REHAB-HF: A Trial of Rehabilitation Therapy in Older Acute Heart Failure Patients

Protocol Outline

Abbreviations:
ADHF- acute decompensated heart failure
SPPB- short physical performance battery
6MWD- 6-minute walk distance
KCCQ- Kansas City Cardiomyopathy Questionnaire
SF-12- 12-item short form health survey
HF- heart failure
QOL- quality of life
PND- paroxysmal nocturnal dyspnea
BNP- B-type natriuretic peptide
ADL- activity of daily living
RPE- rate of perceived exertion
EQ-5D-5L- Euroqol 5-dimension 5-level
GDS- Geriatric Depression Scale
MoCA- Montreal Cognitive Assessment
DSMB- data safety monitoring board
AE- adverse event
SAE- serious adverse event
REDCap- research electronic data capture

1. Overview of the REHAB-HF Study

REHAB-HF: A Trial of Rehabilitation Therapy in Older Acute Heart Failure Patients, is a multicenter, randomized, attention-controlled, single-blind trial designed to examine the hypothesis that, in addition to standard care, a novel, tailored, progressive, multi-domain rehabilitation intervention administered to older patients with acute decompensated heart failure (ADHF) beginning early during hospitalization and continuing for 12 weeks will improve physical function and key clinical outcomes, including the rate of rehospitalization.

Three centers will recruit a total of 360 consenting patients ≥ 60 years old hospitalized with ADHF. Following informed consent and baseline testing, the participants will be randomized in a 1:1 fashion to receive a 12-week novel, progressive, multi-domain rehabilitation and exercise training intervention or attention control. The multi-domain rehabilitation intervention will include endurance, mobility, strength, and balance training and will be tailored based on participant performance in each of these domains. It will begin upon randomization during the hospitalization and will continue 3 times per week in an outpatient setting. Participants randomized to the attention control arm will receive all services ordered by their primary physician and will be contacted bi-weekly by study staff. All participants will undergo measures of physical function and quality of life at baseline, 1 month, and 3 months. Clinical events will be monitored for 6 months following the index hospitalization.

By testing a novel rehabilitation intervention supported by multiple levels of evidence, this trial will address a critical evidence gap in the care of older patients with ADHF. The REHAB-HF results have the potential to shift paradigms by improving physical function and quality of life as well as clinical outcomes. If successful, the results could have a major impact on the management of patients with ADHF, the most common Medicare discharge diagnosis.

2. Study Objectives

2.1 Primary Objective

To conduct a multicenter, randomized, attention-controlled, single-blind trial of a novel, tailored, progressive, multi-domain, 12-week physical function intervention in 360 older patients with ADHF in order to test the following primary specific hypothesis: The REHAB-HF intervention will improve physical function, as measured by the short physical performance battery (SPPB).

2.2 Secondary Objective

To systematically collect clinical outcomes data during the 6 months following the index hospitalization to test the following secondary hypothesis: The REHAB-HF intervention will reduce the 6-month all-cause rehospitalization rate.

2.3 Other Objectives

1. To assess the economic impact of the intervention by comparing medical costs between treatment arms, inclusive of the cost for rehabilitation therapy, relative to its associated changes in health outcomes.

2. To estimate the proportion of the reduction in rehospitalizations explained by the intervention's effect on the SPPB score.

3. To examine the effect of the intervention on these exploratory endpoints:
    1. Change in the Kansas City Cardiomyopathy Questionnaire (KCCQ) total score and physical component score at 3 months
    2. Change in 6-minute walk distance (6MWD) at 3 months

3. Change in component scores of the SPPB at 3 months
4. Change in the 12-item short form health survey (SF-12), depression, and cognition measures at 3 months
5. Change in frailty status at 3 months
6. All-cause rehospitalizations at 1 month and 3 months
7. All-cause combined rehospitalization and death at 6 months
8. Global rank endpoint of SPPB score + all-cause rehospitalization + death
9. Heart failure (HF)-specific rehospitalizations
10. Cardiovascular events
11. All-cause rehospitalization days
12. Total hospitalization days post-randomization
13. Total facility-free days alive
14. Deaths
15. Falls
16. Change in biomarkers at 3 months

3. Background

ADHF is the leading cause of hospitalization in persons > 60 years in the United States. Hospitalized ADHF is associated with severely reduced health-related quality of life (QOL), persistently high rehospitalization rates,(1) markedly increased mortality, and costs over $39 billion per year.(2) Current HF management guidelines, even when perfectly adhered to, have had only modest impact on ADHF outcomes, particularly rehospitalizations in the older population.(1;3-5) Furthermore, several recent trials of new interventions to improve ADHF outcomes, such as telemonitoring,(6;7) alternative diuretic regimens,(8-11) novel agents(11;12) and biomarker guidance have been negative.(9;13) This suggests outcomes in older ADHF patients may be driven partly by mechanisms that are not addressed by current approaches.

Multiple lines of emerging evidence suggest that severely reduced physical function and frailty strongly contribute to adverse outcomes in older patients with hospitalized ADHF.(14) We and others have shown that even when stable with compensated cardiovascular function, older patients with chronic HF have particularly severe impairments in physical function(14-16) due to the combined effects of aging, cardiovascular dysfunction, and impaired skeletal muscle function.(17-27) As patients with chronic HF transition to ADHF, physical function worsens markedly both because of HF decompensation and accelerated physical deconditioning.(19;28;29) This is further exacerbated by the hospital processes, including forced bed rest which can markedly accelerate physical dysfunction.(30-36) We and others have shown that after resolution of the acute HF symptoms and congestion, older ADHF patients continue to have marked impairments in physical function, including strength, balance, mobility and endurance, and that most patients meet formal definitions of frailty.(28;29;37-39) Furthermore, these deficits persist and some patients never recover baseline function.(14;33;40-43) This occurs during the most vulnerable, high risk period for rehospitalization and adverse outcomes - up to 6 months post discharge.(44;45) We hypothesize that this physical frailty predisposes patients to adverse outcomes and that this cascade of events contributes to the persistently high rates of adverse outcomes, including rehospitalization, in older HF patients.(4;16;28;29;37;38;41;42;45-47)

The typical older ADHF patient has > 5 comorbidities(14;48;49) and these contribute to impaired physical function(50) and subsequent adverse outcomes.(4;14;28;47;49;51-56) Impaired physical function and frequent non-cardiac comorbidities may explain the unexpected finding from multiple studies that > 50% of rehospitalizations in older ADHF patients are due to non-cardiac events rather than recurrent ADHF.(4;14;40;48;49;57-59)

In our published model,(14) we have identified 5 factors that contribute to severely impaired physical function and subsequent events in older ADHF patients: aging-related changes, the primary HF disease, deconditioning, multiple comorbidities, and iatrogenesis. Our data and others' from studies in other medical conditions common in older patients support that targeted physical function interventions can improve impairments related to each of these factors.(21;60-67)

However, current ADHF management paradigms do not account for or address the marked physical dysfunction in hospitalized older patients with acute HF.(3;4;50) This may also explain why trials of a wide range of interventions in ADHF have been largely negative(6-8;11;12;12) and disease management programs have had, at most, modest impact on long-term outcomes and mortality.(6;37;68;69)

Furthermore, the exercise training trials in HF to date (n >17) have systematically excluded ADHF patients in this key period of vulnerability.(70-73) The largest of these, the NIH-funded HF-ACTION trial, systematically excluded patients with ADHF and those within 6 weeks of hospital discharge.(73;74) Possibly because of recent instability, the study did not significantly reduce the primary endpoint of all-cause mortality or all-cause hospitalizations.(74) HF-ACTION also enrolled relatively few older patients, excluded those with multiple comorbidities, and utilized a traditional cardiac rehabilitation exercise training intervention that would not have been appropriate for older patients with significant frailty. As a result, and similar to prior trials, it likely missed the patients who are elderly, frail, and have multimorbidity who have the largest potential for improvements in outcomes.(3;3;4;75-77)

