the accelerated cognitive decline in CKD results from a vascular dysfunction-induced reduction in the integrity of the brain white matter and that exercise training provides a cerebro-protective effect by improving cerebral vascular health. We will combine an assessment of cognition with MR imaging techniques to fully evaluate brain structure, blood flow, and behavior relationships at a level previously not conducted in this population. This study is designed to improve or forestall cognitive decline in CKD patients by establishing an intervention that is implemented individually in the community, and will provide the first step in providing an effective treatment designed to delay physical and cognitive function-related loss of independence, and curb the escalating costs in the growing CKD population. This is a population with accelerated brain aging and a high prevalence of cognitive impairment, making the potential clinical impact tremendous.

Anticipated risks associate with the study: We will monitor heart rate and blood pressure during all testing. There is a very small risk associated with the 6 minute walk exercise test and training. The risk of serious adverse events (such as death or heart attack) with maximal exercise testing has been estimated to be 0.5 per 10,000 tests (Stuart, 1980 Chest), the risk of death associated with a 6-minute walk is currently not known, but is considered minimal risk. The exercise test (6 minute walk) and training proposed in this study is considered no more than usual activity of daily living and is considered

moderate intensity exercise. There is a slight risk of abnormally high blood pressure, shortness of breath, muscle injury, and muscle soreness associated with exercise training in a sedentary (not used to exercise) population. There is a slight risk for pain and bruising with the venipuncture. There is a slight risk for loss of confidentiality (being identified) and there may be some discomfort felt by participants when answering questions about their medical history and during cognitive testing: The risks associated with the procedures of this study are minimal – no greater than those encountered during daily life. MRI scans: The MRI does not use x-ray radiation or radioactive material. The magnetism of the machine attracts certain metals, which could put participants at risk. Therefore, people with pacemakers, infusion pumps, metal prostheses, metallic-backed transdermal patches or metallic shrapnel will be excluded from the study. A checklist will be completed that addresses issues of MRI safety. Some people may feel somewhat closed-in (claustrophobic) during the MRI procedure. The MRI scans can get quite noisy and this may cause some discomfort. We will provide padding, a blanket, and ear plugs to ensure comfort. During the vascular testing; the blood pressure cuff could feel too tight and it may cause discomfort and there might be pressure on the neck from the ultrasound Doppler transducer, which could feel uncomfortable. Participants' can withdraw at any time and we will closely monitor them to ensure safety and comfort.

Anticipated Benefits: **This is a pilot study for feasibility** and no benefits should be expected. Walking exercise training has been associated with significant improvement in fitness (aerobic capacity), blood pressure, and ability to perform activities (physical function). The effect of exercise training on cognition is promising, but currently unknown.

Subject population: We anticipate randomizing 72 men and women with and without CKD between 60 and 80 years of age with no contraindications to moderate-intensity exercise that answered "yes" to the question "Do you feel like your memory or thinking skills have gotten worse recently?". (please see detailed inclusion/exclusion criteria, section 4), In order to achieve this we anticipate sending 2000 letters to potential participants at UIC.

2.0 Background/Scientific Rationale

Patients with CKD have more than a two-fold increased risk of cognitive impairment than those without CKD.1-3 As many as 20-50% of patients with moderate CKD have established cognitive impairment or overt dementia.1-7 Cognitive impairment leads to decreased medical care compliance, functional decline and loss of independence.8 There are no recommended treatments to prevent cognitive decline in CKD patients. There is therefore a need for therapies aimed to improve cognitive outcomes in older patients with CKD. The accelerated cognitive decline in older CKD patients is due, in part, to the CKD disease process itself, which creates a toxic vascular milieu that consists of chronic inflammation, oxidative stress, uremia, and systemic vascular endothelial dysfunction. This toxic internal vascular milieu leads to vascular dysfunction related impairment of the white matter that is superimposed on neurodegenerative damage.9 The white matter is important for coordinating interactions between different regions of the brain and is essential for normal functioning of the brain.10-14 Impaired white matter integrity appears to be a primary contributor to cognitive decline in CKD and is strongly affected by the internal vascular milieu.10,11 We have previously demonstrated that exercise training improves the vascular milieu in patients with CKD by reducing systemic inflammation and oxidative stress, and improving vascular function.15,16 Regular exercise and higher fitness levels in non-CKD patients with and without cognitive impairment has been associated with improved cognitive function, white matter integrity, and hippocampal volume suggesting a possible cerebro-protective effect of exercise.17-28 This is conjectured to be due to an improvement in vascular function related increases in cerebral blood flow.18 The effect of exercise training on cognitive function and white matter integrity in CKD patients is unknown.

3.0 Objectives/Aims

This is a pilot study for feasibility. The objective of this study is to test the hypothesis that older participants with moderate/severe chronic kidney disease (CKD) and preclinical cognitive impairment randomized to a 6-month home-based exercise program (n=12), will improve cognitive functioning and white matter integrity (WMI), compared to participants in a usual care control group (n=12). Our central working hypothesis is that the accelerated cognitive decline that occurs in CKD results, in part, from a vascular-dysfunction induced impairment of white matter integrity that is superimposed on a neurodegenerative process, and that exercise training may provide a cerebro-protective effect by improving systemic and cerebral vascular health.

Aim 1: Determine the feasibility and preliminary efficacy of a 6-month home-based exercise program to improve or maintain cognitive function in older participants with moderate/severe CKD and preclinical cognitive impairment, compared to usual care control group.

Hypotheses: Participants in the exercise group compared to the usual care control group at 6-months will:

H1a. Demonstrate a higher score on composite global cognitive functioning.

