Title: Improving Function in Older Veterans With Hospital-Associated Deconditioning

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Project Title: Improving function in older Veterans with hospital-associated deconditioning
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I. Hypotheses and Specific Aims:

Hospitalization with subsequent deconditioning (hospital-associated deconditioning) is a common and profound contributor to functional decline in older adults.[1-3] Skeletal muscle weakness and atrophy are commonly observed in older adults with deconditioning after a hospitalization,[2,4,5] leading to development of chronic functional deficits. This is especially concerning for elderly Veterans, a population who has lower physical function[6] and more comorbidities[7,8] at baseline than the general older adult population, and therefore may be at even higher risk for developing disability in activities of daily living (ADLs) after hospitalization.[9] Thus, our research has the following aims

<u>Specific Aim 1:</u> To determine if PHIT training, initiated upon discharge from an acute care hospital, is as safe and more effective than UC in promoting sustained gains in physical function for older Veterans.
Hypothesis 1.1: There will be greater improvements in gait speed (primary outcome), Short Physical Performance Battery Scores (SPPB), modified Physical Performance Test (mPPT), Timed Up and Go test (TUG), grip strength, and knee extensor muscle strength in the PHIT group compared to the UC group at 60 days following hospital discharge, without increasing adverse events. Benefits of PHIT will be apparent at the end of intervention (30 days), will increase further at 60 days **(**primary endpoint**),** and will persist at 90 and 180 days.

<u>Specific Aim 2:</u> To determine if PHIT intervention, initiated upon discharge from an acute care hospital, improves independence in home and community mobility more than UC in older Veterans.
Hypothesis 2.1: There will be greater recovery in the PHIT group in measures of home and community mobility, as measured by the Nottingham Extended ADL Index, physical activity (PA) monitors, and the Life-Space Assessment (home and community mobility). Assessments will be performed at all time-points.

<u>Specific Aim 3</u>: To determine if PHIT rehabilitation, initiated upon hospital discharge, improves Veteran quality of life (QOL) & cognition, with concomitant reduction in caregiver burden compared to UC.
Hypothesis 3.1: Veterans in the PHIT group will have higher quality of life [measured by the physical function subscale of the Veterans Rand-12 (VR-12)] & better cognition (measured by SLUMS) & caregivers will have lower caregiver burden (Caregiver Burden Inventory).[10,11] Assessments will occur at baseline, 60, and 180 days. Veterans in the PHIT group will be more informed and motivated healthcare consumers [measured by the Patient Activation measure (PAM) at baseline and 30 days].

II. Background and Significance:

<u>B.1. Functional decline after acute hospitalization: a hidden epidemic.</u>
Hospitalization is a profound contributor to functional loss and disability in older adults.[1,2] Considerable evidence exists for hospital-associated deconditioning (HAD),[2] including dramatic and rapid loss of muscle mass and strength,[12] slower walking speed,[13] and greater difficulty

negotiating activities of daily living following hospital discharge.[14] Therefore, it is not surprising that older adults who are hospitalized are 60 times more likely to develop disability.[1] Comorbidities, the concurrent presence of two or more medically diagnosed diseases, further exacerbate the sequelae associated with hospitalization.[15] This is of particular concern to healthcare professionals serving the Veteran population, as this growing population[16] has a higher prevalence of chronic disease,[17] lower level of physical function[6] and decreased health-related quality of life[8] compared to their age-matched peers. Furthermore, older adults experience a sharp decline in home and community mobility after hospitalization. On average, scores on the Life-Space Mobility Assessment—a measure designed to capture activity frequency and dependence in the home and community—decrease significantly in older adults after hospitalization and remain below pre-hospitalization levels 2 years later.[18] Despite these significant declines, many of the healthcare efforts for older adults neglect to specifically address functional deficits stemming from hospitalization.[19,20] Alarmingly, this reduced physical activity and function after hospitalization is also strongly and independently tied to hospital readmission risk.[21] Thus, it appears that many modifiable risk factors (including impaired gait speed and lower extremity weakness) may persist as portents of poor health, re-hospitalization, or death[14] in older adults following acute hospitalization.

B.2. Physical function after hospitalization is a powerful biomarker of health for older adults.
Although the risk factors for the development of disability are likely to be complex and multifactorial, there is evidence to suggest that physical function alone may be a powerful biomarker of overall health following acute hospitalization.[21-24] In older adults, lower extremity weakness is associated with poor mobility and increased fall risk.[25-28] Similarly, in the Veteran population, every 0.10 m/s decrease in gait speed during and after an acute hospitalization is associated with increased self-reported disability, decreased physical health, and increased health-care utilization.[9] These strong associations between physical function and health highlight the need for more intensive interventions which address mobility in older Veterans with HAD. Our preliminary data suggest that mobility is an important modifiable risk factor for poor outcomes in older Veterans with HAD that can be effectively addressed with more intensive rehabilitation strategies.

B.3. Functional decline is associated with increased caregiver burden.
Older Veterans are often cared for by family caregivers,[29] and this assistance may be the difference between staying at home and the need for institutionalization. While many variables contribute to the degree of burden a caregiver experiences, one of the strongest predictors of high caregiving burden is the functional ability of the Veteran being cared for.[30] A Veteran with low ADL function is likely to require more time and assistance with care, both factors which are related to higher levels of caregiver burden.[31] When the burden becomes too great for a caregiver, there is potential for increased healthcare costs through either a need for higher volume of home services or eventual institutionalization. Thus, implementing the PHIT program has the potential to improve function and level of independence of the care recipient, while concurrently decreasing the burden on caregivers. Our intervention may impart long-term benefits on both the caregiver and Veteran care recipient by delaying or eliminating the need for institutionalization, or by reducing the amount of intensive support at home in the form of Home Based Primary Care (HBPC) services.

B.4. Home health physical therapy: tremendous potential to optimize physical function.
Home health care typically occurs during the critical time window when older adults with multiple comorbidities 1) are at a high risk of further health complications and 2) possess a limited capacity to travel to outpatient services. Unfortunately, only half of older adults report improvement in “walking or moving around” after receiving typical HH services.[32] The reasons

underlying these inadequate outcomes are not fully understood. However, based on our own survey results, it appears that both the content and intensity of typical HH physical therapy may be insufficient (see Appendix). In particular, given the profound strength loss that occurs during hospitalization, a more intensive, multi-faceted rehabilitation approach may be necessary to restore patients to or beyond prior levels of functioning. Yet, no evidence exists to support the effectiveness of short duration, higher intensity physical rehabilitation for older adults with HAD in a home environment (see Significance, Section C.1). Our preliminary data strongly suggest the PHIT program, consisting of 1) intensive lower extremity strengthening, 2) motor control-based intervention for gait and balance training, and 3) training in activities of daily living, can safely promote improved mobility in older adults following hospitalization. In this application, we propose to implement this PHIT intervention on a scale that will allow for more definitive conclusions regarding its effectiveness for improving physical function, maximizing home and community mobility, and reducing caregiver burden—goals which have a high potential to both reduce the need for formal caregiver assistance from the Veteran's Health Administration (both HBPC and home health aide services) and possibly reduce the incidence of long-term institutionalization of older Veterans.

B.5. Limitations of previous home health interventions

There is very little research available that evaluates the effectiveness of home-based, short duration, high intensity rehabilitation on older adults with HAD. The studies that do describe home physical rehabilitation generally include low intensity interventions or are not generalizable to the typical population of homebound older adults after acute hospitalization. In addition, studies do not often measure long-term outcomes or outcomes related to community reintegration after hospitalization.

Our research team collected data from a convenience sample of 65 home health physical therapists across multiple geographic locations to better understand usual care practices (see Appendix). The most frequently reported activities included gait training and sit-to-stand transfers. Even when resistance training was reported, the loads produced by elastic bands and cuff weights were equivalent to approximately 2 pounds. Additionally, activities promoting mobility were very basic with less than 10% reported performing more complex or higher level walking activities (e.g. non-linear walking patterns). When we asked therapists why they do not use more intensive rehabilitation strategies, therapists cited two main factors: 1) fear of injury to patients, and 2) lack of concrete evidence/guidelines for applying more intensive strategies in medically complex populations. The results of our therapist interviews and survey suggest the intensity of training and the type of activities chosen are inadequate to return patients to pre-hospitalization levels of function. Therefore, our innovative PHIT intervention represents a novel change in the timing (immediately after hospitalization), frequency (shorter duration), and dose (high intensity) of physical therapy delivered.

Summary: Rehabilitation delivered within the immediate post-hospitalization period has tremendous potential to mitigate HAD.[3] In the current Veteran health care system, home health rehabilitation is extensively utilized, but it remains unclear how to maximize the impact of rehabilitation delivered over the short intervention periods afforded by current payment systems. We propose the PHIT rehabilitation program to address a key modifiable risk factor for poor health outcomes: impaired physical mobility.[21,23,24] Rehabilitation delivered at higher intensities during this critical period of high medical need has the potential to improve strength and function. If successful in improving Veteran physical function, PHIT rehabilitation also holds potential for meaningful reductions in the development of disability and health care utilization.

Short duration, high intensity interventions targeting physical function in Veterans with HAD. Interventions using high intensity exercises during the immediate post-hospitalization period are highly innovative, because **1)** older adults with HAD are commonly excluded from studies, **2)** validation of effective short duration (4wk) rehabilitation programs during the time when patients are at highest risk for re-hospitalization is necessary, and **3)** safe implementation of a high-intensity rehabilitation strategy for HAD in the home setting has not been fully evaluated. Current standard of care almost universally includes low-intensity exercise (see Appendix). Our pilot data suggest that PHIT intervention delivered over 30 days not only facilitates nearly 6 times the improvement in SPPB over UC, but also protects against sharp detraining effects common with low intensity interventions at 60 days post hospitalization (See Fig 2). A recent systematic review concluded that "no RCTs have been conducted to examine the effectiveness of specific reconditioning interventions in rehabilitation… [of] older adults who are deconditioned."[4] Indeed, many rehabilitation research studies on older adults with chronic diseases focus on more clinically stable cohorts,[33,34] making it difficult to generalize the findings to homebound older adults after acute hospitalization. PHIT mobility interventions offered by physical therapists, at this critical juncture, have the highest chance of improving function and returning Veterans to meaningful participation within their homes and communities. Our study would provide the first large scale evidence to more definitively support future implementation and dissemination efforts by validating the benefits of short-duration, intensive rehabilitation strategies in the home setting. These benefits will be assessed in both the short term and long term to examine the full impact of PHIT intervention.