Prior exercise training studies in HF have not addressed the domains of balance and strength which are important for preventing early injuries in frail, older hospitalized ADHF patients(78) and for enhancing gains in function.(79) Prior intervention studies in older hospitalized patients that have included these domains have generally excluded patients with HF. (65;67;78-80) However, the results of such studies informed and support the primary hypothesis of the proposed study.(41;79-82) For instance, Morris et al showed that an early mobility program improved outcomes in older hospitalized patients with acute respiratory failure.(82) In a non-randomized quasiexperimental study, Tinetti et al. recently showed that a restorative home care model that included physical function reduced rehospitalizations by one-third in older patients, some of whom had HF.(41) The primary hypothesis is also supported by our pilot study which showed that in older patients with ADHF, the proposed intervention can improve SPPB score, a strong predictor of hospitalization, disability, and death.(38)

4. Overview of Investigational Plan

The REHAB-HF study is a multicenter, randomized, attention-controlled, single-blind trial of a novel, progressive, multi-domain rehabilitation intervention versus attention control in 360 older patients hospitalized with ADHF. The primary hypothesis is that the REHAB-HF intervention will improve physical function, as measured by the SPPB, the primary outcome.

Patients will be screened and enrolled during the index HF hospitalization. After completion of the baseline testing, participants will be randomly assigned to a novel, progressive, multi-domain, 12-week physical function intervention or to attention control. Participants randomized to the intervention arm will begin a tailored, novel, multi-domain rehabilitation intervention in the hospital which will progress to the outpatient setting. The intervention will focus on four key physical functional domains: endurance, mobility, strength, and balance; and will be tailored based on participant performance in each of these domains. Participants randomized to the

attention control arm will receive all services ordered by their primary physician and will be contacted bi-weekly by study staff. Blinded assessments will be repeated 1 month and 3 months following the index hospital discharge. Data on clinical events and resource use will be collected for 6 months following the index hospital discharge.

5. Study Population

The inclusion and exclusion criteria have been developed to include a broad range of older patients who are hospitalized with ADHF and expected to be discharged to home. To enhance the applicability of the results, the criteria are designed to be inclusive of older patients with multiple comorbidities, heterogeneous functional performance, and both preserved (≥ 45%) and reduced ejection fraction. Specifically, the study has the goal that patients with preserved ejection fraction will compromise at least 30% of the total study population.

5.1 Inclusion Criteria

- Age ≥ 60 years old
- In the hospital setting >24 hours for the management of ADHF, or diagnosed with ADHF after being hospitalized for another reason. ADHF will be confirmed by the study physician, and will be defined according to the Food and Drug Administration definition of hospitalized heart failure as a combination of symptoms, signs, and HF-specific medical treatments, and requires that all 4 of the following are met:

  1) At least **one** symptom of HF which has worsened from baseline: a. dyspnea at rest or with exertion; b. exertional fatigue; c. orthopnea; d. paroxysmal nocturnal dyspnea (PND)

  2) At least **two** of the following signs of HF: a. Pulmonary congestion or edema on exam (rales or crackles) or by chest xray; b. Elevated jugular venous pressure or central venous pressure ≥ 10 mm Hg; c. peripheral edema; d. wedge or left ventricular end diastolic pressure ≥15 mmHg; e. rapid weight gain (≥ 5 lbs.); f. Increased b-type natriuretic peptide (BNP) (≥100 pg/ml) or N-terminal prohormone BNP (≥220pg/ml)

  3) Change in medical treatment specifically targeting HF defined as change in dose or initiation of or augmentation of at least **one** of the following therapies: a. diuretics; b. vasodilators; c. inotropes (including digoxin if for HF); d. other neurohormonal modulating agents, including angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, aldosterone or direct renin inhibitors

  4) The primary cause of symptoms and signs is judged by the investigator to be due to HF

- Adequate clinical stability has been achieved in the judgment of the investigator to allow participation in study assessments and the intervention
- Prior to admission and HF decompensation, patient was independent with basic activities of daily living (ADLs) including the ability to ambulate independently (with or without the use of an assistive device)
- Able to walk 4 meters (with or without the use of an assistive device) at the time of enrollment
- Signed informed consent document indicating that the patient understands the purpose of and procedures required for the study and is willing to participate in the study

5.2 Exclusion criteria

- Acute myocardial infarction (Note: given that cardiac biomarkers such as troponin are frequently elevated in HF patients, the diagnosis of acute myocardial infarction should be based on clinical diagnosis, not biomarkers alone)
- Planned discharge other than to home or a facility where the participant will live independently
- Already actively participating in formal, facility-based cardiac rehabilitation
- Prior cardiac transplantation or planned within the next 6 months
- Severe aortic valve stenosis
- Ventricular assist device or anticipated within the next 6 months
- Already engaging in regular moderate to vigorous exercise conditioning defined as > 30 minutes per day, ≥ twice per week consistently during the previous 6 weeks
- Terminal illness other than HF with life expectancy < 1 year
- Impairment from stroke, injury or other medical disorder that precludes participation in the intervention
- Dementia that precludes ability to participate in rehabilitation and follow study protocols
- Enrollment in a clinical trial not approved for co-enrollment
- Expected use of continuous intravenous inotropic therapy after discharge
- Implantable cardioverter defibrillator with heart rate limits < expected heart rates for exercise and unable to be reprogrammed
- Advanced chronic kidney disease defined as estimated glomerular filtration rate < 20 mL/min/1.73 m2 based upon the Modification of Diet in Renal Disease study equation, current ultrafiltration, or on chronic or intermittent dialysis or dialysis anticipated within the next 6 months
- High risk for non-adherence as determined by screening evaluation
- Inability or unwillingness to comply with the study requirements
- Anticipated hospital discharge before baseline study measures could be completed

6. Participant Enrollment

6.1 Screening

Screening for enrollment will be initiated as early as possible during the patient's hospitalization for ADHF. Patients who are eligible and agree to participate in REHAB-HF will give written, informed consent.

Following informed consent, screening will continue with a brief assessment of walking capability as well as a brief adherence screening tool and behavioral agreement designed to identify participants at high risk of failing to adhere to the study intervention. Participants who are able to ambulate 4 meters independently, are not at high risk for failing to adhere to the intervention, and meet all other inclusion criteria will be enrolled. A record of participants who provided informed consent but were not subsequently enrolled and the specific exclusion reasons will be maintained by the study. In addition, a record of patients screened, but not consented, will be maintained by the study.

6.2 Baseline Testing

Baseline testing of physical function, measures of health status and QOL, and collection of blood samples will be completed as soon as possible after consent (see sections 9 and 10 for details).

6.3 Randomization

Once a participant has been identified who satisfies all enrollment criteria, informed consent has been obtained, and baseline testing is complete, the participant will be randomized to a multi-domain rehabilitation intervention group or to an attention control group. Block randomization will be performed, stratified on clinical center and ejection fraction (<45, ≥45), and will be performed by a centralized, web-based system developed and maintained by Dr. Timothy Morgan.

