

**COMMUNITY AMBULATION FOLLOWING HIP FRACTURE  
PROTOCOL (Version 12.0)**

**Summary of Modifications to Protocol Version 11.0 for Version 12.0**

<b>Version (date)</b>	<b>Section</b>	<b>Brief Summary of Modification</b>
<i>Version 12.0 (10/19/16)</i>	9.2, 10.4.9, 11.2, 12.1.8, Table 2	<p>Prior to Version 12.0 of the protocol, three strategies were used to address participants' nutritional status: 1) Consultation with a study registered dietician (RD) at baseline for participants who are malnourished (Mini Nutritional Assessment-Short Form (MNA®-SF) score <math>\leq 7</math>), at risk for malnutrition (MNA®-SF score 8-11), or with serum albumin <math>\leq 3.5</math> g/dl; 2) Consultation with a study RD if there is weight loss of 2% or more between weight assessments performed every four weeks in the course of the intervention visits, and 3) Referral for follow-up and/or medical evaluation for possible malnutrition if the MNA®-SF score at follow-up is <math>\leq 7</math>.</p> <p>In Version 12.0, to streamline procedures, we eliminated the third strategy (MNA screening for malnutrition at follow-up). Identifying nutritional deficiencies at baseline (the first strategy) and monitoring weight loss throughout the intervention period (the second strategy) will be sufficient for addressing participants' nutritional status.</p> <p>In the event that a weight measurement is not obtained at the last PT intervention visit, the participant's weight at the 16-week follow-up assessment will be compared to his or her baseline weight and, if there has been weight loss of 5% or more, the clinical site principal investigator or clinical site clinician will review the participant's weight trajectory, baseline body mass index, 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.</p>

**Summary of Modifications to Protocol Version 10.0 for Version 11.0**

<b>Version (date)</b>	<b>Section</b>	<b>Brief Summary of Modification</b>
<i>Version 11.0 (8/26/16)</i>	1, 6.1, 8.1, 10, 11	In order to conserve resources, we eliminated several secondary and tertiary outcome measures, while retaining measures needed for the assessment and adjudication of the primary outcome, to determine study eligibility, to ensure participant safety, to monitor adverse events, and to describe characteristics of the participant population.
<i>Version 11.0 (8/26/16)</i>	9.2, 10.6.1, 11.3	In order to conserve resources, we eliminated the collection of information on use of study-provided dietary supplements. However, procedures for drug accountability will remain unchanged.
<i>Version 11.0 (8/26/16)</i>	15.6.2	We expect that, by the time all the approvals for the change described above have been obtained, approximately 160 participants will have been randomized under the existing protocol. The power calculations have been revised accordingly for the secondary and tertiary outcome measures that will no longer be collected.

**Summary of Modifications to Protocol Version 9.0 for Version 10.0**

<b>Version (date)</b>	<b>Section</b>	<b>Brief Summary of Modification</b>
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<i>Version 10.0</i> (6/7/16)	All sections	Prior to Version 10.0 of the protocol, follow-up assessment visits occurred 16 weeks and 40 weeks from the date of randomization, telephone interviews were conducted every four weeks during the 40-week study period for a total of 10 telephone interviews, and participants received vitamin D, calcium, and multivitamin supplements for a total of 40 weeks. In order to conserve resources and preserve the primary outcome, the protocol was revised so that study participation of participants randomized after approval of Version 10.0 of the protocol will end after the 16-week follow-up assessment. The wording of the protocol has been changed accordingly.
<i>Version 10.0</i> (6/7/16)	15.6.2	We expect that, by the time all the approvals for the change described above have been obtained, approximately 150 participants will have been randomized under the existing protocol which includes follow-up to 40 weeks post-randomization. The power calculations for some of the outcome variables have been revised accordingly.
<i>Version 10.0</i> (6/7/16)	16.7	We changed "Monthly reports" to "Regular reports" in the section on study performance monitoring. This was done to accommodate a revised schedule of reports to the Steering Committee.
<i>Version 10.0</i> (6/7/16)	20	Updates were made to the Study Team Roster. Dr. Anne Kenny is leaving the study and was removed from the study team roster. Dr. Yazeed Maghaydah will take her place as the clinical site clinician for the University of Connecticut Health Center clinical site. We also updated contact information for Dr. Ram Miller.

#### Summary of Modifications to Protocol Version 8.0 for Version 9.0

<b>Version (date)</b>	<b>Section</b>	<b>Brief Summary of Modification</b>
<i>Version 9.0</i> (12/18/15)	1, 6.1, 15.6.1, 15.6.2, Table 5	The original target sample size was 150 per group. Because of recruitment difficulties, the DSMB approved a new target sample size of 105 per group. The target sample size was revised in several sections of the protocol and the power calculations with the new sample size were updated in section 15.6.1, section 15.6.2, and Table 5. As recommended by the DSMB, the revised power calculations were based on the rate of loss to follow-up and the rate of nonadherence observed among the first 88 study participants.
<i>Version 9.0</i> (12/18/15)	15.5, Table 4	Due to the change in target sample size, the DSMB approved a change to the critical values used for the four remaining interim analyses. Changes were made to section 15.5 and Table 4 to reflect the revised plan.
<i>Version 9.0</i> (12/18/15)	15, 15.1, 15.6.1	In version 8.0 of the protocol there was inconsistency with respect to the analysis plan for the primary outcome. In several sections it was stated that the primary outcome (community ambulation at 16 weeks) would be assessed using a two-sided 0.05-level test. However, the interim analysis plan (which specified the interim analyses and the final analysis) was to perform a one-sided 0.025-level test at each time point. Therefore, we modified the proposal so that it consistently says that for the primary analysis we will use a one-sided 0.025-level test.

#### Summary of Modifications to Protocol Version 7.0 for Version 8.0

<b>Version (date)</b>	<b>Section</b>	<b>Brief Summary of Modification</b>
<i>Version 8.0</i> (10/2/15)	9.1 and 9.6	Ideally participants will receive 2 intervention visits per week for 16 weeks post-randomization (32 visits total). Previously, missed visits were not replaced. In the proposed protocol, it will be possible for missed visits in a given week to be replaced by performing makeup visits in subsequent weeks (not to exceed 3 visits in any given week) as long as the visits are on non-consecutive days. Furthermore, if the participant has not had 32 visits by the end of 16 weeks, we are allowing makeup visits to be performed during the subsequent two weeks to get as close as possible to the target of 32 visits. The purpose of this modification is to increase intervention adherence.

<i>Version 8.0</i> (10/2/15)	1, 9.2, 10.4.9, 12.1.7, and Table 2	In the previous protocol participants who were at risk of malnutrition and those who were malnourished, based on the Mini Nutritional Assessment-Short Form (MNA®-SF) score and serum albumin level, received an in-person visit from a registered dietician (RD). However, it was found that many participants in the at-risk group did not require an in-person visit. Therefore, in the proposed protocol, participants in the at-risk group based MNA®-SF score and with a normal serum albumin level will receive a phone call from the RD and will only receive a follow-up in-person visit if the RD believes it is necessary.
<i>Version 8.0</i> (10/2/15)	11.5, 15.1	The protocol was revised to reflect changes in the way adjudication will be performed. In the proposed version, all three adjudicators will discuss the case if the two assigned adjudicators do not reach consensus. The three adjudicators will vote on the case if they are unable to reach consensus. Also, cases where the Six-Minute Walk Test was administered but not according to protocol (e.g., using a walking course of less than 10 m) will now be submitted for adjudication.

### Summary of Modifications to Protocol Version 6.0 for Version 7.0

<b>Version (date)</b>	<b>Section</b>	<b>Brief Summary of Modification</b>
<i>Version 7.0</i> (5/5/15)	1, 3, 6, 7, 8, 11.4, and 12.2	In the previous protocol, recruitment of hip fracture patients was limited to acute care hospitals. In this version of the protocol, other mechanisms of recruitment have been added in order to supplement efforts in the acute care hospitals. In addition to augmenting the pool of potentially eligible patients, these approaches will allow us to identify patients who have already received a preliminary level of pre-screening and who have a higher probability of participation than the unselected hip fracture patients who are approached for the study in the acute care hospitals. The new recruitment strategies include screening at rehabilitation facilities, home care agencies, and other agencies that care for older persons after hip fracture; advertising via flyers, print and web postings, radio, and social media; and referral from clinicians (e.g., orthopedic surgeons, physical therapists).

### Summary of Modifications to Protocol Version 5.0.1 for Version 6.0

<b>Version (date)</b>	<b>Section</b>	<b>Brief Summary of Modification</b>
<i>Version 6.0</i> (11/21/14)	All sections	In the previous protocol, participants received three intervention visits per week in the first eight weeks of the intervention and two intervention visits per week in the second eight weeks. In this version of the protocol, the frequency in the first eight weeks has been reduced to two times per week so that participants will receive two visits per week for all 16 weeks. The intensity and total duration of the interventions will not change and there is no evidence in the literature indicating that a frequency of three days per week is superior to two days per week for improving strength or function. Reducing the frequency may increase participation, may increase participants' willingness to start the intervention earlier in the post-fracture period, and may improve adherence to the intervention schedule. Changes were made throughout the protocol to reflect the reduction in the total number of intervention visits from 40 to 32.
<i>Version 6.0</i> (11/21/14)	All sections	Changes were made throughout the protocol to reflect revisions made to the inclusion and exclusion criteria.
<i>Version 6.0</i> (11/21/14)	All sections	We have removed references to the appendices throughout the protocol and removed Section 22 (Supplements/Appendix). Appendices provided with the original protocol submission represented draft documents and are no longer current, as these items continue to be modified to meet the operational needs of the study.