Multi-component exercise interventions are more effective in reducing disability in older adult populations. From these data, we believe our PHIT intervention is highly innovative because our program contains greater intensity of exercise than usual care. Systematic reviews suggest that progressive, high intensity, multi-component exercise programs more effectively reduce disability in frail community dwelling older adults than single focus programs of mobility or strength training alone.[35,36] Additionally, the Center for Disease Control recommends routine application of a multi-component exercise program called OTAGO for older adults at risk of falls and subsequent fall-related disability.[37] Our progressive PHIT program is designed with a similar multi-component paradigm to improve function in older Veterans with HAD by addressing 1) loss of muscle mass with intensive strength training, 2) gait, balance, and endurance impairments with intensive motor control-based mobility training, and 3) ADL disability with a high-intensity functional training. Members of the investigative team have developed and published recommended treatment guidelines for this population using this multi-component treatment framework.[3] We plan to shift current clinical practice by basing our intervention on scientifically valid exercise principles and packaging strength training, motor control, and ADL training into a concise and practical program.

PHIT interventions targets improvements in physical function in a real world home setting. This paradigm-shifting proposal carries low risk to patients because the exercises are supervised by licensed professionals and tailored to the home environment of each person. All testing occurs at home rather than a laboratory setting to increase generalizability and minimize participant burden. Furthermore, the proposed intervention is designed to demonstrate that even in isolated treatment environments (e.g., home setting), more intensive treatments can be safely and effectively implemented. Such evidence will help counter perceptions that conservative intervention approaches are safer in isolated home treatment settings.

Updating practices for older Veterans with hospital-associated deconditioning is a VHA Priority: Our proposal is strongly aligned with the goals outlined in the Veteran's Health Administration (VHA) Office of Geriatrics and Extended Care (GEC) strategic plan,[38] specifically goal 1: Commit to Veteran-centric care, and goal 4: Continuously improve geriatric care through age-appropriate performance indices.

Goal 1: Commit to Veteran-Centric Care

The VHA GEC has proposed a stronger focus on Veteran-centric care, which includes a focus on outcomes important to the Veteran population. Older Veterans have identified many barriers limiting their community mobility after hospital discharge; however, no protocols have been established to prioritize a return to community mobility in this population. Our PHIT intervention will examine how physical therapy influences the changes in life-space mobility after hospitalization, and how these changes are related to therapy dose.

Goal 4: Continuously Improve Geriatric Care through Age-Appropriate Performance Indices

This goal strives to identify and establish benchmarks of physical function in transitionally frail older Veterans. By targeting Veterans with deconditioning after an acute hospitalization, we can start examine what functional measures are biomarkers for adverse health event risk and determine which are most responsive to PHIT interventions. This will help establish functional benchmarks in the older Veteran population, and may contribute to additional care process measures in HBPC to identify and intervene upon these deficits.

In addition, our proposal directly supports the Rehabilitation Research & Development Service (RR&D) mission statement to "advance rehabilitative care and health for our Veterans." Specifically, our PHIT training program is designed to be strongly aligned with the RR&D mission of integrating clinical and applied rehabilitation research and translating the findings into clinical practice.

Potential to reduce long term care costs for older Veterans in the VHA system

The number of older Veterans is estimated to increase in the next decade, with 60% of this growth attributed to an increased proportion of the oldest-old (>85 years old) Veterans.[8,16] Thus, long-term care costs within the VHA system are projected to grow substantially, especially among Veterans over the age of 75. Institutional nursing home services for Veterans in particular are estimated to rise significantly, with previous estimates as high as 22% over a decade.[16] Use of long-term care services increases with increasing disability; thus, reducing ADL disability has the potential to impact utilization of costly long-term care services such as the use of home health aide services or VA Home Based Primary Care services. Similarly, poor lower extremity strength is a major predictor of institutionalization;[39] thus our proposal has the potential to reduce the need for home and institutional long-term care services by facilitating greater and more sustained gains in physical function and ADL ability compared to usual care physical therapy.

III. Preliminary Studies/Progress Report:

Dr. Stevens-Lapsley (PI) (formerly Stevens, JE) has participated in the design, implementation, and publication of a number of clinical research studies involving a variety of patient populations including patients with joint arthroplasty,[40,41] spinal cord injury,[42] ankle fractures,[43,44] and multiple sclerosis.[45] The PI recently completed 2 RCTs in patients following total knee arthroplasty (TKA) (NIH R03 AR054538 and K23 AG029978) and is currently overseeing an RCT investigating the benefits of more intensive rehabilitation following TKA (NIH R01HD065900). These clinical trials involved measurements of functional mobility that are similar to those currently proposed. Furthermore, the PI has spent over 3 years working with interdisciplinary teams focused on medically complex patients in different settings (inpatient, home health, skilled nursing facilities) to strengthen the proposed line of investigation. The PI also recently published a perspective manuscript that provides a treatment framework for rehabilitation of older adults with hospital-associated deconditioning.[3] Dr. Robert Burke (Co-Investigator) is an Academic Hospitalist and Director of post-acute care at the Denver VA Medical Center (VAMC). He has extensive clinical research expertise in transitional care for geriatric populations, which he has applied to the development of the current proposal. He will use his extensive network and influence with the providers who care for elderly patients at the Denver VA to facilitate identification and referral of appropriate patients to the Visiting Nurses' Association (VNA) HH agency. Importantly, all medical inpatients at the Denver VAMC are seen by his hospitalist group, so he will have consistent access to all inpatient candidates. Dr. Bill Sullivan (Co-Investigator) is Chief of the Physical Medicine and Rehabilitation Service at the Denver VAMC and directs all physical therapy and inpatient rehabilitation services. He will facilitate patient recruitment (along with Dr. Burke) and referral to the VNA HH agency through coordinated oversight of his physical therapist staff throughout the Denver VAMC. Finally, Dr. Jeri Forster (Co-Investigator) is a clinical trial biostatistician who has served as the Director of the Data and Statistical Core for the VISN 19 Mental Illness, Research, Education and Clinical Center (MIRECC) for the last 2.5 years, with an additional 5 years of prior collaboration. She is also an Assistant Professor in the Department of Physical Medicine and Rehabilitation, School of Medicine and the Department of Biostatistics and Informatics in the Colorado School of Public Health. She will provide expertise on issues related to study design, database management, quality control, data analysis, and preparation of manuscripts.

D1.3. PHIT Intervention Phase I Preliminary Study

Initial feasibility data to assess the value of the PHIT intervention and safety was performed at Arcadia University by Dr. Kathleen Mangione. This initial proof-of concept investigation involving 10 patients (mean age 82 years taking > 7 medications) suggested that PHIT was both safe and effective compared to usual care. Moderate to large effects were found for six-minute walk distance (effect size; d=0.59), modified Physical Performance Test scores (effect size; d=1.37), fast gait speed (effect size; d=0.51), and disability score on the late life function and disability index LLFDI (effect size; d=2.35). The effects were significant for mPPT and LLFDI, and the magnitude of improvement was clinically meaningful for the six-minute walk distance (58 meters), SPPB (1.5 points), and fast gait speed (0.2 m/sec). Dr. Mangione measured health care events during and for 3 months following the intervention. In the usual care group there were 4 total episodes in (3 re-hospitalizations, 1 emergency room visit), while the PHIT group had only 1 ER visit.

D1.4. PHIT Intervention Phase II Preliminary Study

The strong trends from Dr. Mangione' s feasibility study were used to refine the program for the second phase of preliminary investigation in Denver, Colorado (n=18; Fig. 2) in the following ways 1) reduced the targeted number of PHIT physical therapy visits to target 8-10 visits over ~30 days to more closely approximate the duration of usual care, 2) increased the complexity of the motor control element to challenge patients further, and 3) refined training methods for physical therapists providing PHIT intervention. Preliminary data from this second phase of investigation provide compelling evidence that a more intensive, multi-component approach to rehabilitation results in 1) substantially improved physical function despite short duration, 2) sustainability of improvements, and 3) does not increase the risk for injury (Figure 2). PHIT group patients received on average, 9.6 visits, while UC group received 8.3 visits. Our preliminary data strongly suggest that 1) PHIT intervention was far superior to UC treatment and produced clinically meaningful improvements strongly supporting the importance of treatment strategy, and 2) the benefits of the PHIT intervention continued past the endpoint of the intervention suggesting sustainability (~30 days). In fact, performance in the UC group worsened from 30 to 60 days (after HH physical therapy), while improvements in the PHIT group continued after intervention (30-60 days). Furthermore, though both groups had similar medical complexity, the PHIT group participants had no ER visits or re-hospitalization at 90 days, while 6 episodes (over 2 individuals) were reported in the UC group. Finally, our pilot data included an ethnically diverse group with 23% African American and 5% Hispanic or Latino participants.

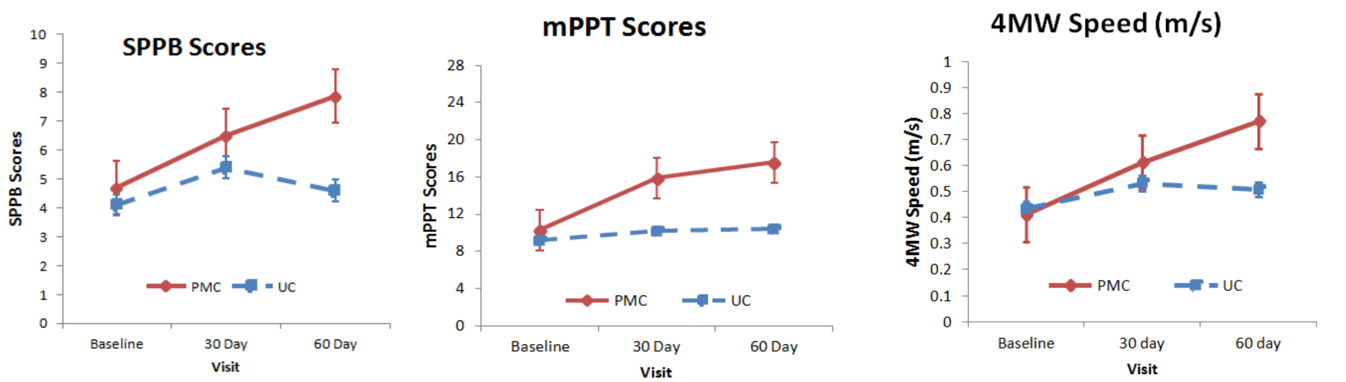

Figure 2. Phase II Colorado Pilot Study outcomes for SPPB, mPPT, and 4MW (n=18). Intervention was complete, on average, by 31.1 days (PHIT) and 35.3 days (UC). Data reported as mean±SE.