7. Investigational Intervention

7.1 Attention Control

Participants randomized to the attention control arm will be notified immediately, and will follow standard care as ordered by their individual, treating physician. Importantly, to reduce the potential for bias from greater attention and surveillance in the rehabilitation intervention group, participants in the attention control group will receive at least bi-weekly contact from study personnel during the first 3 months following the index hospitalization. This contact will be provided as a combination of telephone calls and specified study visits. Specifically, contact will be made with study visits at weeks 4 and 12 and with telephone calls at weeks 2, 6, 8, and 10. Further, in-person contact will be made within the first 2 weeks following discharge for the purposes of retention (section 8.2.2). Consistent with the rehabilitation intervention group, telephone contact will also be made at weeks 14, 16, 20, and 24. Information regarding symptoms, HF transitional management program use, medical compliance, activity level, rehabilitation received, medical resource utilization, and clinical events will be collected at each of these encounters.

Participants in the attention control arm will not receive any specific rehabilitation recommendations or exercise prescription from study personnel. They may, however, receive any physical or occupational therapy deemed appropriate by their usual clinical care providers, both during the hospitalization and as outpatients.

7.2 Rehabilitation Intervention Group

7.2.1 REHAB-HF Rehabilitation Intervention Overview

The multi-domain rehabilitation intervention for this study is a novel integration of rehabilitation therapies developed specifically for older heart failure patients who have been hospitalized for ADHF; a population characterized by heterogeneity in mobility status, multiple co-morbid conditions, and high rates of frailty.(48;50;83-85) The goal of the intervention is to increase endurance, mobility, strength, and balance utilizing reproducible targeted exercises administered by a multi-disciplinary team with specific milestones for progression.

This is a transitional intervention which begins during the acute hospitalization and continues for 12 weeks after discharge in the outpatient setting. The intervention will be administered once daily in the hospital and 3 days per week in the outpatient setting. Each session will include 3 stages: 1) warm-up (seated core exercises, 2-3 minutes light walking if able, and stretching exercises), 2) rehabilitation/training, and 3) cool-down (stretching exercises). The rehabilitation/training portion of each session will include exercises tailored based on participant performance in each of 4 domains: endurance, mobility, strength, and balance.

7.2.2 Initiation of the Rehabilitation Intervention

Participants randomized to the multi-domain rehabilitation intervention will begin the intervention in the hospital as soon as possible after randomization. Though not required for enrollment, when possible the intervention will begin in the hospital. Plans for the initiation / continuation of

the intervention in the outpatient setting will be made prior to hospital discharge and will be scheduled to begin within the first week following discharge.

7.2.3 Initial Exercise Prescription

The initial rehabilitation exercise prescription will be individualized for each participant based upon functional performance level (1-4, from lowest to highest) in each domain using the objective criteria shown in Table 1. Performance level will be assessed in the first rehabilitation session in both the inpatient and outpatient setting. Using a standardized approach, exercises specifically targeted to the participant's functional level in each domain will be selected from the rehabilitation intervention protocols. We anticipate a range of initial performance levels based on the REHAB-HF pilot study where 40% of participants were initially at level 1 for most domains, 33% were at level 2, and 27% were at level 3.

Table 1. Performance Levels for Strength, Balance, Mobility and Endurance

	Level 1	Level 2	Level 3	Level 4
Strength: Rise from chair without hand support	unable	at least once	5 times in > 15 but <60 sec.	5 times in ≤ 15 sec.
Balance: Standing	unable with feet together for 10 sec.	with feet together for 10 sec.	unsupported and reach forward 10 in.	on 1 leg for 10 sec.
Endurance: Continuous walking	< 2 minutes	≥ 2 but < 10 minutes	≥ 10 but < 20 minutes	≥ 20 minutes
Mobility: Gait speed	≤ 0.4 m/sec.	> 0.4 but ≤ 0.6 m/sec	> 0.6 but ≤ 0.8 m/sec.	> 0.8 m/sec.

7.2.4 Exercise Duration

During the hospitalization, each rehabilitation session will last for approximately 45 minutes and will include warm-up (~5 minutes), cool-down (~5 minutes), and rest periods as needed. The outpatient rehabilitation sessions will last for approximately 60 minutes (range 45 - 75 minutes), including 5 to 10 minutes each for warm-up and cool-down periods. The relative time spent on each domain during the rehabilitation session will be tailored to the participant's physical function impairments. Specifically, a participant with poor balance and functional mobility will spend a greater proportion of time performing balance and mobility exercises in the early portions of the intervention. As balance and functional mobility improve, these will comprise a smaller portion of the session and time spent on endurance will be increased. Alternatively, a participant with only modest impairments in balance and functional mobility at baseline will spend most of the exercise session performing endurance and strengthening exercises, even early in the intervention.

7.2.5 Exercise Intensity

Exercise intensity will be based upon patient-reported rate of perceived exertion (RPE) using a 6-20 point scale. While hospitalized and initially following discharge, target intensity will be low (RPE ≤ 12). In the outpatient setting, target intensity will gradually increase over the first 2 weeks of the intervention. For strengthening rehabilitation, the target RPE will progress to 15-16, as this level of intensity may be necessary to obtain significant functional improvement in strength, as previously shown.(67) For the endurance exercises, the target RPE will progress to 13 ("somewhat hard") with a range of 11-15. After 4 weeks of the endurance intervention, intensity within the RPE range will be adjusted to ensure a heart rate response of ≥ 20 beats per minute above the resting heart rate, as exercise increase is needed to achieve $\geq$ 60% of exercise reserve capacity.(86) Using both RPE and heart rate will ensure an adequate training effect and minimize non-responders while maintaining safety(74;87;88)

7.2.6 Exercise Progression

A key aspect of the REHAB-HF intervention is its structured, gradual progression using specific small increments in each exercise. As discussed in section 7.2.3, initial performance level (Table 1) will be assessed at the first inpatient and outpatient session. Using a standardized approach, initial exercises specifically targeted to the participant's functional level in each domain will be selected from the rehabilitation intervention protocols below. Participants will then be continually challenged to safely and effectively improve physical function by advancing through the specified progression for each exercise based on their individual performance. Further, the performance level in each domain will be reassessed bi-weekly in the outpatient setting to re-evaluate functional abilities (i.e. to ensure no under-treatment) and to evaluate progression. Exercise prescription within each domain will be adjusted accordingly. Importantly, as function improves, the duration of endurance-based exercise will be increased as tolerated by the participant. Progression will be monitored by the intervention team under the direction of the site intervention supervisor and in consultation with Dr. Duncan, overall study intervention leader.

7.2.7 Modality of Exercise

The REHAB-HF intervention incorporates 4 exercise domains into each session: endurance, mobility, strength, and balance. A brief description of the types and range of exercises in each of these domains is included below. Generally, exercises range from those adapted to the lowest level of functioning (level 1) to the highest (level 4). A detailed description of each exercise and how it is to be progressed is contained in the manual of operations.

7.2.7.1 Endurance Training

For the most debilitated participants (level 1), endurance training will begin with repeated bouts of ambulation at usual speed with rest breaks as needed, with an initial goal of 5-10 minutes total duration. The endurance training will progress to sustained walking at the target RPE for up to 40 minutes for the highest-functioning participants (level 4). Walking is the preferred mode of endurance exercise, however, endurance exercises utilizing other equipment while still involving major muscle groups of the lower extremities (e.g. exercise bicycle) may be incorporated into the endurance training to supplement walking.

7.2.7.2 Mobility Rehabilitation

One of the primary goals of the rehabilitation intervention is to improve functional mobility, particularly in participants with slower gait speeds (<0.8 meter/second) and impaired dynamic balance. Accomplishing this will involve rehabilitation exercises that combine balance activities with mobility. Such exercises will include dynamic start and stop and changing direction while walking. In addition, participants with a slow gait speed will undergo exercises involving brief episodes of accelerated gait. Close supervision and guarding will be provided to prevent injuries and falls.