H1b. Demonstrate higher scores on executive functioning, learning/memory, and attention/information processing.

Aim 2. Determine the cerebro-protective effect of a 6-month exercise program compared to usual care on white matter integrity as quantified by Diffusion Tensor Imaging (DTI)-derived MRI measures of mean diffusivity (MD) and fractional anisotrophy (FA). Intact white matter is important because it allows the brain to function properly and these are indices of white matter integrity.

H2a. Participants in the exercise group will demonstrate an improvement in overall white matter integrity as measured by DTI, i.e., lower MD and higher FA, compared to control.

H2b. Change in cognitive function will be positively correlated with change in WMI.

Aim 3 (secondary MRI outcomes): Determine the cerebro-protective effect of a 6-month exercise program compared to control on hippocampal volume and cerebral blood flow.
Hypothesis: Participants in the exercise group will have a larger hippocampal volume and improved cerebral blood flow post 6-month intervention, compared to the control group.

Study Duration: 12 months. Study duration for enrolled participants is anticipated to be 27 weeks.

4.0 Eligibility

The eligibility check lists are attached. The PI (Ulf G. Bronas) will ensure that subjects meet eligibility requirements. An eligibility checklist will be completed prior to any study participation during the initial phone screen and during the initial visit following informed consent. Eligibility criteria will be continuously monitored by the PIs and document via an eligibility checklist at baseline and at the 24 week follow up.

4.1 Inclusion Criteria (self-reported and ICD code)

- English speaking men and women
- 60-80 years of age,
- self-experienced persistent decline in cognitive capacity determined as self-reported cognitive complaint (i.e., answering “yes” to the question: “Do you feel like your memory or thinking skills have gotten worse recently?” (before any clinical impairment of cognition has occurred);[26,29,30]
- no history of major head trauma.

4.2 Exclusion Criteria (self reported or ICD code)

- *Diagnosed Dementia or a score of <2 on the mini-cog assessment*
- *Ischemic ulcerations or gangrene on the feet or legs;*
- *Participating in a supervised exercise program with intent to increase fitness levels 3 days/week,*
- *Requires assistive ambulation;*
- *Limited exercise capacity due to conditions other than claudication*
    - *unstable angina,*
    - *Claudication*
    - *severe arthritis,*
    - *extreme dyspnea on exertion,*
    - *unstable coronary artery disease;*
    - *Class III-IV heart failure;*
    - *Current uncontrolled sustained arrhythmias,*
    - *severe/symptomatic aortic or mitral stenosis,*
    - *hypertrophic obstructive cardiomyopathy,*
    - *severe pulmonary hypertension,*
    - *active myocarditis/pericarditis,*
    - *thrombophlebitis,*
    - *recent systemic/pulmonary embolus (within 3 months);*
- *Resting systolic BP >200 mmHg or resting diastolic BP >110 mmHg;*
- *Revascularization procedures within the previous 6 months;*
- *Any unforeseen illness or disability that would preclude exercise testing or training based on patient provider opinion;*
- *Pregnancy*

4.3 **Excluded or Vulnerable Populations**

Vulnerable populations are not included in this study. In addition, the following populations are excluded from this study:
1. Pregnant women: Pregnant women are excluded to limit any potential influence on measures. Non-English speaking population: Non-English speaking population will be excluded to allow patients to fully understand the English speaking study forms, instructions, and procedures used in this pilot study.

5.0 Subject Enrollment

Subjects will be recruited through fliers and a recruitment brochure in Chicago, surrounding communities, and at the outpatient clinics, and a via letters of invitation at UIC. The UI medical center electronic medical records database and the University of Illinois Hospital & Health Sciences System Clinical Research Data Warehouse (CRDW) will be employed to identify potential patients for the study, following HIPPA standards of authorization. The EMR and The University of Illinois Hospital & Health Sciences System Clinical Research Data Warehouse (CRDW) will be searched for diagnosis of CKD using creatinine and estimated glomerular filtration rate. Name, address, email, phone numbers, and medical record number will be extracted into a file for research use.

1. Patients that have a diagnosis code or meet criteria for CKD based on ICD codes or creatinine levels (or estimated glomerular filtration rate) will be sent a letter or an email of invitation mentioning that they might be eligible for a research study and why, and a self-addressed return envelope. Patients will also receive a letter of invitation that that states that they should return the envelop (or email) stating that they do not wish to be contacted by the research staff via telephone and a self-addressed return envelope. We will call all patients that meet criteria for CKD that did not send back the letter stating that they did not wish to be contacted. Phone calls will start 2 weeks after the mailing has been completed.
2. We will post media advertisements on sites such as Craig's list, UIC list-serve, Redeye newspaper, and other relevant media using the advertisement called "media ad".
3. We will send letters advertising the study to persons over 60 years of age in Chicago and surrounding areas using the form titled study interest letter and study brochure.
4. We will send a notice via the CCTS research match service using the form titled "research match"
5. We will approach patients that have expressed an interest in the study to their provider at UIH clinics, this will include a brief medical records review for eligibility.

Individuals who do not qualify for the study will be informed immediately after the telephone screening. Following initial screening by phone interview and if no exclusion criteria are met and with the participant's consent, they will be scheduled for an initial visit during which formal consent procedures will be executed. After completion of the study, we will provide subjects with copies of their records upon request. Any abnormal results will be reported to study participants for appropriate medical follow-up as well as their provider upon consent.

Subjects that contact the study team will be given as much time as they feel necessary to decide if they would like to participate. Subjects will be encouraged to ask any questions at any time throughout the course of the study. Research personnel will be available to answer these questions. Subjects will be informed that participating in this research is voluntary. Subjects will be informed that they may withdraw from the research at any time without penalty. The patient provider is not part of the study team.