<i>Version 6.0 (11/21/14)</i>	7.2 (criterion 1.1)	We have removed the ICD codes from this criterion. The operational definition of hip fracture diagnosis is not based on ICD codes since they are not available at the time of screening.
<i>Version 6.0 (11/21/14)</i>	7.2 (criteria 1.3 and 1.6)	Unilateral hip fracture and stress fracture were deleted as eligibility criteria since patients with these types of fractures can safely perform and can benefit from the study interventions.
<i>Version 6.0 (11/21/14)</i>	7.2 (criterion 1.7)	Orthopedic surgeon permission to contact patient was deleted as a study-wide exclusion criterion since this is not required at all sites.
<i>Version 6.0 (11/21/14)</i>	7.3 (criterion 4.5)	The interval between hospital admission and randomization was extended to 26 weeks. This may help increase participation of people who need more time to complete usual home therapy before starting the study interventions.
<i>Version 6.0 (11/21/14)</i>	7.3 (criteria 5.3-5.10, 5.12, 5.13, 5.16, and 6.11-6.13)	These 14 medical criteria were deleted as exclusions to avoid unnecessarily screening out patients who could safely perform the study interventions and benefit from them. Clinical site clinicians will review all potentially eligible patients to ensure that they can safely participate in the study.
<i>Version 6.0 (11/21/14)</i>	7.3 (criterion 5.18)	Severe lower extremity pain with ambulation was deleted as an exclusion criterion. Significant pain while walking will now be assessed during the baseline administration of the Six-Minute Walk Test (SMWT) (criterion 6.10).
<i>Version 6.0 (11/21/14)</i>	7.3 (criterion 6.10)	This criterion has been revised to exclude patients who develop severe pain during the baseline SMWT.
<i>Version 6.0 (11/21/14)</i>	7.3 (criterion 5.21)	The exclusion criterion was revised to be specific to receiving physical therapy in a hospital or inpatient rehabilitation facility at the time of randomization. Patients receiving physical therapy at home will be eligible to begin the study interventions.
<i>Version 6.0 (11/21/14)</i>	7.3 (criterion 6.7)	This criterion was revised to exclude people who are not fully weight-bearing on either the fractured or non-fractured leg at time of randomization.
<i>Version 6.0 (11/21/14)</i>	Tables 1 and 2	Tables 1 and 2 were removed in order to simplify the study protocol, as this information is already presented in the text.
<i>Version 6.0 (11/21/14)</i>	8.2, 11.5, and Table 3	We have added an out-of-window time interval in order to collect data for the 16-week follow-up visit earlier than the allowable window. The additional out-of-window interval is 0-16 weeks post-randomization, which covers the period from the date of randomization to the earliest date for the 16-week visit. Although assessment visits are always done as close as possible to the target date, this change will increase the probability of obtaining complete follow-up data, even for participants whose assessments are difficult to schedule.
<i>Version 6.0 (11/21/14)</i>	15.1	A few paragraphs were added describing the analysis to address the change in intervention frequency during the first eight weeks of the intervention from three times per week to twice per week.
<i>Version 6.0 (11/21/14)</i>	15.1	We modified the category for age at baseline from “65 to 84 years” to “60-84 years” to reflect the current age eligibility criterion.
<i>Version 6.0 (11/21/14)</i>	20	Updates were made to the Study Team Roster.

#### Summary of Modifications to Protocol Version 5.0 for Version 5.0.1

<b>Version (date)</b>	<b>Section</b>	<b>Brief Summary of Modification</b>
<i>Version 5.0.1 (5/14/14)</i>	7.3 (criterion 6.11) and Table 1	Modified the criterion to remove the word “recent”, which was added in error in version 5.0. The correct wording of criterion 6.11 is "Total hip replacement or prior hip fracture on same side as study index hip fracture." The operationalization of criterion 6.11 has not changed.

#### Summary of Modifications to Protocol Version 4.0.1 for Version 5.0

<b>Version (date)</b>	<b>Section</b>	<b>Brief Summary of Modification</b>
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<i>Version 5.0</i> (4/17/14)	All sections	Changes were made throughout the protocol to capture revisions made to the inclusion and exclusion criteria.
<i>Version 5.0</i> (4/17/14)	7.2 (criterion 1.4)	Eliminated the restriction for surgical fixation within seven days of admission.
<i>Version 5.0</i> (4/17/14)	7.2 (criterion 2.1)	Lowered the age limit to 60 and older at time of randomization.
<i>Version 5.0</i> (4/17/14)	7.3 (criterion 4.5)	Widened the randomization window to 0 to 20 weeks post admission (10± 10 weeks). This will help maximize participation of people who receive a shorter duration of regular PT post hip fracture and of those who receive a longer duration of PT.
<i>Version 5.0</i> (4/17/14)	7.3 (criterion 5.4)	Modified the BMI cutpoint to 17 and deleted the weight restriction due to some older hip fracture patients being of short stature.
<i>Version 5.0</i> (4/17/14)	7.3 (criterion 5.6)	This criterion has been broken out into 3 separate items in order to allow for specific operationalization related to Parkinson's Disease and for multiple sclerosis.
<i>Version 5.0</i> (4/17/14)	7.3 (criterion 5.13)	Deleted this criterion since individuals with contractures will be captured with other criteria.
<i>Version 5.0</i> (4/17/14)	7.3 (criterion 5.20)	Revised the criterion to be specific to receiving PT related to the hip fracture and removed OT since this should not interfere with the study.
<i>Version 5.0</i> (4/17/14)	7.3 (criteria 6.11-6.13)	These three items were edited to capture recent surgeries and fractures of lower extremities to cover both the period prior to the hip fracture but also the period during screening for the study.
<i>Version 5.0</i> (4/17/14)	7.3 (criteria 7.1-7.3)	Deleted these three items since they do not cause a safety risk for participating in the PT interventions. These items will be handled like history of kidney stones and participants will not receive calcium supplementation.
<i>Version 5.0</i> (4/17/14)	Table 1	Table 1 was updated to reflect the edits to the criteria described above.
<i>Version 5.0</i> (4/17/14)	Table 3	Phases 1-3 have been removed from Table 3 since we have widened the window for randomization to include 0-20 weeks.

### Summary of Modifications to Protocol Version 4.0 for Version 4.0.1

<b>Version (date)</b>	<b>Section</b>	<b>Brief Summary of Modification</b>
<i>Version 4.0.1</i> (3/18/14)		When we recently submitted protocol Version 4.0 for approval by the DSMB, we inadvertently submitted a version that was not final. We are now submitting Version 4.0.1 which includes some minor editorial modifications to the version that has already been approved. Edits are limited to the summary table below and Table 3. We apologize for the error.
<i>Version 4.0.1</i> (3/18/14)	All sections	In consultation with our Clinical Direction Committee, we are allowing non-physician medical professionals to perform study activities related to evaluating medical eligibility and safety and to reviewing RAEs, provided those professionals are permitted by law to function autonomously (not under physician supervision) in the jurisdiction and the institution in which the clinical site is located. This change will facilitate clinical sites' access to appropriate clinicians who are available for time-sensitive study activities. "Clinical Site Physician" has been replaced with "Clinical Site Clinician" throughout the protocol.
<i>Version 4.0.1</i> (3/18/14)	Table 3	The allowable interval for telephone interviews has been widened. The telephone interview can occur up to one week before and up to three weeks after the target date. Table 3 has been modified to correctly reflect this time window.

<i>Version 4.0.1</i> (3/18/14)	8.2, 11.5, and Table 3	We have added 2 out-of-window time intervals in order to collect data for the 16- and 40-week follow-up visits outside the allowable window. The first out-of-window interval is 18-38 weeks post-randomization, which covers the period from the latest date for the 16-week visit to the earliest date for the 40-week visit. The second out-of-window interval is 44-68 weeks post-randomization, which covers the period from the latest date for the 40-week visit to 24 weeks later. Although assessment visits are always done as close as possible to the target date, this change will increase the probability of obtaining complete follow-up data, even for participants whose assessments are difficult to schedule.
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### Summary of Modifications to Protocol Version 3.0 for Version 4.0

<b>Version (date)</b>	<b>Section</b>	<b>Brief Summary of Modification</b>
<i>Version 4.0</i> (2/28/14)	All sections	In consultation with our Clinical Direction Committee, we are allowing other medical professionals who can function autonomously (not under physician supervision) to perform study activities related to evaluating medical eligibility, safety and reviewing RAEs. This will vary according to state regulations. This will facilitate clinical sites' access to appropriate clinicians who are available for time-sensitive activities. Clinical Site Physician has been replaced with Clinical Site Clinician throughout the protocol.
<i>Version 4.0</i> (2/28/14)	Executive Summary	Changes were made to the text to clarify that nutritional counseling will be provided to ensure adequate nutrient intake of 1.2-1.5 g protein/kg body weight inclusive of a healthy diet.
<i>Version 4.0</i> (2/28/14)	Table 1	Minor editorial changes were made to the eligibility criteria for clarity.
<i>Version 4.0</i> (2/28/14)	Table 3	The allowable interval of telephone interviews has been widened. The telephone interview can occur up to one week prior and up to three weeks after the target date.
<i>Version 4.0</i> (2/28/14)	10.3.3	A minor editorial change has been made for clarity. For the quadriceps strength test, the participant is not seated on the dynamometer; s/he is seated on the strength testing chair.
<i>Version 4.0</i> (2/28/14)	8.2, 11.5, and Table 3	We have added 2 out-of-window time intervals in order to collect data for the 16- and 40-week follow-up visits beyond the allowable window without resulting in a protocol deviation. The first out-of-window interval is between 18-38 weeks post-randomization, which covers the period from the maximum window for the 16-week visit to the minimum data for the 40-week visit. The second out-of-window interval is up to 68 weeks post-randomization (6 months after the maximum date for the 40-week visit).
<i>Version 4.0</i> (2/28/14)	13.2.3 and 13.4.3	Updated text to include review of RAEs for ancillary studies to CAP.
<i>Version 4.0</i> (2/28/14)	13.6 and 13.6.1	Minor editorial changes were made to expand the categories for RAE status and actions taken in response to the RAE.
<i>Version 4.0</i> (2/28/14)	20	Updates made to the Study Team Roster.