7.2.7.3 Strengthening Rehabilitation

The intervention focuses on functional strengthening exercises of the lower extremities that may be supplemented by general resistance exercises for major muscle groups of the upper and lower extremities. Functional strengthening exercises include: sit-to-stand from chair (or bed in the hospital setting), step-ups (front and side), and calf raises. For the most impaired participants (level 1), this will begin with guarded stands, assisted step-ups on a 4-inch step, and seated toe raises. These exercises will progress to (level 4) rapidly repeated stands with platform in front of chair, unassisted step-ups on an 8-10 inch step, and standing toe raises on one leg. For general strengthening exercises, the most impaired participants (level 1) will begin with assistive or lightly resistive exercises. The interventionists will match the participant's

ability to exercise major muscle groups of the upper and lower extremities. As participants progress, strengthening exercises of the major muscle groups of the upper and lower extremities using resistance bands or free weights will be incorporated. The amount of resistance will be progress so that the participant can perform 1 set of 10 repetitions at the target rate of RPE.

7.2.7.4 Balance Rehabilitation

Balance rehabilitation will include both static and dynamic exercises. For the most unsteady participants (level 1), balance rehabilitation will begin with holding a shoulder-width stance for static balance and standing and reaching forward and backward 6 inches for dynamic balance. For static balance, these exercises will progress to holding an increasingly narrow base of support (feet together to semi-tandem stance to tandem stance to single leg stance) with eyes open and progressing to eyes closed. Close supervision, including the use of a gait belt as needed, will be provided by the study personnel to prevent injuries and falls. For dynamic balance, participants will be challenged to reach further beyond their base of support during seated progressing to standing activities. Dynamic balance will also be integrated within functional strengthening exercises (e.g. step and reach). Close supervision, including the use of a gait belt as needed, will be provided by the study personnel to prevent injuries and falls. As patients progress to level 3 and 4, dynamic balance activities will be incorporated into endurance episodes, such as supervised walking and turning, walking and abrupt stops, walking and talking, and walking and side stepping.

7.2.8 Exercise Safety

During each exercise session, participants will sign an attendance sheet and log any health-related problems or symptoms they are experiencing. These sheets will be reviewed by intervention staff before initiating physical activity. Should a participant report a significant change in health status (see safety parameters below) before or during exercise, a study physician onsite or the participant's primary doctor should be consulted prior to exercise participation. Vital signs, including heart rate, blood pressure and pulse oximetery will be recorded at the beginning and conclusion of each session. Routine assessment of heart rate during the exercise session will also be used to enhance exercise safety. Exercising blood pressure and pulse oximetery will be monitored on a symptom-driven basis as needed during the trial to ensure participant safety.

For participants who meet any of the safety parameters listed below, the following steps and additional monitoring procedures will be conducted:

- Exercise training sessions will be stopped
- The participant will subsequently be re-evaluated for medical contraindications to exercise
- Exercise intensity levels will be re-assessed and modified as needed

Safety Parameters

- Resting blood pressure systolic > 200 mm Hg or diastolic > 100 mm Hg
- Resting heart rate >120 beats/min or < 40 beats/min
- Increase in heart rate ≥90% of age predicted maximum during exercise
- Oxygen saturation < 90% on room air
- Unusual or severe shortness of breath
- Chest pain including chest discomfort or pressure, left arm pain, report of indigestion or stomach discomfort
- Palpitations

- Severe light headedness, dizziness or feeling about to faint
- A physical activity session had to be discontinued because of other symptoms excluding musculoskeletal symptoms (e.g. knees, ankles, hips) reported by the participant
- Decrease in diastolic blood pressure ≥20 mmHg during exercise
- Increase in systolic blood pressure to ≥250 mmHg or in diastolic blood pressure to ≥115 mmHg during exercise
- Decrease in oxygen saturation to <88% on room air during exercise

An automated external defibrillator (AED) will be available at the facility. On-site staff, including a study interventionist, trained in basic life support, will be available to deal with medical emergencies. Also, institutional and community emergency medical services will be activated if needed.

7.2.9 Home Visit and Home Exercise Prescription

All participants randomized to the study intervention will receive one home evaluation within one week following hospital discharge (preferred within 3 days). The home visit will be utilized to:

- Establish patient identified goals
- Prescribe a customized the home exercise program based on patient goals and identified deficits
- Identify areas for safe performance of walking and functional strengthening exercises
- Engage the participant's caregiver/partner to support home exercise
- Identify resources in the home and community (i.e. technology, exercise facilities) to promote adherence to home exercise and goal achievement
- Review use of physical activity monitor to track progress towards goals and promote adherence

Participants will be instructed in low-intensity walking at their usual pace on non-program days, gradually increasing toward a goal of 30 minutes daily. The functional strengthening exercises (sit-to-stand from chair, step-ups, if feasible, and calf raises) will be incorporated as well. Participants will be encouraged to wear a physical activity monitor to both motivate and track adherence to the home exercise (see section 7.4).

7.2.10 Allowance of Supervised Home-Based Exercise

The preferred location of the outpatient intervention is facility-based. However, some patients in the REHAB-HF target population may not be able to immediately begin the intervention in an outpatient facility, particularly in the first 2 weeks following hospital discharge. At the discretion of the investigator, home-based training by appropriately trained personnel following the same intervention as described above (simply different location) is included as an option in the study protocol early after hospital discharge. The investigator must have high confidence that the participant will be able to progress and is willing and able to transition to facility-based training. If a participant requires the home-based intervention, the focus will be to improve functional performance and to remove any barriers so that participants can subsequently transition to facility-based rehabilitation and exercise training.

7.2.11 Maintenance Phase

Following the completion of the outpatient intervention, participants in the intervention arm will be encouraged to continue with exercise training as part of a maintenance phase. Preparations for the maintenance phase will begin after randomization and continue throughout the supervised exercise portion of the intervention. These preparations may include

- Evaluation of home environment for safe and feasible participation in home exercises as described below (home visit section 7.2.9)
- Ongoing encouragement to participate in the home walking exercise as described above (home exercise prescription section 7.2.9)
- Identifying and addressing potential barriers to participation in exercise training after the supervised portion of the protocol is complete
- Discussing the importance of continued regular exercise after the supervised intervention is complete
- Identifying community resources available to the participant for ongoing physical activity and exercise training
- Engagement of spouse or caregiver, when applicable, for ongoing support of continued exercise training

Towards the conclusion of the outpatient intervention, an individualized exercise prescription will be developed by the interventionist and approved by a study physician. This exercise prescription will be given to the participant at the 3-month visit. All participants will receive regularly scheduled phone calls (two in month 4, one in months 5 and 6) to assess clinical status as described below (follow up schedule section 9.1). For participants in the intervention arm, these phone calls will also be used to discuss the maintenance phase exercise prescription.

7.2.12 Management of Conflicts with Physician-Ordered Care

All participants will receive standard care as ordered by their personal, treating physician. Efforts will be made to integrate the REHAB-HF intervention into the standard of care ordered by the treating provider. In the event of conflict between standard care and the REHAB-HF intervention assignment, the study protocol will yield to individual, physician-ordered standard care.

7.3 Intercurrent Illness and Interruption to Study Intervention

Interruptions to the study intervention, including illness and hospitalization, are anticipated. Although this is an intention-to-treat protocol, to help ensure each participant has a reasonable opportunity to complete the study intervention (defined as completing at least 30 outpatient sessions) and that the physical performance outcome measures reflect the intended intervention of this study, limited extensions of the study intervention are included in the study protocol. Participants who suffer an illness, hospitalization or other complications that interferes with participating in the study intervention will resume the intervention once medically stable. Participants will have up to 4 additional weeks beyond the initially planned 12 weeks to attempt to complete the multi-domain intervention.