Precautions to protect subject privacy will be taken throughout the course of the study. All telephone conversations with potential subjects will be conducted in a private setting. Face to face conversations will be conducted within a private setting within the College of Nursing clinical health laboratory with private rooms. Strict procedures will be put in place to minimize the risk of breach of confidentiality. All subjects will be assigned a study code. The master list of the subject's name and the linked code will be kept by the study manager in a locked file cabinet in a locked office. All information provided by subjects will kept strictly confidential and will not be reported on an individual basis. None of the information provided by subjects will become part of the medical record. Hard copy data will be stored in a locked office, and electronic data will be stored on a password-protected computer. Hard copy and electronic data will be coded, with the master list kept separately in a secure file in the principal investigator's office. A HIPAA

authorization form has been developed for this study to use/disclose protected health information. Subjects will be asked to sign the HIPAA consent form. Subjects who refuse to agree to the HIPAA authorization will not be able to participate in this study.

6.0 Study Design and Procedures

This is a pilot study for feasibility. The study is designed as a randomized, controlled study.

Screening procedures:

1. Subjects will be recruited through fliers and a recruitment brochure in Chicago, surrounding communities, and at the outpatient clinics, and a via letters of invitation at UIC. The UI medical center electronic medical records database and the University of Illinois Hospital & Health Sciences System Clinical Research Data Warehouse (CRDW) will be employed to identify potential patients for the study, following HIPPA standards of authorization. The EMR and The University of Illinois Hospital & Health Sciences System Clinical Research Data Warehouse (CRDW) will be searched for diagnosis of CKD using creatinine and estimated glomerular filtration rate. Name, address, email, phone numbers, and medical record number will be extracted into a file for research use.

1. Patients that have a diagnosis code or meet criteria for CKD based on ICD codes or creatinine levels (or estimated glomerular filtration rate) will be sent a letter or an email of invitation mentioning that they might be eligible for a research study and why, and a self-addressed return envelope. Patients will also receive a letter of invitation that that states that they should return the envelop (or email) stating that they do not wish to be contacted by the research staff via telephone and a self-addressed return envelope. We will call all patients that meet criteria for CKD that did not send back the letter stating that they did not wish to be contacted. Phone calls will start 2 weeks after the mailing has been completed.

2. We will post media advertisements on sites such as Craig's list, UIC list-serve, Redeye newspaper, and other relevant media using the advertisement called "media ad".

3. We will send letters advertising the study to persons over 60 years of age in Chicago and surrounding areas using the form titled study interest letter and study brochure.

4. We will send a notice via the CCTS research match service using the form titled "research match"

5. We will approach patients that have expressed an interest in the study to their provider at UIH clinics, this will include a brief medical records review for eligibility.

2. Patients who are interested in participating in the study will have a phone interview to assess exclusion criteria. The phone calls will be conducted in by the study manager in a private room located at the UIC College of Nursing, room 229. It is estimated that the telephone screen will take approximately 10 minutes. This is the document titled "Telephone Screening-Eligibility checklist" and we will follow the telephone screening script titled "Phone Script"

3. a Following initial screening by phone interview the interested participants will be scheduled to come in to the College of Nursing 2nd floor Clinical Research Laboratory (845 S Damen Ave) room 229. During this visit, the study will be

thoroughly explained and all questions will be answered. Comprehension of all study procedures will be ascertained by non-leading open-ended questions. If participants express an understanding of the study and study procedures and would like to participate in the study, written informed consent will be obtained. No study procedures will take place prior to written informed consent.

3. b Following the informed consent process, medical history, the Charlson co-morbidity index questionnaire, blood pressure, heart rate, height, and weight, will be obtained by the PI and/or research assistant. If there are no known contraindications to exercise the participant will continue study participation. These are the documents titled “medical history and “Charlson score tally” We will complete the document titled “In-Person Screening Eligibility Checklist” and ask the participant to fill out the form titled “demographics” and the form titled “Face sheet”.

3. c. Following these procedures participants will be asked to complete several questionnaires to assess their cognitive function. These questionnaires will be performed pre- and post-intervention with alternative forms where available to avoid practice effects. In addition to an overall global composite of cognitive functioning, we will evaluate the following domains of functioning with the below noted tests. (time~1 hour): The forms are titled: Learning & Memory=California Verbal Learning Test-II (CVLT-II); Attention/Information Processing=Trail Making Test Part A (TMT-A) and Digit Symbol Substitution Test (DSST); Executive Functioning, Phonemic and Semantic Fluency=Trail Making Test Part B and part M (TMT-B) and Digit Span subtest (DSp); Global Cognition=MOCA and WTAR (please see enclosed questionnaires). Quality of life will be assessed via the kidney disease quality of life questionnaire. These questionnaires will be administered at baseline and at 24 week follow up. The study satisfaction questionnaire will be administered at 24 weeks only.

