Study Protocol and Statistical Analysis Plan

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Feasibility of Exercise and Cognitive Retraining to Improve Memory, Attention and Concentration in Heart Failure.

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Title: Feasibility of Exercise and Cognitive Retraining to Improve Cognitive Impairment in Heart Failure.

Abstract. Cognitive impairment (CI) is a prevalent problem in persons with HF heart failure (HF) and is associated with adverse clinical outcomes, higher mortality and poorer quality of life. Studies designed to attenuate or alleviate CI in persons with HF are limited, and evidenced based guidelines for screening and provision of care are practically nonexistent. Improvement in cognition has been reported following some therapies in HF and is thought to be the consequence of enhanced cerebral perfusion and oxygenation, suggesting that CI may be amenable to intervention in this population. Exercise is documented to increase cerebral perfusion and oxygenation by promoting neuroplasticity and neurogenesis, and, in turn, cognitive functioning. Brain derived neurotrophic factor (BDNF) is a key mechanism underlying the effect of exercise, but most studies of BDNF have not included individuals with CI or chronic illness populations, and its relationship to cognitive outcomes in HF is unknown. Cognitive retraining techniques, originally developed to treat traumatic brain injury, have also shown efficacy in broader neurologically-affected conditions and may provide added benefit to that of exercise. Animal studies suggest exercise and plasticity-based cognitive training could act synergistically through different neural mechanisms to have a more pronounced and positive impact on cognitive outcomes than either approach alone; but this has not been previously tested as an intervention to improve CI. The proposed feasibility study is designed to test the acceptability and limited efficacy of a combined exercise (Ex) and cognitive training (CT) program to improve CI in stable NYHA class II and III HF patients compared to either exercise alone or a no-intervention, attention-control group. Findings will be used to support the development of a future, large scale study to test the efficacy of this intervention to improve cognitive functioning, quality of life, and physiological markers of improved brain function in HF.

Specific Aims. Persons with heart failure (HF) have a four-fold greater likelihood of developing cognitive impairment (CI) than their age matched healthy counterparts, placing them at high risk for adverse clinical outcomes, poorer quality of life (QOL) and higher mortality.[1-6] CI is a subtle but measurable deficit in one or multiple cognitive domains; it is a deficit greater than cognitive losses associated with normal aging.[5] The few studies that have documented CI in HF are inconsistent. Few have used standard neuropsychological testing, and little is known about change in cognitive function over time in HF. [5,7-10] Further, if CI is detected, there are currently no effective or evidenced-based guidelines to help restore or improve cognition in this population.[3,5-7,11-14] Despite the aging population and projected rise of CI in HF, only 2 small intervention studies[15-16] have been documented, indicating a critical need for further research in this area.[5-6]

The etiology of CI in HF is not fully understood, but several underlying mechanisms are consistently reported: reduced cerebral perfusion and oxygenation, brain structural changes (i.e., hippocampal damage, atrophy, loss of gray matter), and micro emboli.[5,7,11,14,17-22] Clinical studies have shown that CI is improved after cardiac transplantation[23-24] and is modifiable with standard therapies that improve cardiac output, oxygenation, fluid overload, and systemic and cerebral perfusion; these findings are inconsistent and anecdotal.[5,8,13-14,25-27] The ability to positively influence cognitive function has important implications for patient adherence to a complex self-care regimen and the development of interventions that may partially reverse CI.[5-6]

Exercise improves clinical outcomes in HF by altering the deleterious peripheral and central mechanisms that contribute to HF exacerbations, worsen symptom severity, and lead to poor clinical outcomes.[28-38] Less is known about the effect of exercise on cognitive function.[15,39-43] Animal research has provided the most compelling evidence that exercise positively affects neuronal growth and the neural systems involved in learning and memory.[49-51] Similar human findings have emerged;[17,52-55] recent advances in neuroimaging support that participation in regular exercise leads to specific changes in brain structure and function. [56-57] Exercise is also thought to enhance brain plasticity. BDNF appears to play a crucial role in this process: [52-53,58-60] when BDNF levels increase following exercise, cognitive function improves.[52-53,58] The association between exercise, BDNF and cognitive function has not been previously reported in HF.[53] This feasibility study will clarify these important relationships and increase the potential for improving clinical outcomes in a future trial.

Neurogenesis and neuroplasticity are means for the brain to recover from poor perfusion and oxygen deprivation such as that occurring in HF.[5,50,52] Animal studies again provide the strongest evidence to date for using cognitive training (CT) to promote better cognitive functioning and provide a rationale for why a combined exercise and CT approach may be superior to monotherapy.[50,52] Animal studies show that, like exercise, learning tasks and performing cognitively stimulating activities also increase BDNF levels and improve learning and memory.[15,16] The effect of BDNF on brain function due to exercise however, is thought to be different from that occurring with CT. Exercise increases the proliferation and division of neuronal cells through BDNF,[61] whereas CT appears to promote cell survival,[62-63] suggesting a synergistic relationship may exist with greater

benefit obtained when both are used together.[50,52-53] The combination of exercise and plasticity-based CT has not been previously tested in HF or in other populations as an intervention for improving cognitive outcomes,[50,64-66] but may be most optimal for targeting the underlying mechanisms for CI in HF. The proposed feasibility study is designed to test the acceptability, implementation and limited efficacy of a combined exercise (Ex) and cognitive training (CT) intervention in stable NYHA class II and III heart failure patients with cognitive impairment. A total of 60 participants will be randomized to one of three study arms: Ex/CT (N=20), Ex-alone (N=20), and attention control (N=20). The study aims are:

Aim 1: To evaluate the feasibility of a 3-arm intervention (ExCT, Ex, AC) in heart failure patients with CI.
Aim 1a. To test the acceptability and implementation of each study arm.
Aim 2: To ascertain limited efficacy of the 3-arm intervention on changes in cognitive abilities
Aim 3: To ascertain limited efficacy of the 3-arm intervention to improve cerebral oxygenation, physiological status, physical function and QOL.