Clinically meaningful improvements can be summarized as follows: A one point difference in the SPPB represents substantial meaningful change,[46] and we saw differences twice this large in our preliminary data. In fact, PHIT resulted in a 60% improvement in function at 60 days compared to only 9.7% improvement with UC. For walking speed, a 0.1m/s difference in walking speed represents substantial meaningful change,[46] and we saw differences almost twice this large in our preliminary data. In fact, 30% of patients in the PHIT group achieved >1.0m/s walking speed (threshold for independent community ambulation)[47] at 60 days; no UC group patients achieved this walking speed. Importantly, both groups received a comparable number of visits. Furthermore, these results provide evidence for the investigative team's experience managing medically complex patients using the proposed intervention strategy with favorable outcomes.

IV. Research Methods

A. Outcome Measure(s): All measures and time points for each to be assessed are summarized in Table 1. Copies of each tool are attached to this application.

The primary study outcome is self-selected gait speed. This measure was selected because 1) it has been shown to predict risk of mobility and physical disability, higher health care utilization and increased mortality;[39,48,49] 2) it has been established as a meaningful outcome measure in older persons with a wide range of conditions;[50] 3) it is a valid and reliable measure;[51,52] and 4) it is easily performed in the home and well tolerated by patients varying in condition and degree of health.[53] Also, in Veteran populations, improvements in gait speed after hospitalization correlate with reduced disability and health care costs.[9]

Secondary Physical Function Outcomes:

Short Physical Performance Battery (SPPB) is a well-accepted global measure of lower extremity function, which consists of walking speed, chair stands, and balance. It is a well-studied composite measure and a strong predictor of disability, institutionalization, and morbidity in older adults (Table 3).[39] The test takes ~10-15 minutes to administer. The reliability of the individual components, as well as the summary score of the SPPB, are good with intra class correlation coefficients (ICC) >0.88.[54] The continuous scoring system minimizes ceiling effects and scores range from 0-12 with higher scores indicative of better performance.

The **modified Physical Performance Test (mPPT)** assesses 7 tasks. Based on the time it takes to complete each task, a score from 0 (unable to complete) to 4 (performed quickly and easily) is given for each item. The maximum score is 28 and includes tasks that involve upper and lower extremity function.

The **Timed Up-And-Go (TUG)** test will be performed on each participant as a measure of basic mobility skill and evaluation of fall risk. The TUG has excellent inter-rater reliability,[55] and is responsive to changes in mobility status.[56]

Hand-held Dynamometry (Lafayette Instrument Company, Lafayette, IN) will be used to objectively assess muscle performance in the lower and upper extremities. Dynamometric measures of quadriceps and hip strength have been used to quantify gains with resistance training in older adult populations, and are associated with functional performance, gait speed, and ADL performance. Therefore, we will assess knee extensor strength using previously established methodology.[57] Grip strength is widely used as a measure of gross body strength.

Home and Community Mobility Outcomes (Aim 2)
ActivPALphysical activity monitors (PALtechnologies, Glasgow, UK) will be used to obtain an objective measure of physical activity (PA). ActivPAL activity monitors assess PA using accelerometry, which allows objective evaluation of the relative volume (steps/day) and intensity (activity counts) of physical activity with high validity and reliability.[58] Each participant will wear the ActivePAL for 5 consecutive days at all time points to assess average daily PA (steps/day). The ActivPAL monitor will be used only for outcome data (not intervention) and provides no feedback to participants.

Table 1. Describing the planned study time points and assessments

Table 1: Testing measures at each time point

Outcome Measures	Time Points						
	Baseline	**30 days**	**60 days**	**90 days**	**120 days**	**150 days**	**180 days**
Primary Outcome: Self-selected gait	X	X	**X**	X			X
Other Mobility Tests: mPPT, SPPB,	X	X	X	X			X
Activities of Daily Living Performance:	X	X	X	X			X
Home and Community Activity Measures: Life-Space Assessment, **ActiGraph Physical Activity Monitors**	X	X	X	X			X
Caregiver Burden: Caregiver Burden	X		X				X
Quality of Life: VR-12	X		X				X

AE Reporting Script	X	X	X	X	Phone	Phone	X
Cognition: SLUMS	X		X				X
Patient Motivation: PAM Tool	X	X					

Nottingham Extended ADL Index (NEADL) will be assessed at each study time-point to assess Instrumental ADL performance of the participants. This measure was chosen because it specifically examines mobility inside and outside the home, domestic tasks, and leisure activities—all of which are highly important tasks when evaluating community dwelling older adults.[59] The NEADL also has strong psychometric properties. The NEADL has predictive validity for health outcomes after hospitalization in many chronically ill older adult populations.[60] The test has good construct validity, and also has good test-retest reliability.[59]

The Life-Space Assessment (LSA) is a self-report measure assessing a patient's movements, extending from within the home to movement beyond a patient's town or geographic region.[61] The life-space assessment is a continuous measure which can be scored from 0 (totally bedbound and dependent with all activity) to 120 (independent with community ambulation without assistance). The scores take into account both the performance of movement within and outside the home, the frequency of the movement, and the amount of assistance required. Specifically, this measure allows evaluation of actual mobility performed in the home and community, and can be evaluated for older adults across all levels of function. LSA has concurrent validity with physical function measures, as well as self-reported health and ADL disability.[62] The Life-Space Assessment has good test-rest-reliability (ICC=0.96), and is responsive to change in community-dwelling older adults.[61]

<u>Quality of Life and Caregiver Burden (Aim 3)</u>

The Veterans RAND 12 Item Health Survey (VR-12) will be used to assess the quality of life in Veterans. The SF-12 has strong concurrent validity with well-established quality of life measures and is reliable for assessing changes in quality of life in community dwelling adults.[63]

The Caregiver Burden Inventory (CBI) is a multi-dimensional 24-item scale with a five-point scoring system from 0 (never) to 4 (nearly always). The subscales of the CBI demonstrate strong convergent validity with caregiver depression, caregiver satisfaction, and number of caregiver tasks.[31]

Adverse Events Reporting Script will be used to assess any adverse events (e.g. ER visit(s), hospitalization(s), major illness/injury) which occurred since the last study visit and whether the participant is completing their exercises. The AE script will be administered 7 times, once at each of the 5 study visits, and once during each of 2 phone calls.

The **St. Louis University Mental Status Examination (SLUMS)** screens for cognitive impairment by assessing participant function in the areas of attention, calculation, immediate and delayed recall, animal naming, abstract thinking and visuospatial skills.[64] Patient examination with the SLUMS test is used in both clinical and research settings to screen for dementia. The SLUMS test has strong concurrent validity with the Mini-Mental Status Examination, and is a reliable screening tool for the presence of cognitive impairments with a reported sensitivity of 95-98% and a specificity of 76-100%.[65]

The **Patient Activation Measure (PAM)** identifies patient motivation levels regarding their healthcare. The PAM tool can reliably predict future ER visits, hospital admissions, and medication/ therapy adherence. The survey classifies patient activation levels on a scale from 1 (low activation/motivation) to 4 (high activation/motivation). Patients who score higher on the PAM survey tend to be hospitalized less and adhere to medication and therapy schedules more.

B. Description of Population to be Enrolled:

In this study, the target population is community-dwelling older Veterans or spouses of Veterans, 55 years of age and older, who either were hospitalized or who are medically deconditioned (experienced a decline in physical function) as a result of physical activity restrictions due to COVID-19), have several comorbid conditions, and are eligible for home health physical therapy. These patients will either provided with a COMIRB approved flyer describing the study or will be approached in the hospital and asked if they would agree to participate in a study examining the effects of Usual Care (UC) vs progressive high intensity therapy (PHIT) intervention following hospitalization.

Formal inclusion/exclusion criteria are:

Inclusion Criteria for Veterans/spouse of Veteran (All criteria must be met):

1. Veteran status or spouse of Veteran
2. 55 years of age and older
3. Eligible for home care physical therapy
4. Have at least 3 comorbid conditions including those listed below:

o COPD	o Gastrointestinal Bleed	o Urinary Tract Infection
o Pneumonia	o Chronic ulcerative	o Diabetes
o Hypertension	o Depression/mental	o Irritable Bowel Syndrome
o Hernia	o Post-op pancreatic surgery	o Osteoporosis/OA/RA/Gout
o Heart Disease	o Hypercholesterolemia	o Peripheral Arterial
o Spinal Stenosis	o Dehydration	o Syncope
o A fibrillation	o Hypo/Hyperthyroid	o Renal Failure-no dialysis
o Post-op bowel surgery	o Congestive Heart Failure	

The diagnoses most commonly reported for home health patients are diabetes, hypertension, heart failure, chronic ulcerative wounds, and osteoarthritis.

5. Be ambulatory without human assistance prior to hospitalization and be able to maintain a gait speed between 0.3 m/s-1.0 m/s at baseline assessment. Gait speed test may be administered in hospital to determine study eligibility.

Inclusion Criteria for Caregivers:

- Primary caregiver for an enrolled participant in the study

Exclusion Criteria for Veterans/spouse of Veteran (one or more):

1. Acute lower extremity fracture with weight-bearing restriction
2. Elective joint replacement surgery

3. Lower extremity amputation
4. Acute cardiac surgery
5. Terminal illness or end stage kidney disease requiring dialysis
6. Alzheimer's Disease
7. Deep vein thrombosis/pulmonary embolus VT/PE
8. Recent stroke
9. Progressive neurodegenerative diagnosis (e.g. Parkinson's, MS, ALS)
10. Active involvement of Adult Protective Services
11. Active cancer treatment in which exercise is contraindicated
12. Currently enrolled in home health physical therapy upon admission to VAMC
13. Clinical discretion of study physician to exclude patients who are determined to be unsafe and/or inappropriate to participate in high intensity rehabilitation as defined by the inclusion/exclusion criteria

Additional exclusion assessed prior to randomization: the inability to ambulate ten feet with human assistance.