In addition, if a participant is acutely ill or hospitalized within 2 weeks of the anticipated date of the final 3-month visit, the visit will be delayed for up to 2 weeks to allow for up to 6 additional rehabilitation and exercise sessions. Similarly, the final 3-month visit for those in the attention control arm will also be delayed for up to 2 weeks in the event of acute illness or hospitalization within 2 weeks of the date of the visit.

7.4 Monitoring of Exercise and Rehabilitation

The details regarding the number of rehabilitation sessions attended as well as key markers of adherence to the exercise prescription and progression will be recorded and entered into the secure database by the study personnel supervising the rehabilitation and exercise training. In

addition, participants in both the study intervention arm and the attention control arm will keep a diary of any exercise performed or any usual care rehabilitation received.

Participants in the rehabilitation intervention arm will be issued physical activity monitors to promote adherence to home exercise and activity goals. In addition, at specific time points in the study, the attention control arm will wear a physical activity monitor to allow comparison of home activity between the two arms.

Participant adherence with both exercise diary entries and wearing of an accelerometer will be encouraged throughout the study during follow-up visits and phone calls.

8. Retention and Treatment Fidelity

8.1 Overview

In order for the REHAB-HF study to be successful, we will implement proactive procedures to insure that we (1) retain participants in accord with the intent-to-treat principle, (2) deliver the REHAB-HF intervention safely and effectively as outlined in the protocol, and (3) maximize adherence to intervention.

8.2 Retention

8.2.1 Adherence Screening and Behavioral Agreement

Retaining participants in the study will begin prior to enrollment. Following informed consent, a brief adherence screening tool and behavioral agreement will be completed. The adherence screening tool explains the basic commitments of the rehabilitation intervention and asks the participant to rate the degree of: 1) conflicts from other commitments/personal issues interfering with the intervention, 2) difficulty in obtaining transportation, 3) how they think their primary physician would feel about the study intervention, and 4) their confidence in being able to carry out the intervention. The behavioral agreement is a document to be signed by the participant detailing the requirements of REHAB-HF and indicating the participant's willingness to complete the requirements of either treatment arm of the intervention once randomized.

This process will not only allow us to identify adherence risks, but along with informed consent, it will also be used as a mechanism to give participants an in-depth understanding of REHAB-HF and enable us to collect information to assist in the tailoring of treatment.

The study team at each site will carefully discuss the information gleaned from these assessments to make a final determination on behavioral suitability for REHAB-HF.

8.2.2 Retention Promotion Efforts

To promote retention, the following steps will be followed: 1) provision of a clear schedule of all visits, reminders, same-day phone calls for any missed visits, involvement of family and caregivers, and sharing of test results and intervention progress, if applicable; 2) free parking for study visits and intervention sessions; 3) transportation to study visits and intervention sessions as needed for participants of low socioeconomic status; and 4) required in-person contact within the first 2 weeks following discharge, achieved through intervention sessions, home visit, or meeting at a usual care clinic visit or if necessary, a scheduled clinic visit.

8.2.3 Retention for Study Visits

Algorithms are developed to address non-attendance to study visits. These involve procedures (discussed below) that facilitate documentation of these events and how best to rectify the

problem. The following procedures will be implemented (as appropriate in each site) to carefully document and monitor missed study visits:

- Preparing for the next visit at the end of each current visit by making the appointment and giving instructions for the next visit
- Rescheduling the visit within the same window, if possible. Examinations that fall outside of the target window remain important and are used in all analyses. These examinations are assigned to whichever target visit would be the closest in time. If it becomes clear that a visit corresponding to a particular set of forms (e.g. a 3-month visit) is not completed, a Missed Visit form is filled out

The following guidelines are implemented to promote adherence to study visits:

- Fostering personal relationships between participants and individual members of the staff
- Insuring that the clinic environment is warm and pleasant, and oriented to the comfort of the patient
- Using easily accessible clinic locations, providing transportation when necessary, and convenient clinic hours all serve to facilitate study adherence
- Keeping total clinic visit time to a minimum. If waiting is necessary, the situation is explained to the participant and, if possible, an offer is made for the participant to see another staff member, or to reschedule the visit
- Appointment reminders are used to prompt participants to attend clinic visits

8.2.4 Monitoring Recruitment and Retention

The study investigators, including Dr. Jack Rejeski, consultant for retention and adherence, will routinely monitor screening and recruitment yields, and compare these to preset gender and ethnic minority benchmarks for each site. If sites encounter difficulties with recruitment or retention, the investigators will partner with the site in question to establish specific steps to assist in resolving the problem encountered.

8.2.5 Retention and Efforts to Maintain Contact with Inactive Participants

Retention is promoted by:

- Examining and attempting to remove barriers (e.g., by addressing parking and other transportation issues, adjusting clinic hours).
- Incorporating a variety of methods to promote contact with all participants and provide social support for all participants.
- Ensuring that participants' concerns are identified and addressed before they express a desire to reduce their involvement in the study.

REHAB-HF has the goal of maintaining some form of contact (e.g., phone, e-mail) with participants who are unable to continue full engagement in the study and to foster some form of continued involvement (e.g., even an agreement to allow future contact) with participants who are inactive in the study. Priority is given to attending assessment visits.

8.3 Treatment Fidelity: Delivering the Physical Activity Intervention as Detailed in the Protocol

Critical to the success of REHAB-HF is insuring fidelity of the intervention. There are 3 steps taken to address this facet of study conduct.

1. Prior to study launch, all intervention personnel will participate in on-site training sessions. Training materials will include videos, handouts, and case presentations, as well as hands-on

demonstrations for each site. The training will be led by Dr. Pamela Duncan, overall trial intervention leader, who will review, critique, and provide feedback to the interventionists.

2. The intervention will be carried out in a standardized manner across treatment sites. To facilitate this, the intervention protocol contains a standardized protocol for guiding exercise prescription (section 7.3.2) and exercise progression (section 7.3.5), the two most critical pieces to ensure consistent implementation.

3. An intervention committee will regularly review intervention adherence, progression, and fidelity. This committee will comprise of Dr. Duncan and the intervention supervisors from each site along with Dr. Rejeski, as needed. This committee will regularly review real-time reports generated from the study database to track attendance and progression on key measures in each domain (such as walking distance, sit-to-stand level achieved). Bi-weekly teleconferences, including the interventionists, will be used to discuss the progress of individual participants, the performance of interventionists and sites, and to troubleshoot any potential barriers to attendance or progression that may arise.

9. Study Participant Follow-up

9.1 Follow up schedule

All baseline measures (see Table 2) will be collected during the index hospitalization. Follow up visits will occur 4 weeks ± 3 days and 12 weeks ± 10 days (unless intervention is extended, see section 7.3) from the day of discharge from the index hospitalization. These visits will include a brief history and physical and collection of study measures (see Table 2). Historical information will include heart failure symptoms, NYHA class, current medications, the results of any intervening cardiac studies (echocardiogram, stress tests, etc.), and the occurrence of any clinical events. The focused physical examination will include evaluation of the lungs, heart, and periphery. During these visits, the participants will also complete health status and quality of life measures as well as follow-up measures of physical function as detailed in Table 2 below. To promote retention, all participants will receive in-person contact within the first 2 weeks following discharge, achieved through intervention sessions, home visit, usual care clinic visit, or a scheduled clinic visit. In addition to the follow up visits, participants will receive a scheduled phone call at the end of months 2, 3.5, 4, 5, and 6 to evaluate clinical status and for follow-up on adherence to the maintenance phase. Additional telephone contact will be made with the attention control group participants (see section 7.1). Telephone contact will also be maintained with participants unable or unwilling to attend the clinic visits. In some instances, participants unable to attend these visits may receive a home visit to collect important end points.