A. Significance. Approximately 670,000 individuals are diagnosed with HF annually in the United States,[67-70] and over one million hospitalizations occur each year due to HF, especially among adults 65 years of age and older.[71-73] As many as 60% of persons with HF experience cognitive impairment, (CI); this number increases proportionately as HF worsens.[5-6,10,74-76] Increased age and depression are independent predictors of more severe CI in persons with HF.[5-6,77-82] CI often interferes with the ability to engage in effective self-management of HF; this leads to more frequent hospitalizations and contributes to the cost burden on the health care system and reduced quality of life.[6,74-75,83] To reduce these burdens, we propose a nurse-led exercise and cognitive training intervention that targets underlying mechanisms that contribute to CI in persons with HF.
Exercise. Over 130 smaller studies, as well as the recent large, multi-site Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-Action) trial,[28] have established the safety and efficacy of moderate-intensity aerobic exercise in stable HF. The effect of exercise on cognitive outcomes in HF however, remains largely unknown.[5,44-45,52-53] One small study examining the effect of exercise on cognitive functioning and cerebral perfusion in HF revealed significant improvements in 2 cognitive domains (attention and psycho-motor speed) but no changes in cerebral perfusion; the low dose exercise regimen and lack of a true comparison group also interpretation.[15] Evidence from other populations, including those with disabilities and chronic illness, (e.g. renal failure, Parkinson's Disease, multiple sclerosis, stroke, Alzheimer's Disease) suggests that exercise improves cognition via several biological processes: its impact on increased cerebral blood flow and oxygen delivery; its influence on BDNF (thought to enhance neurogenesis); and its effect on certain neurotransmitters.[52-53,58-63] Exercise is reported to improve cerebral oxygenation following moderate intensity aerobic exercise, but few studies have examined clinical populations or the impact on cognitive functioning.[86] Recent meta-analyses also provide strong evidence of a positive and significant effect size for aerobic exercise on cognitive function, despite methodological limitations.[39,41,87] Importantly, the effect of exercise is much greater on selected cognitive processes, especially executive function; this suggests that executive function may be amenable to intervention.[52-55] This finding has important implications for persons with HF whose executive functioning is particularly affected by the underlying pathological changes associated with HF.[82,84] Moreover, because executive functioning is necessary to effectively manage HF disease, it is not surprising that poor cognitive functioning is a significant predictor of mortality in this population.[82]

Cognitive training. The type of CT that produces the best cognitive function outcomes is unknown since many studies have enrolled predominately healthy, well-educated white individuals with no CI.[64-66] Research in adults with CI are inconclusive and have considerable limitations; few randomized trials are available.[64-66,88] Several recent studies suggest that computer-based plasticity interventions may be advantageous, e.g. in memory training.[89-91] Plasticity-based training interventions hinge on the understanding that targeted, repeated cognitive exercises can rebuild and re-organize function through neuronal generation, dendritic sprouting, and axonal sprouting. The only study to date to incorporate plasticity-based cognitive training in HF found that it significantly increased list learning, delayed recall memory, psychomotor speed, and performance of IADLs; participant adherence and satisfaction were high.[16] In another study of community dwelling older adults without CI, improvement in memory and attention was significantly greater in the group that received the plasticity-based cognitive training intervention than in those receiving a program of general cognitive stimulation.

Combined exercise and CT. Evidence of exercise improving cognitive function is **robust;** and similar changes on cognition are noted with plasticity-based CT; the effects of these two approaches are different yet synergistic, and suggest the effect on cognitive functioning may be more pronounced when the two are used in combination versus alone; this provides a strong rationale for the proposed intervention. [52-66] This feasibility study will evaluate the acceptability of the intervention(s), adherence to the intervention protocols, the scope of

recruitment efforts to identify acceptable cases, potential dose responses gleaned from differing amounts of intervention compliance, and estimates of effect sizes to optimize a subsequent, large-scale efficacy trial.

PRELIMINARY STUDIES. We have tested strategies to maximize physical function, reduce psychological distress, and maintain optimal physiological status in persons with HF.[94-100] Our interdisciplinary team published results of one of the largest non-pharmacological trials demonstrating the effectiveness of exercise and CBT to reduce depression in HF patients,[96] using a similar design as the one proposed here, and demonstrating the ability to recruit and retain highly complex HF patients. We have expertise in the design of home-based exercise studies using self-monitoring strategies to increase adherence to exercise (e.g. exercise testing and prescription, HR monitors, pedometers, logs). In our prior work, we collected, stored and analyzed a variety of biomarkers (hsCRP, tumor necrosis alpha and BNP) and findings showed a trend for significance, similar to previous research. This preliminary study will expand our previous work by exploring the influence of exercise and CT on novel biomarkers (BDNF, cerebral oxygenation) not previously examined in HF.

Conceptual framework. The conceptual model for this study, portrayed in Figure 1, is based on the substantial literature of the underlying physiological mechanisms that contribute to CI in HF.[75,93] Heart failure by definition is a state of hypo-perfusion that contributes to poor cerebral perfusion, poor oxygenation and, in turn, CI.[93] The proposed intervention (exercise and CT) is designed to positively alter these underlying physiological processes that contribute to CI in persons with HF. This model aligns well with that of the Center.

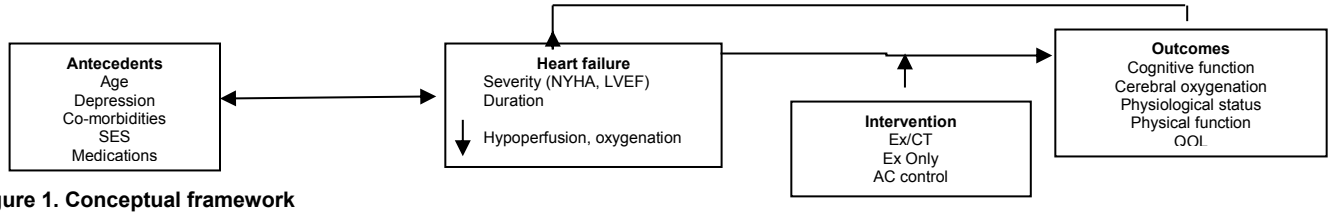


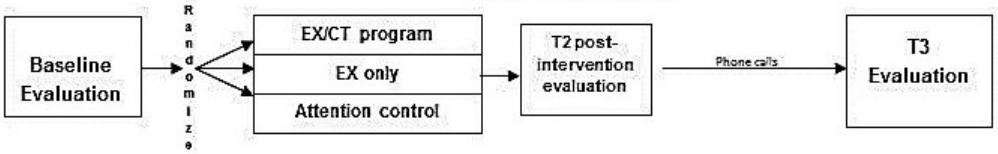
Figure 1. Conceptual framework

B. Innovation: Available evidence to guide care for persons with HF who are cognitively impaired is nonexistent. Our preliminary work using exercise and cognitive behavioral strategies [94-100] has shown improved physical, psychological and QOL outcomes in persons with HF. The proposed study will expand this work and provide important insight on an innovative intervention strategy (exercise and CT) and novel biomarkers (BDNF, cerebral oxygenation) in a diverse population of HF with CI. No study has documented whether exercise improves cerebral oxygenation in persons with HF; the one study measuring cerebral oxygenation in persons with HF found a significantly reduced cerebral oxygenation level using near infrared spectography (NIRS), despite a normal peripheral oxygen saturation.[101] Combination physical exercise and cognitive training have never been evaluated in HF to improve CI. This dual process may provide a synergistic, additive benefit through different yet complementary mechanisms of recovery. This feasibility study will provide essential information to optimize the potential success of a future, large scale research trial.

