PUSH PLUS PROTEIN PILOT STUDY FOR HIP FRACTURE PATIENTS

PROTOCOL (Version 3.0)

Summary of Modifications to Protocol Version 2.0 for Version 3.0

Version (date)	Section	Brief Summary of Modification
9-5-2018	10.1 and 10.2	We removed the Biodex ankle plantarflexion-dorsiflexion measurement from the baseline and 16-week follow-up assessments. We will test Biodex knee flexion/extension only, which is the best representative marker for torque/ power production and importantly related to gait and mobility function. The Biodex ankle test is less reliable and the knee test a better performance predictor. When investigators looked at data from the CAP-MP companion study, they learned that many in this functionally very challenged cohort could not achieve the 60 deg/sec needed to perform the ankle test; thus, the torque/power was not calculated, as there was more missing data for the Biodex ankle test than for the Biodex knee test which was more complete. The ankle test for the selected contraction velocity is more difficult for many in this study population to achieve in order to capture valid measurement. Therefore, experts in the Department of Physical Therapy and Rehabilitation Science (PTRS) suggest using the Biodex knee test only for the current pilot study because it more accurately represents the entire subject cohort being tested. Participants will be able to correctly perform the knee test which was not true for the ankle test in the companion study.
	10.1 and 10.2	We added the Four-Square Step Test (FSST) to be done at the baseline and 16-week follow-up visits as a dynamic balance assessment.

Summary of Modifications to Protocol Version 1.0 for Version 2.0

Version (date)	Section	Brief Summary of Modification
7-24-2018	All sections	Changed study clinician to study physician
	12.5 and Figures 5b-d	Modified procedures for reportable adverse events to coincide with reporting procedures outlined by NIA and the Pepper Center OAIC.
	7.5	Modified recruitment procedures to describe how patients will be contacted after discharge from the hospital and how potential participants who contact the study office will undergo a brief pre-screening to assess eligibility.
	17	Modified the publication policy to state that publications will be overseen by study leadership and added a note that final papers using CAP or CAP-MP data may need to be reviewed by the CAP PASC.

PUSH Plus Protein Pilot Study for Hip Fracture Patients

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Supported by:

The National Institute on Aging
R37 AG009901(PI: J. Magaziner)

Trial Registration

ClinicalTrials.gov

NCT03410823

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List of Abbreviations

Term	Abbr.
Active range of motion	AROM
Activities of daily living	ADL
Adverse event	AE
Arthrogenic muscle response	AMR
Baltimore Hip Studies	BHS
Body mass index	BMI
Cardiopulmonary resuscitation	CPR
Center for Medicare and Medicaid Services	CMS
Data and Safety Monitoring Board	DSMB
Data Management Plan	DMP
Diastolic blood pressure	DBP
Eight-repetition maximum	8-RM
Emergency Medical Service	EMS
Functional Comorbidity Index	FCI
Generalized estimating equations	GEE
Health Insurance Portability and Accountability Act	HIPAA
Heart rate	HR
Heart rate reserve	HRR
Heating, ventilation and air conditioning	HVAC
Incremental net benefits	INB
Independent Safety Monitor	ISM
Information Technology	IT
Informed Consent Form	ICF
Institutional Review Board	IRB
Investigational Drug Services	IDS
Intervention Monitor	IM
Manual of Procedures	MOP
Mini Nutritional Assessment-Short Form	MNA®-SF
Modified Mini-Mental State examination	3MS
National Institute on Aging	NIA
National Institutes of Health	NIH
Peak oxygen uptake	VO_2peak
Pepper Assessment Tool for Disability	PAT-D
Physical therapist	PT
Primary care provider	PCP
Principal investigator	PI
Protected Health Information	PHI
Publications and Ancillary Studies Committee	PASC
Quality assurance	QA
Quality control	QC
Rating of perceived exertion	RPE
Redundant Array of Independent Risks	RAID
Registered dietician	RD
Reportable Adverse Event	RAE
Resource-Based Relative Value Scale	RBRVS
Serious adverse event	SAE
Short Physical Performance Battery	SPPB
Six-Minute Walk Test	SMWT
Skilled nursing facility	SNF
Spine Patient Outcomes Research Trial	SPORT
Standard Operating Procedure	SOP
Statistical Analysis Software	SAS
Systolic blood pressure	SBP
University of Maryland Baltimore	UMB
Weighted estimating equations	WEE

Section 1: Executive Summary

Hip fracture is a common problem among older individuals. This year in the United States approximately 260,000 people aged 65 and older will break a hip. The goal of current standard of care after hip fracture is to achieve independent, household ambulation 2-3 months after surgery, yet decreased functional ability typically persists well beyond three months and many patients never resume independent ambulation outside the home. Previous research has established that one must be able to walk at least 300 meters (~330 yards) within 6 minutes to re-establish routine interactions in the community, such as going to the store or to church. In part, this is based on the average distance from handicapped parking spaces into most facilities. Activity and exercise are believed to be of benefit for reducing disability in older adults, yet the majority of older adults does not participate in regular exercise and is not active. This is especially true for older adults following hip fracture after they complete the usual rehabilitation program.

This research study is being done to test a 16-week, multi-part exercise intervention for hip fracture patients that will be supervised by specially trained physical therapists (PTs). The exercise intervention uses a novel machine to provide strength and endurance training in the home. This has been shown in smaller studies to be safe and effective at increasing strength. We want to test whether adding a protein supplement to the exercise intervention leads to more improvements in a person's ability to walk in their own home and in the local community. With this knowledge, we hope to help a greater number of hip fracture patients enjoy a more complete recovery and improved overall health.

The research is based on the premise that successful community ambulation requires certain factors that are influenced by underlying physical or chemical processes. The key factors include endurance, walking speed, muscle strength, balance, lower extremity function, skeletal integrity, and fracture healing. We believe that physical activity and protein supplementation can impact these factors to improve the ability to walk. We want to gain a better understanding of which factors play a role by performing tests that measure physical function, strength, balance, level of inflammation, bone turnover rate, muscle density, and body composition.

Participant data from this pilot study will be compared to data from participants who received the PUSH intervention without protein in two recently completed studies: 1) Community Ambulation Project (CAP parent study) and 2) Community Ambulation Project- Mechanistic Pathways (CAP-MP ancillary study).

Study Title
PUSH Plus Protein Pilot Study for Hip Fracture Patients (hereafter referred to as PUSH Plus Protein)

Objectives
The primary outcome will be to test whether the PUSH Plus Protein intervention improves community ambulation (as measured by distance walked in six minutes) compared to PUSH intervention alone (from CAP study) at the end of 16 weeks. The effects of PUSH Plus Protein on precursors to community ambulation compared to the PUSH intervention alone (CAP study) and the effects of PUSH Plus Protein intervention on the mechanistic factors compared to PUSH intervention alone (from CAP-MP study) will also be examined. In addition, the safety and tolerability of delivering the PUSH Plus Protein intervention to hip fracture patients will be assessed.

Design and Outcomes
In addition to providing important information on adherence, feasibility, and safety, this pilot study of 30 hip fracture patients has the unique advantage of being able to compare data to two recently completed studies where participants received the PUSH intervention without protein supplementation described below.

Participants in this pilot will receive the same specific multi-component 16-week intervention, PUSH, as participants in the multi-site CAP randomized controlled trial. The PUSH intervention uses a novel machine to provide strength and endurance training in the home. The purpose of this pilot study is to test whether adding a protein supplement to the PUSH intervention leads to greater improvement in a person's functional ability compared to the PUSH intervention alone; therefore, data in this pilot study will be compared to data from participants in the CAP study across the three clinical sites who received the PUSH intervention alone (n=105). Our working hypothesis is that PUSH Plus Protein will lead to greater improvements in ability to walk in the community compared to PUSH measured using the distance walked in six minutes (SMWT).

We will also compare the effect of PUSH Plus Protein intervention to PUSH intervention alone on secondary outcomes in the CAP study believed to be precursors to community ambulation including activities of daily living (ADLs), quality of life, lower extremity physical performance, increase of ≥ 50 meters in distance walked in six minutes, cognitive status, and nutritional status.

We can also compare participants in the pilot study to participants who received PUSH alone in the CAP-MP study (HP-53145) (n=19) to examine whether PUSH Plus
Protein has an impact on the mechanistic factors on the pathway to recovery of ambulatory ability after hip fracture. We will assess whether, at the end of the 16 week intervention, participants in the PUSH Plus Protein intervention, compared to PUSH alone, have: a) greater muscle volume and attenuation (i.e., reduced intra-muscular fat) of the thigh; b) greater lower extremity strength; c) better gait parameters; d) greater bone mineral density and bone strength; e) more bone formation and less bone resorption; and f) lower levels of circulating inflammatory cytokines.

The pilot study will provide important information related to the safety and tolerability of delivering the PUSH Plus Protein intervention to hip fracture patients. We will also be able to estimate the sample size requirements for a more definitive study.

Study activities for participants meeting eligibility criteria will take place after post-acute rehabilitation ends, up to 26 weeks after admission to the hospital for hip fracture. Patients age 60 and older who have had surgical repair for hip fracture will be identified in study hospitals or by self-referral and evaluated for eligibility. Following consent to participate, eligible participants will undergo a comprehensive baseline assessment. Participants completing the required measures of the baseline assessment will be eligible to receive the intervention. All participants will receive the PUSH Plus Protein intervention. The follow-up assessment will occur after the intervention is completed, approximately 16 weeks after baseline testing.

Interventions and Duration
All participants will receive the PUSH Plus Protein intervention. Within a week of completing baseline testing, the study physical therapist (PT) will initiate the exercise intervention and the protein supplement in the home setting. Participants will receive two physical therapy visits a week for 16 weeks, on non-consecutive days, for a total of 32 visits. Each visit will last

approximately 60 minutes. Visits will take place in the participant's place of residence. At the same time, participants will receive a daily whey-based protein powder supplement containing 27.6g of protein. Participants will also receive 2,000 IU of vitamin D3, 600 mg of calcium, and a multivitamin daily during the 16-week study period and counseling with a registered dietician to ensure body weight stability and adequate nutrient intake inclusive of a healthy diet.

PUSH Exercise Intervention

The PUSH exercise intervention is based on improving specific precursors to community ambulation. The intervention addresses endurance with continuous upright exercise for 20 minutes; function by improving fast walking needed to navigate streets outdoors, standing from a chair, and stair negotiation; muscle performance by exercising to enhance lower extremity strength in functionally relevant muscles moving through locomotion-appropriate movements and ranges; and balance by performing unilateral activities and activities with decreased base of support. The components of exercise are woven together into one program that minimizes participant burden. Participants will be instructed to complete the endurance component independently one to two times/week by walking for a similar duration and intensity as they have been doing with the PT during the supervised visits.

The strength components of the muscle performance intervention will be performed using a portable progressive resistive exercise device (Shuttle® MiniPress, Contemporary Design Company, P.O. Box 5089, Glacier, WA 98244). Muscle performance will focus on bilateral hip extensors, hip abductors, knee extensors, and plantar flexors because of their role in function, specifically gait and transfer activities. Balance and strength will be addressed with additional exercises performed while standing. The endurance intervention will begin initially with two to three minutes of continuous upper and lower extremity active range of motion (AROM) with the participant sitting. These exercises are intended to increase the participants' heart rate (HR) or exertion closer to the target zone. The participant will then be asked to walk on level surfaces and up and down a single or multiple steps, if able and available, to keep the HR within the training zone for 20 minutes. The PT may also engage the participant in additional exercises such as upper and lower extremity AROM exercises to keep the HR elevated.

As a measure of treatment fidelity, we will monitor physiologic response (heart rate) during the intervention sessions by measuring heart rate. Heart rate monitoring will provide a dichotomous variable reflecting whether, during each segment of the intervention session, the participant's average HR was equal to or greater than his or her target heart rate (±5 beats).

Protein Supplement

Participants will receive a whey-based protein powder supplement containing 27.6g of protein. This dose induces maximum muscle protein synthesis post-exercise. Participants will mix the supplement in 8 oz. of water (or other beverage) or soft food (e.g., yogurt, soup) and consume immediately following each exercise session with the study PT. On days when they do not have a physical therapy visit with the study PT, participants will be instructed to take the supplement at the meal time closest to the time of scheduled PT visits to maintain regular daily dosing schedule.

Nutrition Intervention

Given the importance of maintaining nutrition in older adults after an acute event, we will provide all participants with 2000 IU vitamin D3, 600 mg of calcium, and a multivitamin daily for the duration of the 16-week study. Nutritional counseling will also be provided to ensure weight stability, adequate nutrient intake of 1.2-1.5 g protein/kg body weight inclusive of a healthy diet (50% carbohydrate, 20% protein, 30% fat). Participants will be screened at the time of baseline

testing to assess nutritional risk using the Mini Nutritional Assessment-Short Form (MNA®-SF). Those who score ≤7 (malnourished) on the MNA®-SF at baseline and participants with serum albumin 2.5-3.5 g/dl (regardless of the score on MNA®-SF) will receive a visit from a registered dietician (RD) in their place of residence within seven days of baseline testing. The RD will evaluate and counsel them on making dietary modifications based on their protein, caloric and other dietary deficiencies using a standardized approach across the three study sites. The RD will follow up with participants by telephone one week after the visit to assess understanding and implementation of recommendations. Participants who score 8-11 (at risk of malnutrition) on MNA®-SF at baseline and have serum albumin level >3.5 g/dl will receive a telephone dietary consultation with the RD within seven days of baseline testing. Based on the participant's eating habits and food intake, the RD may make the clinical determination that an in-person consultation is warranted. In these cases, the RD will schedule an in-person dietary consultation, following the same protocol as those who score in the malnourished range. Those screening in the normal range (with a score ≥12 on the MNA®-SF) at baseline and who have serum albumin level >3.5 g/dl will receive brief telephone contact within seven days of baseline testing from the RD to discuss the importance of calorie and protein intake. Weight will be monitored during home PT visits every four weeks and those who lose 2% or more body weight in a four-week period will receive another telephone consultation by the study RD. This protocol applies to anyone who loses 2% or more of body weight, regardless of whether the participant is trying to lose weight. In the event that a weight measurement is not obtained at the last PT visit, the participant's weight at the 16-week follow-up assessment will be compared to his or her baseline weight and, if there is weight loss of 5% or more, the study physician will review the participant's weight trajectory, baseline BMI, baseline MNA®-SF score, and registered dietician's documentation and, if warranted based on clinical judgment, will refer the participant to a dietician or medical provider for follow-up of possible poor nutritional status.

Sample Size and Population

The target sample size for this pilot study is 30 hip fracture patients who will receive the PUSH Plus Protein intervention. Study inclusion criteria are: 1) Closed, non-pathologic, minimal trauma hip fracture with surgical fixation; 2) Age 60 or older at time of baseline testing; 3) Living in the community at time of fracture and at time of baseline testing; and 4) Ambulating without human assistance during the two months prior to fracture. Participants for whom it is not safe to participate in the intervention will be excluded, as will those who are very unlikely to benefit and in whom the intervention is not feasible.

Section 2: Clinical Site

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Section 3: Study Organization

The PUSH Plus Protein Pilot study is a single-site study conducted at the University of Maryland Baltimore. In addition to the Department of Epidemiology and Public Health (EPH) where the PI has a faculty appointment, the project will utilize resources provided by the Department of Physical Therapy and Rehabilitation Science (PTRS), University of Maryland General Clinical Research Center (GCRC), University of Maryland Investigational Drug Service (IDS), Baltimore Veteran's Affairs Maryland Health Care System (VAMHCS), and the University of Maryland Claude D. Pepper Older American Independence Center (UM-OAIC) Data and Safety Monitoring Board (DSMB). Please see Section 18: for a complete Study Team Roster.

3.1 Study Administration

3.1.1 Study Chair

The principal investigator (PI) of the grant awarded by the National Institute on Aging (NIA) will serve as the study chair. Responsibilities of the study chair will include:

- Providing overall organization and scientific direction of the trial
- Administering logistics for the Data and Safety Monitoring Board (DSMB) in consultation with the NIA program official
- Providing updates on progress to the NIA
- Defining analyses of study data
- Overseeing manuscript preparation

3.1.2 National Institute on Aging (NIA)

This is an investigator-initiated project and funding is provided by a MERIT Award. The funding agency is the NIA. The PI will report study progress to the NIA on an annual basis unless asked to report at a different interval. According to PA-10-067, a Non-Competing Continuation Grant Progress Report (PHS 2590) will be completed by the PI annually and financial statements will be provided as required in the *NIH Grants Policy Statement*. A final progress report, invention statement, and Financial Status Report will be submitted by the PI when the award is relinquished or when it is terminated.

3.1.3 Data and Safety Monitoring Board (DSMB)

The UM-OAIC DSMB reviews all reported adverse events (AEs), serious adverse events (SAEs), and unanticipated problems, and compliance in accordance with NIH/NIA and local UMB IRB guidance/polices. AEs, SAEs and unanticipated problems will be reported to the UM-OAIC center director, UMB IRB, and NIH/NIA. The DSMB will base decisions regarding continuation, modification, or termination on the study's ability to recruit subjects, patient safety/risk changes, audit findings, and study non-compliance to adhere to protocol. The DSMB will discharge itself from its duties when the study is complete.