Exclusion Criteria for Caregivers:

- Being on probation or alternative prison sentencing.

We plan to enroll 150 patients with the goal of 112 completing the study (25% drop-out rate). We will plan to consent up to 250 patients taking into account screening failures or hospital readmissions that occur prior to the first outcome visit. Enrollment in the study will be defined as participation in the first outcome measurement session at baseline once discharged home. The goal of the study is to obtain a representative sample of older adults with multiple comorbid conditions who receive home health physical therapy. Both sexes and all races are included in the study, however the Veteran population is predominantly male and Caucasian, which will be reflected in the enrollment. We will also consent up to 150 Caregivers, for a total of up to 400 consented.

Study Design and Research Methods:

<u>PHIT Rationale</u>

The components of PHIT training as we have designed it is the currently recommended clinical standard by the American College of Sports Medicine for frail older adults, and are practiced by a small percentage of physical therapists as usual care. In fact, multiple professional organizations have endorsed the PHIT guidelines as the recommendations for standard of care for older adults. However, PHIT training is a care standard we believe is not applied consistently in home health by therapists because of the lack of specific data supporting superior efficacy. Our observations of therapists in home settings and our survey results support that 10-15% of therapists practice PHIT principles that are recommended as usual care (PhD student Jason Falvey in my lab was previously an administrator in a home health clinical setting and has firsthand experience observing therapists across the Denver metropolitan area as part of his research in my lab). The other 85-90% of therapists practice a more conservative therapy approach that is based on historical exercise paradigms for older adults. Thus, both paradigms represent a form of usual care that have not been tested against each other in this population—a major goal of the current proposal. We have previously had IRB approvals from COMIRB for pilot work with testing high intensity programs that are applied less commonly but clearly within the auspices of usual care PT practices. These protocols have been approved without concern that we are engaging sites providing one of two types of usual care in research. This is similar to a drug trial in which two commonly used drugs are tested against each other for superior efficacy; we are simply testing two usual care exercise prescriptions to definitively answer which one promotes superior outcomes.

The PHIT program is based on sound physiological principles, relevant clinical literature, and our preliminary data strongly supporting the potential to improve functional mobility in the home setting. Multi-component exercise programs, such as the OTAGO program recommended by the Center for Disease Control, have been shown to be more effective in reducing and preventing disability in frail community dwelling older adults than single focus programs of mobility or strength training alone.[35,36,66] The PHIT intervention will target the greatest deficits in older adults after hospitalization including 1) muscle weakness, 2) mobility deficits from poor balance and coordination, and 3) lack of independence with activities of daily living. To address these deficits, the 3 components of PHIT include 1) progressive intensive resistance training, 2) progressive motor-control program, and 3) progressive training in activities of daily living. The progressive, intensive resistance training for the PHIT intervention is based on ACSM guidelines, observation of high performing therapists, and a previous home health study by Dr. Mangione where she showed that leg strengthening exercise improved strength, walking abilities, and function one year after hip fracture compared to controls.[53] Consistent with Dr. Mangione's findings, a systematic review involving over 6700 participants demonstrated lower extremity, high intensity strength training 2-3 times per week resulted in 1) large effects for increasing muscle strength, 2) small effects for improving physical function, and 3) small to moderate effects for decreasing functional limitations.[67]

Therefore, the second important component of the PHIT intervention is a progressive motor-control based program that develops skill and automatic movement control by progressing speed and accuracy in motor tasks.[68] This program has been shown to significantly improve self-reported mobility and gait speed, decrease the energy cost of walking, and improve self-reported confidence in walking in community-dwelling older adults (mean age 77 years) with slow (≤1.0 m/sec) and irregular gait (increased gait variability).[69] For frail individuals, decreasing energy cost is associated with improved gait speed,[70,71] which could be considered a precursor to endurance training in these frail older adults. In this study, we will indirectly address endurance by targeting the energy cost of walking (gait speed).

Finally, training in activities of daily living (ADLs) remains a fundamental element of all home therapy and represents the third, important component of the PHIT intervention. Training in activities of daily living emphasizes safety and compensation strategies to maximize independence as well as reinforce the gains made through progressive resistance exercise and motor control components of intervention. In general, our ADL training will be carried out as a task specific training program consisting of coordinated, multi-joint movement patterns that simulate the functional patterns required for independence in the home setting[72] (i.e., transfers in and out of bed and sit to stands from seating surfaces within the Veteran's home environment). The PHIT program will perform this task-specific ADL training at high intensity; each task performed will be dosed at the equivalent of an 8-10 RM resistance exercise. Task specific training in homebound Veterans at this intensity is likely to facilitate greater improvements in strength, power, and coordination in important functional patterns, and thus carry over to improved ADL performance.

D2.1. Design Overview

We propose to conduct a single blind, randomized controlled trial in 150 older Veterans with multiple chronic conditions discharged from acute care or medically deconditioned, and referred to home health physical therapy. The two arms will include a PHIT progressive multi-component physical therapy program and a documented UC physical therapy intervention. Veterans admitted to the Denver VAMC will be evaluated for eligibility. Following consent, eligible patients be randomized to either treatment group by the home health coordinator who holds the randomization list. Following hospital discharge, a baseline assessment will be performed within 48 hours of returning to their home. Follow-up assessments will occur at 30, 60, 90, and 180 days following hospitalization (see Figure 1; specific aims). Medically deconditioned participants will complete the same study visit schedule of a baseline assessment with follow-up visits at 30, 60, 90, and 180 days following baseline.

D2.2. Eligibility Criteria*:* Patients can be included if they are Veterans or the spouse of a Veteran ≥ 55 years of age, are eligible for home care physical therapy at the Visiting Nurses Association (VNA) or Berkley Home Health, have at least 3 comorbid conditions, and were ambulatory (with or without an assistive device) prior to hospitalization or deconditioning due to COVID-19 and can maintain a gait speed of 0.3 m/s-1.0 m/s at baseline assessment, which may be determined by a gait speed test conducted in the hospital after patient has been consented. Exclusion criteria include acute lower extremity fractures with weight-bearing restriction, elective joint replacement surgery, active cancer treatment in which exercise is contraindicated, current dialysis treatment, acute cardiac surgery, acute stroke, lower extremity amputation, progressive neurodegenerative diagnosis (e.g. Parkinson's, MS, ALS), use of illegal substances, active involvement of Adult Protective Services, currently enrolled in home health physical therapy upon admission to VAMC or hospital, referred to hospice care, or clinical discretion of study physician to exclude patients who are determined to be unsafe and/or inappropriate to participate in high intensity rehabilitation as defined by the inclusion/exclusion criteria. Additional exclusion: the inability to ambulate ten feet with human assistance at the time of hospital discharge (see Human Subjects for more detail on inclusions/exclusions). These eligibility criteria are consistent with those used for preliminary data and have been successful with identifying patients who benefit from the proposed intervention.

D2.3. Subject identification, recruitment, and randomization*:* Participants will be recruited from the Denver VAMC, UCHealth Highlands Ranch, and UCHealth Broomfield. Two hundred and fifty Veterans will be recruited (3-4 patients per month) with at least 112 expected to complete through the 60 day episode of care to accommodate for the potential re-hospitalization rate of 20-30% among home care recipients[32] and drop-outs for other reasons. We had no difficulty recruiting patients for our preliminary study (3-4 patients/month). The Denver VAMC coordinates home health services for approximately 300 Veterans/month. Of these, approximately 30/month would be eligible for this study (> 55 years old; receiving home health PT services for decreased mobility after an acute hospitalization; living within the Denver metropolitan area). Therefore, recruitment of 3-4 patients/month through the Denver VAMC alone should allow us to meet our recruitment goals

Dr. Raghavan (Co-Investigator), Dr. Torberntsson (Co-Investigator), Dr. Lauren Abbate (Co-Investigator), and Dr. Duc Ha (Co-Investigator) will identify patients at the Rocky Mountain Regional VAMC, Dr. William (Tom) Purcell (Co-Investigator) will identify patients at UCHealth Highlands Ranch, and Dr. John Updike will identify patients at UCHealth Broomfield who meet the inclusion criteria daily (Figure 3) as part of the direct treatment relationship and face to face contact with potential subjects. A PRA under the supervision of Drs. Raghavan, Torberntsson, Abbate, Ha, Purcell, and Updike will also screen medical records daily for potential research subjects who meet study criteria, and review verbally or by phone with the study physicians before approaching patients. The PRA will ask eligible (as identified by the study CO-I physicians) and willing patients to sign a consent form during the hospital stay. If patients are identified in the hospital as eligible in a face-to-face encounter, but are discharged before they are consented, then a research assistant or research physical therapist will ask eligible and willing patients to sign the consent form in the home setting. Additionally, clinicians within the

Denver metro area will be informed of the study and will be provided with study flyers and with HIPAA A forms that they will give to their patients who meet eligibility criteria and who are interested in the study. If the potential participant is interested in learning more about the study, but chooses not to sign the HIPAA A form, they will be provided with a flyer. If the potential participant is interested in learning more about the study and chooses to sign the HIPAA A form, they will be contacted by phone by a study team member and will be asked screening questions from the phone screen script. If potential participants meet all study inclusion criteria and want to participate, a study team member will go to the potential participant's home and will conduct the informed consent process prior to baseline testing. In either case, documentation will be made in the Veteran's medical record (CPRS) indicating they have enrolled in a research study according to VA protocols for clinical research.

After patients are consented, they will be randomized to either the PHIT treatment group or UC group using a randomization table that will be prepared by Dr. Jeri Forester (biostatistician) and held by the home health discharge coordinator at the VA who coordinates all referrals to the home health agency. Randomization assignments will be computer generated using random block sizes of 4 and 6. Randomization will occur via a centralized computer randomization system.

The discharge coordinator will then refer the patient to the home health agency who is delivering the intervention (The Visiting Nurses Association or Berkley Home Health) and inform the agency of the group assignment and ensure that the appropriately trained therapist (UC or PHIT) is scheduled to see the patient. The PRA will then provide the patient contact information to a blinded outcomes assessor (physical therapist or trained research assistant) to complete the baseline evaluation (functional tests and questionnaires). Therapists will be told not to reveal or discuss their assigned protocol to other therapists. Dr. Stevens-Lapsley has successfully worked with the VNA to train PT staff and implement the proposed investigation for the preliminary data. This protocol has been followed for 22 patients recruited to-date without difficulty, and was successfully implemented, assessed, and the pilot data published.

