Supplementary File 1

The Aerobics, Weights and Renal Disease (AWARD) Trial Protocol

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I. Introduction and Rationale

Chronic kidney disease (CKD) is increasingly prevalent in the elderly and carries sequelae that extend beyond progression to kidney failure.[1] These sequelae include neurocognitive and physical dysfunction, both of which occur at markedly higher rates in CKD patients, even after accounting for differences in common co-morbidities including underlying cardiovascular disease and diabetes.[2-7]

For example, among older adults, those with CKD have a 40% greater risk of incident dementia[8], a 75% greater risk of physical frailty[9], and poorer health-related quality of life[10], independent of traditional risk factors. Other factors that may explain these cognitive and physical impairments include inflammation and microvascular endothelial dysfunction, both of which are more frequent in CKD and are associated with compromised cognitive and physical function in the general population.[11-14] To date, no medical interventions are proven to prevent cognitive and physical dysfunction in this exceedingly high-risk population. Given the high prevalence of CKD, the aging US population, and the substantial societal burden associated with cognitive and physical dysfunction for older adults, including loss of independence, this knowledge gap requires investigation.

Aerobic and resistance exercise training is a potentially promising non-pharmacological intervention to improve cognitive and physical dysfunction in CKD. Several pilot studies of supervised exercise training in individuals with CKD suggest improved physical function, and several studies in older patients without kidney disease demonstrate improved neurocognitive function, inflammation, vascular function, and vascular risk factors.[15-27] Accordingly, we hypothesize that exercise training will improve neurocognitive function, physical function, and health-related quality of life in older, non-dialysis CKD patients, and that these results are mediated in part by improvements in inflammation, vascular function, lipids, blood pressure and insulin resistance.

To test this hypothesis, we will conduct a randomized parallel-group clinical trial in 120 older (ages 50 years and older) community-dwelling adults with CKD stages 3b-4 to evaluate the effects of 12 months of aerobic and resistance exercise training versus directed health education on neurocognitive function, physical function, and health-related quality of life, and to evaluate the effect on potential mediating factors including inflammation, microvascular endothelial function, and other vascular risk factors.

This project has the potential to substantially expand current knowledge with the ultimate goals of developing a feasible intervention to improve outcomes in older patients with CKD and furthering the understanding of mechanisms related to the efficacy of this intervention.

II. Recruitment.

Patients with chronic kidney disease (defined by an eGFR below 45 mL/min per 1.73m^2) who are age 50 years and older will be initially approached by their primary nephrologist (for local nephrology practices) or Tufts Medical Center nephrologist with whom they have a relationship in the outpatient clinics at Tufts Medical Center.

Clinic schedules and active clinic patients will be screened using medical records to determine preliminary eligibility; nephrologists will be made aware of their potentially eligible patients in order to facilitate study referrals. Additionally, study posters will be posted in waiting areas and brochures will be available for potential participants.

Local recruitment sites will include:

- Tufts Medical Center Nephrology
- Tufts Medical Center General Medical Associates
- St Elizabeth's Medical Center (Drs. James Strom, Geetha Narayan, Anthony Dash and Bertrand Jaber)
- Dr. Ashraf Selim (practices in Malden and Everett)
- Dr. Michael Cohen (practices primarily in Melrose and is a member of the Tufts Medical Center Division of Nephrology)
- Dr. Anthony Dash (practices primarily at Lawrence Memorial Hospital in addition to St. Elizabeth's Medical Center and is a member of the Division of Nephrology)
- Drs. Andrei Kouznetsov and Valerie Price (practice primarily in Concord and are members of the Division of Nephrology at Tufts Medical Center).

Weekly patient lists will be acquired from the GMA clinic. The list will include individuals scheduled to be seen by the GMA physicians during the next week who are 59 years of age and older who carry a diagnosis of chronic kidney disease.

Only patients who express interest, either by indicating such to their physician or by responding to targeted advertising described above, will be approached further. Subjects identified by medical record screening alone, who are not coming in for a regularly scheduled visit, will be mailed a letter providing more information about AWARD, and offering a system by which they can opt-out of further follow up calls regarding their interest in the study. Letters will only be mailed to potential subjects for which their PCP or Nephrologist has given approval to contact. After referral to the investigating team, research study personnel will describe the study in detail to potential participants, and participants will be asked for informed consent to participate in the study. An informed consent procedure approved by the Tufts Medical Center IRB will be used, and this will include a full description of the purpose of the study, the procedures involved, and potential risks. Individuals who give informed consent to participate will then undergo screening for full eligibility for the study at Tufts Medical Center. A copy of the informed consent document as well as the research authorization form will be provided to all enrolled participants.