3.1.4 Investigative Team

The Investigative Team will be charged with the overall governance of study conduct. Responsibilities will include:

- Approving the final protocol and manual of operations
- Supervising the overall execution of the trial
- Generating and approving study policies
- Considering modifications of the protocol and study operations
- Reviewing issues related to protocol deviations
- Implementing recommendations of the DSMB

All major scientific decisions will be determined by simple majority vote of the members of the Investigative Team. If there is a tie or if investigators disagree, the study chair will make the final decision. The Investigative Team will meet regularly throughout the study. All voting members, as well as other investigators will be invited to participate.

3.1.5 UMB Investigational Drug Services (IDS)

The University of Maryland IDS is responsible for the purchasing, distributing, and accounting procedures for all investigational drugs within the University of Maryland Medical Center campus and will be responsible for preparing the vitamins/supplements for this project. The vitamins/supplements for the study will be purchased and packaged through the University of Maryland IDS. IDS will prepare "treatment kits" for each participant who receives the intervention that will include all vitamins/supplements for the 16-week study period:

1.) 2000 IU vitamin D3, one tablet daily
2.) 600 mg calcium, one tablet daily
3.) Multivitamin, one tablet daily

Each treatment kit will contain four individual packs numbered 1-4. Each pack contains a 4-week supply of vitamin D3, calcium, and a multivitamin. The IDS will prepare appropriate packaging for each item in the treatment kit, with a label and directions for taking each product that complies with legal requirements. Participants who have contraindications for calcium supplementation (i.e., calculated creatinine clearance < 30 ml/min, elevated total or ionized calcium, history of kidney stones, primary hyperparathyroidism, or sarcoidosis) will not be given calcium.

Protein powder will be ordered by the study and shipped directly to IDS for labeling. The IDS will prepare appropriate labeling for each container of protein powder that complies with legal requirements. Each participant will receive four 2 lb. containers of protein powder numbered 1-4. Each container is a 30-day supply of protein powder.

3.1.6 University of Maryland General Clinical Research Center (GCRC)

Study staff will conduct assessments for baseline and 16-week follow-up visits at the University of Maryland General Clinical Research Center (GCRC), located in the University of Maryland Medical Center. The study will utilize GCRC space to draw blood, administer questionnaires, and conduct performance measures, including the SMWT. The GCRC will provide blood draw supplies and staff to process the screening blood samples. GCRC administrative staff will also assist with reserving space for assessment visits.

3.1.7 Study Clinical Site

The study has a single clinical site with a PI and coordinator. The clinical site is located at the University of Maryland Baltimore (UMB).

Responsibilities of the clinical site PI (with assistance from the coordinator) will include:

- Maintaining cooperation of study hospitals and other recruitment sites and ensuring that medical staff involved with the care of hip fracture patients are well informed about the trial
- Recruiting study participants according to the study protocol
- Ensuring retention and adherence of study participants
- Performing all study-related assessments (including complete tracking of outcomes during follow-up)

- Overseeing completion of data collection forms and entering data and processing data edit queries
- Training and supervising study staff; assigning tasks to data collectors, PTs, and dieticians; and providing day-to-day supervision of their work
- Protecting participant safety and verifying that informed consent procedures are followed according to Good Clinical Practice guidelines
- Properly maintaining all study materials and records
- Reporting all RAEs and protocol deviations
- Participating in investigative team meetings and manuscript preparation

Section 4: Study Objectives

4.1 Primary Objective

The purpose of this study is to test whether adding a protein supplement to the PUSH intervention (PUSH Plus Protein) initiated up to 26 weeks pot admission leads to greater improvement in a person's ability to walk in their own home and in the local community 16 weeks after study entry compared to the PUSH intervention alone; therefore, data in this pilot study will be compared to data from participants in the CAP study across the three sites who received the PUSH intervention alone (n=105). Our working hypothesis is that PUSH Plus Protein will lead to greater improvements in ability to walk in the community compared to PUSH.

4.2 Secondary Objectives

We will compare the effect of PUSH Plus Protein intervention to PUSH intervention alone on secondary outcomes in the CAP study believed to be precursors to community ambulation. We can also compare participants in the pilot study to participants who received PUSH alone in the CAP-MP study to examine whether PUSH Plus Protein has an impact on the mechanistic factors on the pathway to recovery of ambulatory ability after hip fracture. Finally, we will assess the safety and tolerability of delivering the PUSH Plus Protein intervention to hip fracture patients.

Section 5: Background

Current standard Medicare-reimbursed rehabilitation therapy fails to restore community ambulation to older persons who have had a hip fracture. A residual mobility disability similar to that reported for stroke occurs in the majority of persons who "recover" from hip fracture.[1,2] In contrast to stroke, heart disease, and cancer, there are few intervention trials focused on decreasing disability following hip fracture. The paucity of intervention trials is surprising since there are over 325,000 hip fractures per year in the U.S.[3] with a predicted increase to over 650,000 per year by 2040.[4] The estimated cost to hip fracture patients, their families and the health care system is between $14 and $20 billion annually.[5-10] A Cochrane Collaboration review on interventions post-hip fracture concluded that there is not sufficient evidence to determine if the interventions evaluated substantially reduce residual disability and enhance community ambulation.[11]

5.1 Residual Deficits in Precursors of Community Ambulation

Effective community ambulation requires sufficiency in five physical precursors: endurance; dynamic balance; lower limb muscle strength; walking speed; and lower extremity function. The precursors enable the person to get up out of bed, get out the front door, and participate in community activities. Previous studies indicate significant residual impairments for persons with hip fracture who have completed "usual" care.

Endurance. Deconditioning is expected following a hip fracture, but there is a paucity of evidence on aerobic capacity from maximal treadmill or cycle ergometry exercise tests.[12-16] The only study that examined peak oxygen uptake (VO_2 peak) values in 20 persons within a month of fracture, reported significantly lower peak values in hip fracture vs healthy community-dwelling older adults.[17] The SMWT has been used as a proxy for aerobic capacity and is considered an endurance measure in elderly, frail and severely compromised patients.[18] Performance on the SMWT by persons post-hip fracture closely resembles that of patients with New York Heart Association class III or IV heart failure who walk 217 meters on average.[19] Mangione reported average SMWT distances of approximately 200 meters after usual care for hip fracture.[20] Work in Baltimore and in the pilot study for this trial indicate an average SMWT distance of 154 m and 184 m, respectively, at six months post-fracture. This contrasts to 400 meters reported for 80-year-olds living in the community[21] or 350 meters reported for a sample of comparable age in the Cardiovascular Health Study.[22]

Balance. Dynamic balance is compromised after hip fracture. For example, at the end of usual care (2-3 months post-fracture), 20% who had regained independence in ADL reported falling; those who had fallen since hospital discharge had poorer balance compared to those who had not fallen.[1,23] Fifty-three percent of patients who were community dwelling pre-fracture fell one or more times in the first six months post-fracture and 18% were readmitted to the hospital for fall-related injury.[1] Balance deficits remain at seven months[24] at a time when physical recovery is reported to approach a plateau.[25,26]

Walking Speed. The proportion of individuals achieving independence in ambulation one year post-fracture is between 30% and 83%, depending on the study.[27-30] Reasons for the variation in reported ambulatory status include the use of different measures, differences in the length of follow-up time and different definitions of recovery. It has also been observed that recovery in gait speed does not reach a plateau until almost a year post-fracture (Magaziner 2000) suggesting that interventions prior to that time might add to the natural recovery process.

Lower Extremity Muscle Strength. Hip fracture is accompanied by rapid loss of muscle mass and weakness.[31] Muscle weakness is not the sole impairment accounting for extensive residual disability post-fracture, but its contribution is significant. Leg, thigh, and hip muscle weakness are related to decreased muscle power and walking speed.[32-35] Muscle weakness appears, therefore, to be a major factor in producing mobility disability.

Lower Extremity Function. A hip fracture results in limited lower extremity function that, in turn, compromises physical, instrumental and social function.[36,37] At six months post-fracture when physical recovery is reported to plateau, a limited proportion of hip fracture patients report climbing a flight of stairs (8%) or walking one half a mile (6%).[26,38] The majority of patients who report independent ambulation also report they do not walk as well they did prior to fracture.[25,39] Even at one year, most hip fracture patients do not return to pre-fracture functional status.[26,38,40-43] They walk more unsteadily and more slowly for shorter distances.[44,45]

Summary: The numbers and costs of hip fracture are significant, and one to two months of usual care is inadequate for restoring function to this patient group. Most hip fracture patients do not regain pre-fracture mobility status. Endurance, dynamic balance, walking speed, lower extremity muscle strength, and lower extremity function are compromised and contribute to failure to achieve community ambulation.

5.2 Exercise Studies in Persons after Hip Fracture

Based on the results of Mangione's survey of 1000 home care PTs,[46] we propose that a reason for the residual disability after hip fracture is an inadequate dose of physical intervention during usual care. A limited number of investigations have examined the direct effect of physical interventions on increasing community ambulation. Only 15 studies were included in a systematic review of physical therapy management of hip fracture. [47] A finding relevant to this study is that usual care outcomes were similar for home, acute rehabilitation, or skilled nursing facilities.

A Cochrane Collaboration review of exercise interventions [11] identified 13 clinical trials in 1,065 patients and concluded that there was insufficient evidence to determine if physical intervention affected outcome post-hip fracture. Seven trials[17,48-53] provided intervention early (approximately two months) after hip fracture. Various combinations of low intensity AROM or flexibility exercises, functional training, strengthening, and balance exercise did not produce outcomes that were different from "usual care" with three exceptions.[17,48,49] Since the Cochrane review, two additional trials intervened with exercise programs early after hip fracture. One offered a one-month intervention focused on falls efficacy and reported initial improvements in walking outdoors and ADLs at two months post-fracture.[54] Another trial reported no benefit in knee extensor muscle strength or walking speed compared to the control group following a 16-week, home-based strengthening program.[55] We believe that differences were not observed because the exercise dose was inadequate. This hypothesis is supported by three small trials which reported between-group differences and demonstrate that higher intensity exercise can be done early and safely. Two of the studies included high intensity exercise very early after hip fracture.[48,49] Strength, gait speed, balance, and balance confidence improved in the experimental groups. The third trial,[17] which included aerobic conditioning during in-patient rehabilitation, demonstrated improved endurance (VO_2 peak), increased mobility, and improved balance.

The other clinical trials began six months or later after hip fracture, with interventions that included various combinations of strengthening exercise, balance training, functional training, and AROM/flexibility. Three of these included endurance training but lacked at least one of the other components of the program we are proposing. Results show positive outcomes in terms of function, gait speed, balance, strength, and endurance.[13,20,56-61] A study conducted in a gym demonstrated improvement in self-reported outdoor mobility in the intervention group who were four years post-fracture, but no changes in dynamic balance or walking speed.[62] Since hip fracture recovery is reported to plateau at six months (which is when the interventions in these studies began), the results of these studies are comparable to the exercise findings reported in older adults without hip fracture, i.e., that older adults benefit from increased activity. These studies indicate that use of higher intensity exercise with endurance training beginning six months post-fracture reduces impairments in precursors to community ambulation.

The unanswered question is whether a higher intensity program performed as soon as usual care is complete will return more people to community ambulation. Mangione described a program that provided function, strength, balance, and endurance training to a single patient three months post-fracture.[63] The patient showed dramatic improvements in all physical precursors to community ambulation. In addition, the recent pilot study of the intervention resulted in a significant between-group difference in distance walked on the SMWT.

A limited number of studies have examined exercise programs post-hip fracture. The most successful in terms of strength, balance, and gait speed outcomes were completed over a 6-month time period in an exercise center.[13,61] The majority of the research published is fraught

with problems including lack of control groups, small samples, and inadequate exercise dose. Prior research suggests that more intensive multi-component training as soon as usual care is complete should be safe and effective.

5.3 Rationale for the Interventions

The significant mobility disability that remains post-hip fracture is remarkable and may account for failure to return to effective community ambulation. Mangione et al. surveyed physical therapists (PTs) nationally to describe usual home care physical therapy following in-patient sub-acute care for hip fracture.[46] The results indicated very similar care regardless of fracture fixation, weight-bearing status, time when physical therapy started, or geographic location. Functional training was one of the most frequently reported interventions. Most of the joint-specific therapeutic exercises reported involved AROM, with very few therapists reporting that they used any form of resistance (manual, elastic bands, or weights) for a specific exercise.

This research study is being done to test a 16-week, multi-part exercise intervention for hip fracture patients that will be supervised by specially trained PTs. The exercise intervention uses a novel machine to provide strength and endurance training in the home. This has been shown in smaller studies to be safe and effective at increasing strength. We want to test whether adding a protein supplement to the exercise intervention leads to more improvements in a person's ability to walk in their own home and in the local community. With this knowledge, we hope to help a greater number of hip fracture patients enjoy a more complete recovery and improved overall health.

The research is based on the premise that successful community ambulation requires certain factors that are influenced by underlying physical or chemical processes. The key factors include endurance, walking speed, muscle strength, balance, lower extremity function, skeletal integrity, and fracture healing. We believe that physical activity and protein supplementation can impact these factors to improve the ability to walk. We want to gain a better understanding of which factors play a role by performing tests that measure physical function, strength, balance, level of inflammation, bone turnover rate, muscle density, and body composition.

PUSH. Older adults improve functional performance when engaging in high intensity multiple component interventions.[64-70] Despite disagreement about exercise type, intensity, frequency, duration, and mechanism, it is known that the older musculoskeletal system adapts to increased demand.[71] Several randomized trials have reported effects of exercise interventions on improved physical function, balance, endurance, mobility and/or falls in community-dwelling elders without hip fracture.[13,68,69,72-76] Studies reporting positive outcomes had similar content (strength, balance, and endurance), used high exercise intensity, and the exercises were tailored to the individual's needs rather than using a generic protocol. Task-oriented functional activities[72,74] were more effective in achieving positive outcomes than traditional regimens that included isometric or isotonic strength training, static standing balance training, and/or cycle ergometry.[68,73]

Principles derived from exercise physiology will be used to determine the intensity of the endurance and muscle performance exercises. According to the overload principle, exercise should be performed at an intensity higher than the usual load to increase the metabolic demand and facilitate a training response.[71,77-79] Overload will be achieved by increasing intensity (effort or load), or frequency and duration (number of repetitions, number of sets). Manipulation of intensity, frequency, or duration alters the exercise dose - heart rate for endurance training or the amount of muscle force produced for muscle strengthening.[77] A review and a meta-analysis emphasize the benefits of endurance training and progressive

resistance training for improvement in functional status, health, and quality of life in older adults.[80,81] Guidelines suggested by these two reviews recommend combining endurance, dynamic balance, and high intensity strength training, which is consistent with the PUSH intervention.

The specificity of training principle has been neglected in many hip fracture intervention programs. Research suggests that the type of muscle contractions used during exercise should match the type of contractions used in the desired activity to achieve the most gain.[71,77] The multi-component PUSH intervention will address endurance by requiring completion of task-specific activities for a continuous period of time. Muscle training will be addressed using a machine that provides progressive resistance training while the lower extremity performs whole limb patterns similar to those used in walking. Upright balance will be challenged in combination with muscle training. Although there is evidence that appropriate training increases endurance and muscle performance, the mechanisms for adaptation in response to exercise in older adults are still being clarified.[82-86] Motor learning principles, theories associated with neural plasticity and exercise physiology must all be considered in the design of an intervention focused on increasing community ambulation.[71] The older person with hip fracture is more complex because of the significant newly acquired deconditioning, muscle atrophy, fracture healing, and other metabolic changes.

Protein. It is hypothesized that the addition of protein will have a beneficial effect on some of the mechanisms on the pathway to community ambulation, specifically muscle and bone. Resistance exercise is a powerful stimulus for muscle protein synthesis.[87-89] and a weaker stimulus for muscle protein breakdown, the net effect of which is a positive protein balance.[88] Protein intake is required to allow muscle protein synthesis in response to resistive exercise. Supplementation with protein or essential amino acids (EAAs) has been shown to simulate post-exercise muscle protein synthesis, and to improve net protein balance,[90,91] with supplementation immediately after exercise resulting in greater quadriceps cross-sectional area and strength compared to supplementation two hours after exercise.[92] Skeletal muscle remains catabolic post-exercise without the presence of the branched-chain amino acid (BCAA) leucine.[93] Supplementation with BCAAs also has been found to reduce muscle soreness resulting from strenuous exercise.[94,95] Although healthy older adults who habitually consume adequate amounts of dietary protein (>0.8 g/kg/d) may not benefit from further protein supplementation with resistance training,[96,97] many elderly hip fracture patients are in a state of protein depletion at the time of fracture and have low protein intake post fracture.[98,99]

Data supporting a positive effect of protein supplementation on bone health as measured by BMD and markers of bone turnover come from two reviews.[100,101] Two studies in elderly hip fracture patients used a protein supplement containing 20 gm per day.[102,103] The proposed mechanism underlying the association between protein supplementation and improvement in bone health is mediated by increases in IGF-1 and both total and free testosterone levels,[104,105] resulting in greater bone formation. This pilot study will test if the addition of a protein supplement immediately following exercise will enhance the mechanistic effects seen with exercise.