### Summary of Modifications to Protocol Version 2.1 for Version 3.0

<b>Version (date)</b>	<b>Section</b>	<b>Brief Summary of Modification</b>
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<i>Version 3.0</i> (2/12/13)	7.1, 7.5, 7.6, 17.2, Figure 2, and Table 1	We have made minor changes to the plan for eligibility screening and obtaining informed consent so that it allows for diversity in the procedures that will be implemented in the three clinical sites, accounting for local differences in staffing and institutional infrastructure. Exclusion criteria collected from the medical chart will continue to be obtained at phase 1. However, assessment of exclusion criteria requiring patient self-report has been moved to phase 2. Each clinical site will follow specific procedures for obtaining appropriate HIPAA authorizations and informed consent as stipulated and approved by their local IRBs.
<i>Version 3.0</i> (2/12/13)	7.3 (criterion 4.2)	Minor editorial changes were made to the eligibility criterion for clarity.
<i>Version 3.0</i> (2/12/13)	9.5.2	Minor editorial changes were made to the schedule for treatment fidelity visits based on recommendation from the Intervention Monitor.

**Summary of Modifications to Protocol Version 1.3 for Version 2.0 and 2.1**  
[Note: The edits made to protocol Version 2.1 originated from review by KAI]

<b>Version (date)</b>	<b>Section</b>	<b>Brief Summary of Modification</b>
<i>Version 2.1</i> (12/17/12)	3.2.3	The plan for distribution of the vitamins and supplements has been modified to be consistent with the MOP. Each treatment kit contains five individual packs, numbered 1-5. Packs 1-4 each contain a 4-week supply of vitamin D3, calcium, and a multivitamin. Pack 5 contains a 24-week supply that will be provided to participants at the conclusion of the 16-week intervention period.
<i>Version 2.1</i> (12/17/12)	6.2	We added clarification that randomization will only be performed by appropriate unblinded study personnel who have received training and certification on randomization procedures, including the clinical site PI, clinical site coordinator, or other unblinded personnel not performing evaluations. This is now consistent with the MOP. Further clarification has also been added about blinding of interventionists to study outcomes and about restricting access to the participant binder which will contain sensitive information about treatment assignment.
<i>Version 2.1</i> (12/17/12)	6.4	We added clarification that clinical site PIs and clinical site coordinators who are responsible for assigning work and assessing treatment fidelity for PTs in both groups are completely unblinded. Only those who will perform evaluations (clinical site visits and telephone interviews) after randomization and the Independent Safety Monitor (ISM) will be blinded to treatment assignment.
<i>Version 2.1</i> (12/17/12)	9.2	The section on the nutritional intervention has been revised to clarify that a participant who loses 2% or more body weight in a four-week period will receive another telephone consultation by the study RD, regardless of whether the participant is trying to lose weight. Nutritional experts serving on the advisory committee providing Specialized Support for Exercise and Nutrition believe that loss of 2% or more body weight in this elderly population warrants follow-up from a registered dietician, who can determine whether weight loss was intentional.
<i>Version 2.1</i> (12/17/12)	13 and Figures 5b-5d	Changes were made to this section to indicate that the responsibility for determining relatedness of RAEs will entirely be the responsibility of the independent safety monitor (ISM), who will remain blinded. RAE reports and supporting documents sent to the ISM will be redacted to conceal treatment assignment.

**Summary of Modifications to Protocol Version 1.3 for Version 2.0**

<b>Version (date)</b>	<b>Section</b>	<b>Brief Summary of Modification</b>
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<i>Version 2.0</i> (10/31/12)	All sections	Minor editorial changes and corrections were made throughout the document for clarity and consistency with the MOP. These changes can be seen with Track Changes. All significant changes are summarized in the remaining sections of this table.
<i>Version 2.0</i> (10/31/12)	All sections	Changes were made to the naming of the physical therapy interventions. “Shuttle Plus” is now PUSH. “TENS Plus” is now PULSE. We wanted to use names for the interventions that did not include the device name and that would be more meaningful and easy for the participants to remember.
<i>Version 2.0</i> (10/31/12)	All sections	In the original proposal, data capture, data management, and randomization were to be implemented by the Veterans Administration Cooperative Studies Program Coordinating Center (CSPCC) in Perry Point, MD. However, because of administrative and regulatory changes at the CSPCC, it was necessary to identify a different data group to handle these tasks. We have contracted with Axio Research, LLC (Seattle, WA) to provide data services. Throughout the current protocol version, “CSPCC” has been changed to “Axio Research, LLC” or “Axio” to reflect this change. References to DataFax (the data capture system that was proposed in the original protocol) have been removed to reflect the change to paper- and web-based data entry.
<i>Version 2.0</i> (10/31/12)	All sections	The name of the administrative database clinical sites will use to facilitate study management activities was changed from “tracking database” to “study management database” to more accurately reflect its role.
<i>Version 2.0</i> (10/31/12)	6.2	The section on randomization has been revised in light of modified procedures related to change to Axio as provider of data services.
<i>Version 2.0</i> (10/31/12)	6.2	“The date and time of randomization is the time of study entry for each participant” was changed to “The date of randomization will mark the start of follow-up for each participant”. This correction was made to avoid contradicting the statement that “Date of enrollment in the trial is defined as the date of informed consent” (7.6.1).
<i>Version 2.0</i> (10/31/12)	7.1 (Figure 2)	The algorithm for screening was updated to include correct terminology for the blood values for eligibility.
<i>Version 2.0</i> (10/31/12)	7.3 and Table 1	These were updated to include newly added exclusion criteria (4.6, 4.7, 4.8 and 4.9). The new items are mostly administrative in nature, but need to be included as reasons why someone is not eligible. A correction was made to item 5.18. The gait speed is still the same, but it is based on walking less than 4 meters in 40 seconds.
<i>Version 2.0</i> (10/31/12)	9.5.3 and 10.6.1	We have added Polar heart rate monitoring to our Treatment Fidelity Plan. This will allow us to monitor the physiologic response during the intervention sessions for all participants.
<i>Version 2.0</i> (10/31/12)	10.3.5	The distance of the fast walking speed test was corrected from 50 m to 50 ft.
<i>Version 2.0</i> (10/31/12)	11.1 (Table 2)	Table 2 was updated to reflect the current data collection form names and to delineate which assessments will be collected on paper forms and which will be submitted via web-entry.
<i>Version 2.0</i> (10/31/12)	11.5 and Figure 4	The process for adjudication of the primary outcome has been modified. The emphasis in the revised adjudication process is on reducing the number of participants with a missing primary outcome by assigning treatment failure status to participants with a high probability of being unable to walk at least 300 m in six seconds. Figure 4 has been revised to correspond to the modified adjudication process.
<i>Version 2.0</i> (10/31/12))	13	Minor editorial changes were made throughout this section to ensure consistency with our definitions of reportable adverse events versus expected adverse events,
<i>Version 2.0</i> (10/31/12)	15.1	The analysis plan was modified to reflect changes in the adjudication procedure.
<i>Version 2.0</i> (10/31/12)	16.1, 16.2, 16.3, 16.4	The sections on data capture, data management, and data security have been revised in light of modified procedures related to change to Axio as provider of data services.
<i>Version 2.0</i> (10/31/12)	20	Updates made to the Study Team Roster.



### Summary of Modifications to Protocol Version 1.2 for Version 1.3

Version (date)	Section	Brief Summary of Modification
Version 1.3 (5/31/2012)	15.5	Changes were made to the text to clarify the inefficacy/harm boundary of the interim analysis plan.