C. APPROACH.

Design. A pre-post randomized controlled design will be used to measure study aims. Sixty participants will be randomized to receive ExCT (N=25), Ex-alone (N=25), or attention control (N=25) intervention conditions for 3 months. Assessments will take place at baseline, intervention completion (3-months) and 6 months post-intervention. Outcomes of interest include cognitive functioning, peak oxygen consumption (peak $V0_2$), BDNF, and Kansas City Cardiomyopathy Questionnaire (KCCQ; HF specific quality of life instrument). After a 4-5 month start-up for hiring and training, enrollment will begin. Recruitment/enrollment will take place over 18 months; the final follow-up appointment in month 30. This will leave 6 months for data analysis and dissemination.

Figure 2. Study Design



Setting and Sample: Patients will be recruited from the Centers of Heart Failure Therapy of Emory University Hospitals (EUH) and clinics, Emory University Hospital Midtown (EUHM), and Grady Health Systems (GHS). A full description of the ethical recruitment of participants is described in the Human Subjects section of this proposal. The Atlanta Cardiomyopathy Consortium (TACC) and HF Network databases at EUH will enable us to rapidly identify HF patients who meet our eligibility requirements. In 2009, over 4,000 inpatient admissions to EUH or EUHM were due to HF, and excluding those for transplant, 5377 local patients with HF were seen in the

Center for HF Therapy; 42% are women and 31% African American. The patients at GHS reflect a more ethnically homogeneous group: 51% are women, 94% African-American, and most are low socioeconomic status. Because the regional population is estimated to be 35% to 40% African American, this range will be used as the recruitment goal. **See Human Subjects for sample characteristics and rationale.**

STUDY CONDITIONS. All 3 groups will receive Usual Care (UC) + group assignment (attention control stretching, EX/CT or EX only) after undergoing baseline measures conducted at the Clinical Integration Network (CIN) clinic of the Atlanta Clinical Translational Science Institute (ACTSI). UC includes pharmacologic therapy according to ACC guidelines [102-103] and patient education and self-management (i.e., low sodium diet, medication instructions, symptom and weight monitoring). All study patients will be given standard printed educational materials (Heart Failure Society of America [HFSA] Modules 1 and 3) regarding HF.[103] Group assignments, schedules and procedures are outlined in Table 1. Education, flexibility and stretching will provide control for the possible confounding variable of receiving attention from a healthcare professional. Instruction on stretching and flexibility movements is also expected to reduce attrition and patient dissatisfaction and to better ensure concealment of group allocation. These time-equivalent, flexibility/stretching movements have been previously piloted and will serve as the "placebo exercise condition." In pilot evaluations they were well received, but were not strong enough to influence outcomes. The AC education placebo component will be delivered as soon as feasible after baseline (T1). The first 2 weeks of the intervention phase will include 2 home visits to demonstrate stretching and flexibility movements and to discuss educational materials. Weekly telephone calls will then be made for the next 10 weeks to discuss educational materials and to answer questions about stretching movements. An appointment will be made for participants to come to the ACTSI to collect T2 measures; this will occur at weeks 13 and 14. From weeks 15-24 bi-monthly telephone contact will be used to encourage continued adherence to the AC intervention. At the end of 24 weeks, a final visit to the ACTSI will be arranged and T3 measures will be taken. For ethical and cardiovascular health reasons, the AC group will be advised to exercise, but will not be provided with an exercise prescription or self-monitoring equipment since these have been shown to influence exercise adherence and exercise self-efficacy and may confound study outcomes.[104-105]

Table 1. Intervention Group Schedules

Group	T1	1-2 wks	3-12 wks	13-14 wks	15-24 wks	24-25 wks
AC	T1	X 2 home visits for HF educ. & stretching	Weekly calls	T2	Bi monthly calls	T3
EX only	T1	X 2 home visits for HF educ. & supervised walk	Weekly calls	T2	Bi monthly calls	T3
EX/CT	T1	X 2 home visits for HF educ. + supervised walk + Brain Fitness training	Weekly calls	T2	Bi monthly calls	T3

Groups 2 and 3 Exercise Prescription. Groups 2 & 3 will receive the same exercise prescription using a progressive moderate intensity aerobic protocol. To ensure that participants achieve adequate training stimulus, dose-specific exercise will be based on maximum heart rate (HR) obtained during symptom limited, modified Balke treadmill tests[106-107] conducted by an exercise physiologist and supervising cardiologist in the CIN. Target heart rate (THR) using the 60% to 70% of maximum HR achieved on the cardiopulmonary exercise test (CPET) will be used to monitor the intensity and training response for aerobic exercise. Each participant will be provided with an individualized THR zone based on CPET results.[107] Under the supervision of a research nurse, participants will begin the walking sessions at 60% of THR and increase to 70% by week 5 as shown in Table 2. In our pilot with HF patients, a progressive moderate intensity level exercise program yielded positive outcomes with no adverse events, was appealing to participants and adherence rates were 80% or higher.

Table 2. Aerobic exercise progression for exercise/CT and exercise only groups

	Wk 1-2	Wk 3-4	Wk 5-7	Wk 8-9	Wk 10-12
Intensity	60%	60%	70%	70%	70%
Duration	30 mins	45 mins	45 mins	45 mins	45 mins
Frequency	3 x/wk	3 x/wk	3 x/wk	3 x/wk	3 x/wk

Group 2: EX/CT (UC + aerobic exercise + cognitive training) The first 2 weeks of the study will consist of 2 consecutive weekly home visits by the research nurse to demonstrate use of the HR monitor, pedometer and the CT program, Brain Fitness (Posit, San Francisco, CA detailed below). The research nurse will supervise one walking session during the first 2 weeks to ensure the safety of the participant and that he/she understands how to use the Polar HR monitor and pedometer and how to complete the walking logs. During the first 2 weeks, the research nurse will also provide training and demonstrate how to use the Brain Fitness computerized cognitive training program designed to be completed in 40 sessions over 12 weeks. We expect that participants will require additional time (at least 30 minutes each time) in the first 2 weeks to learn how to use and access the Brain Fitness program. The weekly schedules are provided in table 1.