Caregivers will be approached and, if eligible and willing, consented in the home setting of an enrolled Veteran. A research assistant will explain the study and the goals, and ask eligible caregivers to participate in filling out the caregiver burden inventory after signing a HIPAA waiver. We will only collect and record age (categories by decade) and gender of the caregiver in addition to caregiver burden scores.

D2.4. Interdisciplinary Coordination of Care: Following enrollment, Drs. Raghavan, Torberntsson, Purcell, Updike, Abbate, and Ha will remain involved in the interdisciplinary coordination of patient care as the physician contact following hospital discharge.

D2.5. Intervention*:* Patients in the PHIT exercise group will receive between 10 and 12 PT visits in their home (45-60 min/session). Data from 3 local home health agencies indicated that the average number of physical therapy visits per episode of care was 8.5 (Agency 1), 7.8 (Agency 2), and 8.6 (Agency 3). Furthermore, the average number of PT visits from the preliminary data for the PHIT and UC groups were 9.8 and 8.4 visits, respectively. Therefore, we chose to target 10-12 PT visits for the proposed study to operate within a reasonable range of the current standards of care and maximize the benefits of the PHIT intervention. Our preliminary data suggest that this frequency of visits (10-12 visits over 4 weeks) will produce neuromuscular and physiological changes that will translate to improved function. Patients in the PHIT group will receive 3-4 visits per week for the first two weeks and 2 visits per week, on non-consecutive days for the remaining 2 weeks (total=10-12 visits). The intervention will consist of progressive resistance exercises for the lower extremity with a portable training device (Shuttle Mini-Press), a motor control-based program of gait/balance training, and ADL training—all designed to improve mobility (see Table 2; Appendix). PHIT participants will also receive specific written nutritional education to emphasize the importance of increasing protein intake by 15 grams/day to support participation in the high intensity program (see Appendix).

The patients in the UC group will also receive 10-12 visits to match the PHIT group over 4 weeks. We will provide a standardized rehabilitation protocol for the UC group to perform over the 10-visit intervention period, which consists of a controlled low intensity program with activities from each of the domains included in the PHIT program (see Appendix). Both groups will also receive a standardized simple home exercise program, which will include identical exercise activities that differ only on intensity (See Appendix).

Progressive High Intensity Therapy*:* The strength component of the PHIT intervention will be performed using a portable progressive resistive exercise machine that uses latex bands providing 6 to 100 pounds resistance (Shuttle Mini Press, Contemporary Design Company, Glacier, WA). The use of the shuttle press allows for standardization of treatment intensity across therapists while ensuring appropriate overload for high intensity strength training. The use of the device will not limit generalizability of study results because a number of alternatives for lower extremity strengthening can be easily implemented in the home setting, and previous research has demonstrated equal benefits for strength training using exercise bands and formal free weights when performed at equivalent intensities.[73] The exercise intensity will be an 8-repetition maximum, and the volume will be 3 sets of 8 repetitions. This protocol has been used safely and effectively in frail elders.[74,75] For the first week, participants will perform 2 sets for 3 different exercises and will increase to 3 sets for the remainder of the program. Intensity will be re-evaluated weekly and resistance will be increased if the participant is able to complete 8 repetitions at the higher load using good movement form. Using the Shuttle Mini-Press will also allow us to estimate total training volume (weight lifted x repetitions) more precisely. We can then use total training volume as an explanatory variable in our analysis to determine if training volume explains additional variability in functional gains within the PHIT group—this will help provide additional evidence for efficacy of the PHIT program in deconditioned Veterans. We will not be collecting any data about the efficacy, feasibility, or safety of the Shuttle Press in promoting the strength gains specifically; we are simply using this device as one of many clinically appropriate modes of delivering exercise for this population (it is equivalent to using theraband, or free weights to deliver exercise). Thus, we do not consider use of the Shuttle Press as a medical device.

The motor control system of PHIT mobility training begins with exercise tasks requiring low skill and progresses to more skilled movements as previously described.[68,69] For example, the patient is instructed to step to a visual target placed in different positions. Stepping activities are performed repeatedly in one direction or to one side, then to the opposite side. As performance becomes skilled (i.e., accurate and smooth), then alternating stepping activities are attempted. Walking activities are also progressed from low skill (e.g., walking in a straight line) to more skilled activities such as walking in a serpentine pattern. Progression is based on increasing speed, accuracy, and finally with holding or manipulating of an object (dual task). Each session begins with practicing a “well-learned task.” Patients are progressed when performance of the task is 80-100% correct. As walking ability improves, this training begins to target patient endurance by prescribing daily walking programs for two 10 minute bouts and increasing to 20 minutes continuous. Before discharge from home therapy, patients will begin to transition to an unsupervised physical activity program by performing a daily walking program and independent home exercises.

The **PHIT Activity of Daily Living (ADL) training** focuses on increasing mobility in activities needed in daily life. Training in ADLs emphasizes safety and compensation strategies to maximize independence. Activities include bathroom transfers, bed mobility (e.g. rolling, supine→sit), and car transfers. These activities will be delivered at higher intensities than UC as described above in section D.1.2.

Nutritional Education Specific to PHIT Program: While all Veteran participants will receive nutrition screening and education at baseline, those randomized to the PHIT group will have ongoing nutritional education from the interdisciplinary team and be encouraged to supplement protein intake by at least 15g/daily to support participation in higher intensity exercise strategies.[76,77] Written education about what foods contain at least 15g of protein will be provided to all PHIT group participants. Along with the rest of the interdisciplinary team, physical therapists will follow up on this education and document compliance each visit (see Appendix).

Usual Care: UC group will undergo a standard home health evaluation, which included basic nutritional screening questions and education (see Appendix). The UC group will then receive 10-12 visits of standardized UC physical therapy intervention. Agency-employed physical therapists will be made aware of the research study, but will not be aware of any specific goals or objectives to avoid contamination and maximize implementation of real world usual care practices. From an extensive survey of home care PTs, existing literature, and our own observations of home health clinical practices, we have included a standardized UC intervention protocol that includes representative activities such as low intensity exercise training, basic training in gait, balance, and transfers, ADL training, and patient education.[78,79] This program will be matched for total rehabilitation time compared to the PHIT group; thus, exercises will differ only in delivered intensity.

Table 2 – Brief Summary of the UC and PHIT Exercise Programs (see Appendix for more detail)

	Group	
Activity	**Usual Care (UC)**	**PHIT**
Strength Training (40% time)	• 3 sets x 8 repetitions: long arc quad (seated), hip extension (standing), plantar flexion (seated), hip abduction (seated) • Progress from no resistance to **0-2 lbs weights or low resistance bands as tolerated**	• 3 sets x 8 repetitions max to failure: leg press (supine), hip extension (standing), plantar flexion (standing), hip abduction (supine) • Uses Shuttle Mini-Press to standardize and progress resistance training each visit • Loads of **74-104 lbs**
Motor Control Gait Program (40% time)	• Stepping Activities: forward only • Gait patterns: Straight line • Gait training: Device training, stairs, and outside gait until not homebound, single speed	• Stepping Activities: forward, backward, diagonal • Gait patterns: straight, oval, spiral, serpentine • Gait training: obstacle course, outdoor surfaces, stairs/curbs, multi-speed
ADL Training (20% time)	• Bed mobility, bathroom transfers, sit to stands, and car transfers x 8 repetitions with no resistance	• Bed mobility, bathroom transfers, sit to stands, and car transfers all performed at high intensities (8 RM maximum)

Other home health services*:* In addition to physical therapy home health services, we recognize individuals may receive additional home services (e.g. nursing, occupational or speech therapy). We expect that the frequency of these additional services will not be different between groups because of randomization, but we will carefully track and report the total numbers of these additional services.

D2.6. Treatment Fidelity across PHIT therapists
Treatment fidelity is critical to the success of the proposed intervention because of the use of multiple physical therapists. Dr. Stevens-Lapsley has extensive experience with treatment fidelity for clinical trials involving rehabilitation of a multitude of patient populations. From these experiences, we have established mechanisms to assure the consistency of treatments across therapists. The availability of three PHIT-trained therapists and 3 UC therapists, covering different geographical areas in Denver through the Denver Visiting Nurses Association and Berkley Home Health will allow us to enroll all eligible patients, regardless of location. Dr. Stevens-Lapsley, and the research physical therapists (Jason Falvey, PT and Allison Kosir, PT) will provide 2-3 initial training sessions to therapists providing UC and PHIT interventions to review treatment protocols and documentation.

A manual will be provided to each clinician with protocol details, clinic and home exercise pictures, documentation forms, and study contact information. Research Physical Therapists will review the intervention data sheets biweekly, and will conduct monthly phone meetings with the PHIT and UC physical therapists. If the treatment fidelity is below 90%, additional training sessions will be scheduled with individual therapists. Treatment fidelity data will provide information on the adherence of the PT to the interventions, the adherence of the participants to the prescribed activities, and will provide an opportunity to address potential study problems (see Appendix). In addition, every month for the first year, and every three months thereafter, treating therapists will meet to discuss treatment guidelines and any issues that have surfaced. For each agency therapist, the research physical therapists will observe 4-5 home sessions for the first 2 patients. These on-site observations may be supplemented with video conferencing during treatment sessions for additional oversight as necessary. Should new therapists require training during the course of the investigation, the same procedures for initial training and monitoring will be implemented. Each treating therapist will fax documentation weekly to ensure protocols are being followed.

Blinding of Research Staff: Only the research physical therapists conducting staff training, and the VNA HH or Berkley Home Health agency manager will have full knowledge of group assignment. Outcome data will be assessed by Physical Therapist Outcomes Assessors who will remain blinded to treatment group. Intervention PTs will only provide either PHIT or UC intervention. Patients will be instructed not to discuss what they do during their home physical therapy sessions with the Physical Therapist Outcomes Assessor to maintain blinding, and also be asked to not share the group assignments during any care coordination meetings.