5.4 Primary Outcome Measure

Community ambulation is a construct that includes the ability to accommodate change in level and terrain irregularity (necessary to enter and leave the home and for curb management), avoid obstacles and walk a requisite distance.[106] Compared to older adults who are active in the community, persons with a mobility disability do not travel alone, take fewer trips and perform fewer activities per trip, walk shorter distances, cross the street less often, carry fewer

objects, and have fewer postural transitions (turning the head, extending their reach, or changing direction).[107] Although community ambulation is complex, covering a minimal distance within a specified period of time is a critical feature.[108,109]

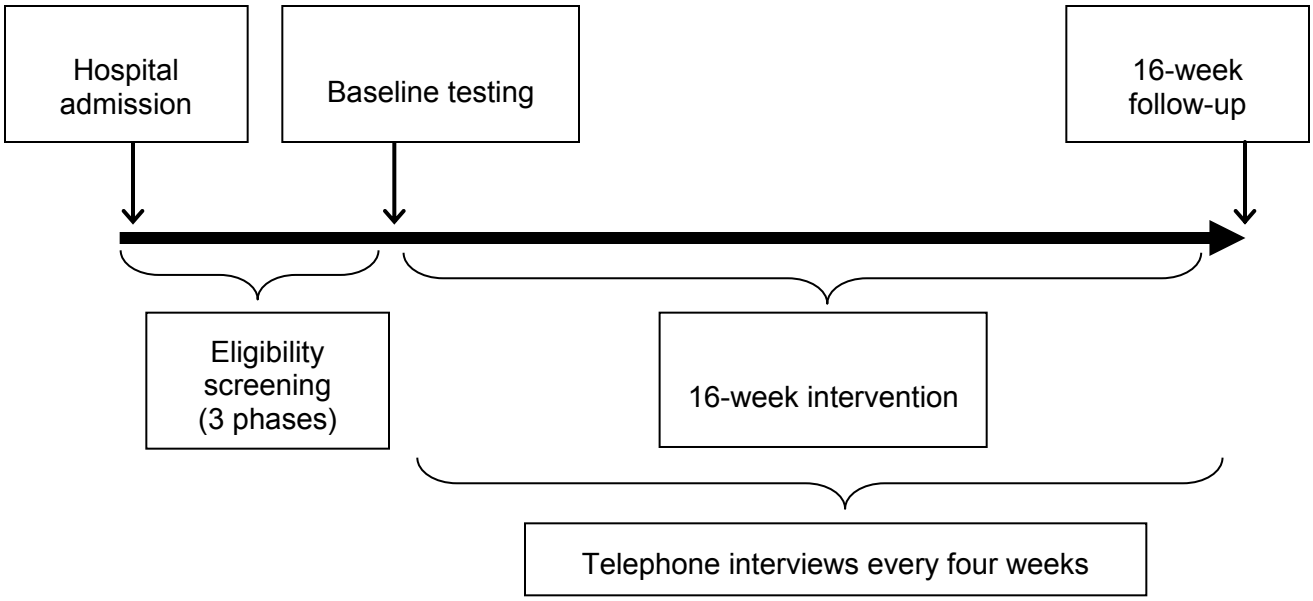
The SMWT is a standardized test that examines both the distance and time components of community ambulation.[110] The Cardiovascular Health Study[111] concluded that the SMWT is safe for use in community samples to measure the impact of multiple comorbidities on endurance in older adults.[22] Harada et al [112] proposed that the SMWT is a useful integrated measure of mobility function taking into account any limitations imposed by major body systems.[112] Lord and Menz[113] concluded that the SMWT provides a measure of overall mobility and physical function in addition to being a measure of cardiovascular fitness. Sixty-nine percent of the variance in the SMWT is explained by physical functioning, lower body strength, standing balance, and gait speed.[112] Construct and predictive validity and responsiveness to change were established for the SMWT in a sample of 108 persons with hip fracture.[114] A high positive correlation was reported between pedometer-determined physical activity and the SMWT test suggesting that both are correlates of community ambulation.[115] The SMWT also has been used as an outcome measure to determine the effectiveness of exercise interventions for elderly patients with and without hip fracture.[20,56,116] In addition to the distance walked in six minutes, gait speed will also be derived. The primary end point for this pilot study is the total distance walked in six minutes.

Section 6: Study Design

6.1 Overview of Study Design

A pilot study including 30 older adults who have experienced a hip fracture will be carried out with participants receiving a specific multi-component intervention with protein supplementation (PUSH Plus Protein). Study activities for participants meeting eligibility criteria will take place after post-acute rehabilitation ends, up to 26 weeks after admission to the hospital for hip fracture. Patients age 60 and older who have had surgical repair for hip fracture will be identified in study hospitals or by self-referral and evaluated for eligibility. Following consent to participate, eligible participants will undergo a comprehensive baseline assessment. Participants completing the baseline assessment will be eligible to receive the intervention. All participants will receive the PUSH Plus Protein intervention. The follow-up assessment will occur after the intervention is completed, approximately 16 weeks after baseline testing. Figure 1 shows the sequence of participant contacts from the time of hospitalization until the 16-week assessment.

Figure 1. Timeline for screening and follow-up



Within a week of complete baseline testing, the physical therapist (PT) will initiate the exercise intervention and the protein supplement in the home setting. Participants will also receive counseling with a registered dietician. The follow-up assessment will take place 16 weeks after baseline testing. Telephone interviews will be conducted every four weeks, beginning four weeks after baseline testing, to obtain information about RAEs and expected AEs, and to help reduce loss to follow-up by maintaining ongoing rapport with participants. An honorarium will be given at the completion of both study assessment visits.

6.2 Interventions

Over a 16-week period, participants will receive two visits per week from a study PT, on non-consecutive days, for a total of 32 visits. These visits will take place in participants' place of residence. Participants will be given a whey-based protein supplement containing 27.6g of protein to be taken daily. Participants will also receive 2,000 IU of vitamin D3, 600 mg of calcium, and a multivitamin daily during the 16-week study period and counseling with a registered dietician to ensure body weight stability and adequate nutrient intake inclusive of a healthy diet.

Section 7: Selection and Enrollment of Participants

7.1 Eligibility

Participants will be evaluated for eligibility in three phases (see Figure 2), all of which must be completed no more than 26 weeks after admission to the hospital for a hip fracture. In phase 1, patients will be assessed for inclusion criteria and medical exclusions. Information for phase 1 will be collected from the patient's medical chart. A HIPAA Partial Privacy Waiver (for recruitment) or verbal consent to review the medical chart for eligibility will be obtained for patients who are identified at study hospitals up to 26 weeks after their admission for hip fracture; this includes patients who were admitted to the hospital for hip fracture up to five months prior to the start of screening.

Patients who are provisionally eligible based on medical chart review at phase 1 will be approached or contacted by telephone to be told about the study in the hospital or after discharge (up to 26 weeks after admission for hip fracture). Interested patients who are approached in the hospital or rehab will be asked to provide written Permission to Contact for additional screening. If we are unable to get written Permission to Contact while the patient is still in the hospital, we will contact patients via telephone to determine their interest in the study and obtain verbal Permission to Contact for additional screening. Patients who are identified through other means of recruitment (e.g., patients who call the study office in response to advertising or physician referral) will undergo a brief pre-screening over the telephone. Potentially eligible patients who are interested in participating will be asked to provide written authorization for release of medical records for review of phase 1 eligibility criteria. Those who agree to further contact will be screened in phase 2 to assess for medical, safety, and feasibility criteria. Informed consent must be obtained prior to any further data collection or research procedures beyond phase 1 screening criteria.

Blood will be collected and tested for hemoglobin (<9 g/dl), serum creatinine to calculate creatinine clearance (<15 ml/min or 15-29 ml/min), serum albumin (<2.5 g/dl), and hemoglobin A1c level (>10%). The blood collection can occur anytime between phases 2 and 3 screening as long as it occurs after informed consent is obtained and no more than 4 weeks prior to baseline testing.

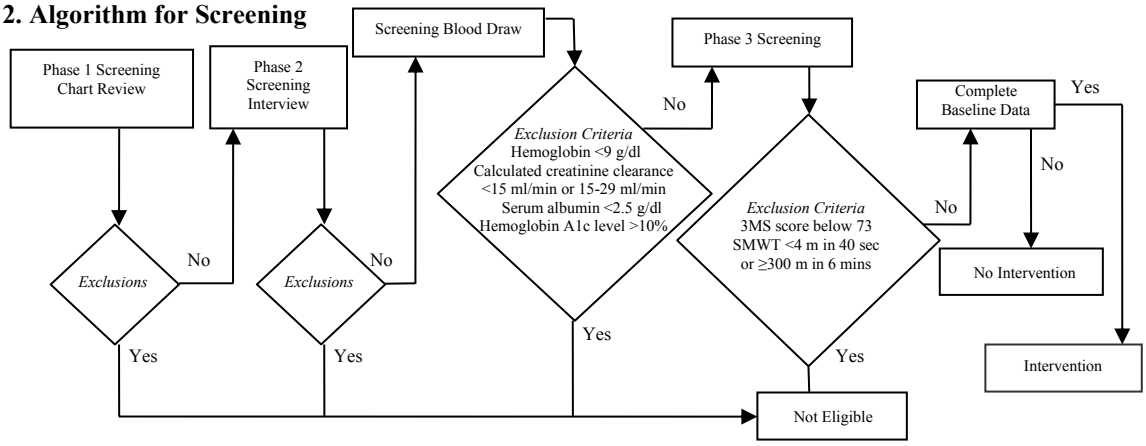
Phase 3 will assess final eligibility at the clinical site center at the beginning of the baseline visit. Phase 3 must be completed no later than 26 weeks after admission to the hospital for hip fracture. Phase 3 will include a review of all disqualifying medical conditions, assessment of cognitive status with the Modified Mini-Mental State examination (3MS), and evaluation of ability to walk 300 meters in six minutes. This final test will be used to exclude participants who are unlikely to benefit from the study interventions because their gait speed is very low (<0.1 m/s) and to exclude those who are able to walk 300 m or more in six minutes and are, therefore, already classified as community ambulators. The study physician must review all study eligibility documents and sign off on final eligibility for all potential participants prior to collection of baseline data. All participants will be seen by the study physician.

Eligible individuals will receive the baseline assessment consisting of questionnaire items, DXA and CT scans, and testing of strength, balance and functional performance.

7.1.1 Required Baseline Data

Certain components of the baseline assessment must be completed by all participants in the pilot study in order to make useful comparisons to data from participants in CAP and CAP-MP and to have enough power to achieve primary and secondary research aims. Participants who perform the required components (identified in Section 10: Study Procedures) no later than 26 weeks after hospital admission for the hip fracture will be said to have complete baseline data and thus be eligible to receive the PUSH Plus Protein intervention.

Figure 2. Algorithm for Screening



7.2 Inclusion Criteria (Target Population)

1. Minimal trauma, non-pathologic hip fracture with surgical repair
   - 1.1 Closed fracture of proximal femur
   - 1.2 Minimal trauma fracture
   - 1.3 Surgical fixation of fracture
   - 1.4 Non-pathologic fracture

2. Age 60 or older
   - 2.1 Age 60 or older at time of baseline testing

3. Community ambulation
   - 3.1 Living in the community at time of fracture
   - 3.2 Ambulating without human assistance two months prior to fracture
   - 3.3 Unable to walk 300 m or more in six minutes without human assistance at time of baseline testing

7.3 Exclusion Criteria

4. Logistical impediments to participation
   - 4.1. Does not live within reasonable distance of the clinical center
   - 4.2. Participant plans to move out of area or otherwise be unavailable during the 16-week intervention period
   - 4.3. Participation in another clinical trial
   - 4.4. Not English speaking
   - 4.5. Baseline testing not completed by 26 weeks post admission for hip fracture
   - 4.6. Final sign off from study physician and/or principal investigator is incomplete
   - 4.7. Incomplete baseline data
   - 4.8. Unable to contact participant
   - 4.9. Participant is unable to provide her/his own informed consent
   - 4.10. Participant refuses the study

5. Medical impediments to participation or low potential for benefit from interventions
   - 5.1. Calculated creatinine clearance < 15 ml/min
   - 5.2. Serum albumin < 2.5 g/dl

5.3. End stage renal disease on dialysis (CKD stage 5 or 6)
5.4. Lower extremity amputation
5.5. Cognitive impairment (3MS score <73)
5.6. Severely diminished lower extremity sensation or ulceration
5.7. Participant walks less than four meters in 40 seconds (<0.1 m/sec)
5.8. Not community-residing (e.g., resident of a skilled nursing facility) at time of baseline testing
5.9. Receiving PT for the hip fracture in the hospital or in an inpatient rehabilitation facility at time of baseline testing

6. Medical contra-indications for exercise
   6.1. Hemoglobin < 9 g/dl
   6.2. Symptoms of angina pectoris
   6.3. Recent myocardial infarction
   6.4. Uncompensated congestive heart failure
   6.5. Chest pain or shortness of breath (including from severe chronic obstructive pulmonary disease)
   6.6. Uncontrolled hypertension
   6.7. Not fully weight-bearing on fractured leg or non-fractured leg at time of baseline testing
   6.8. Study physician thinks participant is not a good candidate for study (e.g., not likely to survive study period)
   6.9. Development of chest pain or substantial shortness of breath or ambulating with severe pain during baseline SMWT

7. Medical contra-indications for whey protein supplement
   7.1. Chronic kidney disease (CKD stage 4)
   7.2. Severe liver disease (e.g., hepatitis, fatty liver disease, cirrhosis)
   7.3. Hemoglobin A1c level > 10%
   7.4. Known dairy allergy
   7.5. Known celiac disease
   7.6. Known history of severe, life-threatening peanut or shellfish allergy
   7.7. Calculated creatinine clearance 15-29 ml/min

7.4 Identification of Hip Fracture Patients

Potential participants will be identified directly from study hospitals, rehabilitation centers, or agencies that care for older adults or they may contact the study directly in response to other recruitment methods such as study recruitment flyers, advertisements, or referral from a clinician (orthopedic surgeon, physical therapist).

Study hospitals will be chosen based on 1) number of hip fracture patients per hospital per year and 2) geographic proximity between hospitals and clinical site. We will review the number of participants recruited in each hospital on a regular basis and initiate enrollment in one or more other hospitals if recruitment numbers are lower than expected. We will obtain approval of our study protocol from the UMB IRB and from each study hospital.

7.5 Informed Consent

Written informed consent and appropriate HIPAA authorizations and/or waivers will be obtained in compliance with procedures reviewed and approved by the UMB IRB and study hospital IRBs prior to any data collection. Informed consent can be obtained anytime upon completion of phase 1 eligibility screening and prior to 26 weeks post hospital admission. Regardless of when

informed consent is obtained, study staff will follow the Good Clinical Practice guidelines for informed consent. A copy of the informed consent form (ICF) will always be provided (either in person or by mail) to potential participants to allow for adequate review of the information and to allow review with family members. Prior to obtaining informed consent, time will be given to the potential participant to review the consent form and ask questions. If a participant has vision impairments that prevent her/him from reading the ICF, the consent form will be read aloud to them and the informed consent process will be witnessed. The witness should also sign and personally date the consent form attesting that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the participant and that informed consent was freely given. Even when the participant reads the consent form on their own, study staff will summarize all components of the ICF and remind potential participants that participation in the study is voluntary and that s/he has the right to withdraw at any time. It will also be explained that signing the consent form allows the study to confirm final eligibility before receiving the intervention. The consent process will be performed without the use of any coercive language or behavior, and with respect for the person's autonomy.

The goal of the informed consent process is to increase potential participants' understanding of the study in order to better enable them to decide whether or not to enroll. Therefore, every effort will be made to help potential participants understand the research project. During the informed consent process, study staff will provide participants with adequate information concerning the study procedures, respond to questions and concerns, and ensure that each individual understands all the information provided by assessing ability to provide informed consent.

Potential participants who choose to enroll will be assessed for their ability to provide informed consent using the Evaluation to Sign Consent measure. Individuals who do not understand the study purpose, methods, risks, and benefits are not able to provide their own informed consent and will not be eligible for participation. The informed consent process will be documented by including the following information in the research records: that the study was explained, questions (if any) were answered, ability to provide informed consent was assessed, subject agreed to participate and signed the consent form and HIPAA Authorization, the presence of a witness for individuals with hearing or vision impairments, and a copy of the signed consent form and HIPAA Authorization was given to participant and, if necessary, left in the chart of facility. For people who provide informed consent, the original signed ICF will be submitted to the study office and a copy of the signed ICF will be given to the participant. If the person provided consent while in a medical facility, a copy of the ICF will go into her/his chart. The PI and/or designee will ensure the accuracy, completeness, legibility, and timeliness of the informed consent process conducted by the study staff before any phase 3 eligibility data are collected.