Patients will be told clearly that they are not required or obligated to participate, and that their medical care will not be influenced by a decision to not participate. Beyond brief introductions, which may occur in a private room in the clinic, detailed discussions between potential participants and investigators regarding eligibility and/or informed consent will take place at the Tufts Clinical and Translational Research Center (CTRC)

in a private interview room. Potential participants will have the opportunity to ask any questions regarding the study and to discuss the decision to participate with family members and others. To ensure continued consent and understanding of the study procedures, participants may, at any time, ask to review individual specific study procedures and any pre-procedure preparation they will need to do. The participants will also be encouraged to take as much time as needed to decide whether they want to participate and will be encouraged to discuss the study with family and friends before signing a consent form.

Release of Medical Information
Participants will be asked to sign a Release of Medical Information form at the screening or randomization visit. This will be used to obtain relevant medical history information and in the case of a Emergency Department visit or Admission to an outside hospital.

III. Randomization

After completing screening, eligible patients will be randomized in a 1:1 ratio to an exercise training intervention group or a directed health and successful aging education control group. Randomization will occur using a permutated block design, with block sizes of 2, 4, 6, 8, and 10. The randomization will be stratified by study site. Primary Investigators will not be blinded. Study staff conducting the cognitive testing will remain blinded to limit the potential for administer bias during the study.

IV. Study Phases

The study processes that occur after informed consent are detailed below:

PHASE 1. SCREENING.
Screening will occur following written informed consent and will include medical history, physical examination, and a resting ECG. The Mini-Mental State Exam, Beck Depression Inventory (BDI), and CHAMPS: Physical Activity Questionnaire for Older Adults will be administered. A stress test (graded exercise test without VO2 collection) will be preformed. Laboratory tests will include eGFR HbA1c, CBC and a chemistry 7 panel. Screening may take place over one or two days. All other portions of the screening process will occur prior to obtaining the exercise stress test. If a potential participant does not qualify for the study for any reason on the initial portions of screening, they will not be given the exercise stress test. Individuals developing inducible ischemia, symptomatic angina or claudication, or who are otherwise unable to complete the test will not be eligible for randomization and will exit from the study. Testing will be performed at the Tufts HNRCA. The study cardiologist, Dr. Robert Peters, is located at the Baltimore site. We anticipate that approximately 30% of subjects undergoing screening/baseline treadmill testing will not qualify and have accounted for this in our recruitment plans.
Participants who meet inclusion/exclusion criteria will proceed to Phase 2.

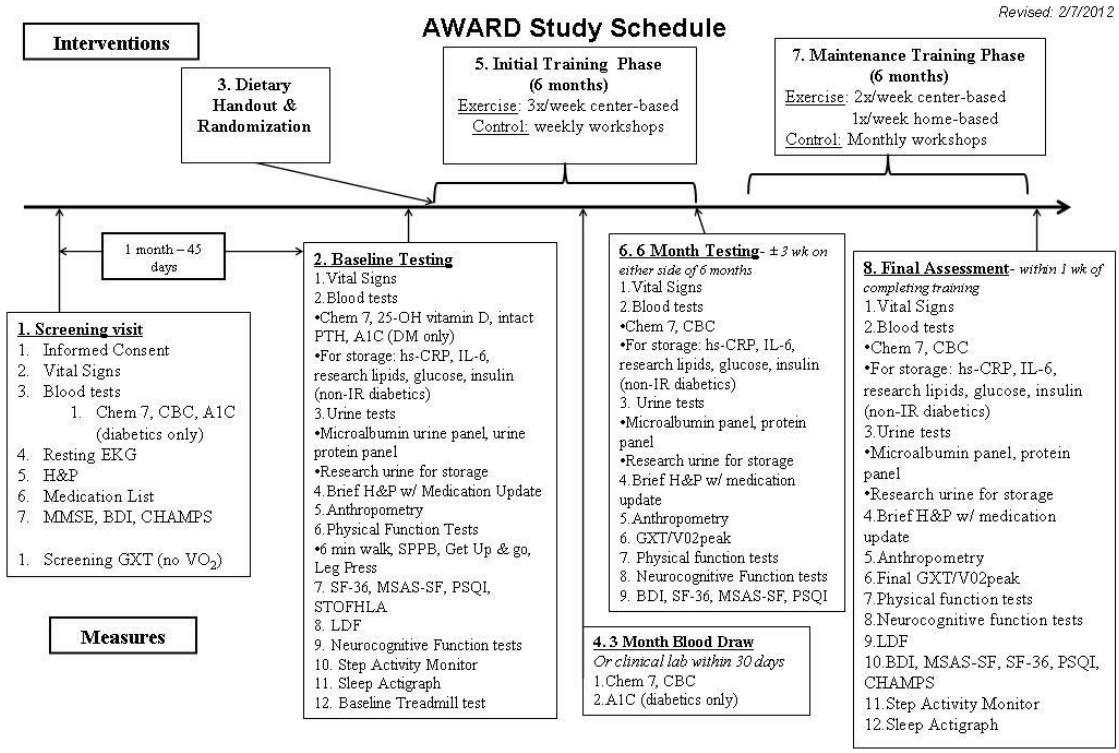
PHASE 2. BASELINE ASSESSMENT.
The baseline assessment will consist of two visit and include:

- Graded exercise treadmill test with assessment of VO_2peak (see below for description of this testing).
- Blood pressure and other vital signs, medication log, anthropometry

- Blood and urine tests, Chem-7, CBC, HbA1c urine protein, urine creatinine, urine albumin, vitamin d, hsCRP, lipids, insulin resistance, IL-6
- Additional blood and urine stored for future assessment of additional mediators (with additional funding)
- Quality of Life Assessments (MSAS-SF and SF-36, San Diego Claudication Questionnaire)
- Health status (EQ-5D-5L)
- Sleep assessment (Pittsburgh Sleep Quality Index (PSQI), Sleep Actigraphy)
- Neurocognitive test battery
- Physical function and strength assessment battery
- Measurement of endothelial function
- Step Activity Monitoring (SAM)
- Health Literacy Assessment (STOFHLA)

PHASE 3. DIETARY COUNSELING.

Baseline dietary information will be provided to all participants to minimize effects of dietary heterogeneity on responses to exercise training. The American Heart Association Therapeutic Lifestyle Changes diet for adults at high vascular risk will be recommended and described in a standardized educational handout.



PHASE 4: 3-MONTH BLOOD DRAW

At 3-months after randomization, a Chem-7, CBC and HbA1c will be drawn for safety assessment. If any of these labs had been run clinically within 30 days of the 3-month time point, they will be used for the safety assessment.

PHASES 5 AND 7. STUDY INTERVENTIONS.
The study interventions are described below, and, for both groups, de-intensify after 6 months.

PHASES 6 AND 8. 6-MONTH AND 12-MONTH ASSESSMENT
Phase 6 is the 6-Month assessment, at which time all baseline measures will be repeated except for endothelial function assessment, step activity monitor, sleep actigraphy assessment and STOFHLA. Phase 8 is the12-Month, at which time all baseline measures will be repeated except for the STOFHLA.

Phase 9: Post-Education Group Exercise
Participants who were randomized into the Health Education intervention group that completed all 12 months of the intervention will be eligible to participate in an optional, abbreviated, exercise training intervention. This exercise intervention will occur twice a week for 3 months. The exercise training sessions will follow the same protocol as the 12-month exercise intervention sessions. The 12-month V02 peak test will be used to determine the target heart rate for the participant. Prior to initiation of this exercise intervention, a study physician will review each participant's medical history and medication lists for interim changes. The study physician will determine that there is no contraindication for exercise in each participant.

At the end of the 3 month exercise intervention, participants will undergo a post-exercise assessment. At this assessment the following will be performed:

- 6-minute Walk Test
- SF-36
- MSAS
- BDI
- EQ-5D-5L
- PSQI
- CHAMPS

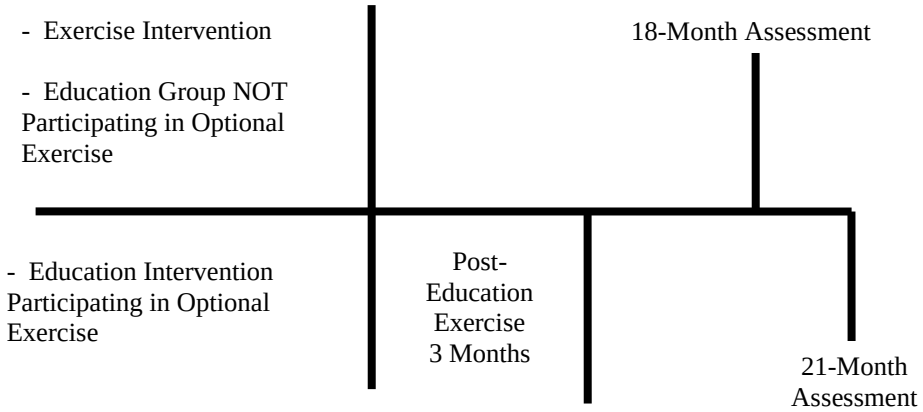
Phase 10: Post-Intervention Assessment
Participants who complete the 12-month assessment will complete a followed up to assess for activity level, quality of life, and sleep. This assessment can take place in-center, by phone, or through the mail.

Exercise Intervention Group: Participants who complete the 12-month exercise intervention group will perform this follow up visit 6 months after the 12-month assessment (+/- 3 weeks). 18-Month Visit

Education Group (NOT participating in optional exercise): Participants who complete the 12-month Health Education group who choose **NOT** to participate in the optional post-education exercise will perform this follow up visit 6 months after the 12-month assessment (+/- 3 weeks). 18-Month Visit

Education Group (PARTICIPATING in optional exercise): Participants who complete the 12-month Health Education group who choose to participate in the optional exercise

regimen will perform this follow up visit 6 months following the post-exercise assessment (+/- 3 weeks). 21-Month Visit



V. Study Interventions

A. EXERCISE TRAINING GROUP

Participants randomized to exercise training will receive 6 months of in-center aerobic and strength training followed by a 6 month maintenance phase. Training will occur at the Tufts HNRCA with a goal of three 50-minute sessions weekly. Sessions will be conducted by an exercise physiologist/trainer under the supervision of Roger Fielding, PhD in small groups comprising up to 4 participants to improve feasibility and efficiency. Aerobic training will consist primarily of treadmill-based walking. Exercise sessions will be preceded by a brief warm-up and will end with a brief cool-down period. Obtaining appropriate exercise intensity is an essential component to a successful training routine, as intensity and duration that is too low may not result in a meaningful improvement in function and capacity while intensity that is too high may both increase the risk of adverse events and may not be sustainable for a sufficient duration. Consistent with our prior studies, aerobic exercise intensity will be prescribed as a target heart rate (THR) corresponding to a percentage of the heart rate reserve (HRR) as defined by the equation of Karvonen. For the first 4-6 sessions, participants will exercise at an intensity of 50-65% for 20 minutes with one or two 5- minute breaks. Intensity will progress to 70–80% over the subsequent 2-4 weeks of the protocol based on tolerance, ultimately including up to 40 minutes of exercise. Each session will be monitored to ensure the safety of participants, including assessment of blood pressure, heart rate, and exertion. For diabetic participants, blood glucose will be measured at the start and completion of each exercise session, with instructions to repeat the measurement 2-4 hours later to screen for post-exercise hypoglycemia.

Given the advanced kidney disease population that is participating in the study, we anticipate that some participants will have acute medical events during the study and may need to curtail or temporarily suspend the exercise intervention. When this occurs, the participant's status will be changed to 'suspended'. When medically cleared, we will perform a modified re-initiation of the training phase until the participant can re-establish exercise intensity of 70–80% of HRR, at which time they will resume the study at the week at which they were assigned suspended status. If an acute medical event occurs in the 2 weeks prior to the planned interim or final month outcome assessment, we will

postpone the assessment until at least 6 thrice or twice-weekly in-center training sessions can be completed at target exercise intensity. Participants will be restarted in the study when it is deemed appropriate by the participant's physician(s) and the study investigators. Resistance training of the upper and lower extremities will follow aerobic training sessions twice weekly, using a strength training routine similar to that employed successfully in the LIFE-P study (which is also being conducted at the HNRCA by Dr. Fielding). This 10 minute regimen focuses primarily on upper and lower extremity strengthening exercises, incorporating standing leg curls, knee extension and side hip raises with ankle weights, arm raises, biceps curls and overhead raises with hand weights, and leg squats and toe stands. Subjects will be encouraged to perform the strength training exercises up to an intensity of 15 to 16 ("somewhat hard" to "hard") on the rated perceived exertion (RPE) scale. This brief moderate intensity resistance training program has previously been shown to maintain muscle strength and size in mobility-limited older adults.