Brain Fitness Computer Training: is based on the principles of positive brain plasticity and designed for use by adults. The training program ("Brain Fitness") is focused on speech reception to strengthen an individual's memory for speech. It has 6 modules names Hi-Lo, Tell Us Apart, Match It, Listen and Do, Sound Replay and Story Teller. Research to date has found: 1) participants with limited or no computer experience were capable of learning to perform the training exercises, 2) the training was safe and well tolerated by participants, and 3) healthy participants who trained on Brain Fitness showed on average a 1/3 standard deviation of improvement in memory, concentration and cognition, and 4) it has been tolerated well in patients in HF in a prior study.[16]
Group 3: Ex only group (UC + aerobic exercise). The same exercise protocol will be used as above without the computer training.
Exercise adherence. To be 100% adherent for exercise sessions, participants in both groups 2 and 3 must document walking weekly at the prescribed intensity/duration on the exercise log. Participants will record on a calendar provided: maximum HR achieved; rate of perceived exertion (RPE) during walk; and number of steps walked during the walking sessions. Polar HR monitors and pedometers (described in instruments) will be used to objectively document exercise intensity (i.e., maximum HR and RPE achieved), duration, walking adherence and progression. The Polar HR monitor and pedometer data will be downloaded during each home visit during the first 2 weeks to track exercise duration and steps walked. At T2, data collected from the HR monitors and pedometers will also be downloaded to document exercise adherence. A total summary adherence score will be calculated by summing and dividing weekly adherence scores by total number of weeks walked.
CT adherence. The total number of minutes for the full Brain Fitness program is approximately 2400 minutes over 8 weeks. Patients will be considered adherent if they meet or exceed 80% of the required minutes for the intervention. Total number of minutes can be accessed from the program to monitor adherence.

VARIABLES, DEFINITIONS AND MEASURES. Variables, operational definitions and methods are described below and in Table 3. Questionnaires will be administered at the time of the visit by a trained research assistant blinded to group allocation. Core services and Center activities will greatly enhance the success of this study. Through training and monitoring in administration and scoring of the core test battery, regular consultation with the BMC to monitor implementation issues, systematic data management and analysis, and support in using these findings to prepare an RO1 application, this study will achieve its aims and further the goals of this Center.
Sociodemographic and clinical variables will be obtained from self-report and medical records. The Charlson Comorbidity Index (CMI)[108] will quantify the cumulative risk of death. **Mini Mental Status Examination**[102] will be used to screen for study inclusion for mild to moderate cognitive impairment (score of 20 for 8-9 yrs of schooling; 22 for 10-12 yrs of schooling; 23 for >12 yrs) [102] and has excellent specificity at this cut-off point.[5] The **Beck Depression Inventory-II** (BDI-II)[109] has been widely used in the HF population. Scores will be used as an effect modifier and explored as a potential outcome variable. **Cognitive Function**. We will use the Center's core neuropsychological testing battery of well-established and validated instruments that are described in the Biobehavior and Methods Core (BMC) portion of this application. The BMC will provide training on test administration and scoring and will aid in data management and interpretation. Cerebral tissue oxygenation will be assessed in the CIN by a cerebral oximeter sensor (Casmed, Blanton, CT) using near infrared spectography (NIRS). NIRS is widely used and validated in a variety of fields to assess cerebral tissue oxygenation.[86,101]

Table 3. Variables, measures, instruments and time of evaluation

Variable	Measure/Instrument	# of items/time	Time of Evaluation
Antecedents Participant Demographics & Clinical information: Co-morbidity, Cardiac Fx, Meds	Age, gender, education, marital status, Charlson comorbidity Index (CMI) LVEF, NYHA class, length of time with HF & etiology, Medications	Chart review & questionnaire Questionnaire	Baseline (BL)
Mild-moderate cognitive impairment	MMSE	30 item/10 minutes	BL only
Depressive symptoms	BDI-II	21 item/15 minutes	BL only
Cognitive function	Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)	30 minutes	BL, 3 and 6 months
	Controlled Oral Word Association Test	5 minutes	
	Color Trails 1 & 2	10 minutes	
	WAIS-III Digit Span/Letter Number Sequence	10 minutes	
	Stroop Test	5 minutes	
	Ruff 2 & 7 Test	5 minutes	
	Rey Auditory Verbal Learning Test	10 minutes	

Physical function	Peak oxygen consumption (Modified Balke)	20 minutes	BL & 3 mos
Physiological status	BDNF	NA	BL & 3 mos
Cerebral oxygenation	Near infrared spectography,	30 minutes	BL & 3 mos
Quality of Life	KCCQ	23 items /15 minutes	BL, 3 and 6 months
Exercise Adherence CT adherence	Polar HR (intensity, duration and frequency), walk calendars, pedometer, nurse telephonic log Brain Fitness program, nurse telephonic log	10 minutes NA	3 and 6 months

Physical Function will be assessed using the **modified Balke maximal treadmill test** [106-107] to determine peak oxygen consumption (peak Vo_2), maximum HR for exercise prescription and to screen for cardiac contraindications to exercise according to the (AHA/ACC) guidelines.[102] **Physiological status.** The serum biomarker **BDNF** will be collected in the CIN by a research nurse or phlebotomist, the assays will be stored at -80 degrees until processed by the ACTSI biocore lab using the manufacturer's ELISA guidelines.

QOL. The **Kansas City Cardiomyopathy Questionnnaire (KCCQ)**[110] is a reliable and well validated 23-item, disease specific questionnaire that quantifies physical function, symptoms, social function, and HRQOL in HF.[111-112]

Adherence. Step counts will be indirectly assessed using the Omron HJ-7201ITC pedometer to count daily steps.[113-117] The 15 point (6-20) **Borg Rate of Perceived Exertion (RPE) Scale**[118] will be used to measure participants' subjective perception of effort. Target heart range (THR) [107] using the HR reserve method will be used to monitor the intensity and training response to walking. Polar Beat ® Watch (FT4)[119] will be used to monitor intensity and duration of walking.[120-121] Actual adherence to intervention protocols and study attrition rates will be included in an intent-to-treat analysis (CT & Ex).

Acceptability. During post-baseline visits and phone contacts, participant's opinions about the intervention, e.g. perceived usefulness, ease of use, barriers to adherence, perceived improvements in health, cognition, mood, quality of life will be collected. The PI will use content analytic techniques to assess acceptability and to identify themes suggesting possible revisions or alterations in the interventions that might improve acceptability.