7.5.1 Enrollment

Date of enrollment in the trial is defined as the date of informed consent.

7.6 Monitoring Recruitment and Retention

Study investigators will monitor recruitment and retention activities throughout the study. We will review the number of patients screened relative to the number of participants recruited through each recruitment source quarterly and initiate additional enrollment strategies if recruitment goals are not being met.

At the completion of baseline testing, participants will receive written instructions about the schedule of follow-up assessments, PT intervention visits, dietician contact, and four-week telephone interviews. To maintain rapport, the same staff member will, whenever possible, contact and visit the participant throughout the study. Minimizing waiting time, providing free transportation for the baseline and follow-up assessment, and providing comfortable waiting room facilities make the visits more pleasant, thereby enhancing participant retention at follow-up. If participants are unable to come to the clinical site for the follow-up assessment, a visit at another location (home or another facility) will be scheduled. Telephone interviews will be scheduled if in-person visits cannot be completed.

Some participants may not actively participate in the study, either by declining the intervention visits and/or by not participating in telephone calls or the follow-up assessment. These participants will be followed until the end of the study unless they explicitly request not to be contacted. Study staff will make contact every four weeks in order to remind the participant that he or she is welcome to rejoin the study at any time. Also, considerable effort will be expended to collect data on the primary outcome at the follow-up assessment.

Section 8: Study Interventions

8.1 Overview

Participants will receive two physical therapy visits a week, on non-consecutive days, for a total of 32 visits and be given a whey-based protein supplement containing 27.6g of protein daily for 16 weeks. Each visit will last approximately 60 minutes. Participants will also receive 2,000 IU of vitamin D3, 600 mg of calcium, and a multivitamin daily during the 16-week study period and counseling with a registered dietician to ensure body weight stability and adequate nutrient intake inclusive of a healthy diet. Missed visits can be replaced during subsequent weeks if there is at least one day in between visits and no more than three visits in the week. Visits will take place in the participant's place of residence.

8.2 Nutritional Support

Given the importance of ensuring adequate nutrition to those who receive the intervention, we will provide all participants with 2000 IU of vitamin D3, 600 mg of calcium, and a multivitamin daily for the duration of the 16-week study and nutritional counseling to ensure weight stability, adequate nutrient intake of 1 g protein/kg body weight inclusive of a healthy diet (50% carbohydrate, 20% protein, 30% fat). Participants will be screened at the time of baseline testing to assess nutritional risk using the Mini Nutritional Assessment-Short Form (MNA®-SF).[117] Those who score ≤7 (malnourished) at baseline and participants with serum albumin 2.5-3.5 g/dl (regardless of the score on MNA®-SF) will receive a visit from a registered dietician (RD) in their place of residence within seven days of baseline testing. The RD will evaluate and counsel them on making dietary modifications based on their protein, caloric and other dietary deficiencies using a standardized approach across the three study sites.[118-120] The RD will follow up with participants by telephone one week after the visit to assess understanding and implementation of recommendations. Participants who score 8-11 (at risk of malnutrition) at baseline and have serum albumin level >3.5 g/dl will receive a telephone dietary consultation with the RD within seven days of baseline testing. Based on the participant's eating habits and food intake, the RD may make the clinical determination that an in-person consultation is warranted. In these cases, the RD will schedule an in-person dietary consultation, following the same protocol as those who score in the malnourished range. Those with a score ≥12 on the MNA®-SF and who have serum albumin level >3.5 g/dl at baseline will receive brief telephone contact within seven days of baseline testing from the RD to discuss the importance of calorie

and protein intake. Weight will be monitored during home PT visits every four weeks and those who lose 2% or more body weight in a four-week period will receive another telephone consultation by the study RD. This protocol applies to anyone who loses 2% or more of body weight, regardless of whether the participant is trying to lose weight. Vitamin D, calcium, and multivitamin adherence will be reviewed by the PT every four weeks (by pill counts) and assessed by self-report every four weeks by telephone interview.

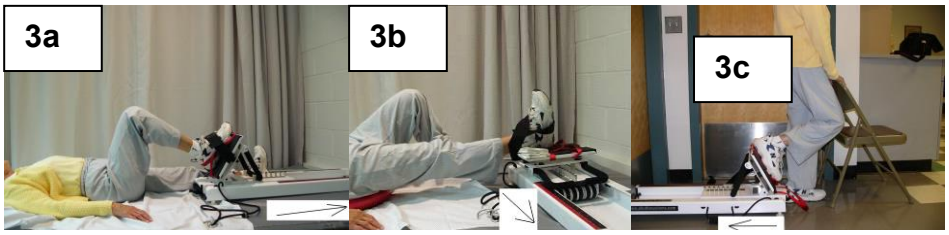
8.3 PUSH Intervention

This intervention is based on improving specific precursors to community ambulation by addressing endurance with continuous upright exercise for 20 minutes in duration; function such as walking, standing from a chair, and stair negotiation; muscle performance by exercising to enhance lower extremity strength and power in functionally relevant muscles moving through locomotion-appropriate movements and ranges; and balance by performing unilateral activities and activities with decreased base of support. These components of exercise will be woven together into one program that minimizes participant burden. By the end of the first eight weeks participants will be instructed to complete the endurance component independently one to two times/week by walking for a similar duration and intensity as they have been doing with the PT during the supervised visits.

The strength components of the muscle performance intervention will be performed using a portable progressive resistive exercise device (Shuttle® MiniPress, Contemporary Design Company, P.O. Box 5089, Glacier, WA 98244). The device has six latex bands each with a starting load equal to approximately seven pounds. At full excursion one band can provide approximately 15 pounds of force. These bands provide the resistance and are attached to the machine by a slotted bar on the frame. Inserting more bands into the slotted bar increases the resistive load for the participant. A progress monitor strip is located on the top of the machine frame. Strips indicate resistance by showing distance that the load is moved. The resistance numbers indicate the force for one band as the carriage is moved. When more than one band is used, the values will be added.[121]

Muscle performance will focus on bilateral hip extensors, hip abductors, knee extensors, and plantar flexors because of their role in function, specifically gait and transfer activities.[122-124] Hip and knee extensor muscle will be trained to work hard and fast during the leg press motion since this mimics the functional activity of rising from a chair or going up a step. Hip abductors will be trained in 5° of adduction and to 10-15° of abduction. Fifteen degrees of movement was chosen because it approximates the 8° of motion associated with gait and takes into account variations in hip positions while standing.[125] Hip extension will also be trained in standing from 35° of flexion to extension to a neutral position. This ROM approximates the time in the gait cycle when the gluteus maximus shows the highest muscle activity, i.e., from heel contact through 20% of stride.[123] Plantar flexors will be strengthened in standing against body weight[68] because of their role in the push-off phase of gait and the strong association of plantar flexion power and walking speed.[68,122-126] The intensity of strength training will be determined during Day 1 of intervention at the participant's residence. The PT will determine the amount of resistance the participant can push against so that s/he can complete a maximum of eight repetitions (eight repetitions maximum (RM) or 8-RM). 8-RM was chosen because it is strongly related to the 1-RM[127] and determining the 8-RM will allow the PT to know the training intensity without further sub-calculations (e.g. 80% of the 1-RM). Studies have shown that the 8-RM is more effective than training at 10-RM or 2-RM[79] yet is not so aggressive that it is associated with injuries.[128,129] This protocol has been used safely and effectively in elders[12,64,65,68,124,130] and specifically in persons post-hip fracture.[20,63] For the first visit, participants will be tested to find the load associated with an intensity of 8-RM. During the second session, participants will

Figure 3. Shuttle Device (arrows indicate direction of lower extremity motion)



perform 2 sets of 8 repetitions at the 8-RM intensity. From the third session through the remainder of the program, participants will perform 3 sets of 8 repetitions at an intensity of the 8-RM. The PT will provide strong verbal encouragement during each repetition for the participant to move as "fast and as hard as possible" during the concentric phase and to move slowly and in a controlled way in the eccentric phase. Intensity will be reviewed every two weeks.

The participants will be supine for two exercises: the combination of hip and knee extension exercise (leg press) and the hip abduction exercise (Figure 3a & 3b). The device will be placed on the bed or floor (if the participant is able to be assisted safely to and from the floor) so that the participant's foot will rest on the footplate and the hip will be flexed to 90°. The participant will push the leg out into full hip and knee extension against the pre-determined resistance. For the hip abductors, the participant will start in 5° of adduction and move 15° into abduction. The participant's foot will be strapped to the footplate as the participant moves the leg outward.

Balance and strength will be addressed with two additional exercises performed in standing. Balance will be addressed by asking the participant to perform one-legged activities or to stand upright with a decreased base of support. The first exercise that combines balance training and strength training will be standing hip extension (Figure 3c). The leg will be flexed approximately 35° of flexion and the participant will extend to neutral position. Upright balance will be challenged as the participant moves the carriage of the exercise device with one leg as the other leg maintains stability.

The second exercise that combines balance and strength training will be standing plantar flexion. Initially, participants will be asked to decrease their standing base of support by rising onto the balls of feet. This exercise also strengthens the plantar flexors. Balance and strength will be progressively challenged by advancing the activity to unilateral heel raises. For hip extension and plantar flexion, the person may hold lightly onto an assistive device for balance or support. The PT will encourage the participant to use less external support for balance during each session. Resistance (load in pounds) and repetitions for each exercise performed will be recorded in a training log.[20]

HR will be measured by palpation of the radial artery recorded every five minutes and it will be averaged over 20 minutes of continuous exercise. The PT will calculate the HR training zone based on the heart rate reserve (HRR) method (HR max-HR rest) multiplied by 50% and then added to HR rest. HR max will be calculated as 220 minus the participant's age. This prescription is consistent with moderate intensity exercise and has been shown to increase aerobic capacity in elders.[131-133] If the person is taking medication that controls heart rate (e.g., beta-blockers), Borg's Rating of Perceived Exertion (RPE) scale will be used.[134] The training intensity using the RPE scale will be "moderate" work as consistent with a 3-5 on the 0-10 scale.

The endurance intervention will begin initially with two to three minutes of continuous upper and lower extremity AROM with the participant sitting. These exercises are intended to increase the participants' HR or exertion closer to the target zone. The participant will then be asked to walk on level surfaces and up and down one or more steps, if able and available, to keep the HR

within the training zone for 20 minutes. The PT can also engage the participant in additional exercises such as upper and lower extremity AROM exercises to keep the HR elevated. The target HR will be 30% of HRR in the first week of the program, 40% of HRR in the second week, and 50% of HRR in weeks 3 through 16.

8.4 Protein Supplement

Participants will receive a whey-based protein supplement containing 27.6g of protein. This dose induces maximum muscle protein synthesis post-exercise.[130] Participants will mix the supplement in 8 oz of water (or other beverage) or soft food (e.g., yogurt, soup) and consume immediately following each exercise session with the study PT. On days when they do not have a physical therapy visit with the study PT, participants will be instructed to take the supplement at the meal time closest to the time of scheduled PT visits to maintain regular daily dosing schedule.

8.5 Treatment Fidelity Plan

Treatment fidelity[135,136] will be evaluated with regard to: (1) design, which focuses on whether the intervention (PUSH plus protein) is consistent with underlying theories, and whether the study is free of contamination such as unintended motivational interventions; (2) training, which addresses skill acquisition and maintenance in PTs; (3) delivery, or the assessment that the intervention was implemented as intended; (4) receipt, which focuses on whether or not the participant understood and received the intervention as intended. Overall, treatment fidelity data will provide information on the adherence of the PTs to the intervention, and the adherence of the participants to the prescribed activities. Monitoring treatment fidelity also will provide an opportunity to address potential study problems, such as drift from the intervention protocol which could threaten the study's ability to detect treatment effects.

8.5.1 Initial Training for Procedural Reliability

The Intervention Monitor (IM) will train PTs in PUSH intervention procedures. Knowledge of procedures will be tested by written examination and by psychomotor skills observation via video. The IM will document that PTs are "certified" and provide a certificate of completion after they demonstrate competence on the written exam and video observation. PTs also need to bring evidence to the training session that they are currently CPR certified. As new PTs join the study, training will be conducted on an individualized basis following the same procedures.

8.5.2 Ensuring Ongoing Competency

We will use a multi-faceted approach to ensure ongoing treatment fidelity. The approaches include direct observation of skills by the IM, mandatory monthly telephone calls with all active PTs, periodic review of PT log books, and access to online discussion boards.

Direct Observation: Direct observations of PTs as they perform the intervention will be conducted by the IM. The IM will document observations using a structured checklist that addresses data completeness, physical performance, qualitative observations, and verbal and non-verbal communication. The checklist will also document whether the participant completed the necessary repetitions at the appropriate intensity and whether the participant completed 20 minutes of aerobic exercise at the proper intensity. There will be two observation visits during the PT's first assigned participant's 16-week intervention period and then one observation per quarter for PTs who have conducted a complete 16-week intervention period for at least one participant. If the total score on the checklist is less than 90%, the PI will be notified. A remediation plan will be proposed that will offer refresher training to ensure accurate understanding of the protocol, follow-up observation visits, and possible dismissal if warranted.

Mandatory Conference Calls with PTs: The IM will conduct monthly telephone calls with the PTs who are currently active with participants and take minutes of the telephone meetings to document ongoing training. During these calls, the IM will ask questions to identify problems with delivering the intervention. If problems are identified, the IM will schedule an individual telephone call and review of PT log books. Additional follow-up will be mandated if there are modifications to the exercise prescription that are due to PT factors. A remediation plan will be followed if there is ongoing lack of progress.

Periodic Review of Intervention Logs: The IM will review PT intervention logs on a regular basis to confirm that PTs are completing logs correctly and identify whether there are modifications to the intervention protocols. This information will be discussed during the monthly phone calls.

8.6 Scheduling Intervention Visits

There are three requirements for scheduling of intervention visits:

1. The first intervention visit should occur on Day 7 or earlier, where the last day of baseline testing = Day 0.
2. The schedule of intervention visits is anchored to the date on which baseline testing is completed regardless of when the intervention starts.
3. Intervention visits should never occur on two consecutive days, even when moving from one week to the next.

Participants who provide required baseline data are eligible to receive the intervention; however, the intervention will not begin until after the date all baseline measures are completed. Baseline data collection must be completed within 14 days of the SMWT. Week 1 will begin on the day of the first intervention visit or on Day 7 after baseline testing is complete, whichever is earlier. Subsequent weeks will start on the same day of the week as Week 1. For example, if the participant's first intervention visit is on a Wednesday, each intervention week for that participant will extend from Wednesday to Tuesday (inclusively). Alternatively, if the first visit has not yet occurred by Day 7 and Day 7 is a Monday, then the participant's intervention weeks will extend from Monday to Sunday (inclusively).

In certain circumstances (e.g., illness, travel), the first intervention visit may be scheduled after Day 7.

Ideally participants will receive 2 visits per week for 16 weeks after complete baseline testing (32 visits total). However, missed visits in a given week can be replaced by makeup visits in subsequent weeks (not to exceed 3 visits in any given week) as long as the visits are on non-consecutive days. If the participant has not had 32 visits by the end of 16 weeks, makeup visits can be performed during the subsequent two weeks to get as close as possible to the target of 32 visits.

Section 9: Study Measures

A list of study measures is provided below. All of the measures will be interview-based or based on observations of performance or physiological assessments. No proxy data will be allowed at baseline. However, at the 16-week follow-up visit, a proxy may be contacted to provide information about the participant's walking ability. Also, the four-week phone calls to obtain information on recent health events will be conducted with a proxy when the participant is not available

9.1 Screening Evaluations

There will be three primary components to the screening process: the chart review in the acute care setting (phase 1), the phase 2 screen, and screening for final eligibility (phase 3) that includes the 3MS and the SMWT. These components will be typically administered over three contacts. Those who qualify after phases 1 and 2 will be invited for the first study visit for phase 3 screening.

9.1.1 Modified Mini-Mental State Examination (3MS)

The 3MS is a test of global cognitive function which assesses a broad variety of cognitive dimensions and is an expanded 100 point version of the original Folstein Mini-Mental State Exam.[137,138] The 3MS will be used at the baseline visit to identify and exclude participants with cognitive impairment (3MS score <73).[139]

9.2 Primary Outcome Measure: Community Ambulation

The Six-Minute Walk Test (SMWT) will be used to obtain a continuous measure of total distance walked in six minutes. The SMWT is highly correlated with workloads, heart rate, oxygen saturation, and dyspnea responses when compared to bicycle ergometry and treadmill exercise tests in older persons. It has been performed by elderly, frail and severely compromised participants who cannot perform standard maximal treadmill or cycle ergometry exercise tests. Performance of the SMWT at the baseline assessment also will be used to define final eligibility prior to the collection of additional baseline data. Participants who walk less than four meters in 40 seconds (<0.1 m/sec) or who walk 300 meters or more in six minutes will be excluded from the trial. Participants with angina, extreme shortness of breath, or ambulating with severe pain during the SMWT also will be excluded.