B. HEALTH EDUCATION GROUP

The Health Education Group will receive lifestyle counseling in a social setting, incorporating a Successful Aging Workshop series adapted from the LIFE-P clinical trial and to be utilized in LIFE. Participants will receive information on a variety of topics of relevance to older adults (e.g., effective negotiation of the health care system, safe travel, age appropriate preventive services and screenings, resources for reliable health information, etc.) with further discussion of factors relevant to CKD (e.g., kidney replacement therapies, dialysis access, etc.). The program includes an experiential component, in which participants learn how to 'take charge' of their health in seeking out appropriate medical information and services. In addition to educational offerings, an instructor led program (5-10 minutes) of upper extremity gentle stretching exercises and relaxation techniques are performed during each class. To promote involvement, additional upper extremity stretches will be added during the study. As demonstrated in the LIFE-P, this 'placebo exercise' activity helps foster adherence to the control arm of the study and increases the perceived benefit of the Successful Aging Workshop series without directly affecting study outcomes. Workshops will occur weekly during the initial phase and monthly during the maintenance phase. Following study completion, individuals randomized to Health Education will have the option of joining in an abbreviated structured exercise program, conducted under the direction of a trained exercise physiologist at the HNRCA similar to the research exercise intervention; this is intended to improve compliance and retention in the control group and will not be part of the study protocol. The program will entail two sessions with an exercise physiologist to tailor a patient-appropriate exercise program which can be performed by the patient at home. All education presentations will be submitted to the IRB for approval prior to their use.

VI. Study Outcomes

As described above, assessments will be performed at baseline and after 6 and 12 months of intervention.

Table. Study outcomes (*primary study outcomes; ^among non-insulin requiring patients only)

Neurocognitive	Physical	Cardiovascular	QoL	Biochemical	Sleep
Executive function* Psychomotor speed* Memory and learning*	6-minute walk* Timed 'get up and go' Short physical performance battery Lower extremity muscle power	$V0_2$peak* Blood pressure Laser Doppler flowmetry	SF-36 BDI MSAS-SF EQ-5D-5L	eGFR, Lipids Insulin, glucose^ hs-CRP, IL-6	PSQI Sleep Actigraphy

A. Neurocognitive Tests

A 14-test cognitive battery that examines a range of domains including executive functions, psychomotor speed, attention, verbal and non-verbal memory and learning, and visuospatial functions will be administered to all participants. This is summarized in the table below.

B. Physical Function Tests

The primary outcomes of peak aerobic capacity on graded exercise treadmill test ($V0_2$peak) and performance on the 6-minute walk test, as well as several secondary outcomes, including score on the short physical performance battery, performance on the timed "get up and go" test, and assessment of muscle power.

a) $V0_2$peak will be measured during a maximal treadmill exercise test using a modified Balke protocol. During the test, O_2 consumption, CO_2 production, and minute ventilation are measured breath-by-breath using a metabolic cart (Quark Cardio Pulmonary Exercise Testing metabolic analyzer, Cosmed, Rome), with values averaged for 20 second intervals. We recognize that not all participants will be able to obtain a true maximal aerobic capacity as defined by a plateau in oxygen consumption. Therefore, we plan to use the peak oxygen consumption as our main outcome measure. Blood pressure and ECGs are monitored during exercise testing and recovery; testing is stopped if termination criteria are achieved.

b) Six-minute walk test: Participants are instructed to "cover as much distance as they can" over a flat 100 foot walking surface demarcated by traffic cones

c) The Short Physical Performance Battery (SPPB) includes the following components: 1) Timed 4-meter walk; 2) Repeated chair stand; and 3) Balance tests. For each component, a score of 0 to 4 is assigned, with the sum of components comprising a final score

d) The Timed "Get Up and Go" Test: Beginning in a seated position in a chair, participants are asked to stand up, walk 6 feet, turn around, return to the chair, and sit down. The time required to complete this task is recorded.

e) Muscle Power: 1-Repetition Maximum (RM) Muscle Power for a leg press will be determined using KeiserA420 pneumatic resistance equipment.

Table. The neurocognitive test battery.