### Summary of Modifications to Protocol Version 1.1 for Version 1.2

Version (date)	Section	Brief Summary of Modification
Version 1.2 (4/17/2012)	13.4.3	Edited this section for clarity using the term injury consistently to delineate events that need to be reported while under study supervision.
Version 1.2 (4/17/2012)	7.2 (criterion 1.7)	Moved this item from eligibility section 6 since it is an initial inclusion criterion.
Version 1.2 (4/17/2012)	7.3 (criterion 4.5)	Added a criterion to capture the maximum randomization date of 14 weeks post admission.
Version 1.2 (4/17/2012)	7.3 (criterion 5.20)	Added a criterion for still receiving PT or OT at time of randomization.
Version 1.2 (4/17/2012)	7.3 (criterion 6.11)	Added a criterion that excludes patients with a prior hip fracture or total hip replacement on the same side as the study index hip fracture to avoid misclassification of the injury when the source could be due to failure of prior surgery or prosthesis.
Version 1.2 (4/17/2012)	7.3 (criteria 6.12 and 6.13)	Added 2 criteria to exclude patients who are in the process of recovering from another recent lower extremity musculoskeletal event or procedure.
Version 1.2 (4/17/2012)	13.5, 13.6, 13.7, 13.8	Updated text and figures 5b-5d to incorporate revised plan for reporting SAEs such that the CCC will be responsible for reporting SAEs to the DSMB and NIA. Clinical site staff will report SAEs to the CCC which then forward to the DSMB and NIA directly.
Version 1.2 (4/17/2012)	15.5	In response to a query from the DSMB, we have clarified that we are not proposing a futility analysis and have provided more details about our approach to the interim analyses.
Version 1.2 (4/17/2012)	15.6	Power was re-calculated using R software to account for 1) the group sequential design and 2) the impact of non-compliance on variances.

### Summary of Modifications to Protocol Version 1.0 for Version 1.1

Version (date)	Section	Brief Summary of Modification
Version 1.1 (1/26/2012)		<i>Incorporates recommendations from the DSMB meeting on 12/12/2011 and Steering Committee's edits</i>
Version 1.1 (1/26/2012)	Executive Summary, 4.2, 10.4.5, 15.2.2	Corrected wording of tertiary outcome to be consistent across the protocol: "increase of 50 meters or more in distance walked."
Version 1.1 (1/26/2012)	Executive Summary, 3.2.3, 6.3, 9.3, 12.1.7	Increased the amount of time participants will receive study medications to include the period beyond the 16-week intervention period. Participants will now receive vitamin D, calcium, and multivitamin daily for the entire 40-week study period, as per the DSMB recommendation.
Version 1.1 (1/26/2012)	Executive Summary, 3.2.3, 6.3, 9.3	Removed one-time loading dose of 100,000 IU of vitamin D3 at randomization due to safety concerns in the recent literature and as per DSMB recommendation.
Version 1.1 (1/26/2012)	Executive Summary, 3.2.3, 6.3, 9.3	Edited the amount of calcium provided from 1000 mg (500 mg twice a day), to 600 mg once a day as per DSMB recommendation.
Version 1.1 (1/26/2012)	Executive Summary, 9.2, 12.1.7	Changed procedure for nutritional intervention based on recommendation of Clinical Direction Committee. If a participant has a serum albumin level 2.5-3.5, he/she will receive a diet consultation visit from the registered dietitian following the same protocol as for those who are at risk according to the Mini Nutritional Assessment –Short Form.

<i>Version 1.1</i> <i>(1/26/2012)</i>	3.1.6 (DCC)	Added "...implement the data analysis plan" to DCC's list of responsibilities.
<i>Version 1.1</i> <i>(1/26/2012)</i>	3.2.3, 12.1.7	Added calculated creatinine clearance < 30 ml/min obtained from blood draw as a contraindication for calcium supplementation. Participants with contraindications for calcium will receive vitamin D and multivitamin.
<i>Version 1.1</i> <i>(1/26/2012)</i>	6.1 (Figure 1)	Included revised Figure 1 for clarity.
<i>Version 1.1</i> <i>(1/26/2012)</i>	4.2	Corrected an error. "...following initiation of the intervention" was replaced by "...following randomization."
<i>Version 1.1</i> <i>(1/26/2012)</i>	7.1, 10.1, 11.4 (Table 3)	Based on the DSMB's recommendations, we have added three exclusion criteria: hemoglobin < 9 g/dl, calculated creatinine clearance < 15 ml/min, and serum albumin < 2.5 g/dl. The blood can be obtained between phases 2 and 3, but no more than 4 weeks prior to randomization.
<i>Version 1.1</i> <i>(1/26/2012)</i>	7.1	Updated Figure 2 incorporating the blood draw and additional exclusion criteria and possibility of phase 2 being an in-person visit.
<i>Version 1.1</i> <i>(1/26/2012)</i>	7.1, 7.5, 7.6, 17.2	We are no longer requiring that informed consent be obtained at the baseline visit (phase 3 screening). For greater flexibility and to maximize enrollment, we are now allowing informed consent to be obtained at any time prior to data collection that is not covered by the HIPAA Partial Privacy Waiver.
<i>Version 1.1</i> <i>(1/26/2012)</i>	7.2 (criterion 3)	Edited item for clarity.
<i>Version 1.1</i> <i>(1/26/2012)</i>	7.2 (criterion 3.3)	Moved this item from eligibility section 5 since it is defining our target population.
<i>Version 1.1</i> <i>(1/26/2012)</i>	7.2 (criterion 5.1)	As per DSMB, added new exclusion criterion of calculated creatinine clearance < 15 ml/min as a medical impediment to participation.
<i>Version 1.1</i> <i>(1/26/2012)</i>	7.2 (criterion 5.2)	As per DSMB, added new exclusion criterion of serum albumin < 2.5 g/dl as a medical impediment to participation.
<i>Version 1.1</i> <i>(1/26/2012)</i>	7.2 (criterion 5.5)	Deleted "legally blind" since we capture this in criterion 5.4 (severe sensory impairment (visual or hearing)).
<i>Version 1.1</i> <i>(1/26/2012)</i>	7.2 (criterion 5.7)	"History of Parkinson's disease, multiple sclerosis...." moved from eligibility section 6 since the criterion captures medical impediments to participation.
<i>Version 1.1</i> <i>(1/26/2012)</i>	7.2 (criterion 6.1)	As per DSMB, added new exclusion criterion of hemoglobin < 9 g/dl for safety.
<i>Version 1.1</i> <i>(1/26/2012)</i>	7.2 (criterion 7)	Edited the category so that it is just contraindications for calcium supplementation.
<i>Version 1.1</i> <i>(1/26/2012)</i>	7.2 (criterion 7.2)	Deleted glomerular filtration rate (<30 ml/min) obtained from the medical chart since we are now obtaining a calculated creatinine clearance from blood drawn within 4 weeks prior to randomization. A calculated creatinine clearance <30 ml/min will be a contraindication for receiving calcium supplementation.
<i>Version 1.1</i> <i>(1/26/2012)</i>	7.2 (criterion 8)	Deleted "Other" as a criterion.
<i>Version 1.1</i> <i>(1/26/2012)</i>	7.2 (Table 1)	Edited Table 1 to reflect all changes to the eligibility criteria.
<i>Version 1.1</i> <i>(1/26/2012)</i>	9.2, 10.6.1, 11.3	Previously, we planned to assess adherence to study medications only during the 16-week intervention period. We now propose to also assess adherence to study medications during the 24-week post-intervention period using self-report questions administered during the 4-week phone calls.
<i>Version 1.1</i> <i>(1/26/2012)</i>	10.1.1	Correction: Height will be measured in feet and inches and weight will be measured in pounds.
<i>Version 1.1</i> <i>(1/26/2012)</i>	10.3.2	Added clarification on the scoring of the balance measure.
<i>Version 1.1</i> <i>(1/26/2012)</i>	10.3.5	Clarified that the time required to walk 50 meters is the measure for fast walking speed.
<i>Version 1.1</i> <i>(1/26/2012)</i>	10.4.6	Removed incorrect statement about summing the scores for obtaining the standing balance subscale.
<i>Version 1.1</i> <i>(1/26/2012)</i>	11 (Table 2)	Updated the table to reflect the timing of informed consent, addition of a blood draw, and assessment of adherence to study medications beyond intervention period.

<i>Version 1.1</i> <i>(1/26/2012)</i>	11.4 (Table 3)	With the addition of the blood, the timing of informed consent and phase 2 screening has been widened. The new time windows reflect that each can occur between 4-14 weeks post-admission
<i>Version 1.1</i> <i>(1/26/2012)</i>	11.5	<p>We now require that the Six Minute Walk Test (SMWT) be administered only by study staff whereas previously we allowed administration by non-study staff. We have clarified that, at follow-up, self-report or proxy-report of walking ability will be used for participants who cannot perform the SMWT because of non-physical reasons (e.g., cognitive or sensory impairment).</p> <p>We have clarified that our approach to classification will reduce bias by maximizing the number of participants who are included in the analysis for the primary outcome.</p> <p>We have removed the sample self/proxy-report question that will be used to assess walking ability. The actual question will be added to the data collection forms and the Manual of Procedures.</p> <p>The adjudication process has been clarified.</p>
<i>Version 1.1</i> <i>(1/26/2012)</i>	11.5, 15.1	At follow-up, participants who cannot perform the SMWT because of illness, sickness, or death will be considered treatment failures in both the primary and secondary analyses. They were considered missing in secondary analysis in the previous version.
<i>Version 1.1</i> <i>(1/26/2012)</i>	11.5 (Figure 4)	Updated Figure 4 to reflect changes to the classification of the primary outcome as described in section 11.5.
<i>Version 1.1</i> <i>(1/26/2012)</i>	13.5, 13.8	Updated text and Figures 5b-5d to incorporate NIH reporting timelines for serious adverse events. SAEs will be reported to the DSMB and NIA by the study chair within 48 hours of when the event is known and reported by study staff.
<i>Version 1.1</i> <i>(1/26/2012)</i>	15.1	Clarified primary outcome as "...able to walk 300 meters or more in six minutes..."
<i>Version 1.1</i> <i>(1/26/2012)</i>	15.5	<p>We have replaced "beta spending" with "lower bound spending" because the spending is actually computed under the null hypothesis.</p> <p>Our interim analysis is asymmetrical, but we plan to perform a two-sided (symmetrical) test at the end. To clarify, we have added: "The two-sided test with nominal alpha=0.05 will be operationalized at the final analysis by rejecting if <math> Z  &gt; 2.03</math>."</p>
<i>Version 1.1</i> <i>(1/26/2012)</i>	15.6.2	The detectable effect size for the economic evaluation was recalculated with alpha=0.05, instead of alpha=0.01.
<i>Version 1.1</i> <i>(1/26/2012)</i>	16.4	Clarified that site visit reports will only be sent to the Steering Committee (SC) not to the DSMB and the SC.
<i>Version 1.1</i> <i>(1/26/2012)</i>	20	Updates made to the Study Team Roster.