Participants will be asked to walk back and forth on a measured path marked clearly at both ends for turning purposes, while being told when each minute has passed, and receiving verbal encouragement ("you're doing well" or "keep up the good work") every 60 seconds. Test-retest reliability in older adults is excellent (r = .95).[112] Concurrent validity with $V0_2$ peak (r=.64) and cycle ergometry (r=.58) have been reported.[110,140,141]

9.3 Secondary Outcome Measures

9.3.1 Cognitive Function (3MS)

The Mini Mental Status Exam (MMSE) is one of the most widely used screening instruments for dementia. The Modified Mini-Mental State (3MS) test was developed to overcome shortcomings of the MMSE, specifically its narrow range of possible scores and ceiling effects. The 3MS incorporates four additional items (on long-term memory, abstract thinking, category fluency, delayed recall), more uniform administration, and refined scoring, in order to sample a broader variety of cognitive functions, cover a wider range of difficulty levels, and enhance the reliability and validity of the test scores. The 3MS test has a score range of 1-100. It can provide an estimated score of the MMSE, and can also be used to monitor cognitive change over time.

9.3.2 Short Physical Performance Battery (SPPB)

The SPPB evaluates lower extremity performance in older persons based on timed short distance walk, repeated chair stands, and a set of balance tests.[142-144] Each of the tasks is assigned a score ranging from 0 to 4, with 4 indicating the highest level of performance and 0 an inability to complete the test. The test takes about 10-15 minutes to administer and was designed to be administered by a lay interviewer in a setting with limited space. The battery has

an excellent safety record. It has been administered to well over 10,000 persons in various studies and no serious injuries are known to have occurred. The SPPB components and total score are derived from normative values obtained from a population-based study.[142,144] The total score ranges from 0 to 12; there are three subscales embedded in the SPPB.

Standing balance. For the test of standing balance, participants are asked to maintain balance in three positions, characterized by a progressive narrowing of the base support: with feet together (side-by-side position), the heel of one foot beside the big toe of the other foot (semi-tandem position), and the heel of one foot in front of and touching the toes of the other foot (tandem position). For each of the three positions, participants are timed to a maximum of 10 seconds.

We will use an enhanced balance measure that includes the balance subscale of the Short Physical Performance Battery (SPPB) and two additional single leg stands (eyes open and eyes closed), as used in the National Health and Aging Trends Study (NHATS).[160] For the test of standing balance, participants are asked to maintain balance in three positions, characterized by a progressive narrowing of the base support: with feet together (side-by-side position), the heel of one foot beside the big toe of the other foot (semi-tandem position), and the heel of one foot in front of and touching the toes of the other foot (tandem position). For each of the three positions, participants are timed to a maximum of 10 seconds. Participants are then asked to stand on one leg (on the side of the fracture) with eyes open and again with eyes closed. Each of the single leg stands are held for up to 30 seconds. The number of seconds is then summed across the 5 items to obtain the measure of balance. These tests are hierarchical such that when a participant fails an item, the harder ones are not administered and receive a score of 0.

Walking speed. Walking speed is assessed by asking participants to walk at their usual pace over a 4 m course. Participants are instructed to stand with both feet touching the starting line and to start walking after a specific verbal command. Participants are allowed to use walking aids (cane, walker, or other walking aid) if necessary, but not the assistance of another person. Timing begins as soon as the participant starts to walk and the time in seconds needed to complete the entire distance is recorded. The faster of two walks is used to compute walking speed.

Chair stands. The repeated chair stands test is performed using a straight-backed chair, which is placed with its back against a wall. Participants are first asked to stand once from a sitting position with their arms folded across their chest. If they are able to perform the task, they are then asked to stand up and sit down five times, as quickly as possible. The time to complete the task is recorded.

9.3.3 Activities of Daily Living (ADLs)

We will measure ADLs using the Pepper Assessment Tool for Disability (PAT-D)[145,146] with two modifications. First, two items (walking a quarter mile and walking across a small room) were added to address perceived gaps in the original PAT-D scale. This modification is consistent with the version used in the Lifestyle Interventions and Independence for Elders study.[147] Second, two items (walking several blocks and lifting heavy objects) were deleted to avoid duplication with other items in the scale. The resulting 19-item scale allows examination of three subscales (basic ADL, functional limitations, and instrumental ADL).

9.3.4 Quality of Life (SF-36)

We will use an interviewer-administered version of the SF-36, a health survey that assesses quality of life in eight subscales (physical function, social function, role-physical, role-emotional, bodily pain, mental health, general health, and vitality).[148] The measure has been validated as a generic measure of quality of life in many different populations, including patient and non-patient samples.[148 61,149,150]

9.3.5 Nutritional Status

Nutritional status will be assessed using the Mini Nutritional Assessment-Short Form (MNA®-SF),[117,151] a validated and widely used malnutrition screening tool.[151-154] We are using a modified version of the MNA®, approved by the scale's developer (the Nestlé company), to facilitate use as an interviewer-administered tool in a research setting. Scores range from 0 to 14; participants scoring ≤7 will be considered malnourished; those scoring 8-11 will be considered to be at risk of malnutrition; and those scoring 12-14 will be considered to have normal nutritional status.[117,151]

9.3.6 Muscle and Fat Mass

Lean mass will be estimated using dual-energy x-ray absorptiometry (DXA) (GE LUNAR, Madison, WI). DXA calculates fat and lean tissue mass from the total body scan. The coefficient of variation of these measurements in our previous studies for fat and lean mass was 1.4% and 1.3%, respectively.

9.3.7 Muscle Composition: Intramuscular fat and muscle volume

Thigh CT will be performed every 4 cm starting at the patella and ending at the femoral head (Siemens Somatom Sensation 64 Scanner) to quantify skeletal muscle area, total fat area, low density lean tissue area, and muscle attenuation of the thigh. Scans will be analyzed using MIPAV (Medical Image Processing, Analysis and Visualization, v.7.0, NIH). The cross-sectional area of each axial slice will be multiplied by the distance between slices (4 cm) and summed across slices representing volume expressed in cm3. The average attenuation of muscle tissue and the percentage of low-density lean muscle to total muscle volume is associated with skeletal muscle lipid content, and a measure of muscle quality.

9.3.8 Strength

A Biodex System 3 PRO dynamometer will measure concentric isokinetic peak normalized joint torque over the entire range of motion (strength) for bilateral ankle plantarflexion-dorsiflexion and knee flexion-extension. Strength is measured in Newton-meters (Nm). Testing will utilize standardized positioning and joint motion excursions. Subjects will perform two blocks of three repetitions with a rest period between blocks.

9.3.9 Power

A Biodex System 3 PRO dynamometer will measure strength per unit of time (power) for bilateral ankle plantarflexion-dorsiflexion and knee flexion-extension. Power is measured in Watts (W). Testing will utilize standardized positioning and joint motion excursions. Subjects will perform two blocks of three repetitions with a rest period between blocks.

9.3.10 Bone Mineral Density

BMD will be estimated using DXA as described above. DXA of the contralateral (non-fractured) femur will be measured to yield measures of total hip and femoral neck BMD.

9.3.11 Gait and Balance (GAITrite)

A GAITrite instrumented walkway system will measure spatial and temporal gait parameters. Subjects will walk at their safest fast and natural speeds. In addition, the Dynamic Gait Index, a clinical assessment of balance and mobility while walking, will be administered. Measures will include: step length, walking speed, single and double leg support time, and cadence.

9.3.12 Bone Turnover Markers

Bone turnover markers. a) bone formation (serum aminoterminal propeptide of type 1 procollagen; P1NP) and b) bone resorption (serum cross-linked C-telopeptides of type I collagen; CTx-I) will be assessed.

9.3.13 Hormones

Parathyroid hormone, intact (iPTH) will be measured by ELISA.

9.3.14 Inflammatory Cytokines

a) interleukin-6 (IL-6), b) soluble TNF- α receptor 1 (sTNF- αR1), c) IL-1 receptor antagonist (IL-1ra), and d) interleukin-10 (IL-10). All cytokines will be measured in serum by ELISA (R&D Systems Inc., Minneapolis, MN).

9.3.15 Cognitive Function (Trail Making Test (Trails A and B))

The Trail Making Test is a neuropsychological test of visual attention and task switching. It consists of two parts in which the subject is instructed to connect a set of 25 dots as quickly as possible while still maintaining accuracy. The test can provide information about visual search speed, scanning, speed of processing, mental flexibility, as well as executive functioning. It is sensitive to detecting cognitive impairment associated with dementia.

9.3.16 Waist Circumference

Waist circumference (cm) reflects adipose tissue distribution and is believed to be influenced by glucocorticoid activity. Waist measurement will be taken by measuring tape of the waist circumference (narrowest section between the ribs and iliac crest). Waist circumference will be measured in centimeters.

9.4 Improvement in Walking

Whether or not there was an increase of at least 50 meters in the distance walked on the SMWT will be assessed as a tertiary outcome. This distance has been shown to be clinically meaningful.[142,160]

9.5 Clinical and Background Characteristics

Information on a small number of other patient characteristics will be collected to allow description of the study population, to allow analyses of differential effects in subgroups (i.e., effect modification), and to help in the interpretation of results.

9.5.1 Demographic and Surgical Characteristics

For descriptive purposes, information on the following participant characteristics will be collected either during screening or at the baseline assessment: age, gender, race, living situation, marital status, educational level, fracture type, and surgery type.

9.5.2 Functional Comorbidity Index

The Functional Comorbidity Index (FCI) is a clinically based measure developed by Groll *et al.* This index includes a checklist of 18 comorbid conditions scored 1 or 0. A maximum score of 18

indicates the highest number of comorbid illnesses. The FCI was specifically developed to predict physical functioning.[161]

9.5.3 Weight, Height, and BMI

Height (in feet and inches) will be measured once at the baseline visit using a standard stadiometer. Weight (in pounds) will be measured using a digital scale at baseline and follow-up visit. Measured height and weight will be used to calculate BMI.

9.6 Other Measures to be Monitored

9.6.1 Adherence

Adherence with PUSH intervention. PTs will submit a visit form for each of the 32 visits that records date of visit; start and end time of the visit; reason for missed visit; what activities were performed; and whether activities were performed as prescribed. We will also obtain information about the intensity of each activity at initiation of the intervention and every four weeks during the intervention period. Logs completed by PTs will record the detail of each designated activity during intervention sessions as well as any precautions or modifications to activities. Reasons for protocol variations will be noted in the PT log books.

Adherence with protein supplement. We will monitor adherence to the protein supplement by weighing the container(s) of protein powder every 4 weeks during the 16-week intervention period and by self-report during the 4-week telephone calls.

Adherence with study vitamins/supplements. Vitamin D, calcium, and multivitamin adherence will be monitored by pill counts every four weeks during the intervention period and by self-report during the 4-week telephone calls for the entire16-week study period.

9.6.2 Weight Loss

Weight will be monitored by the PTs every four weeks during the 16-week intervention period using a standard digital scale.

9.6.3 Reportable Adverse Events (RAEs)

Reportable adverse events (RAEs), which include serious adverse events (SAEs), unexpected AEs or injury that occurs under supervision by study staff, will also be obtained during the study. Participants will be screened for possible RAEs every four weeks during the telephone interviews using standardized questions. Participants (or their proxies) will be asked about life-threatening or significant medical events and the outcomes of these events. RAEs will also be asked about by study staff prior to each PT visit and clinical site follow-up assessment. RAEs may be spontaneously reported to any study staff member throughout the study (see section 12.4.1).

9.6.4 Expected Adverse Events (AEs)

Expected AEs will be assessed every four weeks during the telephone interview. Participants (or their proxies) will be asked a series of standardized questions related to pain (feet, hip, back, knees, digestive and stomach); breathing problems or chest pain; bloating or puffiness in legs, ankles, or feet; drowsiness, dizziness, or confusion; shakiness, anxiety, clammy skin, or irritability; and falls (with and without injury).

Section 10: Study Procedures

10.1 Baseline Assessments

The baseline assessments will be performed immediately following screening for phase 3 criteria.

Certain components of the baseline assessment are required by all participants in the pilot study in order to make useful comparisons to data from participants in CAP and CAP-MP and to have enough power to achieve primary and secondary research aims. Other assessments at the baseline visit will allow comparisons for other outcome measures. Participants who perform the required components (marked with a pound sign (#) in the list below) will be eligible to receive the PUSH Plus Protein intervention. All baseline data collection must be completed within 14 days of the SMWT.

The items with an asterisk (*) are collected as part of phase 3 screening:

- Baseline Anthropometry #
- Demographics and Blood Draw Information # *
- Modified Mini-Mental State Examination # *
- Six-Minute Walk Test # *
- Baseline Interview #
- Short Physical Performance Battery #
- SF-36 Health Survey #
- Pepper Assessment Tool for Disability #
- Mini Nutritional Assessment-Short Form #
- Trail Making Test (Trails A and B)
- Blood draw (for serologic and genetic tests)
- Reportable Adverse Events
- CT scan of thigh #
- DXA scan of whole body #
- DXA scan of hip
- GAITrite
- Four-Square Step Test
- Biodex strength testing (knee flexion/extension)

10.2 Follow-up Assessment

The following measures will be obtained at 16 weeks after baseline testing.

- Reportable Adverse Events
- Six-Minute Walk Test
- Modified Mini-Mental State Examination
- Short Physical Performance Battery
- SF-36 Health Survey
- Weight and waist circumference
- Pepper Assessment Tool for Disability
- Mini Nutritional Assessment-Short Form
- Trail Making Test (Trails A and B)
- Blood draw (for serologic and genetic tests)
- CT scan of thigh
- DXA scans of hip and whole body
- GAITrite

- Four-Square Step Test
- Biodex strength testing (knee flexion/extension)

10.3 Telephone Interviews

Structured telephone interviews will be conducted every four weeks for 16 weeks starting four weeks after the last date of baseline testing. The following measures will be administered:

- Reportable Adverse Events (RAE) Form
- Expected Adverse Events (AE) Form
- Self-reported adherence to protein and supplements

10.4 Timing of Study Procedures

The target date for completion of the pre-baseline testing (i.e., screening) assessments will be anchored to the date of admission to the hospital for hip fracture. The target date for completion of all other assessments will be anchored to the date on which all baseline testing is completed (see Table 1).

Note: In cases where the participant performs all required baseline measures and then performs additional baseline measures, the date on which baseline testing is completed is defined as the date on which the participant performed the last assessment within the allowable window for baseline testing (up to 26 week post hospital admission). In cases where additional baseline measures have been scheduled but cannot be completed within the allowable window for baseline testing, (e.g., scheduling conflict, not safe), the date on which baseline testing completed is defined as the date on which staff establishes definitively that no additional baseline measures can or will be attempted.

Table 1. Timing of Study Procedures

PROCEDURE	TARGET DATE	ALLOWABLE INTERVAL
Phase 3 screening	As early as possible following admission	Up to 26 weeks post-admission
Baseline assessment	As early as possible following admission	Up to 26 weeks post-admission
Dietitian consult	1 week after baseline testing is completed	+1 week
First intervention visit	1 week after baseline testing is completed	+16 weeks
First telephone interview	4 weeks after baseline testing is completed	-1 week, +3 weeks
Subsequent telephone interviews	At 4-week intervals from date on which baseline testing is completed	-1 week, +3 weeks
First follow-up assessment	16 weeks after baseline testing is completed	+2 weeks
Out-of-window assessment	16 weeks after baseline testing is completed	0-16 weeks and 18-38 weeks after baseline testing is completed

At baseline, all participants will, by design, be tested at the clinical site. At the follow-up visit, we will attempt to test all participants at the clinical site. When this is not possible, we will attempt to have study staff administer the test in a non-study clinical facility or, failing that, at another non-study location or the participant's home.

Section 11: Safety Assessments

11.1 Participant Safety Parameters: Methods and Timing

11.1.1 Pre-Intervention Safety Screening

Potential participants will be excluded during the screening phases if they have cardiovascular diseases or other conditions that would make it unsafe for them to participate in one or both of the study interventions. Information about these conditions will be obtained through chart review, interviews, and consultation with a medical professional familiar with the potential participant (e.g., primary care provider, orthopaedic surgeon). The study physician and PI will be responsible for giving permission for potential participants to receive the intervention, based on thorough review of all eligibility information. In addition, persons who develop chest pain or substantial shortness of breath during the SMWT will be excluded using a protocol to evaluate cardiovascular reserve similar to the one suggested by Gill et al.[162]

11.1.2 Safety Considerations for Study Assessments

All study assessments will be done by certified staff who will be trained to perform the tests safely. If, during the SMWT or the SPPB a participant reports chest pain, tightness or pressure, significant shortness of breath or difficulty breathing, or feeling faint, lightheaded, or dizzy, the test will be stopped. If the participant weighs more than 400 pounds or if s/he is unable to lie supine, the whole body and hip DXA scans will not be done. Participants with prior hardware in the non-fractured hip will not have a hip DXA scan. If a participant is unable to lie supine or be left alone in a room, the thigh CT scan will not be done. Participants unable to put full weight on the fractured side or unable to stand for 30 seconds without an assistive device will not perform the GAITrite or Biodex measures. All research staff who come in contact with study participants will be CPR certified and will be trained to provide immediate care when faced with medical emergencies. Also, institutional and community emergency medical services will be activated if needed.