Table 2: Collection of Outcome Measures

	Index Hospitalization (Baseline)	1 Month (Visit)	2 Months (phone call)	3 Months (Visit)	3.5, 4, 5, & 6 Months (phone call)
6MWT	X	X		X	
SPPB	X	X		X	
Grip	X	X		X	
Biomarkers	X			X	
KCCQ	X	X		X	
SF-12	X	X		X	
EQ-5D-5L	X	X		X	X (6M only)
GDS-15	X			X	

MoCA	X			X	
Clinical Events	X	X	X	X	X
Medications Review	X	X	X	X	X
Medical Resource Use		X	X	X	X

9.2 Blinding

The study will use a single-blind design where the study personnel assessing outcomes will be blinded to the study arm to which participants are assigned. To enhance continued blinding of assessors, participants will be asked not to disclose their assigned group during the assessment sessions.

10 Outcomes

10.1 Measures of Physical Performance

The primary efficacy outcome for this study will be the SPPB. The 6MWD, gait speed, and handgrip strength are other important measure of physical function that will be assessed.

10.1.1 SPPB

The SPPB was chosen as the primary outcome because: 1) physical function is an independently important outcome in older persons; 2) the SPPB is a well-accepted, reliable, validated measure of physical function in the older population,(89) and is safe and feasible in clinic, home, and hospital settings,(90) including hospitalized older ADHF patients HF;(28;29;37) 3) the SPPB score is highly predictive of important clinical outcomes, including disability, hospitalization, nursing home admission, and death;(89;91-94) 4) it is sensitive to change in health status(95) and responsive to exercise training;(65;67;96;97) 5) interventions that improve SPPB also improve clinical events, providing independent confirmation of validity;(98;99) 6) the SPPB is a key outcome in LIFE, the largest NIA-funded physical function intervention trial; 7) in our pilot study, the improvement in SPPB explained 90% of the improvement in rehospitalizations, providing a mechanistic link; and 8) the SPPB is standardized, simple, and relatively brief (<10 minutes). The SPPB measures physical function using 3 components: usual gait speed over 4 meters, time to complete 5 chair rises, and standing balance with progressively narrow base of support. Each component is scored on a 0-4 scale and summed for an overall score range of 0-12. Each component of the SPPB is independently associated with important outcomes including mortality.(100;100) Gait speed is associated with survival at increments of 0.1 m/s in community-dwelling adults(101) and is associated with survival in hospitalized older adults with coronary disease.(102)

10.1.2 6MWD

The 6MWD test is a well-established outcome measure in HF. It is valid and reproducible in patients with a wide range of physical function, predicts clinical events, and responds to interventions.(103-106) We showed that it is as predictive of clinical events as exercise oxygen consumption,(107) and improves with exercise training including in older HF patients.(74;108) Although most studies involved outpatients with stable HF, the 6MWD is safe, feasible and predictive of outcomes in an inpatient population(109) and was feasible, safe, and responsive to the intervention in the REHAB-HF pilot study.(28) The 6MWD will be conducted in an unobstructed hallway, utilizing a standardized script as recommended and as previously reported.(106;107;110) Total distance covered, the number of times and duration of rest, along with symptoms, will be recorded.

10.1.3 Handgrip Strength

Handgrip strength is a simple measure of upper extremity strength that correlates well with lower extremity strength and may serve as a marker of mobility.(111) The measurement is obtained in only a few minutes using a handheld dynamometer. Lower handgrip strength has been associated with increased risk of clinical outcomes including ADL disability (112) and mortality.(100) Cut-off points of < 20 kg in women and < 30 kg in men have been recommended to help identify patients with sarcopenia, a geriatric syndrome characterized by progressive loss of muscle mass and strength (111;113) and has been used as an indicator of frailty.(114)

10.2 Health Status and Quality of Life Measures

10.2.1 Kansas City Cardiomyopathy Questionnaire (KCCQ)

To assess change in health status and health-related QOL, participants will complete the KCCQ, a 23-item self-administered questionnaire that quantifies physical function, symptoms, social function, self-efficacy, and QOL in patients with HF. Scores range from 0-100; higher scores indicate better function. The KCCQ score is an independent predictor of clinical outcomes such as hospitalization and mortality in outpatients with HF,(115;116) and those recently hospitalized for ADHF.(117) It is a reliable and valid measure in HF patients, more sensitive to change than other measures of QOL.(118;119) The KCCQ is also reliable, valid, and responsive in patients with comorbidities.(120) A change in score of as little as 5 points is clinically significant and is associated with changes in clinical status(119) and physical function. A one standard deviation change in 6-minute walk distance correlates with a 5 point change in KCCQ.(121;122) A 5-point change in KCCQ is associated with all-cause mortality, cardiovascular death and hospitalization in patients with HF complicating acute myocardial infarction.(123)

10.2.2 12-Item Short-Form Health Survey (SF-12)

Given the high rates of comorbidities that frequently drive events in this population and which may be impacted by the study intervention, participants will also complete the 12-Item Short-Form Health Survey (SF-12). The SF-12, a quick (2 minute)(124) 12 item health survey is valid and reliable in older adults (125;126) and in HF.(127)

10.2.3 EuroQol (EQ-5D-5L)

This instrument assesses patient-specific health utilities used in cost-effectiveness analyses to capture QOL.(128) It performed well in HF-ACTION(129) and the PROTECT trial of ADHF.(130) It consists of five items that measure difficulty with 1) mobility; 2) self-care; 3) usual activities; 4) pain/discomfort; and 5) anxiety / depression and a self-rating (0-100) "thermometer" of the respondent's overall health. We will use the 5-level version which has improved sensitivity and reduced ceiling effect. It takes approximately 90 sec to complete.(131) When administering the EQ-5D-5L we will discern if participants require assistance with any essential ADLs as identified with responses of 'severe problems' or 'unable to' wash or dress (i.e. the self-care domain).

10.3 Depression and Cognitive Status

10.3.1 Geriatric Depression Scale – 15 (GDS-15)

Depression is common in patients hospitalized with heart failure and is associated with worse clinical outcomes (132;133) and quality of life.(134;135) The Geriatric Depression Scale is a depression screening questionnaire developed specifically for the elderly. The original version consists of 30 'yes/no' questions. A shorter, 15 item version that was subsequently developed

(GDS-15) has also been shown to be a valid and reliable screening instrument for depression in an elderly population (136) with sensitivity and specificity similar to the longer 30-item GDS.(137)

10.3.2 Montreal Cognitive Assessment (MoCA)

Cognitive impairment is common in HF patients(138) particularly when recently hospitalized,(139) and is associated with worse clinical outcomes, decreased independence with ADLs, and poorer functional mobility.(139;140) The MoCA, a widely used, sensitive instrument for this purpose, will be used to identify participants with cognitive impairment and assess changes in cognitive status.(141)

10.4 Biomarkers

To determine if the intervention alters the HF disease course, we selected two well-accepted biomarkers of HF disease severity and prognosis, NT-proBNP(142) and galectin-3;(142) both of which were responsive in HF-ACTION and ASCEND. Tumor necrosis factor alpha, C-reactive protein, and interleukin-6 were selected because we found they were increased in older HF patients and correlated with their SPPB score(143) and are known to predict prognosis. The latter two were also responsive to the physical function intervention in the LIFE study.(144) Twenty mL of venous blood will be drawn at the baseline visit and the 3-month follow-up visit, spun, and frozen at -20^{o}C in 1 mL aliquots, stored locally at -80^{o}C, and shipped in batches to Wake Forest Health on dry ice via overnight transport. Samples will be analyzed later in paired fashion (baseline and follow-up) to minimize inter-batch variability and cost.