# **Improving Community Ambulation after Hip Fracture**

**Study Chair and Principal Investigator:**

Jay Magaziner, PhD, MSHyg

**Supported by:**

**The National Institute on Aging**

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## Table of Contents

Section 1: Executive Summary .....	1
Section 2: Participating Clinical Sites .....	4
Section 3: Study Organization.....	5
3.1 Study Administration .....	5
3.1.1 Study Chair.....	5
3.1.2 National Institute on Aging (NIA) .....	5
3.1.3 Data and Safety Monitoring Board (DSMB) .....	6
3.1.4 Steering Committee (SC) .....	6
3.1.5 Clinical Coordinating Center (CCC) .....	7
3.1.6 Data Coordinating Center (DCC) .....	7
3.1.7 Economic Evaluation Core (EEC) .....	8
3.2 Scientific Oversight .....	8
3.2.1 Scientific Oversight Committees (SOC) .....	8
3.2.2 Specialized Support for Exercise and Nutrition .....	9
3.2.3 UMB Investigational Drug Services (IDS) .....	9
3.2.4 Study Clinical Sites.....	10
3.3 Organizational Chart .....	11
Section 4: Study Objectives .....	12
4.1 Primary Objective.....	12
4.2 Secondary Objectives .....	12
Section 5: Background .....	12
5.1 Residual Deficits in Precursors of Community Ambulation .....	13
5.2 Exercise Studies in Persons after Hip Fracture.....	14
5.3 Rationale for the Interventions .....	15
5.4 Primary Outcome Measure .....	17
5.5 Economic Evaluation of Interventions to Reduce Post-fracture Disability.....	18
Section 6: Study Design .....	18
6.1 Overview of Study Design .....	18
6.2 Randomization .....	19
6.3 Interventions.....	19
6.4 Blinding of Study Staff.....	20
Section 7: Selection and Enrollment of Participants.....	20
7.1 Eligibility .....	20
7.2 Inclusion Criteria (Target Population).....	21
7.3 Exclusion Criteria .....	21
7.4 Identification of Hip Fracture Patients .....	22
7.5 Participant Screening and Recruitment.....	23
7.6 Informed Consent.....	23
7.6.1 Enrollment .....	24
Section 8: Retention .....	24
8.1 Retention Promotion Efforts .....	24
8.2 Drop-out Prevention Efforts.....	25
8.3 Monitoring Recruitment and Retention.....	25
8.3.1 Monitoring and Quality Control of Recruitment and Retention .....	25
Section 9: Study Interventions.....	26
9.1 Overview .....	26
9.2 Nutritional Intervention .....	26
9.3 PUSH Intervention .....	27
9.4 PULSE Intervention.....	29
9.5 Treatment Fidelity Plan .....	29
9.5.1 Initial Training for Procedural Reliability .....	29
9.5.2 Ensuring Ongoing Competency .....	30

9.5.3	Monitoring Physiologic Response .....	30
9.6	Scheduling Intervention Visits .....	31
Section 10:	Study Measures .....	32
10.1	Screening Evaluations .....	32
10.1.1	Weight, Height, and BMI .....	32
10.1.2	Modified Mini-Mental State Examination (3MS) .....	32
10.2	Primary Outcome Measure: Community Ambulation .....	32
10.3	Secondary Outcome Measures - Precursors to Community Ambulation .....	33
10.3.1	Endurance .....	33
10.3.2	Balance .....	33
10.3.3	Quadriceps Muscle Strength .....	33
10.3.4	Lower Extremity Function .....	33
10.3.5	Fast Walking Speed .....	34
10.3.6	Cost Effectiveness: Health Care Utilization .....	34
10.4	Tertiary Outcomes.....	34
10.4.1	Activities of Daily Living (ADLs).....	34
10.4.2	Quality of Life (SF-36) .....	35
10.4.3	Balance Confidence .....	35
10.4.4	Yale Physical Activity Survey (YPAS) .....	35
10.4.5	Improvement in Walking .....	35
10.4.6	Short Physical Performance Battery (SPPB).....	35
10.4.7	Depressive Symptoms .....	36
10.4.8	Cognitive Status .....	36
10.4.9	Nutritional Status .....	36
10.5	Clinical and Background Characteristics.....	36
10.5.1	Demographic and Surgical Characteristics .....	37
10.5.2	Functional Comorbidity Index.....	37
10.5.3	Psychological Measures.....	37
10.6	Other Measures to be Monitored .....	37
10.6.1	Adherence .....	37
10.6.2	Weight Loss.....	38
10.6.3	Reportable Adverse Events (RAEs).....	38
10.6.4	Expected Adverse Events (AEs) .....	38
Section 11:	Study Procedures.....	38
11.1	Baseline Assessments .....	38
11.2	Follow-up Assessment .....	39
11.3	Telephone Interviews .....	39
11.4	Timing of Study Procedures.....	39
11.5	Primary Outcome Classification .....	40
Section 12:	Safety Assessments.....	43
12.1	Participant Safety Parameters: Methods and Timing.....	43
12.1.1	Pre-Intervention Safety Screening .....	43
12.1.2	Safety Considerations for Study Assessments.....	43
12.1.3	Safety Considerations for the PUSH Intervention .....	44
12.1.4	Safety Measures during the PUSH Intervention.....	45
12.1.5	Safety Considerations for the PULSE Intervention.....	45
12.1.6	Safety Measures for the PULSE Intervention.....	47
12.1.7	Safety Considerations for the Nutritional Intervention .....	48
12.1.8	Safety Measures for the Nutritional Intervention .....	48
12.2	Confidentiality.....	49
12.3	Participant Education about Potential Risks .....	49
Section 13:	Reportable Adverse Events (RAEs) and Expected Adverse Events (AEs).....	49
13.1	Overview .....	49
13.2	Classifying Adverse Events.....	50

13.2.1	Severity .....	50
13.2.2	Expectedness .....	50
13.2.3	Relatedness .....	51
13.3	Expected AEs.....	51
13.4	Reportable AEs .....	51
13.4.1	Serious Adverse Event (SAE) .....	51
13.4.2	Unexpected Adverse Event.....	52
13.4.3	Injury that Occurs while Under the Supervision of Study Related Personnel.....	52
13.5	Expected AE and RAE Collection and Reporting.....	52
13.6	Evaluation and Follow-up of RAEs.....	57
13.6.1	Action Taken .....	57
13.7	Responsibilities .....	58
13.7.1	Clinical Site Clinician .....	58
13.7.2	Independent Safety Monitor (ISM).....	58
13.8	Reporting Expected AEs and RAEs to the DSMB .....	58
Section 14:	Intervention Discontinuation .....	59
Section 15:	Data Analyses .....	59
15.1	Primary Aim.....	59
15.2	Secondary Objectives .....	61
15.2.1	Delayed and Sustained Effects .....	61
15.2.2	Secondary and Tertiary Outcomes.....	62
15.2.3	Cost-Effectiveness of Interventions.....	62
15.3	Missing Data .....	63
15.4	Nonadherence.....	63
15.5	Interim Analyses.....	64
15.6	Sample Size Adequacy .....	64
15.6.1	Primary Aim.....	64
15.6.2	Secondary Aims .....	65
Section 16:	Data Capture, Data Management, and Quality Assurance .....	66
16.1	Overview .....	66
16.2	Data Capture.....	67
16.3	Data Management.....	67
16.3.1	Processing of Paper Data Forms .....	67
16.3.2	Processing of Web-Entry Data .....	68
16.3.3	Reportable Adverse Events Coding .....	68
16.3.4	Extraction of Data for Analysis and Reporting.....	68
16.4	Protection of Data .....	69
16.4.1	Physical Security and Backup .....	69
16.4.2	Software Systems Security.....	71
16.5	Study Management Database.....	71
16.6	Quality Assurance (QA) .....	71
16.6.1	Training .....	72
16.6.2	Quality Assurance Oversight.....	72
16.6.3	Protocol Deviations .....	72
16.7	Monitoring .....	73
Section 17:	Participant Rights and Confidentiality.....	74
17.1	Institutional Review Board (IRB) .....	74
17.2	Informed Consent Forms (ICF) .....	75
17.2.1	Disposition of Informed Consent Forms .....	75
17.2.2	HIPAA Authorization.....	75
17.3	Participant Confidentiality.....	75
Section 18:	Research Publication Policy.....	76
Section 19:	Ancillary Studies Policies .....	77
19.1	Concurrent Studies .....	77