Table 2 describes a summary of safety alerts and the appropriate action during clinical assessments.

Table 2. Safety Alerts and Actions for Study Assessments

ALERT	ACTION
Resting blood pressure SBP > 145mm Hg or DBP > 90mm Hg	Qualified staff will inform the participant if noted on more than one occasion.
Resting blood pressure SBP > 170mm Hg or SBP < 90mm Hg or DBP > 100mm Hg or DBP < 50mm Hg	Qualified staff will encourage the participant to seek additional follow-up and/or medical evaluation. Physical performance testing will be deferred until consultation with the study physician.
Resting blood pressure or after SMWT SBP > 185mm Hg or SBP < 90mm Hg or DBP > 110mm Hg or DBP < 50mm Hg	Qualified staff will consult with the study physician and follow up as needed.
Resting pulse Rate > 120 or < 40 beats/min	Qualified staff will consult with the study physician and follow up as needed.

Table 2. Safety Alerts and Actions for Study Assessments

Chest pain, dizziness, significant shortness of breath, or severe musculoskeletal pain during the intervention or study assessment.	Qualified staff will consult with the study physician and follow up as needed.
MNA®-SF Score ≤ 7 at the follow-up assessment	Qualified staff will talk to the participant and provide a referral for additional follow-up and/or medical evaluation for possible malnutrition.
Weight loss ≥ 2% body weight in four weeks during intervention period	Participant will be referred to the registered dietician for follow-up by telephone.
Participant expresses desire to commit suicide	Call primary care provider and report findings. Report to study coordinator/study physician for follow-up and clearance.

11.1.3 Safety Considerations for the PUSH Intervention

There is no expectation that the PUSH intervention will evoke serious cardiovascular responses; however, participants will be warned of a possible risk. Cardiac events are rare, with estimates of one event per 60,000 participant-hours in aerobic exercise programs.[163] No significant cardiac events were reported after performing 1-RM testing for over 6600 healthy subjects.[164] The American Heart Association's guidelines for resistance training for adults with and without cardiovascular disease reports the safety of high intensity resistance training and testing in persons with coronary disease which found an absence of anginal symptoms, ischemic ST-segment depression, abnormal hemodynamics, complex ventricular dysrhythmias, and cardiovascular complications.[165,166] Less serious risks may include chest pain, fainting, hypotension, or muscle strain. We have minimized risk to participants by following the guidelines suggested by Gill et al.[162] Blood pressure and heart rate will be monitored using a standard blood pressure cuff and palpation of peripheral pulse.

Another concern is the presence of osteoporosis and the risk of inducing a compression fracture or a lower extremity fracture. The exercises have been designed to minimize this risk. The risk of inducing a compression fracture will be minimized because the exercises are performed in supine and upright standing positions with minimal to no trunk flexion.[167] The PT will also remind the participant to minimize flexion to the spine during all standing exercises. Using an exercise device that eliminates the risk of weights falling on a person, and using only voluntary muscle contractions during isometric testing, will reduce the risk of lower extremity fracture. We do not anticipate additional risk for the PUSH intervention for the following reasons: 1) by 12 weeks post-fracture, there is moderate stability from the bone callus formation, 2) participants will only be included if they have medical clearance to participate in full weight bearing activities, and 3) the device limit is 100 pounds (which in most cases is less than body weight) resulting in less load than walking up and down stairs. 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. If a participant reports continued discomfort, the study physician will discuss this with the participant and contact their primary care provider (PCP) as necessary. Please see Table 3 below for a summary of alerts and appropriate action during the PT intervention visits.

11.1.4 Safety Measures during the PUSH Intervention

The PUSH intervention will be conducted in the participant's place of residence and all sessions will be conducted and supervised by trained PTs, who monitor potential adverse experiences and symptoms. PTs will be trained to deal with medical emergencies that occur during the PUSH sessions and will be CPR certified. Also, community EMS services will be activated if needed.

In order to minimize discomfort and maximize safety, participants will be taught the proper method for performing each exercise and the importance of following the proper method. Intensity is gradually increased, and exercise technique is commented on during each session. Participants will be instructed to talk with the PTs about any muscle soreness, pain or discomfort.

Every effort will be made to prevent harm by stopping intervention activity when the participant reports chest pain, dizziness, significant shortness of breath, or severe musculoskeletal pain. PTs will 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 170/100, the participant will rest quietly for a few minutes. The PT will monitor the participant for signs of muscle strain, dizziness, or hypotension and appropriate palliative methods will be discussed with the participants and appropriate medical referrals will be made. Please see Table 3 for a summary of alerts and appropriate action during the PT intervention visits.

11.1.5 Safety Considerations for the Protein Intervention

Although the protein supplement used in this study is virtually lactose (sugar) free, small amounts of lactose may trigger digestive upset (abdominal pain, gas, and diarrhea) for participants who suffer from lactose intolerance. Although this product may not contain one or all of the following, this product is manufactured in a facility that handles milk, soy, egg, peanut, nut, tree, fish, crustaceans/shellfish, and wheat products. Those who have celiac disease or who have a known allergy to dairy, peanuts, or shellfish are excluded from participation. Whey provides no fiber to the diet, and excessive consumption may lead participants to experience constipation unless they consume high-fiber foods in addition to whey. There is an extremely low risk of renal (kidney) or liver damage related to whey protein supplementation. Those with a history of severe liver disease (e.g., hepatitis, fatty liver disease, cirrhosis), chronic kidney disease (CKD stage 4), or a calculated creatinine clearance 15-29 ml/min are excluded from participation. There is an extremely low risk that participants with poorly controlled type 2 diabetes could experience hypoglycemia (low blood sugar). Those with hemoglobin A1c level greater than 10% are excluded from participation. Please see Table 3 for a summary of alerts and appropriate action for the protein intervention.

Table 3. Safety Alerts and Actions for Interventions

ALERT	ACTION
Resting blood pressure SBP > 170mm Hg or SBP < 90mm Hg or DBP > 100mm Hg or DBP < 50mm Hg	1. If initial BP check is high (systolic > 170; diastolic >100), have participant sit for 5 minutes and rest then check BP again. This may be done twice. 2. If three BP readings are greater than 170/100, then individual should not exercise. 3. The PCP, study coordinator, and study physician should be called before exercise is initiated. 4. If initial BP is low for that person (systolic<90; diastolic<50) follow same protocol.
New chest pain Reported chest pain that occurred between visits	Call 911. 1. Cancel treatment and call PCP. 2. Report to study coordinator and study physician to follow-up until cleared.
Acute shortness of breath	1. Have participant stop exercising and rest. 2. Take vital signs. 3. If the shortness of breath does not resolve itself in 10 minutes, and vital signs are not within normal limits for participant, call 911. 4. Report to PCP, study coordinator, and study physician.
Fall	1. If there is bleeding/wound, apply pressure using emergency kit for wound; call 911 if needed. If participant is unable to stand or move the injured part, call 911 and keep them warm and comfortable. 2. Report all falls to study coordinator. 3. Complete an incident report.
Stroke symptoms	Call 911 immediately.
Dizziness during exercise	1. Stop exercise and have person sit or lie down. 2. If sitting is not sufficient to resolve dizziness, then check vital signs. 3. Call 911 if clinically unstable. 4. Report to PCP if heart rate is less than 60 (and not usually so), the dizziness is new in onset; or if the BP is > 160/100 or systolic <90. 5. Report event to study coordinator and study physician.

ALERT	ACTION
Resting pulse Rate > 120 or < 40 beats/min	1. PT will stop delivery of the intervention. 2. Qualified staff will consult with the study physician and follow up as needed. 3. PT will resume delivery of the intervention only after the participant receives medical clearance.
New irregular heart rate with complaint of heart palpitations	1. Do not exercise and call PCP. 2. Report to study coordinator and study physician for follow-up. 3. Wait for medical clearance to resume exercise.
New acute musculoskeletal pain during exercise (pain > 5 on VAS)	1. Have the participant stop the exercise and rest. 2. Attempt to alter position of participant to reduce pain. If pain persists, do not continue specific exercise. Attempt to do other exercises. 3. If pain does not resolve, refer to PCP or orthopedist and study physician.
New, acute, non-musculoskeletal pain (pain > 5 on VAS)	1. Do not exercise. 2. Take pain history and call PCP. 3. Report to study coordinator and study physician for follow-up and clearance.
Acute change in mental status	1. Do not exercise. 2. Call PCP or if unavailable, call 911. 3. Report to study coordinator and study physician for follow-up and clearance.
Participant expresses desire to commit suicide	1. Call PCP and report findings. 2. Report to study coordinator and study physician for follow-up and clearance.
Participant exhibits signs of allergic reaction to protein.	1. Do not give protein supplement. 2. Call PCP and report findings. 3. Report to study coordinator and study physician for follow-up and clearance.

11.1.6 Safety Measures for the Protein Intervention

In order to minimize discomfort and maximize safety, PTs will instruct participants on how to take the protein supplement. We will monitor for potential adverse events. A participant who exhibits signs of allergic reaction to the protein will stop receiving the protein supplement and the study physician and PCP will be consulted.

11.1.7 Safety Considerations for Nutritional Support

Individuals who have sustained a hip fracture are frequently at risk for protein and calorie malnutrition and have low calcium and vitamin D intake.[168] Individuals enrolled in the study will be screened with the MNA®-SF and if their scores indicate that they are malnourished, they will receive in-person nutritional counseling by a registered dietician. Individuals enrolled that have a serum albumin value 2.5-3.5 will also receive in-person nutritional counseling by a registered dietician, regardless of score on the MNA®-SF. Participants who are at risk or not at risk for malnutrition will receive a telephone consultation from the dietician on maintaining proper diet.

The RD will schedule an in-person visit for those at risk if he/she feels it is necessary based on the telephone consultation. All subjects will receive vitamin D, calcium, and multivitamin supplementation for the 16-week study period, all of which represent best practices for this disabled group of participants. There are small risks associated with vitamin D, calcium, and multivitamins including gastrointestinal complaints (including mild constipation or diarrhea, stomach upset) and kidney stones. Those with a calculated creatinine clearance less than 30 ml/min, elevated total or ionized calcium, or history of kidney stones, primary hyperparathyroidism, or sarcoidosis will not receive calcium supplements. A participant who experiences an episode of kidney stones during the study period will stop receiving calcium supplements.

11.1.8 Safety Measures for Nutritional Support

If a participant loses 2% or more body weight in a four-week period, the participant will be referred to the registered dietician for follow-up by telephone.

11.2 Confidentiality

Confidentiality of data will be maintained by using research identification numbers and letter codes that uniquely identify each individual. Safeguards will be established to ensure the security and privacy of participants' study records. Data will be stored in locked files and on computer disks, with access limited to the investigators and key study personnel. Computer data files will not include participant names, addresses, initials, hospital record number, or any other personal identifiers. Computer security procedures, including multiple levels of password protection will be instituted. Data for publication will be presented only in aggregate form, preventing identification of individual participants. After the study is completed, local data will be archived in a secured storage area.

In compliance with the Health Insurance Portability and Accountability Act (HIPAA) and the Standards for Privacy of Individually Identifiable Health Information of the Department of Health and Human Services, CAP will access personal health information and medical records only after receiving approval for a HIPAA Partial Privacy Waiver for Recruitment. Only information necessary for determining eligibility will be obtained.

11.3 Participant Education about Potential Risks

Potential risks associated with study-related activities and interventions will be explained to each participant by trained study personnel during the informed consent process. Each participant will be instructed to report the occurrence of an AE to appropriate study staff at scheduled data collection times, to PTs administering the intervention, or spontaneously at any other time. Participants also will be encouraged to report concerns about the safety of participating in the study.

Section 12: Reportable Adverse Events (RAEs) and Expected Adverse Events (AEs)

12.1 Overview

In this study we will capture study-defined expected adverse events (AEs) through structured telephone interviews every four weeks. Reportable AEs (RAEs) are defined as serious adverse events (SAEs), AEs that have potential implications for participant safety, unexpected AEs, and injury that occurs while a participant is under the supervision of study related personnel. These

RAEs will require individual event reporting as described in section 12.4. The timely and complete account of RAEs will be a critical requirement for the protection of human subjects in this study.

The University of Maryland Claude D. Pepper Older American Independence Center (UM-OAIC) DSMB will review and approve study-defined expected AEs and will be involved in regular monitoring of the RAE reporting system.

12.2 Classifying Adverse Events

An AE is any unfavorable or unintended medical occurrence in a human study participant that has taken place during the course of a research project, including any abnormal sign, symptom, or disease, whether or not related to participation in the research

For the purposes of this study, any event that meets the criteria for an SAE, is unexpected, or results in injury to the participant while s/he is under the supervision of study related personnel will be classified as an RAE.

Adequate review, assessment, and monitoring of RAEs require that they be classified as to severity, expectedness, and potential relatedness to the study intervention.

12.2.1 Severity

The study physician will use the following guidelines to determine level of severity:

Mild: Awareness of signs or symptoms, but easily tolerated and causing no loss of time from normal activities. No specific medical intervention is required.

Moderate: Discomfort enough to cause a low level of inconvenience or concern to the participant and may interfere with daily activities. Symptoms may require minimal, local, or noninvasive medical intervention only.

Severe: Events interrupt the participant's normal daily activities and are usually incapacitating. Significant symptoms may require hospitalization or invasive medical intervention.

Life threatening: Events that may involve acute, life-threatening metabolic or cardiovascular complications (such as circulatory failure, hemorrhage, sepsis) or life-threatening physiological consequences. Intensive care or emergent invasive procedure is required.

Fatal: Causing death.

Severity is not synonymous with seriousness. A severe headache is not necessarily an RAE. However, mild chest pain may result in a day's hospitalization and thus would be classified as an RAE.

12.2.2 Expectedness

An independent safety monitor (ISM) will assess AEs as to whether they were expected or unexpected based on current knowledge. Categories are:

Expected: An AE that is anticipated on the basis of prior experience with the intervention under investigation; an event that can be attributed to the underlying condition of the participant being

studied; or an event that can be attributed to the patient population being studied (see section 12.3). Expected AEs are captured in a standardized way every four weeks.

Unexpected: An AE that was not anticipated on the basis of prior experience with the intervention under investigation; an event that cannot be attributed to the underlying condition of the participant being studied or to the patient population; or an expected event whose frequency or severity exceeds what was anticipated (see section 12.4.2). Unexpected AEs are reportable.

12.2.3 Relatedness

The ISM will determine the degree to which RAEs are related to study procedures.

Definitely related: The adverse event is clearly related to the investigational procedure – i.e., an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected pattern of response to the study intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure, and that could not be reasonably explained by the known characteristics of the participant's clinical state.

Possibly related: An adverse event that follows a reasonable temporal sequence from administration of the study intervention or that follows a known or expected pattern of response to the study intervention, but that could readily have been produced by a number of other factors.

Not related: The adverse event is clearly not related to the investigational procedure (i.e., another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible).

12.3 Expected AEs

Expected AEs will be captured through telephone interviews every four using the Expected Adverse Events Form. Following are expected adverse events that have been listed in the ICF:

- foot pain
- hip pain
- back pain
- knee pain
- digestive or stomach pain
- breathing problems
- chest pain or discomfort
- bloating or puffiness in the legs, ankles, or feet
- drowsiness, dizziness, or confusion
- shakiness, anxiety, clammy skin, or irritability
- fall (with or without injury)

12.4 Reportable AEs

RAEs are events that have potential implications for participant safety and that require individual reporting. RAEs will be defined as events that fall into at least one of the following categories:

1. Serious adverse events (SAEs)
2. Unexpected AEs, and
3. Injury that occurs while a participant is under the supervision of study personnel.

Events that cannot be clearly defined as “reportable” will be discussed with the study physician and PI to determine if they should be reported.

12.4.1 Serious Adverse Event (SAE)

SAEs will be defined as any event that:

- Results in death
- Is life threatening, or places the participant at immediate risk of death (e.g., MI, stroke/TIA)
- Requires or prolongs hospitalization
- Causes significant disability or incapacity (e.g., torn muscle or ligament)
- Requires medical or surgical intervention to prevent significant disability (e.g., hip fracture)

SAEs will be assessed through telephone interviews every four weeks using the Reportable Adverse Events Telephone Screening Form. SAEs will also be assessed at the beginning of each PT visit and clinical site visit, and by any study staff who learns of a serious event.

12.4.2 Unexpected Adverse Event

Unexpected AEs will be defined as medical events that occur during study participation, but do not commonly occur in the study population and which are not listed in the ICF or study protocol (section 12.3). An unexpected AE may be witnessed by a member of the research team, or staff may be told about an unexpected event that may meet the criteria for reporting. Unexpected AEs that have a potential relationship to study procedures and activities will be captured on an Incident Report and submitted to the study office where they will be logged in the participant binder and then reported to the Independent Safety Monitor (ISM).