Cognitive Outcomes (Table 1) will be performed pre- and post-intervention with alternative forms where available to avoid practice effects. In addition to an overall global composite of cognitive functioning, we will evaluate the following domains of functioning with the below noted tests. (time~1 hour)

Table 1. Cognitive Protocol

Domain	Tests	Outcome variables
Learning & Memory	California Verbal Learning Test-II (CVLT-II)	CVLT-II: Trials1-5 and learning slope; Long Delay Free Recall and Recognition Memory Discriminability
Attention/Information Processing	Trail Making Test Part A (TMT-A); Digit Symbol Substitution Test (DSST)	TMT-A time to completion and errors; DSST time to completion and errors
Executive Functioning	Phonemic and Semantic Fluency; Trail Making Test	Total correct words produced for Phonemic and Semantic fluency

	Part B (TMT-B); Digit Span subtest (DSp)	separately; TMT-B time to completion and errors; DSp total score
Global Cognition	MOCA and WTAR*	Total MOCA score; WTAR Estimated verbal IQ

*WTAR will only be given once as premorbid IQ is not anticipated to change with intervention

3. d. Following these procedures a CCTS travel nurse will perform a standard venipuncture. Ten milliliters will be collected for determination of complete blood cell count and basic metabolic panel in order to characterize the sample. Coded blood samples will be analyzed by Quest diagnostics. An additional 10 ml will be collected for analysis of vascular health biomarker in Dr. Bronas lab.

3. e. Following blood draw we will ask the participants to perform the short physical performance battery; participants attempt to stand for 10 seconds with their feet side by side, standing with the side of the heel of one foot touching the big toe of the other foot for about 10 seconds; and with the heel of one foot in front of and touching the toes of the other foot for about 10 seconds, they will then walk at a normal speed for a total of 4 meters (this test is repeated twice); the last part is called a chair rise where participants stand up from a chair 5 times (see manual in the appendix). Thereafter a 6-minute walk will be performed to determine total walking distance. Participants will follow standard testing procedures for older patients. Participants will be asked to walk up and down a 100 foot long corridor as fast as they can without running. They will turn around a cone placed at each end of the walk. No encouragement will be given and participants will be allowed to stop and rest whenever they need. Heart rate (measured by a polar heart rate monitor) will be monitored at rest, during and following the walking test to ensure safety. Blood pressure will be assessed prior to and immediately following the 6-minute walk. The 6-minute walk is considered to be within usual activities of daily living and should not pose any risk to participants. The 6-minute walk test is an accepted method for determination of total walking distance in older adults with chronic illness (see appendix for manual). The document used are titled “6 minute walk test” and Short Physical Performance Battery”. These will be administered at baseline and at the 24 week follow up.

The total time estimated for visit 1 is 2-3 hours.

Following completion of the initial visit we will ask the participants to wear a physical activity monitor, similar to a fancy pedometer, (actigraph GXT3 the size

of a small matchbox) on their hip for one week in order to collect their usual activities of daily living.

Visit 2 (about 1 week following visit 1): If able to undergo MRI scan: The patient will return to UIC and the center for Magnetic Resonance Imaging Center UIC **2242 W. Harrison St. Chicago IL 60612**. During visit 2 we will ask participants to have their brain imaged by an MRI machine for assessment of their brain structure. The imaging will be performed on GE 3T MRI research dedicated scanner (MR 750) pre- and post-intervention. Padding will ensure comfort and limit excessive motion during scanning. After a brief scout image for localization, we will acquire the following whole brain images using diffusion tensor imaging, DTI; T1- and T2-weighted imaging; and arterial spin labeling (ASL). (time~1hour)

Image acquisition will be performed on GE 3T MRI research dedicated scanner (MR 750) pre- and post-intervention. After a brief scout image for localization, we will acquire whole brain images using diffusion tensor imaging (DTI); and high-resolution 3D T1-weighted imaging. We will determine and quantify white matter integrity (DTI-FA/MD); and hippocampal volume (T1). These are indices of alterations of brain inter-connections, structure, and function, which are associated with cognitive functioning (details, table 2).

Table 2. Imaging Parameters

Technique	Purpose	Parameters (TE=echo time; TR=repetition time; BW=bandwidth; FOV=field of view; TI=inversion time)
DTI	White matter integrity (FA/MD) quantification	single-shot EPI & parallel imaging using the same 32-channel phased-array head coil; TE/TR~70/5525ms, b-values 0,1000s/mm^2, 33 directions, FOV=20cm^2, matrix 160x160, NEX 2, parallel imaging acceleration factor 2; 6 B0 images, Slice thickness 3 mm
T1/BRAVO	Hippocampal Volume Quantification	Coronal; TI=4.5, Flip=13º, 1.5mm slice thickness, no gap, BW=±25kHz, FOV=22cm^2
T2-FLAIR	White matter hyperintensity quantification	Coronal; TE/TR=104.5/9500ms, TI=2.5sec, FOV 22cm^2
ASL	Cerebrovascular perfusion Cerebral blood flow	axial; Spiral-FSE acquisition; post-label delay time = 1.8 sec, TE/TR=minimum, flip angle=90°, slice thickness = 3-5 mm, matrix size = 128x128, FOV 22cm^2
Resting-state fMRI	Resting state networks	Subjects will be instructed to keep their eyes open, focus on a fixation point, and “not think of anything in particular”. Resting-state data will be acquired: total scan time = 8 minutes.

Image Analyses DTI: FSL with TBSS, we will quantify FA and MD from whole brain and tract specific white matter. T1/FSPGR: Using FreeSurfer, we will extract hippocampal volumes (right and left) as well as sub-fields of the hippocampas adjusted for intracranial volume.T2-FLAIR: Using standard software, we will quantify white matter hyperintensity volumes across the entire brain white matter. We will use a seed-based approach to measure resting state networks of interest. *Functional connectivity networks:* Functional brain networks will be generated using the resting-state fMRI toolbox, CONN (*http://www.nitrc.org/projects/conn*; (Whitfield-Gabrieli and Nieto-Castanon, 2012)). In brief, raw EPI images are realigned, co-registered, normalized, and smoothed before analysis. Any confound effects from motion artifact, white matter, and CSF are regressed out of the signal. Using the same label maps as the structural brain networks, functional brain networks will derived using pairwise BOLD signal correlations.