Procedures Recruitment, Screening and Enrollment of participants will occur through physician and other health care provider referrals and patient self-referral. These methods have proved successful in our prior work. The recruitment nurse will arrange a time for laboratory, and treadmill tests at the CIN. Baseline (T1) measures will be taken in the CIN by a trained data collector blinded to group assignment. All participants will be given the same measures, in the same sequence at each time point. Questionnaire completion should take 30 minutes or less, the neuropsychological testing is anticipated to take 75 minutes. Laboratory samples will be taken prior to the treadmill test. The BDNF samples will be stored at -80 in the CIN until processed. After the laboratory work is completed, the modified Balke treadmill test will be conducted by an exercise physiologist; emergency equipment, doctors and nurses are available. After BL, participants will be randomized to study groups by computerized sheet prepared by the study statistician. At 3 and 6 months we will follow the same procedures used at Evaluation 1. After Evaluation 3, participants will be discharged from the study, and all participants provided with study results. A $50 honorarium will be provided at each measurement time point, to total $150/patient for completing the study. Intervention process measures (evaluation, attendance) will be tracked and evaluated to maintain internal validity. Protocol adherence will be calculated for both groups.

Data Management and Analysis. The Biobehavioral and Methods Core (BMC) will coordinate the collection, integration, and analysis of biological and psychosocial data for this study. Data will be analyzed using both descriptive and inferential test statistics. We will build multivariable statistical models to examine the relationship between an Ex/CT intervention to exercise alone and attention control (AC) on cognitive functioning (P-30 Neuropsychological Battery), cerebral oxygenation (NIRS, 3 months only), physiological status (BDNF), physical function (peak V02) and QOL (KCCQ) in HF at BL, 3 and 6 months controlling for but not limited to age, gender, SES, depression, social support, NYHA class, medications and comorbidities.

Since the intent of this study is exploratory; hypothesis testing will not be the primary focus of the statistical analysis. Rather, we will analyze data with the specific intent of establishing population parameters (e.g., effects sizes) for the variables being investigated. Confidence intervals will be calculated for all effect sizes associated with the predictor variables, other significant outcome effects, and for changes over time. These effect size estimates will be used to design the future R01 study. Given the relatively small sample size of n=60 at 80% power, and α=.05, we will have the ability to detect a moderate (d=.5) to large effect size (d=.8). We will use

general linear and/or mixed models as the main modeling framework for analyses of the outcome measures in the projects. We will build full factorial models to test for interactions and review estimated marginal means. We will use Using G*Power 3, to estimate actual power for the GLM analysis both a priori and post hoc.

E. HUMAN SUBJECTS RESEARCH

Inclusion criteria: (a) 75 outpatient men and women between the ages of 40 and 75; (b) English speaking; (c) live independently within a 60 mile radius of Atlanta; (d) meet education corrected cut-offs on the MMSE indicating cognitive impairment (score of 20 for 8-9 yrs of schooling; 22 for 10-12 yrs of schooling; 23 for >12 yrs) [102]; (e) have a computer with internet connection;(f) documented medical diagnosis of NYHA class II or III systolic. (g) Left ventricular ejection fraction (LVEF) ≥ 10% that is documented within the last year by echocardiogram, cardiac catheterization ventriculography or radionuclide ventriculography; (h) Receiving medication therapy for HF according to American College of Cardiology (ACC) American Heart recommendation guidelines[103]for at least 8 weeks prior to study enrollment. Exclusion criteria: a) NYHA class I or IV; (b) change in HF therapy within 8 weeks; (c) worsening HF symptoms within last 5 days; (d) unstable angina; (e) renal insufficiency (serum creatinine > 3.o mg/dL); (f) fixed rate pacemaker; (g) uncontrolled hypertension; (h) not involved in any structured exercise program or exercising 3 or more times per week for a minimum of 30 minutes and; (i) not hospitalized within the last 30-days; (j) not diagnosed with any neurological disorder that may interfere with cognitive function; (k) Beck Depression Inventory II (BDI-II) score greater than 25; and (l) any disorder interfering with exercise participation.

It is anticipated that approximately 50% of patients approached regarding the study will be eligible and will agree to participate. Based on the PI's earlier studies, a retention rate of 85% is expected. The actual acceptance and retention rates will be included as part of the information gleaned from this feasibility study to inform the design and methods for a subsequent, large scale efficacy trial.

Rationale for sample characteristics. The age range was selected to avoid confounding effects of age and sarcopenia with outcomes such as aerobic capacity, BDNF and HRQOL; participants below the age of 40 years are likely to have HF for other reasons than the majority of the general HF population. Older age (>75) is associated with reduced exercise capacity and age related cognitive decline which may confound physical function cognitive outcome measurement. In addition, persons over the age of 75 are at higher risk for adverse events during exercise testing and with aerobic exercise. Although we anticipate most participants to be receiving optimal medication therapy, treatment decisions regarding individual care will be based on patient's clinician; evidence-based care will be encouraged. If any participants are not being treated with what is considered optimal medication therapy according to ACC guidelines, the reason (eg, intolerance) will be recorded and tracked by group and statistically controlled as a covariate. We recognize that both resting and exercise heart rates are influenced by beta-blockers, which is considered optimal therapy for HF patients. For both exercise testing and training we will use the heart rate reserve method which takes into account the patient's resting heart rate, thereby reducing the effect of beta-blockade. We will attempt to schedule patients for their exercise testing and training a minimum of 3 hours after taking beta blockers.[28-29] For patients who are unable to schedule exercise during this time frame or exercise up to the prescribed heart rate, Borg's 6-20 rate of perceived exertion scale (RPE) between 12-15, will be used to guide exercise intensity, consistent with a moderate intensity level exercise. Patients with an ICD may be enrolled if their heart rate limits are set to be higher than the target heart rate for the exercise regimen. In our last preliminary study, approximately 90% had an ICD; there were no firings during exercise or any increase in adverse events. Although unlikely to occur, participants with a fixed rate pacemaker would not be able to participate because heart rate may be set at a lower rate than required to achieve prescribed target heart rate. Participants who have recurrent angina, more severe symptoms have uncontrolled hypertension will be excluded due to the higher risk for adverse cardiovascular events during exercise testing and the walking intervention. Because moderate to severe depressive symptoms are a major predictor of exercise attrition and more severe CI, participants will be excluded who have a BDI-II score of 25 or higher. These severely depressed subjects will be evaluated for suicidal risk, and referred to psychiatric care. Because the benefit of exercise is being evaluated, participants who are currently enrolled, or were recently enrolled in an exercise program for the past 8 weeks, currently exercising at regular intervals (more than twice per week for 30 minutes) will not be eligible for the study.