Neurocognitive Test	Primary Neurocognitive Domain Assessed	Minutes to Complete*
Preliminary Screens		
Mini-Mental State Exam	General cognitive screen	5
Beck Depression Inventory	Depression screen	7
Study Outcomes		
Trail Making Test Part A	Perceptuomotor and psychomotor speed	4
Trail Making Test, Part B^	Mental flexibility, attention, perceptuomotor speed	6
Grooved Pegboard Test	Manual dexterity, psychomotor speed	6
Stroop Color Word Test^	Set-shifting, mental flexibility	6
Digit Symbol Substitution Test^	Working memory, attention	5
California Verbal Learning Test	Verbal memory & learning	20
Brief Visuospatial Memory Test	Non-verbal memory	15
Controlled Oral Word Association Test^	Letter fluency	4
Judgment of Line Orientation	Visuospatial ability	7
Digit Vigilance Test^	Complex attention, concentration	9
Digit Span subscale^	Attention, concentration, working memory	5
Montreal Cognitive Assessment (MoCA)	General cognitive screen	15

* Based on published data or results of pilot testing in older stage 3-4 CKD patients.
^ Tests assessing aspects of executive functioning

C. QUALITY OF LIFE AND SYMPTOM BURDEN

These elements will be assessed using the Medical Outcomes Study Short-Form 36 (SF-36) and the Memorial Symptom Assessment Scale Short Form (MSAS-SF), respectively. The BDI, a 21-item self-report scale validated in individuals with CKD, will be administered at the screening visit and in follow-up to assess symptoms of depression. The San Diego Claudication Questionnaire is a 9-item scale to assess for symptoms and severity of Claudication symptoms.

D. SLEEP ASSESSMENT

The sleep quality and patterns of study participants will be assessed using the validated Pittsburgh Sleep Quality Index as well as the sleep actigraphy monitor. This will be administered at baseline and follow-up assessments. The sleep actigraphy monitor will be worn for approximately 5 days and nights at Baseline and 12-month follow up. This device is worn on the wrist and measures movement and ambient light. During the period which the participant is wearing the actigraph, they will be instructed to maintain a sleep log to increase the interpretability of the actigraphy results.

E. HEALTH STATUS

Health status of study participants will be assessed using the EQ-5D-5L measure. This is a short validated measure for participant's subjective assessment of their health status. This will allow for analysis of quality-adjusted life years in future cost effectiveness analyses.

F. VASCULAR HEALTH AND INFLAMMATORY MARKERS

Interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP) will be measured on plasma stored at -80C. The vascular health assessment utilizes Laser Doppler Flowmetry (LDF) to measure microvascular endothelial function. LDF uses a laser light source and doppler shift effect to non-invasively measure microvascular blood flow, permitting measurement of the relative change in microcirculatory perfusion in response to various interventions. The thermal-hyperemic response will be used, induced by heating the probe on forearm skin to 44C for over two minutes; LDF flow is recorded for

another 30 minutes. An occlusive test will also be assessed. This will entail using a blood pressure cuff to occlude blood flow to the arm of interest for 4 minutes, at which point the cuff will be released and the return of blood flow will be assessed over the subsequent minutes.

G. OTHER VASCULAR RISK FACTORS

Insulin concentration will be measured in stored plasma by radioimmunoassay (Millipore, Billerica, MA). Total cholesterol and triglycerides will be measured using enzymatic methods; LDL cholesterol will be calculated using the Friedwald equation; total HDL cholesterol and HDL sub-fractions will be measured after precipitation with dextran sulfate. For blood pressure, the average of the second and third of three seated measures will be recorded; the dose of each antihypertensive medication will also be recorded.

H. Physical Activity Assessment

Participant's daily physical activity will be assessed at baseline and follow-up. This assessment will be made using the CHAMPS, a validated questionnaire and through Step Activity Monitoring (SAM). The SAM is a device worn around the ankle which measures movement. This will be worn for 5 days in conjunction with the sleep actigraph.

VII. Data Management.

Data collection will use the StudyTrax data system, a secure Web-based application designed to provide easy user access and monitoring, incorporating role-based access for multi-user studies. StudyTrax will be housed on dedicated Tufts servers, and accessed using standard browsers. Working with study investigators, Tufts computing staff, guided by the study biostatistician, Hocine Tighiouart, will create data entry screens, data and range checks, and standard reports as well as create programs to link existing data and to merge with other electronically transmitted data as needed. Following informed consent, participants' data will be entered into the StudyTrax system with generation of a study ID. Each center will perform double data entry, followed by assessment of data discrepancies, and subsequent correction of any errors.