C. Description, Risks and Justification of Procedures and Data Collection Tools:

All assessments and interventions in this study are considered to be a part of physical therapist clinical practice. We see little or no additional risk resulting from participation in this study. To minimize risk of falls and injury, the PHIT training protocol will be conducted with licensed physical therapists (PTs) trained to minimize risk of falls and will not be undertaken in subjects who report inability to perform the tasks. In all conditions of outcome testing in which the participant is standing and/or walking (e.g. conditions with a potential risk for falling), the participant will be directly supervised by a member of the research staff (PRA or research physical therapist) who has been trained on all measures by a physical therapist, and a licensed physical therapist will be available by telecommunication at all times.

There is no expectation that the proposed multi-component intervention will evoke serious cardiovascular responses. Gardner et al[80] reviewed controlled clinical trials with exercise interventions for older adults at-risk for falling. No cardiac events or falls were reported in the 12 clinical trials reviewed. No significant cardiac events were reported after performing one repetition maximum (1-RM) testing for over 6600 healthy subjects.[81] A recent review of 12 articles examining the safety of high intensity resistance training and testing in persons with coronary disease found an absence of anginal symptoms, ischemic ST-segment depression, abnormal hemodynamics, complex ventricular dysrhythmias, and cardiovascular complications.[82] Less serious risks may include chest pain, fainting, hypotension, or muscle strain.

We have minimized risk to patients who are not undergoing exercise stress tests by following the guidelines suggested by Gill et al. which are outlined below.[83] Every effort will be made to prevent adverse events including stopping exercise when the patient reports shortness of breath, angina or dizziness. A licensed physical therapist will supervise all of the training sessions and will additionally monitor blood pressure at the start of the training session, mid-session, and when participants are finished with the session. Blood pressure and heart rate will be monitored using a standard blood pressure cuff and palpation of peripheral pulse. If blood pressure is elevated above 160/100, the participant will rest quietly for a few minutes. The PT will monitor the patient for signs of muscle strain, dizziness, or hypotension. As needed, appropriate palliative methods will be discussed with the participants and reported to the primary care physician, although these adverse events are also not expected. All PTs and PRAs will be trained in a standardized way to address all safety precautions.

Delayed onset muscle soreness is a common occurrence after the initiation of an exercise program. The soreness occurs in the muscle belly 1-3 days after the initiation of exercise and lasts 2-3 days. There is no effective way to eliminate the risk of delayed onset muscle soreness, but it is hoped that the orientation process and gradual increase in intensity will reduce the risk. The participants will be informed about the condition, what it feels like, how long it lasts, and suggested ways of decreasing the pain including the use of superficial heat or ice.

There is also a small risk of rash on the area of skin on which the TegaDerm patch is applied. We anticipate that these risks are minimal, and have low potential for any long-term harm. Nonetheless, if any abnormal skin reactions are observed, we will notify either the home health agency nursing staff, the patient's physician, or a study physician to determine the appropriate medical care.

Other outcome assessments are also expected to be minimal risk to participants. Use of ActiGraph monitors to assess physical activity is common in older adult populations, and has not been associated with adverse events of a serious nature. Physical therapists treating patients will monitor for skin irritation over the areas where the Actigraph straps come into contact with skin and discontinue use if any skin breakdown occurs.

We have established the following apriori stopping criteria for removing a Veteran from the study to maintain the safety of the participant.

Participants will be withdrawn from the study by the investigators if:

a.) They are admitted to the hospital after enrollment and the study physician determines the Veteran unsafe or inappropriate for high intensity rehabilitation as defined by the inclusion/exclusion criteria b.) They develop a new medical or psychiatric condition after enrollment which precludes participation in exercise training based on ACSM criteria or the determination of a physician, safety officer, or investigator (i.e. new cardiac diagnosis such as unstable angina, marked change in cognition, acute illness, pneumonia)

Expected Adverse and Serious Adverse Events:
The following are expected AEs and SAEs for this study: High risk behavior, e.g. drug use and/or alcohol abuse; hospitalizations due to poor functional mobility, e.g. falls; and complication from or exacerbation of current medical diagnoses and comorbidities.

Data Management Risks: As with any study, there is a risk of data breach or disclosure of study data outside the study team (e.g through accidental loss of data, theft, inadvertent electronic or paper disclosures). We will minimize these risks through the following protocol for collecting data:

1.) Medical data relevant to the study (hospital length of stay, comorbidities, age, sex, etc) will be extracted from the VA EMR and recorded for each patient in the VA version of RedCap by a member of the investigative team. The VA Informatics and Computing Infrastructure (VINCI) will be used as a central location for data processing and management. Vanderbilt University, with collaboration from a consortium of institutional partners, has developed a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap (Research Electronic Data Capture) data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process. REDCap servers are housed at the VA Informatics and Computing Infrastructure (VINCI). VINCI servers are physically located at the VA Austin Information Technology Center (AITC), located in Austin, Texas. REDCap was developed specifically around HIPAA-Security guidelines. REDCap has been disseminated for use locally at other institutions and currently supports 240+ academic/non-profit consortium partners on six continents and over 26,000 research end-users (www.project-redcap.org). All EMR access will occur behind the VA firewall, and directly input into RedCap, thus minimizing the risk of accidental disclosure outside the VA and maintaining strict access only to VA employees. RedCAP access will only be granted to PRAs in a data entry capacity only, and other investigators will only be granted access consistent with their duties in database management or data checking. Computer access will occur either at VA buildings, or using a VA computer set up in the lab space of Dr. Jennifer Stevens-Lapsley on the University of Colorado Campus in Room EG308 in Building 500.

2.) All paper documents generated (e.g. consent forms, outcome measures collected in the home setting, HIPPA B forms) will be transported between patient homes and different VA sites (downtown 9th Street hospital, Clinical Building South, Fitzsimons Building) only using lockable bags that are approved by the VA. These documents will be stored in a locked cabinet, within a locked office in the RSC (Rehabilitation Science Consortium) in the Fitzsimons Building. These documents will be also scanned directly into a VA computer and stored electronically on a VA server to be accessed electronically with minimal transportation of sensitive data.

D. Potential Scientific Problems:

Missing Data. All patients with outcome measurements will be included in the intent-to-treat analysis. Although we will encourage patients to be fully compliant to their assigned treatment regimen and testing sessions, they will not be dropped from follow-up measurements for lack of compliance. Although statistical methods can be used to “adjust” for missing data, these methods rely on the untestable assumption that data are “missing at random” so that the effect of the missingness can be removed through statistical modeling. We will instead focus on preventing missed follow-up visits and evaluate missingness to determine whether the data are consistent with the hypothesis of missing at random or missing completely at random.

F. Data Analysis Plan:

Primary and Secondary Outcomes*:* The primary outcome for this study is gait speed measured 60 days following hospital discharge. Secondary outcome measures include SPPB measured at other study time points, mPPT, LSA, NEADL, VR-12, and CBI, measured at designated study time points (see Table 3). The 60 day time point is chosen for clinical relevance because it helps establish not only efficacy but also sustainability of the effects after the initial 30-day intervention period. Preliminary descriptive and graphical analyses (including boxplots, scatterplots, profile plots) will be used for data cleaning and visualization.

Primary Analysis (*Aim 1*)*:* The primary analysis will be an intent-to-treat comparison of the differences between treatment groups in change in gait speed 60 days following hospital discharge. Statistical inference regarding the difference between treatment groups will be based on the estimated coefficient for a treatment group indicator variable in a linear regression model with 60 day change in walking speed as the response variable, and explanatory variables that include an indicator of treatment group and the baseline value of gait speed. The baseline gait speed value is included to improve the precision/power of the inference about treatment differences. The conclusion about the statistical significance of differences between groups will be determined by this single statistical test to protect against an elevated risk of false-positive conclusions. Sensitivity analysis will be done to evaluate whether conclusions would differ when other important covariates are added to the model (length of hospital stay, inflammatory molecules, presence of the frailty phenotype [Fried’s criteria[84]], days of intensive care unit stay, days of inpatient rehabilitation, age, comorbidity burden, social status, gender]. These variables will be extracted from the VA EMR and stored in the VA version of RedCAP using unique ID numbers for each Veteran. **Secondary Analyses** ***(Aim 2****)**:* Differences between groups at 60 days following hospital discharge in other outcomes (SPPB, mPPT, PA, dynamometry, LSA, PAM NEADL, CBI, SLUMS, and VR-12) will be analyzed as described above. Follow-up measures at 90 and 180 days will be analyzed to evaluate the long-term impact and sustainability of our PHIT interventions. Secondary analyses will be evaluated for their consistency with the conclusions of the primary endpoints. We anticipate that group differences in secondary measures will be correlated with the primary so that significant differences in the primary endpoint will be reinforced by similar effects on secondary endpoints. Failure to observe consistency in the primary and secondary endpoints will be taken as evidence that the effects of PHIT are not clear, and that further study is necessary to resolve any inconsistencies. This approach will reduce the risk of false-positive conclusions resulting from multiple statistical tests.

The characteristics of the time trajectory (30, 60, 90 and 180 days of follow-up) for treatment effects will also be analyzed in secondary analyses to elucidate the mechanism and inform the development of methods to improve long-term outcomes. The analytic methods will include maximum likelihood estimates from a repeated measures model of the mean effect at each of the measurement times.[85] The trend in means will be evaluated using a linear contrast as the summary measure of greatest interest.[86] This approach will evaluate whether there are differences in the first-order trends (slope) between intervention groups. Finally, we will estimate adverse events rates (falls, emergency department visits, nursing home days, or re-hospitalizations) for each arm and compare rates between arms using a likelihood ratio test. We will additionally investigate whether training volume significantly explained additional variability in functional gains within the PHIT group using regression analysis.

Sample Size Estimates
Statistical power was estimated based on the results of a pilot study of 18 participants: 8 were randomized to PHIT, 10 to the UC interventions (results for SPPB, gait speed, and mPPT are shown in Figure 2). We observed a between group difference ± SD in gait speed of 0.18 ± 0.29 meters/second (m/s) in the preliminary study. Thus, a sample size of 112 patients completing the study (56/group) will provide 90% power (assuming the same pooled SD in both groups to be conservative) to detect differences at least that great. This represents 1.8 times a clinically important difference of 0.1m/s.[46] This estimate is conditional upon using a 2-sided, alpha = 0.05 level 2-group t-test.