Based on the practice patterns at enrolling institutions, we expect the recruitment pool to be approximately 35% African American, with very small numbers of Hispanic/Latino, Asian/Pacific Islander or American Indian racial/ethnicity groups. We anticipate our recruitment to represent this population (Tables 3 and 4). Subjects

will not be excluded due to race or ethnicity. Based on our prior experience with this population, we anticipate most participants will have computer access.

Sources of research material will include responses to questionnaires **obtained at baseline, 3 and 6 months;** data will also be obtained at these time points in the form of laboratory serum samples, treadmill and neuropsychological tests. Polar HR monitors and pedometers will be downloaded weekly during the first 2 weeks to obtain data on adherence to prescribed exercise intensity and duration and at 3 and 6 months. Calendar walking logs will be used to obtain data on exercise adherence for the exercise sessions. The participant's medical history, medication history and sociodemographic information will be obtained from the medical record. It is expected to take approximately 30 minutes for the participants to complete the questionnaires at each time point. The neuropsychological tests are anticipated to take approximately 75 minutes. Each participant is anticipated to spend approximately 3 hours at each time point for data collection purposes. A trained research assistant blinded to study group assignment will administer the questionnaires at the ACTSI at each visit in the same sequence for each time point. All data will be obtained specifically for research purposes and in the same order and sequence at each testing period. Participants in each group will have 2 home visits during the first 2 weeks of the study followed by weekly telephone contact from 3-12 weeks and bi-monthly telephone contacts from 15-24 weeks. Participants randomized to the exercise/CT and exercise only group will have one supervised walking sessions to establish safety, explain use of pedometers, HR monitors and calendars. Participants randomized to the exercise/CT group will have 2 home visits during the first 2 weeks to explain and review how to use the Brain Fitness program (in combination with one supervised walk session). The AC group will also have 2 home visits in the first 2 weeks to demonstrate stretching and flexibility exercises and to review HF educational materials. At the end of 12 weeks, the participants will undergo T2 measures at the ACTSI at weeks 13 and 14 (3 months evaluation). At the end of the 6 months, T3 measures will be scheduled at weeks 25 and 26. Printed education materials will be standardized across all groups. The total participation time over 12 weeks is anticipated to be 40 hours for the exercise only and AC groups, including testing time. The total estimated time for the exercise and CT group is anticipated to be approximately 80 hours including testing time.

After a 4-5 month start-up for hiring and training, enrollment will begin. Recruitment/enrollment will take place over 18 months; the final follow-up appointment in month 30. This will leave 6 months for data analysis and dissemination.

Participants will be recruited through two mechanisms **following HIPPA guidelines**- health provider referral and self-referral. We will track method of referral and examine this in relation to demographic and outcome variables. Physicians, physician assistants, and nurse practitioners working in the HF clinics of the enrolling sites will identify patients who meet eligibility criteria and provide them a brief letter describing the study and asking if they are interested to hear more about the study. If interested, the patient will either be briefed at that time by a member of the research team if available, or be asked to provide his or her phone number at the bottom of the letter, and a member of the research team will pick up such forms at the end of each week and will follow-up by phone with each potential subject within 48 hours. Recruitment flyers, posters, and print/media advertisements will be placed in strategic places for patient access, with a phone number to call if they are interested in participating. The Atlanta Cardiomyopathy Consortium (TACC) database and NIH funded HF network at EUH will also be used to identify potential participants. Those who are identified as eligible using the TACC or HF network database will be mailed letters with research team contact information for them to call if they are interested in participating or want further information about the study. Recruitment fairs may also be held in areas where HF patients are likely to be present, such as HF patient education conferences and congregate housing facilities. Community-sponsored events such as health fairs and cardiac support groups are also potential venues to elicit study participants. Once eligibility has been established via phone or in person, the study will be fully explained and written informed consent will be obtained from each participant by a member of the research team. Prior to beginning the study, recruitment materials will be reviewed and approved by the Institutional Review Board (IRB) of Emory University, which serves as the oversight committee for each of the enrolling institutions. IRB approval for the overall study will be obtained prior to participant recruitment or enrollment.

<u>Potential Risks</u> are expected to be minimal since participants will be referred from an academic health sciences center under the care of a cardiologist and receiving optimal medication and device therapies. In addition, excluding patients who are over the age of 75 years, NYHA class IV and have a LVEF < 10 will reduce risk of adverse cardiac events. The cardiologist will be contacted and agree that potential participants are eligible for the exercise program. We will conduct a brief history and physical examination before aerobic

capacity tests (modified Balke) are conducted at the ACTSI. If a participant becomes fatigued and does not wish to continue, they will be rescheduled for an additional appointment to complete the remainder of the tests.

The risks associated with administering the modified Balke treadmill tests are anticipated to be minimal but may include: atrial and ventricular arrhythmias, sudden death, angina, ICD firings, adverse blood pressure changes (high or low), dyspnea, fatigue, falling orthopedic/musculoskeletal complaints, dizziness, and electrocardiographic evidence of ischemia. We will administer the modified Balke, a symptom limited treadmill test, in the ACTSI by an exercise physiologist and under the sponsorship of the study cardiologist according to the ACC/AHA guidelines.[123] The treadmill test will be performed with commercially available equipment (VMAX Spectra 29 CPET Instrument, Yorba Linda, CA) according to the recommendations of the ACC/AHA guidelines.[123] Before the exercise testing, each participant will undergo spirometry and remain seated for 2 min to obtain resting oxygen consumption (VO_2); and will walk for 1 min to warm up to avoid potential muscle soreness. Emergency equipment, medical and nursing staff are immediately available should the participant have any adverse response. A continuous electrocardiogram and blood pressure readings every 1 minute will be recorded. If ST elevation or multiple ventricular ectopy occur the treadmill test will be stopped immediately. The participant will be continuously monitored during the treadmill test and VS taken every 1 minute for 5 minutes after the test, then every 5 minutes. If there are any untoward vital sign changes such as lower or higher BP, arrhythmia, chest pain or dizziness the study cardiologist (Dr. Butler) will be notified. Data from the HF-ACTION study provides evidence of the safety of symptom limited exercise tests. Of the 4,411 symptom-limited exercise tests during 5 years, no deaths and only 2 nonfatal, major CV events occurred (0.45 events/1,000 tests). There were also no test-related ICD discharges requiring hospitalization. It was concluded that in NYHA class II-IV patients with severe left ventricular systolic dysfunction, that symptom-limited exercise testing is safe based on no deaths and a rate of nonfatal major CV events that is <0.5 per 1,000 tests[123]