VIII. Adverse Event Reporting

Given the minimal risk nature of the current study (such that participants could engage in similar interventions in an unsupervised fashion outside of the purview of this research study), we will be utilizing the Internal Data Safety Monitoring Board (DSMB) of the Geriatric Research Education and Clinical Center (GRECC) of the VA Maryland Healthcare System.

<u>Current voting members/positions of the GRECC include:</u>

- Leslie Katzel, M.D., Ph.D., Chair (GRECC Clinical Care Associate Director)
- Marianne Shaughnessy, Ph.D., C.R.N.P., Vice-Chair (GRECC Associate Director Education)
- Gretchen Zietowski, M.S., R.N. (UM-OAIC clinical coordinator)
- GRECC Nurse Manager (GRECC clinical coordinator)
- Ivy Dorsey, B.S.N., R.N. (GRECC clinical staff member)
- The Research Compliance Officer VA Research Services Baltimore VA Maryland Health Care System

- Kathleen Michael, Ph.D., R.N., C.R.R.N. (UM-OAIC and Maryland Exercise & Robotics Center of Excellence investigator)
- Peter Normandt, C.R.N.P. (GRECC and Maryland Exercise & Robotics Center of Excellence clinical staff)
- John Sorkin, M.D., Ph.D. (Biostatistician, UM-OAIC Biostatistics and Informatics Core principal investigator)

Alternate Voting Members of the GRECC include:

- Jacob Blumenthal, M.D. (GRECC investigator)
- Ronald Prigeon, MD (Biostatistician, GRECC investigator)
- Dawn Jacobs, CRNP (GRECC clinical staff member)
- Lynda Robey, MS (GRECC clinical research coordinator)

Non-Voting Members of the GRECC include:

- Andrew Goldberg, M.D. (UM-OAIC principal investigator and GRECC Director)
- Kara Longo, M.S. (UM-OAIC and Division of Gerontology Health Program Manager)

In general, the GRECC and Division of Gerontology investigators, and support staff, work in a collaborative fashion on GRECC sponsored protocols. This collaboration enhances the quality of the research and strengthens the medical oversight of the research. The degree of cross-collaboration varies considerably from protocol to protocol. Any internal review of the protocols by Division of Gerontology faculty will result in some degree of conflict of interest. However, as licensed physicians in Maryland and the Federal Government, they practice good clinical practice in reaching all decisions to insure the proper, safe conduct of research in the GRECC and Division of Gerontology

To minimize conflicts with the current protocol, Dr. Katzel, a co-investigator of this protocol, Dr. Goldberg, a co-investigator of this protocol, and Kathy Brandt, a recipient of salary support from the GRECC, will be excluded from the study evaluation process.

Furthermore, to avoid conflict, the GRECC Internal SMB will provide its findings to both the GRECC internal and external advisory committees.

Review Process

DSM review and reporting will occur semi-annually (twice per year), and safety monitoring results will be reported both to the relevant IRBs as well as to the GRECC internal and external advisory committees. There will be no interim efficacy analysis.

Data reviewed will include:

- Adverse Events, both serious and non-serious
- Patient Charts/Clinical Summaries when indicated
- Laboratory Tests
- Procedure Reports as part of QA audits
- Enrollment Numbers as part of review of SAEs
- QA audit results, operating procedures and consent forms when indicated

The DSMB is just one part of the administrative oversight of research that will be undertaken in this study and that occurs in the Division of Gerontology at the University of Maryland.

As per IRB requirements all protocols are reviewed for safety and scientific merit prior to their submission to the IRB. In general each protocol is reviewed by 3 reviewers. All procedures are reviewed by the research testing staff and signed off by the GRECC Director. The PI presents the protocols at the weekly Geriatric Assessment Clinic conference to their fellow GRECC investigator, nursing and metabolic staff prior to implementation. Quality management plans will be reviewed with the GRECC quality management nurse specialist.

The DSMB reviews will be open to the investigator as this clinical trial is not placebo-controlled and is not blinded to the investigators. The reviews will be HIPAA compliant. In reviewing adverse events, the board will have access to patient identifiers and PHI as needed. All specific patient identifiers will be removed in the DSMB report. The DSMB will review the data described above from both the University of Maryland ("Maryland") site and from the Tufts Medical Center ("Boston") site. Consistent with other exercise intervention trials and in keeping with the minimal risk nature of this trial, there are no formal interim stopping criteria.