The total estimated time during visit 2 is 1-2 hours.

Visit 3. (about 1 week following visit 2): During this visit we will assess vascular health (arterial stiffness, endothelial function, and carotid artery compliance).

Participants will be asked to come back the college of nursing in the morning between 7-11:00 am following an overnight fast with no caffeinated or sugary beverages in the morning of the test. This is done to avoid any diurnal variability. Following a 15-minute supine rest will assess several vascular health indices listed below:

Arterial Stiffness will be measured using carotid-femoral pulse wave velocity following standard procedures:
1. A blood pressure cuff is placed around the upper arm and is automatically inflated and deflated for determination of blood pressure and for pulse wave form analysis. This is similar to a usual blood pressure assessment during a clinical visit.
2. A blood pressure cuff will be placed around the upper thigh of the subject and a hand-held tonometer (similar to the eraser end of a pencil) will be placed overt the carotid (neck) artery. Once the tonometer detects a carotid pulse the blood pressure cuff is inflated (similar to a blood pressure obtained in a clinical visit, but on the upper thigh) and the pulse wave form is automatically collected. This measure will be repeated 3 times and the average pulse wave velocity will be used. Total time=10 minutes

Endothelial function will be assess using brachial artery flow mediated vasodilation following standard guidelines:
1. The participant's brachial artery in the upper arm will be imaged using ultrasound. The ultrasound transducer will be placed on the participant's upper arm and a baseline picture of the brachial artery will be obtained.
2. A blood pressure cuff will be placed on the forearm of the participant. The blood pressure cuff will be inflated to 20 mm Hg above the systolic pressure for 5

minutes followed by a rapid deflation of the cuff. The brachial artery will be imaged for 3-5 minutes follow deflation of the cuff. Total time=10 minutes

Carotid artery compliance will be assessed using ultrasound of the carotid artery. The carotid artery will be imaged using ultrasound. The ultrasound transducer will be placed over the carotid artery and the carotid artery will be imaged for approximately 30 seconds.

Following the vascular assessment, the NIH Toolbox measures for Cognitive function will completed using the standard NIH Ipad (see administration manual):
C.2.1 NIH Toolbox Picture Vocabulary Test page 46
C.2.2 NIH Toolbox Flanker Inhibitory Control and Attention Test page 49
C.2.3 NIH Toolbox List Sorting Working Memory Test page 61
C.2.4 NIH Toolbox Dimensional Change Card Sort Test (DCCS) page 82
C.2.5 NIH Toolbox Pattern Comparison Processing Speed Test page 109
C.2.6 NIH Toolbox Picture Sequence Memory Test page 118
C.2.7 NIH Toolbox Oral Reading Recognition Test page 137
C.2.8 Oral Symbol Digit Test page 140
C.2.9 Auditory Verbal Learning Test (Rey) page 142

Following the NIH Toolbox measures for Cognitive function, the NIH toolbox motor measures will completed using the standard NIH Ipad (see administration manual):
Pegboard dexterity test
Balance measures with the addition of iPod app for assessment of sway.
Two-minute walk (already assessed at visit 1, already IRB approved)
Timed-up and go (TUG)
Grip strength (using handheld dynamometer)
4 meter walk (already IRB approved and assessed during visit 1)

Upon completion of Visit 3, the patient will be randomized to the 24-week walking program or usual care. The randomization will be assignment by chance using a 1:1 chance of being assigned to the exercise group over the usual care group. Participants cannot choose which exercise group they will be in. The assignment is done by a randomized numbers table in computer program that acts like flipping a coin to decide which group they will be placed in.

The total estimated time during visit 3 is 1-2 hours.

The exercise training group will participate in an educational session on walking exercise for CKD during visit 2. Participants will receive a packet of information previously developed by the PI with exercise prescription and information, and a heart rate monitor that monitors the exercise. The documents handed out to the exercise group are titled “Exercise Recommendations” and “work effort scale”.We will work with the participant to 1) set up a schedule that

fits with the participant's schedule for home-based exercise; 2) identify time-slots for exercise; 3) work with the participants to assess their readiness to do exercise; 4) address perceived barriers to exercise, and 5) build a relationship with the participants to provide support and address concerns. This will be done to empower participants to take individual control of the exercise program. Participants will be asked to exercise (a brisk walk) at home, 3 times per week, for 30-60 minutes for 24 weeks.

Participants randomized to the exercise group will be contacted via phone biweekly or more frequently if they are slightly behind the exercise routine, and we will meet with them once per month to provide encouragement and progression of exercise, and to download the heart rate monitor. Participants will have to option to upload their physical activity remotely if they prefer, but they will still be asked to meet in person as scheduled. This system will allow us to monitor and address any issues to achieve optimal compliance to the intervention. We have successfully conducted this type of partially supervised exercise program in CKD patients with excellent adherence and compliance rate (80-87%).

The monthly meetings (once per month) will occur at months, 1, 2, 3, 4, and 5 following randomization. The PI and study staff will continue to work with the participants to assess their readiness to do exercise; 2) address perceived barriers to exercise, and 3) provide support and address concerns related to the exercise program. The meetings will last 30 minutes. We will assess for any adverse events during the bi-weekly phone calls using the document title "Adverse Event Monitoring". The total number of visits in the exercise group is 11.

Usual medical care control group

The usual care group will receive standard instructions on exercise for patients with kidney disease. These documents are titled "Exercise Recommendations" and "work effort scale".This is similar to what is commonly done in clinical practice. The control group will not receive an exercise prescription or heart rate monitor. Participants will be contacted via phone biweekly to answer any questions and ensure continued study participation. In order to minimize any feeling of disenfranchisement in the control group we will offer them the exercise training prescription following all post-test data collection procedures. The usual care group will NOT meet monthly. We will assess for any adverse events during the bi-weekly phone calls using the document title "Adverse Event Monitoring". The total number of visits for the usual care group is 5.