The potential risks associated with the walking intervention are anticipated to be minimal. Any potential cardiovascular (CV) events that poses risk to the participant is anticipated to be detected during the modified Balke maximal treadmill test. In addition, the duration of walking will be limited to 30 minutes during the first 2 weeks and at an intensity level (60%) that is not likely to result in any adverse CV events; if necessary participants can rest as needed until the 30 minute duration of walking is completed. Participants will wear a Polar HR monitor so that HR and intensity level can be closely monitored. Participants will undergo 2 supervised walking sessions prior to walking at home unsupervised; the risk associated with the unsupervised session therefore, is anticipated to be minimal. Participants in the study will be provided with detailed instructions on self-monitoring HR, BP and symptoms associated before, during and after walking. Each participant will be provided with a target heart rate range to stay within during the study period. Participants will be instructed to wear the Polar HR monitor during each exercise session. The participants will take their HR, and BP (if machine available) and weight prior to and after each walking session and record it in their walking calendar. Participants will be instructed to call the research nurse if their BP or HR is outside their normal range. If participants are symptomatic, experience increased shortness of breath or have a greater than 2 pound weight gain over the previous 24 hours, they will be instructed not to exercise. The participants will be instructed to take their medications as usual prior to exercise and instructed on proper attire for exercising. Demonstrations and return demonstrations of the Polar HR monitor will ensure they know how to wear the monitor around the chest as well as trouble shoot when the monitor does not display a HR. They will be instructed that if their HR approaches within 5-10 beats of the target HR range to slow the walking pace down. The will also be instructed if they have an ICD, to keep their HR 15 beats below the firing range at all times (usually set at higher than 170 beats per minute, so it is unlikely to interfere with training stimulus). In addition, they will be instructed to monitor their RPE using the Borg 6 to 20 scale, and to keep their RPE at 12-13 during the initial weeks and to gradually progress with instructions to 15 as stipulated in the protocol. Participants in the intervention groups will be advised to carry a cell phone when they walk at home in the event of an emergency or sudden event. Specifically, participants will be instructed to slow their pace if their HR increases to near THR as previously noted or if they become short of breath. Participants who have ischemic heart disease and prescribed nitroglycerin (NTG) will be instructed to carry their NTG with them during each walking sessions. If chest pain occurs during exercise, the participants will be told to stop exercising and to take a NTG as directed by their cardiologist. The participant will also be instructed if the chest pain continues to sit down and to call a relative or friend and to take another NTG if the chest pain does not subside. If the chest pain continues and is not relieved by NTG within 10 minutes they will be instructed to call 911. If the participant becomes moderately to severely dyspneic where they cannot talk while walking they will be instructed to stop walking until the dyspnea subsides. If the dyspnea continues once they have stopped walking for several minutes they will be instructed to call a relative or friend; if not dissipated they will be

instructed to go the nearest emergency room. If a participant becomes dizzy while walking they will be asked to sit down and to get up slowly once the dizziness passes. If an ICD fires, the participant will be instructed to call 911 if symptoms are present; to notify their cardiologist if no symptoms for possible evaluation. In our preliminary work, 90% of participants had an ICD and there were no ICD shocks using a very similar protocol. If symptoms are present at current intensity level or duration of walking the participant will not be progressed until exercising at current level with RPE at 15 or below for 45 minutes. This will better ensure the participant is not progressed too rapidly.

The *potential risk to participants in the CT* is anticipated to be minimal. Participants will be taught how to use the computerized CT program by a research nurse. It is possible that some participants may have additional stress or anxiety related to participation in the CT. The 2 home visits that will be used to review the CT program are anticipated to alleviate any unusual stress or concern about participation in CT. In addition, the research nurse will be contacting the participant on a weekly basis to discuss any concerns or issues related to CT from weeks 3-12. In a prior study that used the same CT program in persons with HF, Brain Fitness (Posit, San Francisco, CA), there were no adverse events, and satisfaction and adherence were reported to be high.[16]

The *potential risk to participants in the AC control stretching/flexibility* movement group is anticipated to be minimal. Participants will be taught how to use stretching and flexibility movements by a research nurse who is not involved with the intervention groups. In our preliminary work, participants enjoyed this placebo exercise, but it was not strong enough to influence outcomes. Although some participants did experience a better QOL from contact with the research team but this was not as strong as the intervention, and it was of shorter duration.

Potential risks related to questionnaire completion include the possibility of distress after the instrument administration or teaching session. Based on the preliminary work and patient responses to these types of questionnaires and interventions, we anticipate this risk to be minimal. The intervention should not increase distress over usual care. We also observed no increase in patient depressive symptom scores over time in other studies suggesting that the intervention did not introduce greater distress. However, if participants do indicate significant symptoms of depression by their responses on the BDI-II, mental health referral information will be provided and they will be asked if they would like a research team member to assist them in setting up a referral. If at any time a participant indicates serious depressive symptoms or an intent to hurt him or herself, a family member will be informed (as agreed in the Informed Consent form) and/or their primary care provider (or cardiologist) alerted (again as agreed to in the Informed Consent). Other risks that occur are increased burden of participating in the intervention or attention control follow up calls and clinic visits. The blood sample will be collected by a research nurse or laboratory assistant in the ACTSI at each time point. The needles and syringes will be disposed in appropriate biohazard containers. The BDNF sample will be labeled by participant identification number, time point and stored in the ACTSI at -80 degrees until analyzed using the recommended ELISA procedures by the manufacturer. All laboratory specimens will be run twice to ensure reliability of blood tests. Slight bruising at the site of the venipuncture is possible. For participants on anticoagulant therapy, additional pressure to site will be applied.

The study was designed to minimize and protect against potential risks by careful training of staff, emphasis on confidentiality, and efforts to increase convenience to the subject for each study activity. To reduce anxiety and emotional responses to the intervention, we will address these concerns as part of the sessions. In the rare event that subjects experience emotional distress, they will be referred to their provider, a clinical psychologist or clinical nurse specialist available to HF patients. The total BDI-II will be reviewed as part of screening and those with moderate to severe depressive symptoms will be excluded. If BDI-II scores reveal that moderate depression (BDI-II>25) is present, the participant will be informed and asked for permission to share this information with their primary physician because of the established increased CV risk as a consequence of depression in this patient population. This will be a part of the study explanation prior to informed consent. It is important to note that the BDI-II does not confer a diagnosis of clinical depression but is a useful screening tool for those needing further assessment by a clinical psychologist or psychiatrist.

All patient records will be kept in a locked file cabinet in the research office and will be accessible only to the PI and the research team. All data will be coded by subject identification number, and no identifying information will be recorded on the data collection forms. The master list that will connect the codes to identifying information will be secured in the research project office. All data maintained in the computerized database will be accessible only with a login and protected, encrypted password. After the study is completed, all data will be kept according to regulations in a locked file.