We expect that we will consent 250 Veterans and spouses for the study, with allowance for a 25% screening failure. Screening failures that occur after consent is obtained and before enrollment in the study may include a change in medical status during hospitalization requiring a discharge to a location other than home health (e.g skilled nursing facility) , a hospital re-admission which occurs after hospital discharge but prior to the baseline assessment being completed, or a failure to meet specific performance inclusion criteria (e.g. a Veteran or spouse who lacks the ability to ambulate 10 feet without at least minimal physical assistance [more than supervision or light touching for steadiness] from another person)

Enrollment in the study will be defined as participating in the baseline functional performance measures. We expect to enroll 150 Veterans and spouses into the study, with 112 needed to complete to meet study goals. From our experiences and available data, we anticipate a 25% drop out. Caregivers will be consented after a Veteran or spouse is enrolled in the study, thus we anticipate enrolling 150 caregivers. Caregivers will undergo assessment of caregiver burden on the outcome measurement schedule above until the conclusion of the 180 day study period, or until the Veteran or spouse for whom they give care is lost to the study (e.g re-hospitalized)—similarly, we anticipate to need 112 to complete.

Thus, in total, we anticipate consenting 250 Veterans and spouses for the study, enrolling 150 of them, and expecting 112 to complete. We will additionally be consenting 150 caregivers with 112 expecting to complete. For the total study, we will be consenting 400 participants (250 Veterans and spouses, 150 caregivers) and expecting 224 to complete (112 Veterans and spouses, 112 Caregivers). These numbers have been provided to as part of the grant application process to the Veterans Administration Rehabilitation Research and Development Service and were favorably reviewed and pending a funding announcement for a Merit Award (R01 equivalent).

G. Summarize Knowledge to be Gained:
There is a growing recognition that acute hospitalization contributes to long-term disability for hospitalized older adults—who are 60 times more likely to develop disability than those who are not hospitalized. Older Veterans are particularly vulnerable to functional decline after

hospitalization, as this population has lower function and more comorbidities than age-matched peers. Home Health (HH) physical therapy may be the ideal venue for addressing these mobility deficits. However, as currently structured, these services do not appear to adequately address deconditioning often resulting from acute hospitalization as evidenced by poor functional recovery, and poor community and home mobility, up to 2 years after acute hospitalization. A more intensive approach to HH physical therapy delivered within the immediate post-hospitalization period in older Veterans has great potential to maximize physical function, home and community mobility, and quality of life. Therefore, we have developed a short duration, progressive high intensity therapy (PHIT) intervention that directly addresses the functional deficits seen after acute hospitalization. If successful in improving patient function, PHIT intervention holds potential for future health care cost savings by reductions in the need for formal caregiving services and institutionalization in the older Veteran population.

References:

1. Gill TM, Allore HG, Holford TR, Guo ZC. Hospitalization, restricted activity, and the development of disability among older persons. *JAMA.* 2004;292(17):2115-2124.
2. Kortebein P. Rehabilitation for Hospital-Associated Deconditioning. *American Journal of Physical Medicine & Rehabilitation.* 2009;88(1):66-77.
3. Falvey J, Mangione K, Stevens-Lapsley J. Rethinking Hospital-Associated Deconditioning: Proposed Paradigm Shift. *Physical therapy.* 2015.
4. Timmer AJ, Unsworth CA, Taylor NF. Rehabilitation interventions with deconditioned older adults following an acute hospital admission: a systematic review. *Clinical Rehabilitation.* 2014.
5. Krumholz HM. Post-hospital syndrome--an acquired, transient condition of generalized risk. *N Engl J Med.* 2013;368(2):100-102.
6. Peterson MJ, Crowley GM, Sullivan RJ, Morey MC. Physical function in sedentary and exercising older veterans as compared to national norms. *Journal of rehabilitation research and development.* 2004;41:653-658.
7. Frayne SM, Parker VA, Christiansen CL, et al. Health status among 28,000 women veterans. *Journal of general internal medicine.* 2006;21(S3):S40-S46.
8. Selim AJ, Berlowitz DR, Fincke G, et al. The health status of elderly veteran enrollees in the Veterans Health Administration. *Journal of the American Geriatrics Society.* 2004;52(8):1271-1276.
9. Purser JL, Weinberger M, Cohen HJ, et al. Walking speed predicts health status and hospital costs for frail elderly male veterans. *Journal of rehabilitation research and development.* 2005;42(4):535.
10. Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: correlates of feelings of burden. *The Gerontologist.* 1980;20(6):649-655.
11. Dellasega C. Caregiving stress among community caregivers for the elderly: does institutionalization make a difference? *Journal of community health nursing.* 1991;8(4):197-205.

12. Kortebein P, Ferrando A, Lombeida J, Wolfe R, Evans WJ. Effect of 10 days of bed rest on skeletal muscle in healthy older adults. *JAMA.* 2007;297(16):1772-1774.
13. Gill TM, Gahbauer EA, Han L, Allore HG. The relationship between intervening hospitalizations and transitions between frailty states. *J Gerontol A Biol Sci Med Sci.* 2011;66(11):1238-1243.
14. Boyd CM, Landefeld CS, Counsell SR, et al. Recovery of Activities of Daily Living in Older Adults After Hospitalization for Acute Medical Illness. *Journal of the American Geriatrics Society.* 2008;56(12):2171-2179.
15. Donze J, Lipsitz S, Bates DW, Schnipper JL. Causes and patterns of readmissions in patients with common comorbidities: retrospective cohort study. *BMJ (Clinical research ed.).* 2013;347:f7171.
16. Kinosian B, Stallard E, Wieland D. Projected use of long-term-care services by enrolled veterans. *The Gerontologist.* 2007;47(3):356-364.
17. Yu W, Ravelo A, Wagner TH, et al. Prevalence and Costs of Chronic Conditions in the VA Health Care System. *Medical Care Research and Review.* 2003;60(3):146-167.
18. Brown CJ, Roth DL, Allman RM, Sawyer P, Ritchie CS, Roseman JM. Trajectories of life-space mobility after hospitalization. *Annals of internal medicine.* 2009;150(6):372-378.
19. Naylor MD, Brooten D, Campbell R, et al. Comprehensive discharge planning and home follow-up of hospitalized elders: a randomized clinical trial. *Jama.* 1999;281(7):613-620.
20. Coleman EA, Parry C, Chalmers S, Min S. The care transitions intervention: Results of a randomized controlled trial. *Archives of Internal Medicine.* 2006;166(17):1822-1828.
21. Fisher SR, Kuo YF, Sharma G, et al. Mobility after hospital discharge as a marker for 30-day readmission. *J Gerontol A Biol Sci Med Sci.* 2013;68(7):805-810.
22. Portegijs E, Buurman BM, Essink-Bot ML, Zwinderman AH, de Rooij SE. Failure to regain function at 3 months after acute hospital admission predicts institutionalization within 12 months in older patients. *J Am Med Dir Assoc.* 2012;13(6):569.e561-567.
23. Hoyer EH, Needham DM, Atanelov L, Knox B, Friedman M, Brotman DJ. Association of impaired functional status at hospital discharge and subsequent rehospitalization. *Journal of Hospital Medicine.* 2014;9(5):277-282.
24. Nguyen HQ, Chu L, Amy Liu IL, et al. Associations between physical activity and 30-day readmission risk in chronic obstructive pulmonary disease. *Ann Am Thorac Soc.* 2014;11(5):695-705.
25. Rantanen T, Guralnik JM, Izmirlian G, et al. ASSOCIATION OF MUSCLE STRENGTH WITH MAXIMUM WALKING SPEED IN DISABLED OLDER WOMEN1. *American Journal of Physical Medicine & Rehabilitation.* 1998;77(4):299-305.
26. Skelton DA, GREIG CA, DAVIES JM, Young A. Strength, power and related functional ability of healthy people aged 65–89 years. *Age and ageing.* 1994;23(5):371-377.
27. Moreland JD, Richardson JA, Goldsmith CH, Clase CM. Muscle weakness and falls in older adults: a systematic review and meta-analysis. *Journal of the American Geriatrics Society.* 2004;52(7):1121-1129.
28. Fukagawa NK, Brown M, Sinacore DR, Host HH. The relationship of strength to function in the older adult. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 1995;50(Special Issue):55-59.
29. Stone R, Cafferata GL, Sangl J. Caregivers of the Frail Elderly: A National Profile. *The Gerontologist.* 1987;27(5):616-626.
30. Buhr GT, Kuchibhatla M, Clipp EC. Caregivers' reasons for nursing home placement: clues for improving discussions with families prior to the transition. *The Gerontologist.* 2006;46(1):52-61.
31. Caserta MS, Lund DA, Wright SD. Exploring the Caregiver Burden Inventory (CBI): further evidence for a multidimensional view of burden. *The International Journal of Aging and Human Development.* 1996;43(1):21-34.
32. Medicare.gov. Home Health Compare.
33. Jankowska EA, Wegrzynowska K, Superlak M, et al. The 12-week progressive quadriceps resistance training improves muscle strength, exercise capacity and quality of life in patients with stable chronic heart failure. *International journal of cardiology.* 2008;130(1):36-43.
34. Vonbank K, Strasser B, Mondrzyk J, et al. Strength training increases maximum working capacity in patients with COPD – Randomized clinical trial comparing three training modalities. *Respiratory Medicine.* 2012;106(4):557-563.