Section 20: Study Team Roster .....	79
Section 21: References .....	91



## List of Tables

<b>Table</b>	<b>Title</b>	<b>Section</b>
Table 1	Timing of Study Procedures	11.4
Table 2	Safety Alerts and Actions for Study Assessments	12.1.2
Table 3	Safety Alerts and Actions for Interventions	12.1.5
Table 4	Anticipated Critical Values for Each Planned Analysis	15.5
Table 5	Power to Detect Differences in Proportions	15.6.1

## List of Figures

<b>Figure</b>	<b>Title</b>	<b>Section</b>
Figure 1	Timeline for Recruitment, Randomization, and Follow-up	6.1
Figure 2	Algorithm for Screening	7.1
Figure 3	Shuttle Device	9.3
Figure 4	Classification and Analysis of Primary Outcome	11.5
Figure 5a	Collection and Reporting Process for Expected AEs	13.5
Figure 5b	Collection and Reporting Process for RAEs Collected During Standardized Telephone Interviews	13.5
Figure 5c	Collection and Reporting Process for RAEs Identified Anytime Other than During a Standardized Telephone Interview	13.5
Figure 5d	CCC Reporting Process for RAEs	13.6

## List of Abbreviations

<b>Term</b>	<b>Abbr.</b>	<b>Term</b>	<b>Abbr.</b>
Active range of motion	AROM	Life Orientation Test-Revised	LOT-R
Activities of daily living	ADL	Manual of Procedures	MOP
Activities-Specific Balance Confidence	ABC	Mini Nutritional Assessment-Short Form	MNA®-SF
Adverse event	AE	Modified Mini-Mental State examination	3MS
Arcadia University	AU	Modified Physical Performance Test	mPPT
Arthrogenic muscle response	AMR	National Health and Aging Trends Study	NHATS
Baltimore Hip Studies	BHS	National Institute on Aging	NIA
Body mass index	BMI	National Institutes of Health	NIH
Cardiopulmonary resuscitation	CPR	Peak oxygen uptake	VO <sub>2</sub> peak
Center for Epidemiologic Studies Depression scale	CES-D	Pepper Assessment Tool for Disability	PAT-D
Center for Medicare and Medicaid Services	CMS	Physical therapist	PT
Clinical Coordinating Center	CCC	Primary care provider	PCP
Community Ambulation Project	CAP	Principal investigator	PI
Data and Safety Monitoring Board	DSMB	Protected Health Information	PHI
Data Coordinating Center	DCC	Publications and Ancillary Studies Committee	PASC
Data Management Plan	DMP	Quality-adjusted life year	QALY
Diastolic blood pressure	DBP	Quality assurance	QA
Economic Evaluation Core	EEC	Quality control	QC
Eight-repetition maximum	8-RM	Randomized controlled trial	RCT
Emergency Medical Service	EMS	Range of motion	ROM
Functional Comorbidity Index	FCI	Rating of perceived exertion	RPE
Generalized estimating equations	GEE	Redundant Array of Independent Risks	RAID
Health Insurance Portability and Accountability Act	HIPAA	Registered dietician	RD
Heart rate	HR	Reportable Adverse Event	RAE
Heart rate reserve	HRR	Resource-Based Relative Value Scale	RBRVS
Heating, ventilation and air conditioning	HVAC	Scientific Oversight Committee	SOC
Incremental net benefits	INB	Serious adverse event	SAE
Independent Safety Monitor	ISM	Short Physical Performance Battery	SPPB
Information Technology	IT	Six-Minute Walk Test	SMWT
Informed Consent Form	ICF	Skilled nursing facility	SNF
Institutional Review Board	IRB	Spine Patient Outcomes Research Trial	SPORT
Investigational Drug Services	IDS	Standard Operating Procedure	SOP
Intention-to-treat	ITT	Statistical Analysis Software	SAS
Intervention Monitor	IM	Steering Committee	SC
		Systolic blood pressure	SBP

<b>Term</b>	<b>Abbr.</b>	<b>Term</b>	<b>Abbr.</b>
Transcutaneous electrical nerve stimulation	TENS	University of Maryland Baltimore	UMB
University of Connecticut Health Center	UCHC	Weighted estimating equations	WEE
		Yale Physical Activity Survey	YPAS

## Section 1: Executive Summary

Despite improvements in medical management, significant residual disability remains in older persons after a hip fracture.<sup>1-3</sup> The goal of current clinical practice is independent, safe *household* ambulation two to three months after surgery.<sup>4</sup> Hip fracture-acquired dependency in functional activities of daily living persists well beyond three months post-surgery. One year after hip fracture, 20% of patients need help putting on pants, 50% need assistance to walk, and 90% need assistance to climb stairs.<sup>2</sup> This residual disability indicates that current standard Medicare-reimbursed post-hip fracture rehabilitation (i.e., usual care) fails to return many patients to pre-fracture levels of function. In contrast to stroke and heart disease, other commonly occurring acute conditions in the older population, there are few intervention trials focused on decreasing disability following hip fracture. None of the trials for hip fracture has examined the effect of early post-fracture intervention on the ability to ambulate at a level required for independent function in the community (i.e., *community ambulation*). Thus, there is a paucity of evidence to justify extending medical management beyond usual care in persons following hip fracture to achieve community, rather than merely household, ambulation.

### Study Title

Improving Community Ambulation after Hip Fracture (hereafter referred to as the Community Ambulation Project or “CAP”)

### Objectives

The primary outcome will be ability to walk 300 meters or more in six minutes at the end of the 16-week intervention period. The goal is to enable older adults who have experienced a hip fracture to recover sufficiently to become community ambulators. In addition, the effect of the interventions on five precursors for community ambulation will be examined, as will the cost-effectiveness of the interventions, and the effect on a set of tertiary outcomes. Precursors to community ambulation include measures of endurance, dynamic balance, walking speed, quadriceps strength, and lower extremity function. Tertiary outcomes include activities of daily living (ADLs), quality of life, physical activity, lower extremity physical performance, balance confidence, increase of 50 meters or more in distance walked in six minutes, nutritional status, cognitive status, and depressive symptoms.

### Design and Outcomes

A randomized controlled trial (RCT) including 210 older adults who have experienced a hip fracture will be carried out at three clinical sites with half of the subjects receiving a specific multi-component intervention (PUSH) and the other half receiving a non-specific multi-component intervention (PULSE). Randomization of 210 participants meeting eligibility criteria will take place after post-acute rehabilitation ends, up to 26 weeks after admission to the hospital for hip fracture. The primary endpoint will be measured using the Six-Minute Walk Test (SMWT) at 16 weeks after randomization. Patients age 60 and older who have had surgical repair for hip fracture will be identified at the three clinical sites and evaluated for eligibility. Following consent to participate, eligible participants will undergo a comprehensive baseline assessment. Participants completing the entire baseline assessment will be randomized to one of the two treatment groups.

The two groups will be compared on measures of endurance, dynamic balance, walking speed, quadriceps strength, and lower extremity function using the distance walked in six minutes, Short Physical Performance Battery (SPPB), dynamometry for quadriceps strength, and Modified Physical Performance Test (mPPT). Resource utilization will be tracked using

telephone calls every four weeks beginning four weeks post-randomization. The economic value of the interventions will be determined by assessing the impact on quality-adjusted life years (QALYs), cost, and cost per QALY gained over the period following randomization. The cost-effectiveness analyses will address both the within trial comparison of the study interventions and a model-based comparison of the study interventions and usual care. This RCT will also compare the effect of the interventions on the following tertiary outcomes that are related to community ambulation: ADLs, balance confidence, quality of life, physical activity, lower extremity physical performance, depressive symptoms, increase of 50 meters or more in distance walked in six minutes, cognitive status, and nutritional status. Telephone interviews every four weeks will also obtain information on adverse events (AEs), and will help reduce loss to follow-up by maintaining ongoing rapport with participants.

For participants randomized prior to version 10.0 of the protocol, follow-up assessment visits occurred 16 weeks and 40 weeks from the date of randomization and telephone interviews were conducted every four weeks during the 40-week study period for a total of 10 telephone interviews. For participants consented under version 10.0 of the protocol, all follow-up will end at 16 weeks post-randomization.

In version 11.0 of the protocol, we will eliminate several secondary and tertiary outcome measures.

### **Interventions and Duration**

Participants will be randomly assigned to one of two treatment groups: 1) PUSH or 2) PULSE. Within a week of randomization, participants will initiate the intervention with a physical therapist (PT) in their home and receive counseling with a registered dietician to ensure body weight stability and adequate nutrient intake inclusive of a healthy diet. Participants in both intervention groups will also receive vitamin D, calcium and multivitamin supplements during the 16-week study period.

Both groups will receive 32 visits of approximately 60 minutes duration from a study PT. Participants will receive two visits per week, on non-consecutive days, for 16 weeks. Visits will take place in the participant's place of residence.

#### PUSH Intervention

The PUSH 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. 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). 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.

### PULSE Intervention

The PULSE intervention group will receive flexibility exercises, AROM for the upper and lower extremities, breathing exercises and transcutaneous electrical nerve stimulation (TENS). During the AROM exercises, participants will be working to increase flexibility and range of motion in order to increase the motion the participant produces. The exercises will include the neck, shoulders, arms, trunk, hips, knees and ankles. During all of the AROM exercises, the participant will focus on deep breathing techniques. Progression will be gradual by beginning with three repetitions and slowly progressing to 10 repetitions. We will add a second set of exercises when necessary. This portion of the session will last approximately 20-30 minutes.