Ten participants with an eGFR of >60 ml/min will only undergo baseline testing and not partake in the intervention or follow up. We will ask if the participants with an eGFR >60 ml/min prefer to only to the baseline versus intervention.

Follow-up testing will occur at 24 weeks over 2 visits about 1 week apart. During the follow up testing we will ask participants to perform one 6-minute walk test and the short physical performance battery, and the NIH toolbox measures as described above, as well as completing the questionnaires and imaging procedures described above.

During the 24-week visit we will query patients using structured interviews and open-ended questions as to whether participants liked the independent home-based walking program. Study satisfaction will be assessed using a likert scale and open-ended question at the end of the 24 week follow up test..

<u>Physical activity and exercise monitoring and Assessment of Adherence to Exercise Rehabilitation Program (fidelity of treatment):</u>
1. Adherence to the exercise program in the intervention group will be tracked using a heart rate monitor. The heart rate monitor will track when exercise training has been performed (date), duration of the exercise, and the intensity of the exercise. These data will be downloaded at each monthly visit to assess adherence to the program (this is coded data). Adherence and volume of exercise will be calculated as number of exercise sessions performed divided by number of prescribed exercise session x 100.

2. We will also ask all participants regardless of group assignment to wear the lightweight accelerometer worn on the hip (Actigraph GTX3, Actigraph) for 7 days at weeks 6, 12, 18, and 24 following randomization. Participants will be mailed the actigraph and reminded to wear it during the biweekly phone calls. They will be asked to return the actigraph after 1 week using a stamped self-addressed return envelope. This is done to assess daily physical activity and is not an intervention.[56]

The study manager will be trained and checked off by the PI in the measurement of the 6-minute walk and short physical performance battery. Fidelity and competence will be continuously monitored by the PI and protocol fidelity will be ascertained during bi-weekly phone calls and the once per month visits.

7.0 Expected Risks/Benefits

Risk associated with the medical history assessment

Discomfort could be felt by participants when answering questions about their medical history.

Risk associated with the physical function battery

There is a slight risk of falling during the balance testing.

Risk associated with the 6 minute walk

There is a slight risk of abnormally high blood pressure, shortness of breath, muscle injury, and muscle soreness. The risk of serious adverse events with maximal exercise testing has been estimated to be 0.5 per 10,000 tests (Stuart, 1980 Chest), the risk of death associated with a 6-minute walk is currently not known, but is considered minimal risk. The exercise test (6 minute walk) proposed in this study is considered no more than usual activity of daily living and is considered moderate intensity exercise. There is a risk that underlying disease may be uncovered during study participation. This would most likely be undiagnosed cerebrovascular disease, previous stroke or mini-stroke. These findings would be immediately related to the patient and the providers (upon patient approval). These findings may require additional testing and procedures as deemed necessary by the patient's provider.

Risks associated with the walking exercise training

There is a slight risk of injury associated with exercise training in a sedentary. population. There is a slight risk of abnormally high blood pressure, shortness of breath, muscle injury, and muscle soreness associated with exercise training in a sedentary (not used to exercise) population. The risk of serious adverse events with maximal exercise testing has been estimated to be 0.5 per 10,000 tests (Stuart, 1980 Chest), the risk of death associated with walking exercise training is currently not known, but is considered minimal risk. The exercise training proposed in this study is considered no more than usual activity of daily living and is considered moderate intensity exercise. There is a risk that underlying disease may be uncovered during study participation. This would most likely be undiagnosed cerebrovascular disease, previous stroke or mini-stroke. These findings would be immediately related to the patient and the providers (upon patient approval). These findings may require additional testing and procedures as deemed necessary by the patient's provider.

Risks associated with the venipuncture (blood draw)

The blood draw may cause pain and bruising. There is a slight risk for infection, lightheadedness and fainting.

Risk associated with the cognitive function questionnaires.

There is a slight risk that participants will feel uncomfortable with filling out the questionnaires. Participants could find answering the questions boring and/or tiring. We will monitor the progress and allow participants to take breaks as needed. If they become upset or uncomfortable, they may skip a given question.

Risks associated with the MRI:

The MRI does not use x-ray radiation or radioactive material. The magnetism of the machine attracts certain metals, which could put participants at risk. Therefore, people with pacemakers, infusion pumps, metal prostheses, metallic-backed transdermal patches or metallic shrapnel will be excluded from the study. A checklist will be completed that addresses issues of MRI safety. Some people may feel somewhat closed-in (claustrophobic) during the MRI procedure. The MRI scans can get quite noisy and this may cause some discomfort. We will provide padding, a blanket, and ear plugs to ensure comfort. This risk is minimized by careful screening by qualified research personnel prior to entry into the MRI room. Subjects with metal implantations will not be recruited. Participants' can withdraw at any time and we will closely monitor them to ensure safety and comfort.

Risks associated with ultrasound procedure:

There could be pressure felt on the neck from the hand-held tonometer, which might make participants feel uncomfortable. The inflation of the blood pressure cuffs might feel too tight and cause discomfort (similar to that of having a blood pressure measured in clinic).
The blood pressure cuff could feel too tight and it may cause discomfort and pain.
There might be pressure on the neck from the ultrasound Doppler transducer, which could feel uncomfortable
If any of these occur the measurement will stop immediately.