A reportable unexpected AE will be one that meets <u>all</u> of the following criteria:

- Unexpected, in terms of nature, severity, or frequency, given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and ICF; and (b) the characteristics of the study population;
- Related or possibly related to participation in the research (meaning that there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

The medical and scientific judgment of the study physician and the PI will be exercised in deciding whether an occurrence should be reported. In addition, difficulty determining whether or not an event is unexpected and/or attributable to the intervention will be addressed by the ISM, who will determine if the event is to be reported.

12.4.3 Injury that Occurs while Under the Supervision of Study Related Personnel

Any injury that occurs while the participant is under the supervision of study-related personnel is reportable. The injury can happen on site (during an assessment visit) or off-site (in the participant’s home during a PT visit or if the study offers supervision during transportation). These events will be captured on the Reportable Adverse Events Form.

12.5 Expected AE and RAE Collection and Reporting

The requirements for reporting RAEs will begin when the participant provides informed consent and will end 30 days after the participant's involvement in the study has ended. Expected AEs will be assessed every four weeks after baseline testing. Figures 5a-d provide algorithms describing the reporting process.

Figure 5a. Collection and Reporting Process for Expected AEs

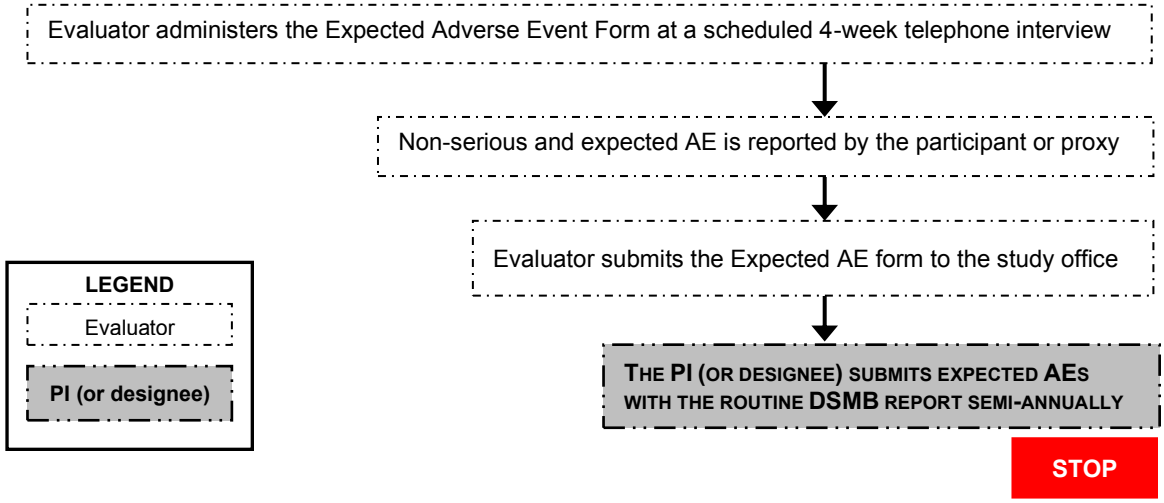


Figure 5b. Collection and Reporting Process for RAEs Collected during Standardized Telephone Interviews

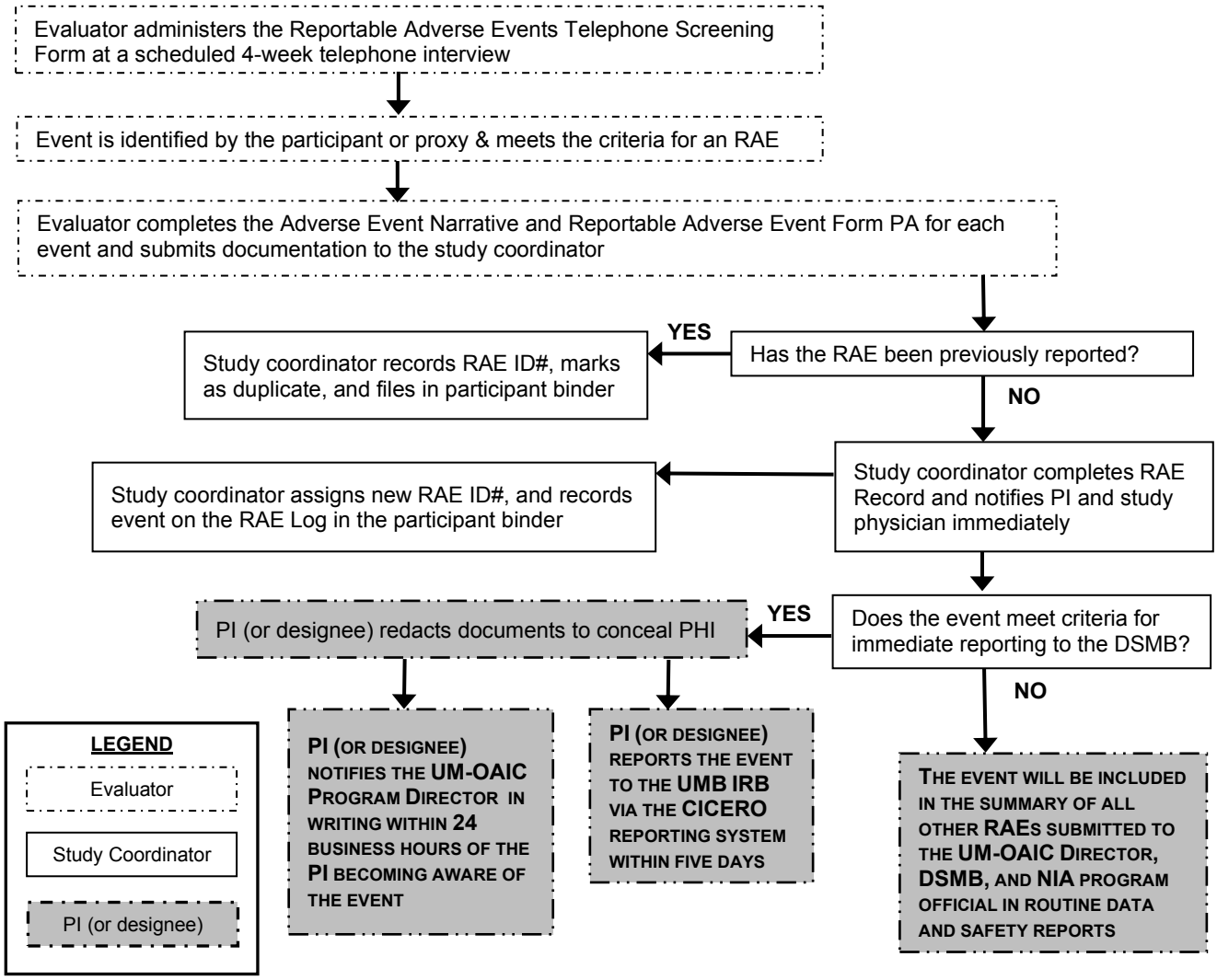


Figure 5c. Collection and Reporting Process for RAEs Identified Anytime Other than During a Standardized Telephone Interview

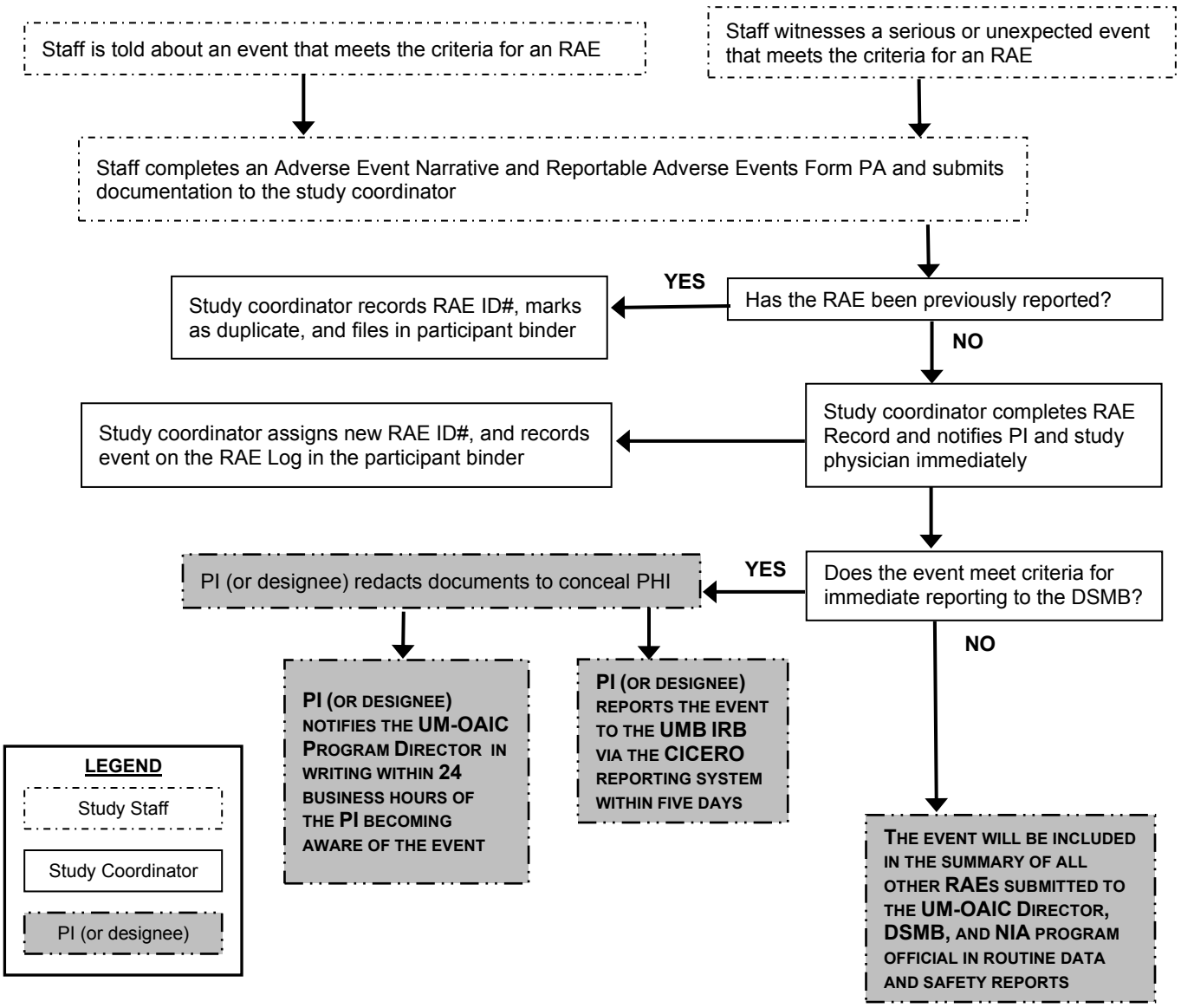
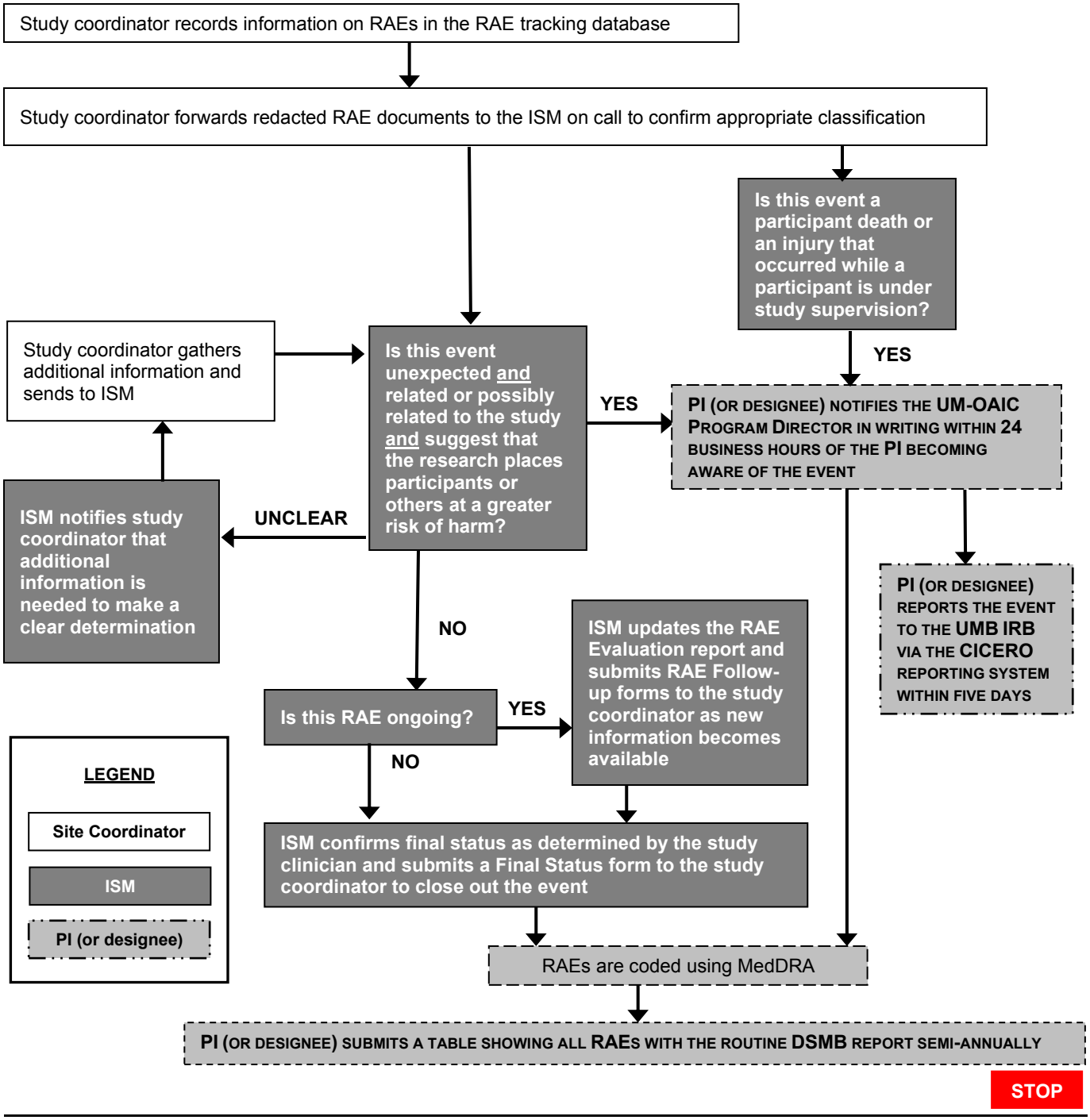


Figure 5d. Review and Reporting Process for RAEs



Timeline for Reporting Events

The RAE reporting schedule is shown below:

1. Staff will report RAEs to the PI and study physician as soon as the event is known and submit documentation of the event to the study coordinator in real time.
2. All injuries that occur while a participant is under the supervision of study personnel and all participant deaths (regardless of relatedness) will be reported to the OAIC Program Director within 24 business hours (excluding weekends and holidays) of the PI becoming aware of the event.
3. Events that are reviewed by the ISM and subsequently classified as related or possibly related to the research will also be submitted to the OAIC Program Director.
4. All other RAEs, SAEs, expected AEs, and protocol deviations will be requested semiannually by the OAIC to be presented to the DSMB.

12.6 Evaluation and Follow-up of RAEs

All RAEs will be forwarded to an ISM for adjudication and follow-up. The ISM may contact the study coordinator to request additional information from the participant, significant other, or their health care provider and may seek medical records from a physician or care setting if needed to make a determination about relatedness to the study. If the event is potentially related to the study, the ISM will consider whether the event was listed in the protocol and ICF and whether modifications to the protocol and ICF should be considered. To ensure the appropriate classification of events, the study physician and/or PI may also be called on to provide additional information.

The ISM will be responsible for providing follow-up for ongoing reportable events, as follows:

1. The ISM will make a determination about relatedness and expectedness of the event and submit a Reportable Adverse Event Evaluation to the study coordinator.
2. If there are follow-ups to an event (and the event is ongoing), the ISM will complete the RAE Follow-up Form to record any updates and submit to the study coordinator.
3. The ISM will follow up on RAEs until a final status has been determined for the event (e.g., recovered, ended in death, is still present, or status is unknown). Some RAEs may have a status of still present at the conclusion of the study. These are the categories of RAE status:
    a. ‘Resolved’ is an event that has ended, with or without residual deficits.
    b. ‘Still present’ is an event that is ongoing.
    c. ‘Unknown’ should be used when the site is unable to make contact with the participant or proxy or to obtain additional information in any other way.
    d. ‘Died’ is for an event that ended in death.
4. Once the event is no longer ongoing and a final status for the event has been determined by the study physician, the ISM will confirm the final status, record the closed date, and sign and date the RAE Final Status Form that will be submitted to the study coordinator.