The major focus of the monitoring board is on safety, particularly on expected and unexpected adverse events directly attributable to participation in the research; i.e. phlebitis due to an IV line insertion, fall during treadmill testing, etc. All protocols will adhere to good clinical practice guidelines. In the review of the adverse events, the board will review policies and procedures and make recommendation accordingly. If there is a serious unexpected adverse event that brings into question the safety of a procedure or of the protocol, the board will temporarily suspend new enrollment into the protocol and work in concert with both the Maryland and Tufts IRBs as well as the VA Research Committee to further evaluate the situation and determine if additional steps are necessary.

All adverse events will also be reported directly to the Tufts Medical Center IRB in accordance with their guidelines. All unexpected serious adverse events will be reported to the IRB with proper paperwork within 5 days of the event. Other serious adverse events will be reported with proper paperwork within 15 days of the event. All other adverse events will be reported during continuing reviews of the study.

Safety and Event Reporting (Exercise Intervention)

All adverse events and serious adverse events will be reviewed by the study doctor at each site and reported to the site principal investigator. Serious adverse events will be reviewed immediately and reported to the IRB. All adverse events will be reviewed by the site principal investigators monthly.

Adverse event monitoring: Study subjects will be monitored for the occurrence of events defined as any undesirable experience. Subjects will be monitored from the day of enrollment throughout the duration of the study period. All adverse events will be recorded on an adverse event case report form and will include a description of all undesirable experiences, required interventions, subject's condition after the event, an estimate of the extent of injury and potential strategies to prevent future occurrences. The Principal Investigator will classify the relationship of the study protocol to the event (see below). As stated, the Principal Investigator, in consultation with the study physician, is responsible for reporting serious adverse events (life threatening, new,

serious or permanent disability, new kidney failure, death) to the IRB. Other adverse events will be summarized annually for the IRB.

Adverse events: In the current protocol, an adverse event or experience is defined as any health-related unfavorable or unintended medical occurrence that happens during the process of screening, the study assessments and during the randomized intervention. Minor adverse events are defined as conditions that may be unpleasant and bothersome to the participant, such as a head cold, but that do not require discontinuing participant in the study. Examples of minor adverse events include but are not limited to the following: anxiety, fatigue, decreased appetite, insomnia, dizziness, muscle or joint stiffness, muscle strain or soreness, ankle or knee pain, foot pain, and other minor symptoms that may have restricted the participant's usual activities for at least ½ day. Minor adverse events will be reported to the IRB during annual recertification.

Serious adverse events: In the current protocol, serious adverse events are defined to include: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or new kidney failure. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse experiences if they might jeopardize the participant or might require medical or surgical intervention to prevent one of the outcomes in the definition. An example of this in the current protocol is an injurious fall resulting in a fracture that occurred in the HNRCA during a study visit. All serious adverse events will be reported promptly to the IRB.

The Principal Investigator, in consultation with the study physician, will classify the relationship of the study protocol to the event as follows:

Not Related: The event is clearly related to factors such as the subject's clinical state, not to interventions associated with the study protocol.

Remote: The event was most likely related to factors such as the subject's clinical state, not to interventions associated with the study protocol.

Possible: The event follows a reasonable temporal sequence from interventions associated with the study protocol but is possibly related to such factors as the subject's clinical state.

Probable: The event follows a reasonable temporal sequence from interventions associated with the study protocol and cannot be reasonably explained by factors such as the subject's clinical state.

Highly Probable: The event follows a reasonable sequence from interventions associated with the study protocol and cannot be reasonably explained by factors such as the subject's clinical state.

Data safety and monitoring plan: If any of the blood draws show lab values newly and unexpectedly different from the normal range, these events will be reported to the principal investigator and the study physician. All adverse events will be reported to the principal investigator or a co-investigator within 5 working days of the incident. All serious adverse events will be reported promptly to the IRB.

Potential adverse events for study related activities and interventions are explained to each participant by trained study personnel during the informed consent process. Each participant is instructed to report the occurrence of an adverse event at scheduled data collection times. Participants also have access to study personnel at other times to report serious adverse events or concerns about the safety of participating in this study.

References:

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