After the AROM exercises, the second part of the session will use sensory level electrical stimulation on lower extremity muscle groups. The TENS portion of intervention is intended to decrease pain thereby allowing greater ease of mobility. Conventional TENS uses low-level electrical current to stimulate superficial cutaneous nerve fibers through the skin. The amount of current for sensory level stimulation is that level which the participant detects as a "tingling" sensation and is not high enough to produce a visible muscle contraction (below motor threshold).<sup>5</sup> Flexible carbonized, disposable electrodes coated with a self-adhesive conductive polymer will be applied to the skin. The electrodes will be placed bilaterally near the motor points on muscle bellies (the gluteal complex, the quadriceps, and the gastrocnemius) for seven minutes per muscle group. The muscle regions selected are important for function after hip fracture.

### Nutrition Intervention

Given the importance of maintaining nutrition in both study groups, we will provide all participants (regardless of group) with 2000 IU vitamin D3, 600 mg of calcium, and a multivitamin daily for the 16-week study period. 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 randomization to assess nutritional risk using the Mini Nutritional Assessment-Short Form (MNA®-SF).<sup>6</sup> Those who score  $\leq 7$  (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) from our study in their place of residence within seven days of randomization. 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.<sup>7-9</sup> 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 randomization. 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  $\geq 12$  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 randomization 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.

Participants randomized prior to version 10.0 of the protocol received vitamin D, calcium, and multivitamin supplements for a total of 40 weeks. Participants consented under version 10.0 of the protocol will receive vitamin D, calcium, and multivitamin supplements for 16 weeks post-randomization.

### **Sample Size and Population**

The target sample size is 210 randomized hip fracture patients across three clinical sites (with approximately 35 in each treatment group at each site). Study inclusion criteria are: 1) Closed, non-pathologic, minimal trauma hip fracture with surgical fixation; 2) Age 60 or older at time of randomization; 3) Living in the community at time of fracture and at time of randomization; and 4) Ambulating without human assistance during the two months prior to fracture. Participants for whom it is not safe to participate in the interventions will be excluded, as will those who are very unlikely to benefit and in whom the interventions are not feasible.

## **Section 2: Participating Clinical Sites**

### **Arcadia University (1)**

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### **University of Maryland Baltimore (2)**

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### **University of Connecticut Health Center (3)**

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## Section 3: Study Organization

The Community Ambulation Project (CAP) is a multi-center clinical trial with a Clinical Coordinating Center (CCC) and Data Coordinating Center (DCC) at the University of Maryland Baltimore, an Economic Evaluation Core (EEC) at Dartmouth College, and three clinical sites. In addition to these units, the project will have a Steering Committee (SC) and three Scientific Oversight Committees (SOCs) that will provide expertise needed to conduct this investigation. There will also be a sub-committee that includes a group of experts who will provide support on exercise and nutrition in older adults. A project Organizational Chart is provided in section 3.3. Each clinical site will be affiliated with a university (University of Maryland Baltimore, Arcadia University, and University of Connecticut) and will be recruiting older adults who have experienced a hip fracture in their surrounding geographic areas. All key personnel have collaborated on the design of this trial; most will have multiple roles in its execution, based on individual areas of expertise. Please see Section 20: 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
- Serving as chair of the SC
- Administering logistics for the Data and Safety Monitoring Board (DSMB) in consultation with the NIA program official
- Working with investigators and staff in the CCC, DCC, EEC, clinical sites, and SOCs to maximize collaboration
- Providing updates on progress to the NIA
- Participating in visits to clinical sites to assess quality and assist with problems
- Defining analyses of study data
- Overseeing manuscript preparation

In the unlikely event the study chair becomes unable to serve, the next most senior investigator from UMB and deputy director of the DCC for the trial will replace the study chair and become co-chair of the SC; the current co-chair will become study chair.

#### 3.1.2 National Institute on Aging (NIA)

This is an investigator-initiated project and funding is provided by an R01 grant. The funding agency is the NIA. The NIA will appoint members of the DSMB, who will review study data and safety and report to the NIA program official. The NIA program official will then report the outcome of DSMB review to the NIA director following established internal procedures. 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)**

Members of the DSMB will be appointed by and report to the NIA. They will monitor accruing data in order to confirm that the participants in the trial are being cared for safely.

Responsibilities of the DSMB will include:

- Review the research protocol, informed consent documents and plans for data and safety monitoring
- Advise the NIA on the readiness of the study staff to initiate recruitment
- Evaluate the progress of the trial, including periodic assessments of data quality and timeliness, recruitment, accrual and retention, participant risk versus benefit, performance of the trial sites, and other factors that can affect study outcome
- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial
- Review, approve, and monitor ancillary studies
- Review study performance, make recommendations and assist in the resolution of problems reported by the PI
- Protect the safety of the study participants
- Report to NIA on the safety and progress of the trial
- Make recommendations to the NIA and the PI concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study
- If appropriate, review the results of interim analyses in accordance with stopping guidelines, which are clearly defined in advance of data analysis and have the approval of the DSMB
- Ensure the confidentiality of the study data and the results of monitoring
- Assist the NIA by commenting on any problems with study conduct, enrollment, sample size and/or data collection

The DSMB will discharge itself from its duties when the study is complete. Study completion will be considered in consultation with the PI and NIA after no further outcome data are being collected in the main study and the main paper reporting on the primary outcome has been published.

### **3.1.4 Steering Committee (SC)**

The SC 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 and making final determinations regarding continued participation by a clinical site
- Appointing and charging the oversight committees and subcommittees described below
- Implementing recommendations of the DSMB

Voting membership has been established within the SC and includes the co-chairs of the SC, CCC director, DCC director, EEC director, and one member from each clinical site. All major scientific decisions will be determined by simple majority vote of the voting members of the SC. The study chair and co-chair will share one vote and will only vote if there is a tie. If the study

chair and co-chair disagree, the study chair will make the final decision. The SC will meet regularly (no less than monthly) throughout the study. All voting members, as well other investigators and the NIA program official, will be invited to participate.

### **3.1.5 Clinical Coordinating Center (CCC)**

The CCC will be primarily responsible for managing study operations and ensuring adherence to the study protocol. Responsibilities will include:

- Developing protocols and the manual of procedures (MOP)
- Tracking protocol amendments and ensuring their implementation
- Providing study materials to clinical sites
- Procuring equipment and materials
- Tracking protocol deviations and developing Corrective Action Plans
- Tracking the implementation of the Corrective Action Plans
- Organizing and providing staff support for meetings of SOCs
- Recording minutes from meetings
- Organizing training sessions of site coordinators, evaluators, dieticians, and PTs
- Providing training related to clinical operation of study
- Producing documents and forms in collaboration with the DCC
- Developing study management databases for monitoring study activity at each clinical site
- Classifying reportable adverse events (RAEs)
- Developing quality assurance plans
- Participating in quality assurance visits to the clinical sites
- Tracking submissions and amendments to the UMB Institutional Review Board (IRB)
- Tracking human subjects training and certification
- Interfacing with UMB Investigational Drug Services (IDS) to ensure proper dispensing of the vitamins/supplements (Please see section 3.2.3 for more information on the IDS.)

### **3.1.6 Data Coordinating Center (DCC)**

The DCC's primary responsibility will be to manage data operations, monitor adherence to the study protocol and implement the data analysis plan. Responsibilities will include:

- Developing, implementing, and monitoring the data and safety monitoring plan, the data management plan, and the randomization plan
- Overseeing training of clinical site staff with regard to data entry, data correction, and randomization procedures
- Assisting CCC on development of data collection form templates and overseeing the implementation of paper-based and web-based forms
- Monitoring completion and timeliness of form submissions and query responses
- Developing and implementing data edit specifications
- Monitoring distribution of data queries to clinical sites
- Monitoring sites' responsiveness to queries
- Participating in quality assurance visits to the clinical sites
- Preparing reports on study progress and study results for the DSMB (twice per year and on request), the NIA (annually and on request), IRBs (annually and on request), and the SC (on request)
- Preparing final data files and performing data analyses for publications and presentations
- Preparing data files for the EEC and to be shared with any ancillary studies that are approved by the SC

- Developing and maintaining a website to ensure up-to-date study documents (e.g., data collection forms, manuals, protocol, study personnel contact information)

Data capture, data management, and randomization will be implemented through a subcontract with Axio Research, LLC (hereafter referred to as Axio) in Seattle, WA.

### **3.1.7 Economic Evaluation Core (EEC)**

The EEC will be responsible for assessing the cost-effectiveness of the interventions. The economic value of the interventions will be determined by assessing the impact on QALYs, cost, and cost per QALY gained over the study period. The EEC will conduct analyses of within trial comparisons for the economic endpoints (costs and QALYs) as well as develop and implement a decision-analytic modeling framework that will incorporate within trial findings regarding costs and QALYs.

## **3.2 Scientific Oversight**

### **3.2.1 Scientific Oversight Committees (SOC)**

There are four SOCs that will provide scientific oversight for distinct aspects of the trial. CCC and DCC staff and SOC leadership will provide day-to-day guidance on issues pertaining to the implementation procedures for recruitment, measurement, intervention delivery, and data management and analysis. SOCs will perform their responsibilities under the guidance of the SC and with assistance from CCC and DCC personnel. The areas of responsibility and membership of each committee are described briefly below.