The potential risks to subjects are anticipated to be minimal, and the anticipated benefits to patients enrolled in the study are potentially high. The majority of those who participate in combined exercise and exercise only are expected to show an improvement in cognitive function, physiological status, aerobic capacity and QOL. Because CI and physical inactivity contributes to physical function decline and poor clinical outcomes in persons with HF, improvement of physical function has the potential to significantly reduce the burden associated with this disorder and has potentially cost savings benefits. Based on our previous experience, we anticipate that the AC stretching/flexibility group may have an improvement in psychological functioning and QOL as a result of the contact with the research team members, but it will likely be of shorter duration than the intervention groups, and have no benefit on any of the other outcome variables. In addition, potentially AC education only participants may improve in HF self-care behaviors based on the additional knowledge and education provided in the education sessions. The potential knowledge to be gained from this study includes a better understanding of the underlying mechanisms that contribute to CI and the influence of a combined exercise and CT program on cognition, aerobic capacity and novel biomarkers. We will provide funds to cover transportation and parking costs associated with laboratory and physical function testing. In addition, costs for travel, parking and membership at the ACTSI will be provided. A payment of $50 will be used at each measurement time point to total $150/patient for completing the study.

Inclusion of Women

Based on the practice patterns of the enrolling institutions, we expect 60% of the HF patients to be male. Enrollment targets are set for 40-50% of the HF patient sample to represent women. This is congruent with the population at the enrolling sites and will result in data generalizable to the overall population of HF patients. We will over sample women at all sites to assure attainment of the gender distribution. We will monitor the gender of enrolled HF patient subjects and alter recruitment strategies to increase the representation of women if needed. In our pilot studies we were able to recruit 47% women.

Inclusion of Minorities

The greater Atlanta area census data reflects that approximately 35% of the population is African American. Based on the practice patterns at the enrolling institutions, we expect the minority recruitment pool of HF patients to be approximately 35% to 40% African American, with very small numbers representing Hispanic/Latino, Asian/Pacific Islander or American Indian racial/ethnicity groups. Enrollment targets are set for at least 30% of the enrolled HF patients sample to represent minorities, primarily African Americans, which will be congruent with the populations of the enrolling sites and the greater Atlanta area. We will monitor minority enrollment for HF patient subjects and alter recruitment strategies to increase the representation of minorities if needed. In our previous studies 39%-52% were African American HF participants. We have been diligent in selecting the sites for this study for their access to potential minority participants.

Inclusion of Children

Children are excluded from this study. This is due to the low prevalence of HF under the age of 21 years, the difference in the etiology, disease process and self management behaviors in children and the extraordinary scientific effort and financial resources that would be essential to include children in this study.

Data and Safety Monitoring Plan. A data and safety monitoring plan will be developed and implemented following the guidelines of the Institutional Review Board and the ACTSI of Emory University. The plan will include anticipation of adverse risks, monitoring of study progress and safety of patients, assurance of compliance with requirements regarding reporting of adverse events, and plans for performing data reviews and it will incorporate a data safety and monitoring board (DSMB). This board will be composed of Dr. Monica Parker, Chairperson, Dr Andrew Lee Smith, cardiologist and Director of the Heart Failure Therapy Center, Emory University School of Medicine, Dr. Ann Rogers, Professor at Emory University School of Nursing; this board will be supported by Dr. Amita Manatunga, PhD, biostatistician in the School of Public Health. Each of the DSMB members have extensive experience serving on a DSMB and are well qualified to serve in this capacity.

The PI will assume responsibility for developing and implementing the data and safety monitoring plan. This study is considered to present minimal risks to participants. Adverse events, that is, unfavorable or unintended symptoms temporarily associated with the intervention or evaluation, are expected to be minimal. Possible mild adverse events could include shortness of breath, fatigue, chest pain, dizziness, or rapid beating heart beat during the symptom limited modified Balke treadmill test and muscle strength testing. Subjects will

be informed of these and will be asked to notify the research staff if any of the symptoms occur; they will also have telemetry in place during the tests to detect any heart rhythm changes, blood pressure will be monitored as well before and after these tests. The risks for the adverse events during the home based walking and resistance intervention are also anticipated to be minimal. If symptoms occur during the home-based intervention, participants will be counseled on ameliorating strategies and asked to contact their provider. Before the modified Balke, all participants will receive a brief history and physical by a cardiology fellow or advanced practice nurse, and will be asked if they feel well enough to perform the test. If they experience any untoward symptoms, the treadmill test or muscle strength testing will be stopped and the participant seated and evaluation of symptoms performed by the ACTSI, nursing research team member or study cardiologist. If symptoms persist, the person will be taken to the Emergency Department for further evaluation and treatment. All adverse events will be reported to the IRB, ACTSI and DSMB for review.

The research team will meet periodically to review screening, enrollment and randomization data and to identify any human subject issues that arise. All staff will be trained in the protection of human subjects according to university and NIH regulations, and will be required to be certified in human subject's research in accordance with the Emory University IRB procedures. We will conduct random and periodic audits of research records to ascertain that informed consents are signed, witnessed and complete for each subject, and that confidentiality procedures are being maintained.

The DSMB will meet with the PI and study team at the beginning of the trial, after 30 patients have been enrolled and completed the study, as well as annually or as needed to review the conduct of the trial, including accrual, recruitment and retention, violations in protocols, adverse events, breaches in confidentiality, or other data related to protection of human subjects. The first meeting of the DSMB will review and make recommendations about consent procedures, and situations within which confidentiality may be broken, for example, if a participant indicates suicide tendencies on the BDI-II. The primary role of the DSMB will be to ensure data integrity and the safety of participants. They will have the power to recommend termination of the trial if significant negative trends emerge. In the highly unlikely event that serious risks occur, they will also have the power to recommend termination of the trial. In addition, study recruitment, and retention procedures will be examined for timeliness, practicality, safety, and protection of all human subjects.

At subsequent regular annual meetings, the DSMB will review adherence to the goals for recruitment and retention; adherence to study protocols; cumulative data for evidence of study related adverse events; quality, completeness, and timeliness of the data collected; factors that could affect the outcome or compromise participant/data confidentiality; and other factors outside the study (e.g., therapeutic developments, agency related policies) that could impact the safety of participants or the ethical conduct of the study. General recommendations the DSMB may include these: continuation of the study without change; modifications to the study protocol; suspension or early termination; alternative approaches to consider. Formal minutes and reports of the DSMB will be maintained and made available to NIH as required. All materials, discussions and reports of the DSMB are considered confidential and will be treated as such in the maintenance of records.

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