35. Daly JJ, Ruff RL. Construction of efficacious gait and upper limb functional interventions based on brain plasticity evidence and model-based measures for stroke patients. *ScientificWorldJournal.* 2007;7:2031-2045.
36. Daniels R, van Rossum E, de Witte L, Kempen GI, van den Heuvel W. Interventions to prevent disability in frail community-dwelling elderly: a systematic review. *BMC Health Serv Res.* 2008;8:278.
37. (CDC) CfDC. http://www.cdc.gov/HomeandRecreationalSafety/Falls/compendium/1.2_otago.html.
38. Shay K, Hyduke B, Burris JF. Strategic plan for geriatrics and extended care in the veterans health administration: background, plan, and progress to date. *Journal of the American Geriatrics Society.* 2013;61(4):632-638.
39. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol.* 1994;49(2):M85-94.
40. Petterson SC, Mizner RL, Stevens JE, et al. Improved function from progressive strengthening interventions after total knee arthroplasty: a randomized clinical trial with an imbedded prospective cohort. *Arthritis Rheum.* 2009;61(2):174-183.
41. Stevens-Lapsley JE, Bade MJ, Shulman BC, Kohrt WM, Dayton MR. Minimally invasive total knee arthroplasty improves early knee strength but not functional performance: a randomized controlled trial. *J Arthroplasty.* 2012;27(10):1812-1819 e1812.
42. Jayaraman A, Gregory CM, Bowden M, et al. Lower Extremity Skeletal Muscle Function in Persons with Incomplete Spinal Cord Injury. *Spinal Cord.* 2005;Epub ahead of print (Dec 13).
43. Pathare N, Walter GA, Stevens JE, et al. Changes in inorganic phosphate and force production in human skeletal muscle after cast immobilization. *J Appl Physiol.* 2005;98(1):307-314.
44. Stevens JE, Pathare NC, Tillman S, et al. Relative Contributions of Muscle Activation and Muscle Size to Plantarflexor Torque during Rehabilitation after Immobilization. *J Orthop Research.* 2006;24(8):1729-1736.
45. White LJ, McCoy SC, Castellano V, et al. Resistance training improves strength and functional capacity in persons with multiple sclerosis. *Mult Scler.* 2004;10(6):668-674.
46. Perera S, Mody SH, Woodman RC, Studenski SA. Meaningful change and responsiveness in common physical performance measures in older adults. *Journal of the American Geriatrics Society.* 2006;54(5):743-749.
47. Fritz S, Lusardi M. White paper: "walking speed: the sixth vital sign". *Journal of geriatric physical therapy (2001).* 2009;32(2):46-49.
48. Cesari M, Kritchevsky SB, Penninx BWHJ, et al. Prognostic value of usual gait speed in well-functioning older people-results from the health, aging and body composition study. *Journal of the American Geriatrics Society.* 2005;53(10):1675-1680.
49. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-Extremity Function in Persons over the Age of 70 Years as a Predictor of Subsequent Disability. *New Engl J Med.* 1995;332(9):556-561.
50. Mudge S, Barber PA, Stott NS. Circuit-based rehabilitation improves gait endurance but not usual walking activity in chronic stroke: a randomized controlled trial. *Archives of physical medicine and rehabilitation.* 2009;90(12):1989-1996.
51. Jette AM, Jette DU, Ng J, Plotkin DJ, Bach MA. Are performance-based measures sufficiently reliable for use in multicenter trials? Musculoskeletal Impairment (MSI) Study Group. *The journals of gerontology. Series A, Biological sciences and medical sciences.* 1999;54(1):M3-6.
52. Bohannon RW. Comfortable and maximum walking speed of adults aged 20-79 years: reference values and determinants. *Age and ageing.* 1997;26(1):15-19.
53. Mangione KK, Craik RL, Palombaro KM, Tomlinson SS, Hofmann MT. Home-Based Leg-Strengthening Exercise Improves Function 1 Year After Hip Fracture: A Randomized Controlled Study. *Journal of the American Geriatrics Society.* 2010;58(10):1911-1917.
54. Investigators LS, Pahor M, Blair SN, et al. Effects of a physical activity intervention on measures of physical performance: Results of the lifestyle interventions and independence for Elders Pilot (LIFE-P) study. *The journals of gerontology. Series A, Biological sciences and medical sciences.* 2006;61(11):1157-1165.

55. Lin MR, Hwang HF, Hu MH, Wu HDI, Wang YW, Huang FC. Psychometric comparisons of the timed Up and Go, One-Leg stand, functional reach, and tinetti balance measures in community-dwelling older people. *Journal of the American Geriatrics Society.* 2004;52(8):1343-1348.
56. van Iersel MB, Munneke M, Esselink RA, Benraad CE, Olde Rikkert MG. Gait velocity and the Timed-Up-and-Go test were sensitive to changes in mobility in frail elderly patients. *Journal of clinical epidemiology.* 2008;61(2):186-191.
57. Stevens-Lapsley JE, Kramer LR, Balter JE, Jirikowic J, Boucek D, Taylor M. Functional performance and muscle strength phenotypes in men and women with Danon disease. *Muscle & nerve.* 2010;42(6):908-914.
58. Berlin JE, Storti KL, Brach JS. Using Activity Monitors to Measure Physical Activity in Free-Living Conditions. *Physical therapy.* 2006;86(8):1137-1145.
59. Harwood RH, Ebrahim S. The validity, reliability and responsiveness of the Nottingham Extended Activities of Daily Living scale in patients undergoing total hip replacement. *Disability and Rehabilitation.* 2002;24(7):371-377.
60. Yohannes AM, Roomi J, Waters K, Connolly MJ. Quality of life in elderly patients with COPD: measurement and predictive factors. *Respiratory medicine.* 1998;92(10):1231-1236.
61. Baker PS, Bodner EV, Allman RM. Measuring Life-Space Mobility in Community-Dwelling Older Adults. *Journal of the American Geriatrics Society.* 2003;51(11):1610-1614.
62. Peel C, Baker PS, Roth DL, Brown CJ, Bodner EV, Allman RM. Assessing Mobility in Older Adults: The UAB Study of Aging Life-Space Assessment. *Physical therapy.* 2005;85(10):1008-1019.
63. Cheak-Zamora NC, Wyrwich KW, McBride TD. Reliability and validity of the SF-12v2 in the medical expenditure panel survey. *Quality of Life Research.* 2009;18(6):727-735.
64. Feliciano L, Horning SM, Klebe KJ, Anderson SL, Cornwell RE, Davis HP. Utility of the SLUMS as a Cognitive Screening Tool Among a Nonveteran Sample of Older Adults. *The American Journal of Geriatric Psychiatry.* 2013;21(7):623-630.
65. Tariq SH, Tumosa N, Chibnall JT, Perry Iii MH, Morley JE. Comparison of the Saint Louis University Mental Status Examination and the Mini-Mental State Examination for Detecting Dementia and Mild Neurocognitive Disorder—A Pilot Study. *The American Journal of Geriatric Psychiatry.* 2006;14(11):900-910.
66. Thomas S, Mackintosh S, Halbert J. Does the 'Otago exercise programme' reduce mortality and falls in older adults?: a systematic review and meta-analysis. *Age and ageing.* 2010;39(6):681-687.
67. Liu CJ, Latham NK. Progressive resistance strength training for improving physical function in older adults. *Cochrane Database of Systematic Reviews.* 2009(3).
68. Brach JS, Vanswearingen JM. Interventions to Improve Walking in Older Adults. *Curr Transl Geriatr Exp Gerontol Rep.* 2013;2(4).
69. VanSwearingen JM, Perera S, Brach JS, Cham R, Rosano C, Studenski SA. A randomized trial of two forms of therapeutic activity to improve walking: effect on the energy cost of walking. *The journals of gerontology. Series A, Biological sciences and medical sciences.* 2009;64(11):1190-1198.
70. Wert DM, Brach JS, Perera S, VanSwearingen J. The association between energy cost of walking and physical function in older adults. *Archives of gerontology and geriatrics.* 2013;57(2):198-203.
71. Schrack JA, Simonsick EM, Ferrucci L. The relationship of the energetic cost of slow walking and peak energy expenditure to gait speed in mid-to-late life. *American journal of physical medicine & rehabilitation / Association of Academic Physiatrists.* 2013;92(1):28-35.
72. Liu C-j, Shiroy D, Jones L, Clark D. Systematic review of functional training on muscle strength, physical functioning, and activities of daily living in older adults. *Eur Rev Aging Phys Act.* 2014;11(2):95-106.
73. Andersen LL, Andersen CH, Mortensen OS, Poulsen OM, Bjørnlund IBT, Zebis MK. Muscle activation and perceived loading during rehabilitation exercises: comparison of dumbbells and elastic resistance. *Physical therapy.* 2010;90(4):538-549.
74. Fiatarone MA, Marks EC, Ryan ND, Meredith CN, Lipsitz LA, Evans WJ. High-Intensity Strength Training in Nonagenarians - Effects on Skeletal-Muscle. *Jama-Journal of the American Medical Association.* 1990;263(22):3029-3034.

75. Fiatarone MA, O'Neill EF, Ryan ND, et al. Exercise training and nutritional supplementation for physical frailty in very elderly people. *N Engl J Med.* 1994;330(25):1769-1775.
76. Cermak NM, Res PT, de Groot LC, Saris WH, van Loon LJ. Protein supplementation augments the adaptive response of skeletal muscle to resistance-type exercise training: a meta-analysis. *The American Journal of Clinical Nutrition.* 2012;96(6):1454-1464.
77. Carlsson M, Littbrand H, Gustafson Y, et al. Effects of high-intensity exercise and protein supplement on muscle mass in ADL dependent older people with and without malnutrition—A randomized controlled trial. *The journal of nutrition, health & aging.* 2011;15(7):554-560.
78. Murkofsky RL, Alston K. The Past Present, and Future of Skilled Home Health Agency Care. *Clinics in geriatric medicine.* 2009;25(1):1-+.
79. Mangione KK, Lopopolo RB, Neff NP, Craik RL, Palombaro KM. Interventions used by physical therapists in home care for people after hip fracture. *Physical therapy.* 2008;88(2):199-210.
80. Gardner MM, Phty M, Robertson MC, McGee R, Campbell AJ. Application of a falls prevention program for older people to primary health care practice. *Prev Med.* 2002;34(5):546-553.
81. Gordon NF, Kohl HW, 3rd, Pollock ML, Vaandrager H, Gibbons LW, Blair SN. Cardiovascular safety of maximal strength testing in healthy adults. *Am J Cardiol.* 1995;76(11):851-853.
82. Wenger NK, Froelicher ES, Smith LK, et al. Cardiac rehabilitation as secondary prevention. Agency for Health Care Policy and Research and National Heart, Lung, and Blood Institute. *Clin Pract Guidel Quick Ref Guide Clin.* 1995(17):1-23.
83. Gill TM, DiPietro L, Krumholz HM. Role of exercise stress testing and safety monitoring for older persons starting an exercise program. *JAMA.* 2000;284(3):342-349.
84. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci.* 2001;56(3):M146-156.
85. Pinheiro JC, Bates DM. *Mixed Effects Models in S and S-Plus* New York: Springer-Verlag; 2000.
86. Kittelson JM, Sharples K, Emerson SS. Group sequential clinical trials for longitudinal data with analyses using summary statistics. *Stat Med.* 2005;24(16):2457-2475.