8.0 Data Collection and Management Procedures

Results from all measurements, and questionnaires will be recorded on coded source documents before being entered into the electronic database that is password protected and housed on a secure CON server that only the PIs and statistician have access to. Source documents will be stored in a locked file cabinet in a locked office that only the PIs have access to. coded exercise data from the heart rate monitor and actigraph will be downloaded at each follow-up

visit to a password protected secure CON server and analyzed before being entered into the main database as described above.

9.0 Data Analysis

Dr. Alana Steffen of the College of Nursing statistician will conduct all analyses. The apriori stated analysis is listed below.

This is a pilot study for feasibility**.** For these pilot data we will emphasize descriptive statistics such as means, standard deviations, effect sizes, medians, interquartile ranges, frequencies, and percentages to demonstrate the feasibility of recruitment, adherence, and retention, treatment effects over time, and proof of concept. Our statistical approach for a full trial of these hypotheses will be Generalized Linear Mixed Models (GLMM) with an identity link function for a continuous outcome or a logit link function for a binary outcome. Conceptually, GLMM is a more advanced version of repeated measures ANOVA that can account for potential correlation among multiple measurements over time while having flexibility in fitting outcomes with different distributions (such as normal, binomial or Poisson, etc.). One advantage of this approach over repeated measures ANOVA is that there is no assumption that participants are measured at every, or even the same, time points. Therefore, these models are very flexible at handling missing data. Participants who have a missing observation are not excluded, thus, this produces the intention to treat (ITT) full information maximum likelihood (FIML) model. Conducting these models on pilot data help with sample size calculations for a future R01 submission.

10.0 Quality Control and Quality Assurance

Data will be evaluated for protocol adherence during weekly meetings with the PIs and the study manager. Dr. Bronas will evaluate all data for quality during weekly study meetings. Biweekly visits will be conducted by the PI to ensure that data collection is carried out according to the protocol.

11.0 Data and Safety Monitoring

Serious adverse events will be monitored and tracked at each follow-up period and biweekly phone calls. Patients will be queried at the biweekly phone calls and at 24 weeks if they have had any visits to the emergency department or hospitalizations (see attached checklist). We will also ask if they have had any symptoms of cardiac-related problems such as chest, arm or jaw pain while exercising or not exercising. Data will be recorded on an excel spreadsheet and reviewed by the PI at weekly study meetings. Any unanticipated adverse events or problems will be reported to the IRB within 7 days on notification. Ulf G. Bronas, PhD, ATC, FSVM, FAHA will monitor safety data. Subjects are free to withdraw from the study at any time. If a subject withdraws from the study we will ask the subject (only once) if they are willing to come back for the follow-up tests. If the subject does not want to complete the study, not further contact attempts will be conducted and the subject will be discontinued from the study (this will be reported at the annual continuing review).

This study is funded by the Midwest Roybal Center for Health Promotion and Translation and is required to follow their NIH approved DSMB plan outlined below: The PI will be responsible for ensuring participants' safety on a daily basis. The Safety Officer (SO; Dr. Susan Hughes, Roybal PI) in conjunction with a Data Safety Monitoring Roybal Center Committee will act in an advisory capacity to the NIA Director to monitor participant safety, evaluate the progress of the study, to review procedures for monitoring the confidentiality of the data, the quality of data collection, management, and analyses.

Safety Officer Membership and Affiliation.
Dr. Susan Hughes, Midwest Roybal grant PI, has accepted the position as the Safety Officer and will work with the study PI to review pilot study data and safety monitoring.
Title: Co-Director, Center for Research on Health and Aging and
Professor, Community Health Sciences

Organization/Affiliation: Institute for Health Research and Policy and School of Public Health, UIC

Data Safety Monitor Committee
Dr. Susan Hughes will serve as chair of the committee, and as SO for any adverse event reports. Other members will include David Marquez, PhD (Kinesiology), Margaret Baumann, MD (Medicine), and Laurie Ruggiero, PhD (School of Public Health)

Conflict of Interest for SO.

The SO and DSM committee will adhere to the Conflict of Interest Policy and procedures of the University of Illinois.

The PI will meet semiannually with the DSM Committee, either in-person or by teleconference call to review study progress, data quality, and participants' safety. Written summary reports will be submitted twice a year and will include a detailed analysis of study progress, data and safety issues. The PI will be informed of serious adverse events as soon as they occur and will notify the SO within 24 hours of notification. In addition, serious adverse events will be reported to the UIC IRB and NIA consistent with their established protocols.

Content of Data and Safety Monitoring Report/SO Reports.

The content of the SO report will include study status/quality, participant descriptive information, adverse events, and dropout rates/reasons.

Protection of Confidentiality.

Data will be presented to the SO and DSM committee in a blinded manner during meetings and in written reports. The content of the SO reports and discussions will be treated as confidential. Participant identities will not be known to the SO.

SO and DSM committee Responsibilities.

The responsibilities of the SO DSM committee include:

- Review the research protocol, informed consent documents and plans for data safety and monitoring;
- Recommend subject recruitment be initiated after receipt of a satisfactory protocol;
- Evaluate the progress of the trial, including periodic assessments of data quality and timeliness, recruitment, accrual and retention, participant risk versus benefit, performance of the trial sites, and other factors that can affect study outcome;
- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
- Review study performance, make recommendations and assist in the resolution of problems reported by the Principal Investigator;
- Protect the safety of the study participants;
- Report to NIA on the safety and progress of the trial;
- Make recommendations to the NIA and the Principal Investigator concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
- Ensure the confidentiality of the study data and the results of monitoring; and
- Assist the NIA by commenting on any problems with study conduct, enrollment, sample size, and/or data collection.