10.5 Clinical Measures

Clinical events will be collected prospectively from randomization until 6 months after discharge from the index hospitalization, the highest risk period for older ADHF patients,(44) by interviewing participants and family at each visit, phone calls, and medical records review.

10.5.1 Rehospitalizations

All-cause rehospitalization was chosen as the secondary outcome because: 1) it is the most frequent adverse outcome in ADHF; 2) it is associated with impaired physical function, reduced quality of life, increased mortality, and increased cost; and 3) our pilot data and others' suggest that it is responsive to physical function interventions. A rehospitalization will be defined as a hospital stay > 24 hours, including prolonged emergency department visits or observational unit stays, for any cause and categorized according to the recommendations of Horwitz et al.(145) Rehospitalizations will be categorized by the site investigators as primarily due to non-cardiovascular, HF, or other cardiovascular (myocardial infarction, acute coronary syndrome without myocardial infarction, arrhythmia, peripheral vascular) cause, and whether they were related to the study intervention or assessments.

10.5.2 Other Clinical Events

The study will also capture deaths, emergency department visits < 24 hrs, stays at observational units < 24 hrs, unscheduled, urgent medical visits, nursing home placement, myocardial infarction, stroke, serious arrhythmia, syncope, and falls. A fall will be defined as ‘‘an unexpected event in which the participants come to rest on the ground, floor, or lower level" as recommended by a recent consensus statement on defining falls as an outcome.(146)

10.6 Frailty

Frailty has been described as a geriatric syndrome characterized by decreased physiologic reserve due to impairment in multiple interrelated systems that results in increased vulnerability to stressors and increased risk for adverse events (147;148). Fried et al developed an

operationalized definition of frailty(114)'(149) based on five characteristics: unintentional weight loss; self-reported exhaustion; weakness; slow walking speed; and low physical activity.(150) This now widely adopted frailty phenotype is associated with multiple adverse events, disability and death(114;149) and in HF patients is strongly associated with increased risk of hospitalization.(151) It is dynamic(152) and responds favorably to interventions.(97) For this study, frailty status will be based on modification of the Fried assessment described by McNallan et al(153) for older HF patients using: a) slowness (gait speed by SPPB); b) low physical activity (physical component of SF-12); c) weakness by handgrip strength (dynamometer); d) unexpected weight loss by self report or body mass index <18.5; e) exhaustion based on KCCQ questions 5,6. Participants meeting $\geq$ 3 of these criteria will be classified as frail; those meeting 1 or 2 as pre-frail; and those meeting none as non-frail.

10.7 Timing and Order of Outcome Measures

All baseline assessments are to be collected prior to hospital discharge. Ideally, all measures at all visits will be performed consecutively in 1 period with short-term (~2-5 minute) rest breaks as needed. However, at baseline, extended rest breaks or interruptions to outcomes testing will be allowed to accommodate usual care procedures, visitors, or unusual fatigue.

The order of testing should be kept constant for each participant at each visit. Measures of health status and quality of life should be collected prior to measures of physical performance. Within physical performance, the SPPB should be performed first.

11. Economic Analysis

11.1 Direct Medical Costs

The case report form will be used to collect patient-level information on all-cause medical resource use (hospitalizations, emergency department and urgent care visits, major medical procedures, home and skilled nursing facility care, and outpatient visits) and personnel and capital resources required to provide the REHAB-HF intervention. Medical resource use data will be ascertained by patient self-report and caregiver interviews and supplemented by their medical records. Intervention-related information will be documented by study personnel throughout the study. Direct medical costs will be valued from the societal perspective.(154) Professional services and costs for skilled nursing, home nursing and outpatient visits will be valued using Medicare fee schedules.(155) Costs for emergency department visits and hospitalizations will be estimated using models developed from HF-ACTION based on hospital-level variables (length of stay, reason for admission, major procedures).(156) Cost for the REHAB-HF study intervention will be estimated using our recently-developed TEAM-HF Costing Tool.(157)

11.2 Direct Non-Medical Costs

At 3 months and 6 months, patients will be asked to report information on direct non-medical costs incurred to comply with the REHAB-HF intervention including costs associated with transportation and/or parking and fees for health club memberships, exercise equipment or other services or resources that patients have chosen to purchase to help them adhere to exercise training.

11.3 Indirect (Patient Time) Costs

To estimate time spent on REHAB-HF intervention, we will use information reported within the trial pertaining to adherence to protocol-required rehabilitation sessions and patient-reported information on time spent on home exercise. We will also ask patients to report the total amount

of time they spend getting to each rehabilitation session. Indirect costs associated with patient time will be valued using the average hourly wage in the USA.(158)

11.4 Short-term Cost Analysis

We will compare mean direct medical costs, indirect (patient time) costs, total costs and quality-adjusted survival over the six-month follow-up period in the REHAB-HF intervention patients versus attention control. We will generate utility weights from the EQ-5D-5L collected data.

11.5 Long-term Cost-Effectiveness Analysis

We will also perform a cost-effectiveness analysis of the REHAB-HF intervention by combining estimated long-term costs and quality-adjusted survival with rehabilitation versus attention control. We plan to use our TEAM-HF Cost-Effectiveness Model(157) developed with NIH funding (R01 NR011873) to generate long-term estimates of costs, survival and quality-adjusted survival for patient-centered interventions in heart failure. We will conduct sensitivity analyses to evaluate the impact of varying the time horizon for the study and costs associated with the intervention.

11.6 Sustainability of the Intervention

To evaluate the sustainability of the intervention after the trial concludes, we will determine the extent to which the cost of the rehabilitation program is offset by savings from reductions in readmissions and other medical resources. This information will be used to propose payment models for 3rd party payers (e.g. CMS) and accountable care organizations and health maintenance organizations who provide care to heart failure patients on a capitated basis. If the intervention does not produce a net cost-savings, the cost-effectiveness analysis will assess gains in health outcomes vs. incremental costs of the intervention, which will provide important information for coverage decisions.

12 Efficacy Parameters

12.1 Primary Efficacy Parameter

The primary outcome for assessing the efficacy of the REHAB-HF intervention will be change in physical function, as measured by the SPPB score, at 3 months.

12.2 Secondary Efficacy Parameter

The secondary outcome for assessing the efficacy of the REHAB-HF intervention will be the total number of all-cause rehospitalizations during the 6 months following discharge from the index hospitalization.

12.3 Exploratory Efficacy Parameters

The study will explore several other possible endpoints:

1. Change in the Kansas City Cardiomyopathy Questionnaire (KCCQ) total score and physical component score at 3 months
2. Change in 6-minute walk distance (6MWD) at 3 months
3. Change in component scores of the SPPB at 3 months
4. Change in the 12-item short form health survey (SF-12), depression, and cognition measures at 3 months
5. Change in frailty status at 3 months
6. All-cause rehospitalizations at 1 month and 3 months
7. All-cause combined rehospitalization and death at 6 months
8. Global rank endpoint of SPPB score + all-cause rehospitalization + death
9. Heart failure (HF)-specific rehospitalizations

10. Cardiovascular events
11. All-cause rehospitalization days
12. Total hospitalization days post-randomization
13. Total facility-free days alive
14. Deaths
15. Falls
16. Change in biomarkers at 3 months

13. Safety Monitoring and Adverse Events

Safety Monitoring and Adverse Events, including falls, will be collected at all visits, recorded with clinical details on the case report form, discussed during the regular Operations Committee meetings (Section 16), and forwarded to institutional review boards and the data safety monitoring board (DSMB; see section 12.2). An independent DSMB, appointed by NIH and governed by NIH policy, will meet semi-annually (or more frequently as indicated) and will monitor study-wide safety and clinical events.