12.6.1 Action Taken

The PI, in consultation with the study physician and the ISM, will decide whether or not an RAE requires that the participant be removed from the study intervention. The UM-OAIC DSMB will be notified of the recommended course of action by the PI in the routine DSMB report. Actions taken in response to the RAE will fall into one of five categories:

- Study intervention modified
- Study intervention suspended temporarily
- Study intervention stopped permanently
- Study assessment modified
- No action taken

12.7 Responsibilities

The PI has primary responsibility for the safety of participants as it relates to the study protocol. The study coordinator will be responsible for reviewing RAEs and assuring accurate and timely reporting of RAEs. The study physician will be responsible for reviewing RAEs. ISMs will evaluate and classify RAEs and provide follow-up for events until they are resolved. The UM-OAIC DSMB will be responsible for reviewing monitoring data for evidence of harm attributable to participation in the study.

12.7.1 Study Physician

The study physician will be responsible for being "on call" for study-related emergencies and will be available by telephone for consultation with study personnel during all time periods when participants are engaged in the home-based interventions or at clinical assessment visits. In addition, the study physician will be responsible for reviewing RAEs requiring immediate notification to the UM-OAIC DSMB and NIA. The study physician will assess severity and consider whether participation in the study should change for reasons related to safety. The physician will also make a determination about final status once the event has resolved.

The study physician may delegate responsibilities related to immediate notification to a "covering" physician who has been trained on the protocol.

12.7.2 Independent Safety Monitor (ISM)

Physicians will serve as ISMs to review RAEs on a rotating basis. When a RAE is identified the information will be redacted to conceal PHI and then forwarded to the on-call ISM to make a determination. The ISM will be responsible for:

- reviewing reports of RAEs;
- confirming or refuting classification of the event as an RAE;
- evaluating the expectedness of the RAE;
- making a determination about relatedness of the RAE;
- requesting additional information as needed in order to make a determination;
- providing the study coordinator with follow-up reports for ongoing RAEs as new information becomes available;
- confirming the final status for the event once it has been determined by the study physician; and
- submitting a final status report to the study coordinator.

12.8 Reporting Expected AEs and RAEs to the UM-OAIC DSMB

The UM-OAIC DSMB will review tabulated data on non-serious and expected AEs on a semi-annual basis and monitor for adverse event rates out of proportion to those expected. The PI (or designee) will forward the individual Reportable Adverse Event Record and AE Narrative for each event requiring immediate notification to the UM-OAIC DSMB and NIA as well as a table showing all RAEs to the UM-OAIC DSMB and NIA semi-annually. The UM-OAIC DSMB will review all RAEs that are temporally related to the intervention in aggregate form at its scheduled meetings.

All RAEs that relate to hazards of the study intervention or are cause for urgent concern will be reported to the UM-OAIC DSMB chair, NIA, and the UMB IRB immediately after recognition of their importance. The DSMB chair may conclude that an RAE is of universal and immediate concern. The DSMB chair may also recommend convening the UM-OAIC DSMB to review participant safety based on any individual report or accumulating evidence.

Section 13: Intervention Discontinuation

Certain RAEs may result in a temporary interruption or early discontinuation of the trial assessments and interventions or components of these assessments and interventions. Please refer to the appropriate MOP chapter(s) for specific instructions on stopping criteria during screening, intervention, and follow-up assessments.

After such RAEs occur, a participant may resume the trial intervention when the study physician and the primary care provider (if participant has one) agree that it is appropriate. For mild problems that require temporary cessation of intervention, the PI, in consultation with the study physician and participant, may agree to reintroduce the participant to the study intervention.

At any time, the UM-OAIC DSMB may recommend discontinuation of any component or intervention group of the study for any of the following reasons:

1) Compelling evidence from this or any other study of an adverse effect of the study intervention(s) that is sufficient to override any potential benefit of the interventions to the target population.
2) Compelling evidence from this or any other study of a significant beneficial effect of the study intervention(s), such that its continued denial to other study group(s) would be unethical.
3) A very low probability of addressing the study goals within a feasible time frame.

Section 14: Data Analyses

14.1 Primary Aim

The primary aim is to compare the PUSH Plus Protein study subjects (n=30) to those who received PUSH from CAP (n=105). The primary outcome is the distance walked in six minutes (6MWT). Previous analyses of various physiologic measures in the Baltimore Hip Studies data ("BHS"; data unpublished) have shown a r>0.80 within subject correlation of measures across time. Preliminary data from CAP-MP have shown a within subject correlation of r=0.78 for initial subjects in usual walking speed (n=13).

14.2 Secondary Objectives

A longitudinal analysis using Generalized Estimating Equations (GEEs) will be employed. A model of the form Y(t) = a + b1 X + b2 t4 + b3 Xt4 will be used where: Y(t) is the dependent variable Y at time t (which is 0 or 4 months post baseline testing); a is the intercept; X is an indicator variable for treatment group (PUSH vs PUSH+ Protein); t4 is an indicator variable for time at 4 months post baseline testing; Xt4 is an interaction term for treatment and time; and b1 through b3 are empirically derived regression coefficients. An unstructured covariance matrix, an identity link function, and robust standard errors will be used. The effect of intervention on each mechanistic factor will be assessed by estimating the magnitude of the coefficient b3, which is interpreted as mean change in outcome from baseline to 4 months comparing PUSH Plus Protein to PUSH alone. The primary outcome will be the 6-minute walk test (6MWT). Other potential outcomes include: activities of daily living (ADLs), quality of life, lower-extremity physical performance, increase of ≥ 50 meters in distance walked in six minutes, cognitive status, and nutritional status.

14.3 Missing Data

By design, there will be no missing data at baseline because only participants with complete baseline data will be randomized. At follow-up, scores for scales that have published rules for handling missing scale items (e.g., the CES-D and the SF-36) will be calculated using those rules. All other scales will be considered missing if any part of the scale is missing. To correct for potential selection bias from missing data, we will perform a weighted estimating equations (WEE) analysis.[169] This method involves two steps. First the probability of being observed (not missing) is calculated as a function of predictors of missingness. Next the relationship of treatment group to outcome is assessed using the inverse probability of being observed as a weight in the GEE model. WEEs are advantageous because a) they are consistent with the ITT principle because participants with missing data are included in the analysis through the estimated weight, and b) unlike other methods for addressing missing data, they can be performed in conjunction with marginal structural modeling by multiplying both weights together.

14.4 Sample Size Adequacy

Power analyses were conducted for detectable mean changes from baseline (conservatively) assuming a within subject correlation of r=0.70. For between group differences, assuming 10% loss to follow up from all causes (mortality, attrition, etc.) by 16 weeks post randomization (CAP n=105 in the PUSH arm and this study will have n=30, so effective n=94 compared to n=27 including attrition). The study will have 80% power to detect differences of 0.475 standard deviations assuming two-sided tests and an alpha level of 0.05. These differences are considered small-to-moderate effects using Cohen's criteria for interpretation of effect sizes (where 0.2 is "small" and 0.5 is "medium). Given a 6MWT mean of 186.7 and SD=55.8 in the most recent overall sample from CAP (n=199, DSMB report May 2017), this would translate into a difference of 22.9. Similar magnitude of effects (SD=0.41) are detectable comparing to other measures available in the CAP study (e.g, SPPB, 3MS, etc.).

For outcomes only available in the CAP-MP study, the comparison sample is 19 subjects in CAP-MP PUSH. Assuming 10% loss to follow up (n=17 in CAP-MP PUSH group vs n=27 in pilot study), the study will have 80% power to detect between group differences of 0.62 standard deviations assuming two-sided tests and an alpha level of 0.05. This is considered a moderate-to-large effect size by Cohen.

Section 15: Data Capture, Data Management, and Quality Assurance

15.1 Data Management

15.1.1 Processing of Paper Data Forms

Field staff will bring in data forms within 1 week of the visit and place them in the appropriate tray in the study office. Office staff will review each form for completeness and check any required fields. Submitted data forms will be tracked in an Access® database. Forms are then double entered into the appropriate data entry database and filed in the participant binder.

15.1.2 Reportable Adverse Events Coding

RAEs will be coded using MedDRA (version 15.1, release date September 1, 2012). The MedDRA coding dictionary is integrated with the study database.

15.1.3 Extraction of Data for Analysis and Reporting

Data will be extracted using StatTransfer and converted to SAS data sets for analysis and reporting. Where required, data will be merged and recoded using validated SAS code to create "analysis data sets". Specifications for these analysis data sets will be drafted and updated as needed.

15.2 Protection of Data

15.2.1 Physical Security and Backup

All tracking and data entry databases are password protected with limited access. Each are stored on the School of Medicine's secure server. The server is backed up daily. SAS programs and datasets are also stored on the server and backed up daily.

15.3 Study Management Database

An Access® database will be used to track study visits, generate schedules of future study visits, status of participants, activities of study staff members, form completion, and form submission. The database will provide a standard way to track time-sensitive study activities throughout the study. The study management database will be password-protected and saved on the server that will be automatically backed up daily. Access to the database will be restricted to office staff. There will be several standard reports available in the database to use for a variety of tracking issues. Additional reports will be created as needed. Data for the tracking database will come from tracking forms completed by study staff.

15.4 Quality Assurance (QA)

Quality assurance (QA) will be a shared responsibility of all study personnel. The goal of QA monitoring will be to track study progress and develop the information necessary to ensure: 1) enrollment of the required number of participants; 2) adherence to treatment protocol; 3) that data are reported completely, verifiably and in a timely fashion; and 4) participant safety, by accounting for expected AEs and RAEs. Study monitoring will be based on early implementation of reviews of accumulating data with rapid feedback to the PI regarding problem areas. The Investigative team will regularly review progress.

15.4.1 Training

Staff will be trained at the initial training session(s). Certification and recertification will be required in order to assure that staff have a clear understanding of the study protocol and Manual of Procedures (MOP). Separate training sessions will be provided for staff conducting study assessments, telephone interviewers, PTs providing the PUSH intervention, staff conducting screening and informed consent procedures, and the registered dieticians. The study coordinator will attend all training sessions.

Training sessions will cover recruitment; obtaining informed consent; collection of protocol-specified data (both questionnaire and performance-based measures); scoring; completion of forms; capturing and reporting expected AEs and RAEs; administering the intervention; performing diet consults; and using the paper-based data forms.

In preparation for training, staff will be asked to read background material (e.g., designated chapters in the MOP). The training session will involve both didactic and interactive components. Training for the different sessions will be provided by investigators with the appropriate expertise. For example, training the PTs to deliver the study interventions will be provided by the IM. Whenever appropriate, trainees will be required to demonstrate acquired

skills. These demonstrations will be observed and critiqued by the trainers and other staff. Trainees will be certified to perform study procedures after successfully completing written and (when appropriate) performance tests.

The study coordinator will be responsible for documenting that certification has been completed.

15.4.2 Protocol Deviations

Protocol deviations may jeopardize the study by breaching assurances made to the participants or by diminishing the validity of the study. Major deviations will be those that endanger participants, such as failure to protect safety during the intervention, or that undermine fundamental premises of the study, such as failure to provide the assigned intervention according to protocol or enrolling an ineligible participant. Minor deviations will be those that impede the progress of the study, such as not submitting data in a timely fashion.

Major deviations will be reported annually to the UMB IRB and tracked using a protocol deviation log. The following classifications of protocol deviations will be captured, documented, and reviewed:

1) Enrollment and consent deviations
   a. Enrollment of an ineligible participant
   b. Failure to obtain informed consent
   c. Enrollment of participant into another study

2) IRB deviations
   a. Failure to keep IRB approval up to date
   b. Failure to submit study modification for approval

3) Intervention deviations
   a. Required aspects of intervention not administered (e.g., dietician referral)

Section 16: Participant Rights and Confidentiality

16.1 Institutional Review Board (IRB)

The study protocol will be reviewed by the UMB IRB. Subsequent modifications must be approved by UMB IRB before submission to the IRBS at respective study hospitals.

16.2 Informed Consent Forms (ICF)

It will be the sole responsibility of the PI to ensure that informed consent was properly obtained for every participant who entered into the study. The ICF will describe the purpose of the study, the procedures to be followed, alternatives to participation, and the risks and benefits of participation. It will also be explained that signing the consent form allows the study to confirm eligibility before starting the intervention. Written informed consent will be obtained according to procedures reviewed and approved by the IRB. Informed consent can be obtained anytime upon completion of phase 1 eligibility screening and prior to 26 weeks post hospital admission. Consent by a legally authorized representative will not be accepted.

In some cases, a local hospital will allow the use of the UMB IRB approved consent form and/or the HIPAA Authorization Form. However, local hospital IRBs may require that language be added to the consent form to correspond to local requirements. Staff will be responsible for ensuring that the correct version of the ICF is used.

If there is a change in any of the study procedures or risks that may affect the participant, the ICF must be revised and undergo appropriate IRB review and approval. Any participants enrolled in the study prior to such changes and who are still active in the study must sign the amended consent form.

The study consent form will be provided to a potential participant for review prior to obtaining informed consent. The ICF may also be mailed to the participant and/or a family member so that s/he has sufficient time to read the document and, if desired, to have a family member or friend review the form before signing. During the informed consent process, study staff will provide participants with adequate information concerning the study procedures, respond to individuals' questions and concerns, and ensure that each individual understands all the information provided by assessing ability to provide informed consent. A more detailed description of the informed consent process can be found in section 7.5.

16.2.1 Disposition of Informed Consent Forms

Because ICFs contain subject identifiers and protected health information (PHI), these forms will not be submitted with the data collection forms. Originals of the ICF will be filed and maintained by the study coordinator in the participant binder which will be secured in a locked cabinet or office, separate from source documents that include no PHI. A copy of the signed consent form will be given to the participant and this fact will be documented in the participant's record.

16.2.2 HIPAA Authorization

The HIPAA Authorization for Research is an individual's signed permission to allow the study investigators to use or disclose the individual's PHI described in the authorization. Once an individual has agreed to participate in the study and written informed consent has been obtained, the HIPAA Authorization for Research must also be explained and signed. The HIPAA Authorization may be a stand-alone document or wording for the HIPAA Authorization may be incorporated into the text of the ICF. The original signed authorization will be submitted to the study office and a signed copy will be given to the participant.

16.3 Participant Confidentiality

Potential participants will be provided with a clear understanding of how the information they provide will be used. All investigators and staff involved in the study will be required to complete training on the protection of human subjects and HIPAA and to maintain proper certifications.

To ensure confidentiality of study data, completed questionnaires and study forms will be kept in participant binders stored in locked offices, no unauthorized person will be permitted to see the binder or forms, names will be used only for the necessary purpose of making sure that the recorded information is for the person to whom it refers, and data will be summarized so that published results cannot be traced to individuals.

On data collection forms, participants will be identified only by a unique study identification number. Staff will record names, contact information, and other direct identifiers to enable them to maintain contact with participants. Logs accessible only to the PI and key study personnel will link the study identification number to names.

To protect study data from theft or unauthorized perusal or alteration, access to all computer files will be restricted to designated personnel through the use of passwords. Access to the database and programs will be on a "need to use" basis (e.g., coordination staff cannot access main system programs).

Computer security procedures, including multiple levels of password protection will be instituted. The study records will be identified by a unique participant identification number. Identification numbers will be recorded on each page of the paper forms. Names and addresses of participants corresponding to each identification number will be kept in secure files at the clinical site. Final analysis data sets will not contain any directly or indirectly identifying information. Thus, dates of birth will be converted to age, other dates will be changed to counts of days from study entry, identification numbers will be replaced with sequence numbers, variables that could lead to deductive disclosure of the identity of individual participants will not be included nor will indirect identifiers such as infrequently occurring (e.g., fewer than 20 participants) outwardly manifest characteristics.

Section 17: Research Publication Policy

Publications will be operationally defined as manuscripts for publication; abstracts for platform or poster presentation at scientific and other professional meetings; slides for presentation at scientific and other professional meetings; doctoral dissertations; and master's theses.

The goal of our publication policy is to encourage and facilitate the publication of study results. The purposes of this policy are to ensure the following: 1) Publications will be of the highest scientific quality; 2) the study will be described in a consistent manner across publications; 3) measures are reported in consistent ways across publications; 4) proper acknowledgements are included; and 4) appropriate authorship credit is determined prior to submission of manuscripts for publication consideration.

Publications will be overseen by the PUSH Plus Protein Pilot Study leadership (Drs. Magaziner, Orwig, and Gruber-Baldini). These investigators will make recommendations to the Investigative team. Final papers using data from CAP or CAP-MP may also need to be reviewed by the CAP Publication and Ancillary Studies Committee.

A document describing the Publication Policy and Procedures appears in the Manual of Procedures.

17.1 Concurrent Studies

Study investigators agree not to conduct studies which would compete with or have a detrimental effect on the conduct of the PUSH Plus Protein Pilot study during the period of recruitment and follow-up. However, it is understood that each investigator has the right to conduct concurrent studies with participants who do not meet criteria for enrollment into PUSH Plus Protein. Concurrent studies of patients who meet eligibility criteria for PUSH Plus Protein but are not enrolled in PUSH Plus Protein must be disclosed and reviewed by the Investigative team.

Section 18: Study Team Roster

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Section 19: References

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