Serious adverse events will be monitored and tracked during each phone call (every two weeks). Patients will be queried they have had any visits to the emergency department or hospitalizations. We will also ask if they have had any symptoms of cardiac-related problems such as chest, arm or jaw pain while exercising or not exercising. Lastly, we will ask patients if they have had any falls. Data will be recorded on an excel spreadsheet and reviewed by the PI and study team at weekly study meetings.

12.0 Statistical Considerations

Dr. Alana Steffen of the College of Nursing statistician will conduct all analyses. The apriori stated analysis is listed below.

This is a pilot study for feasibility. For these pilot data we will emphasize descriptive statistics such as means, standard deviations, effect sizes, medians, interquartile ranges, frequencies, and percentages to demonstrate the feasibility of recruitment, adherence, and retention, treatment effects over time, and proof

of concept. Our statistical approach for a full trial of these hypotheses will be Generalized Linear Mixed Models (GLMM) with an identity link function for a continuous outcome or a logit link function for a binary outcome. Conceptually, GLMM is a more advanced version of repeated measures ANOVA that can account for potential correlation among multiple measurements over time while having flexibility in fitting outcomes with different distributions (such as normal, binomial or Poisson, etc.). One advantage of this approach over repeated measures ANOVA is that there is no assumption that participants are measured at every, or even the same, time points. Therefore, these models are very flexible at handling missing data. Participants who have a missing observation are not excluded, thus, this produces the intention to treat (ITT) full information maximum likelihood (FIML) model. Conducting these models on pilot data help with sample size calculations for a future R01 submission.

This is a pilot study investigating the feasibility and proof-of-concept. There is no power-calculation for this study: This study may not be powered to find statistically significant differences between groups due to the smaller sample size. Based on previous studies, we do expect to find at a minimum a trend for improvement cognitive function and brain structure. We expect to be able to use these data for determination of the necessary sample size for detection of significant differences between groups

13.0 Regulatory Requirements

13.1 Informed Consent

Each interested subject will be mailed a copy of the consent form 1 week prior to scheduling the initial consent visit. This will be done to allow potential subjects sufficient time to consider participation. Informed consent will be obtain in the CON Health Research Laboratory 229 at the baseline visit. Informed consent will be obtained using procedures and documents understandable to the subject. Individuals who are unable to give informed consent will be excluded from participation in this research. All study personnel will have received the required UIC CITI and HIPAA training prior to initiation of the study. The PI (Ulf Bronas), and the study manager will obtain consent. Subjects that contact the study team will be given as much time as they feel necessary to decide if they would like to participate. Subjects will be encouraged to ask any questions at any time throughout the course of the study. Research personnel will be available to answer these questions. Subjects will be informed that participating in this research is voluntary. Subjects will be informed that they may withdraw from the research at any time without penalty. Patient providers are not part of the study team. Informed consent documents will be kept in a locked file cabinet in a locked office separate from other study documents. Only the PI (Ulf Bronas) will have access to these files.

We have requested approval for a waiver of consent for recruitment purposes only to identify potential subjects from the medical records. We will only obtain patients name, address, medical record number, and whether they have the ICD code for diagnosis of CKD. This is minimal risk. We are requesting an alteration of consent to conduct the telephone screening for all potential subjects that have expressed an interest in the study and would like to be contacted by the stud team. The telephone screen will be used to determine initial eligibility and to schedule the consent visit. The telephone screen is minimal risk. The only potential risk to participating in the telephone screen is loss of confidentiality. The initial telephone screening and interview is a component of the study and involves an assessment to determine if individuals potentially interested in participating meet the preliminary qualification criteria and attests to their interest in participating in the entire study. Candidates who meet the screening criteria and agree to participate will be invited to schedule an initial visit during which formal written consent processes will be executed. The telephone screening obviates the need for unnecessary visits to UIC. This represents an alteration in the consent process

13.2 Subject Confidentiality

Precautions to protect subject privacy will be taken throughout the course of the study. All telephone conversations with potential subjects will be conducted in a private setting. Face to face conversations will be conducted within a private setting within the College of Nursing clinical health laboratory with private rooms. Strict procedures will be put in place to minimize the risk of breach of confidentiality. All subjects will be assigned a study code. The master list of the subject's name and the linked code will be kept by the study manager in a locked file cabinet in a locked office. All information provided by subjects will kept strictly confidential and will not be reported on an individual basis. None of the information provided by subjects will become part of the medical record. Hard copy data will be stored in a locked office, and electronic data will be stored on a password-protected computer. Hard copy and electronic data will be coded, with the master list kept separately in a secure file in the principal investigator's office. A HIPAA authorization form will be developed for this study to use/disclose protected health information. Subjects will be asked to sign the HIPAA consent form. Subjects who refuse to agree to the HIPAA authorization will not be able to participate in this study. Study data will be coded in numerical order (e.g. CKD001, CKD002 etc.). The link to the code will be maintained by the project manager and will be kept in a locked file cabinet in a locked office separate from study data. An electronic copy of the masterfile will be kept in a folder, separate from the data and study forms, on a UIC secured drive. The project manager and PIs will have access to the code. The link to identifiers will be destroyed after 6

years. The study statistician will have access to the de-identified database for analysis purposes.

13.3 Unanticipated Problems

- All study-related, serious, unanticipated adverse events will be reported to the IRB within 48 hours of discovery. Other unanticipated events will be reported to the IRB at the time of continuing review. We will comply with university policies and procedures regarding any unforeseen identifiable data loss.

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APPENDICES

Recruitment documents

Eligibility Checklist

Data Collection Tables/Forms

Questionnaires