13.1 Adverse Events (AE) and Serious Adverse Events (SAE)

The following standard definitions of an adverse event and a serious adverse event are based on NHLBI policy as follows.

1. Adverse event (experience):
Any untoward medical occurrences in participants will be captured, regardless of causal relationship with the intervention and procedures. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptoms, or disease temporally associated with the investigational intervention, whether or not considered related to the investigational intervention.

2. Serious adverse event (experience) (SAE):
Any untoward medical occurrences that may result in any of the following outcomes:

- Death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Important medical event that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, it may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed above

Disability is defined as a substantial disruption of a person's ability to conduct normal life's functions (Federal Code of Regulations 21 CFR 312.32)

For the purpose of the REHAB-HF study, the following AE's and SAE's will be reported to the DSMB: death, hospitalization, hospitalization/observation unit stay lasting less than 24 hours, emergency room visit, urgent clinic visits, and adverse events occurring while participant performing the REHAB-HF intervention (including angina, syncope/presyncope, palpitations, symptomatic hypoglycemia and/or falls). All cardiovascular events (including worsening heart failure, acute coronary syndrome, arrhythmia, and stroke) will be collected and reported to the DSMB. For the purpose of this protocol, hospitalizations will be identified as planned or not planned. We will not be collecting specific information on congenital anomalies. At the end of

the study or at death, an attempt will be made to ascertain if any permanent disabilities occurred related to the intervention.

SAE's resulting in a death associated with REHAB-HF intervention, defined as occurring while undergoing the multi-domain intervention or within 3 hours after the multi-domain intervention will be reported within 5 days to the REHAB-HF study investigators who will forward this information to the DSMB chairperson. If it is unknown whether a SAE resulting in a death occurred while undergoing treatment or within 3 hours after treatment, this event will also be reported within 5 days to the investigators and forwarded to the DSMB chairperson.

13.2 Data Safety Monitoring Board (DSMB)

An independent DSMB, appointed by NIH and governed by NIH policy, will be charged with monitoring study-wide safety and clinical events on a regular basis (semi-annually). In particular, the DSMB will review the following SAE's and the following specific clinical and safety events: death, hospitalization, hospitalization/observation unit stay lasting less than 24 hours, emergency room visit, urgent clinic visits, and adverse events occurring while participant performing the REHAB-HF intervention (including angina, syncope/presyncope, palpitations, symptomatic hypoglycemia and/or falls), cardiovascular events (including worsening heart failure, acute coronary syndrome, arrhythmia, and stroke), nursing home placement, and injury (or fall) during rehabilitation.

14. Statistical Considerations

14.1 Statistical Methods

The primary aim of the study is to assess the efficacy of the REHAB-HF intervention on physical function measured by the total SPPB score. The effect of the intervention on SPPB score measured 3 months post-randomization will be estimated and tested for significance using analysis of covariance, where the randomized arm is the between-subject grouping variable and the pre-randomized measure of SPPB score, clinical site, age, gender, and ejection fraction category (preserved vs. reduced) will be covariates. Least square means will be used to estimate the intervention effect. Tests will be conducted at the 5% two-sided level of significance.

The secondary aim of the study is to assess the intervention's effect on the total number of all-cause rehospitalizations during the 6 months following discharge from the index hospitalization. Since the count of all-cause rehospitalizations per participant may not be normally distributed, the effect of the intervention on total all-cause rehospitalizations will be estimated using a Poisson model for modeling count data, where the randomized arm is the between-subject grouping variable and clinical site, age, gender, and ejection fraction category will be covariates.

The proportion of the intervention's effect on total all-cause rehospitalizations that can be explained by its effect on 3-month SPPB score will be analyzed by multivariable regression between total number of all-cause rehospitalizations and the residual of the analysis of covariance model for 3-month SPPB omitting intervention from the model.

Similar statistical methods as described above will be used for all of the exploratory efficacy parameters.

14.2 Sample Size Justification

The REHAB-HF pilot study showed an estimated intervention effect of an increase of 1.13 units in 3-month SPPB score (the primary outcome) or a 17.9% relative increase above the least

square mean for the attention control group, with a mean square error from the analysis of covariance model of 3.269. A clinically meaningful but small change in SPPB score is 0.5 units and a substantial change is 1.0 units.(159) This study is designed to have 80% power to detect a 10% treatment difference (0.63 absolute difference) in the 3-month least square mean of SPPB score. This requires 258 evaluable participants. In our pilot study, the observed retention rate was 89%. Conservatively assuming an 85% retention rate, the study requires randomizing 304 participants (25.3 per site per year).

In the completed pilot study, the number of all-cause rehospitalizations within 6 months was reduced 29.3% by the intervention (1.673$\pm$0.392 per patient in the attention control group vs. 1.157$\pm$0.349 in the intervention group). We performed additional work with an analysis of a contemporaneous sample of 239 consecutive patients aged $\geq$ 65 years admitted with the primary diagnosis of ADHF. This confirmatory sample yielded a 6-month rehospitalization event rate estimate within 0.5% of our attention control group, giving confidence in our pilot study estimate. This study is designed to have 80% power to detect a 25% reduction (0.41 absolute difference) in the total number of all-cause rehospitalizations during the 6 months following the index hospitalization. This requires 334 evaluable participants. In the pilot study we were able to evaluate the number of hospitalizations within 6 months in 100% of participants. Conservatively assuming up to 5% inevaluability, the study requires randomizing 352 total participants. Rounding up to 30 patients per site per yr, this study will randomize a total of 360 patients, providing > 80% power for the primary and secondary aims.

14.3 Data Management

The REDCap (Research Electronic Data Capture) data management system developed by the Clinical and Translational Science Award-funded Centers (NIH) will be used. The REDCap system is a secure, web-based database. The system will be developed and maintained by the study Data Manager. The REDCap system is hosted through the Bio-medical Informatics program of the WFU Translational Science Institute.

15. Privacy protection

The data analyses will pool data from all 3 sites. Before transmission to a data center, identifier information will be stripped and replaced with a unique code while the code linking the specimen with the participant's identity will remain in the security of the local site principal investigator. Data de-identification will be in full compliance with section 19.8 of the Wake Forest Office of Research Investigator page: http://www.wakehealth.edu/IC_Office-of-Research/IC_Investigator-Resource-Page.htm. Only individuals trained and certified in privacy protection will have access to data.

16. Organizational structure

REHAB-HF is comprised of 3 clinical centers and an administrative center. The Steering Committee is comprised of the directors of the 3 clinical centers (Drs. Kitzman, O'Connor, Whellan, Reeves, Patel), study biostatistician (Dr. Morgan), intervention leader (Dr. Duncan), and economic analysis leader (Dr. Reed). All key decisions will be made by this group which will meet by teleconference every other week (or weekly as needed). The Operations Committee will consist of the study investigators, research nurse coordinators, intervention supervisors, study manager and data manager from the administrative center, and will meet by bi-weekly teleconference. The Intervention Committee, led by Dr. Duncan, includes the intervention supervisors from each site and will meet every other week. The Administrative Center at Wake Forest will: 1) administer subcontracts with clinical centers, matching timelines and deliverables; 2) maintain the Manual of Operations, protocol and intervention materials, questionnaires and forms; 3) coordinate training and certification of clinical center staff; 4)

maintain the centralized web-based data management system and randomization procedures; 5) monitor data collection, measurement and intervention reliability; 6) generate data quality reports for study sites, steering committee and DSMB meetings; and 7) schedule and lead all teleconferences.

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