#### Recruitment and Evaluation

The Recruitment and Evaluation SOC will refine and optimize procedures and strategies for recruitment and retention of study participants and for maintaining adherence to the protocol. It will be this group's responsibility to oversee recruitment progress at all sites, intervene in cases of under-recruitment, and report recruitment progress to the SC. The committee will oversee retention efforts and investigate and intervene when a site is having retention problems. A study management database will be developed by the CCC to provide a standardized way for clinical sites to monitor study-related activities in a timely way (see section Section 16:). The Recruitment and Evaluation SOC will utilize reports from this database which will allow monitoring of recruitment, retention, and data collection by clinical site. Another responsibility of this committee is ensuring that protocols are followed for data collection procedures and that each clinical site establishes standard operating procedures and maintains a current version throughout the study. The Recruitment and Evaluation SOC will also monitor data collection for the CAP study and approved ancillary studies. This committee will be led by the director of the CCC and will include the clinical site PIs and the director of the EEC.

#### Clinical Direction

The Clinical Direction SOC will contribute to protocol implementation from the perspective of orthopaedic surgery and clinical gerontology, reviewing clinical practice-related issues and overseeing the clinical safety of all study participants. The group will monitor the scientific literature, scientific meetings, and input received from colleagues on medical topics that are relevant to the project and advise the SC on emerging scientific issues that may affect the conduct of the study. Committee members will be on call on a rotating basis to answer questions about eligibility from clinical staff and to serve as Independent Safety Monitors (ISMs) to review RAEs. They may be asked to provide medical advice in study-related emergencies

and to address IRB issues related to participant safety.

### Intervention

The Intervention SOC will finalize and refine the intervention protocols and work closely with the CCC and clinical sites to ensure the QC procedures and training for the intervention. The committee will develop the Intervention Manual, and together with the Recruitment and Evaluation SOC, will implement strategies to enhance and monitor treatment fidelity and adherence to the interventions. This committee will be responsible for selecting, training, and certifying all PTs involved in the intervention protocols.

### Publications and Ancillary Studies Committee (PASC)

The PASC will be responsible for: (a) encouraging production of high quality publications and presentations in a timely fashion, (b) encouraging broad participation by the study investigators in publications, abstracts, and presentations, c) reviewing ancillary studies with regard to scientific value and participant burden, paying particular attention to avoiding interference with the main study, and (d) assuring accurate maintenance of a database on study publications, presentations and ancillary studies. The PASC will review proposals for and final versions of research abstracts, presentations, manuscripts to be submitted to journals, and proposals for ancillary studies. The PASC will report its recommendations to the SC for ratification. Standing members will include two committee co-chairs, and the study chair and co-chair of the SC. Additional committee members will be recommended by standing members; at a minimum, the directors of the DCC and CCC will each be invited to nominate one representative to serve as a standing member of the PASC.

### **3.2.2 Specialized Support for Exercise and Nutrition**

This advisory committee will provide guidance and expertise to the SC and Oversight Committee Chairs in the areas of exercise and nutrition in older adults as required during the development of the protocol, MOP, and training materials; execution of the project; and interpretation of study findings as they relate to the interventions. The committee will convene on an as-needed basis at the request of the SC. This advisory committee will be involved in providing guidance on the development and implementation of the dietician protocol and will work closely with the Intervention Oversight Committee to ensure the successful and safe implementation of the interventions.

### **3.2.3 UMB Investigational Drug Services (IDS)**

The University of Maryland IDS will be 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 and shipping the vitamins/supplements for this project to each of the clinical sites. The vitamins/supplements for the study will be purchased and managed through the University of Maryland IDS. IDS will prepare “treatment kits” for each randomized participant 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.

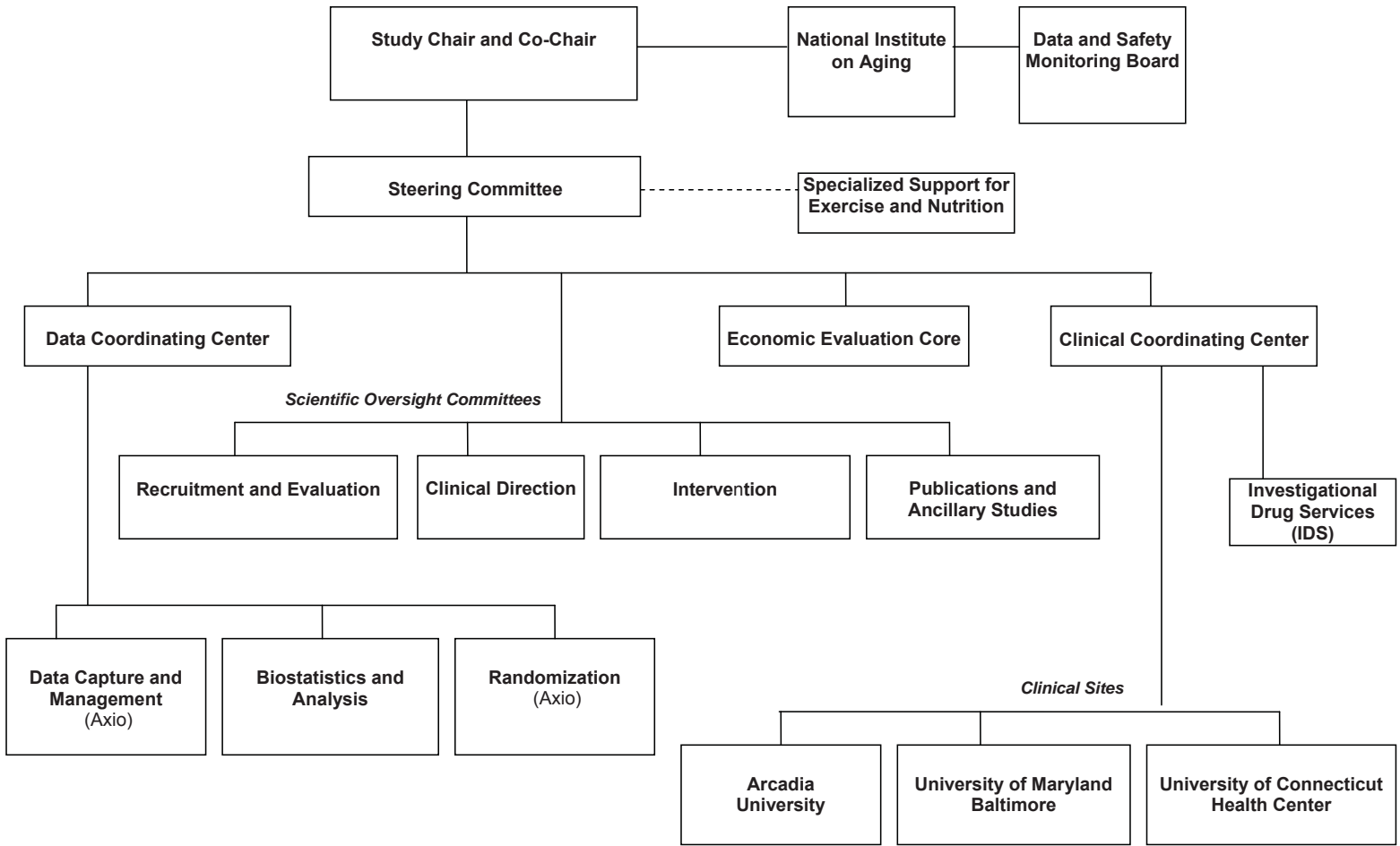
### **3.2.4 Study Clinical Sites**

The study has three collaborating clinical sites each with a clinical site PI and coordinator. The three clinical sites are Arcadia University (AU), University of Maryland Baltimore (UMB), and University of Connecticut Health Center (UCHC).

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, enrolling participants using the automated randomization system, and entering data and processing data edit queries
- Training and supervising staff at the clinical site; 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 clinical site study materials and records
- Reporting all RAEs and protocol deviations
- Participating in the study oversight committees and manuscript preparation

### 3.3 Organizational Chart



## Section 4: Study Objectives

### 4.1 Primary Objective

The primary objective will be to determine if a specific multi-component 16-week intervention based on aerobic conditioning, specificity of training, and muscle overload (the PUSH intervention), initiated up to 26 weeks following admission to the hospital for hip fracture, will be more successful in producing community ambulation at 16 weeks after study entry (approximately six months post-fracture) compared to a non-specific multi-component intervention of transcutaneous electrical nerve stimulation (TENS), flexibility activities, and AROM exercises (the PULSE intervention).

The primary hypothesis is that there will be a 20 percentage point or greater difference in the proportion of PUSH compared to PULSE participants who achieve community ambulation 16 weeks after randomization. Community ambulation will be defined as walking at least 300 meters in six minutes on the Six-Minute Walk Test (SMWT).

### 4.2 Secondary Objectives

Delayed and sustained effects. A secondary objective will be to determine whether the proportion of community ambulators differs between the PUSH and PULSE interventions at 40 weeks post-randomization and, for the subset of participants who were followed for 40 weeks, whether the difference in proportions at 40 weeks changed from the difference in proportions at 16 weeks.

Effect on secondary and tertiary outcomes. There are five variables (endurance, dynamic balance, walking speed, quadriceps strength, and lower extremity function) that are hypothesized to be precursors to community ambulation. To gain a better understanding of the interventions' mechanisms, the two groups will be compared at 16 weeks post-randomization on each of these outcomes and at 40 weeks post-randomization for the subset of participants who are followed for 40 weeks. In addition, this study will assess the effect of the interventions on several tertiary outcomes including ADLs, balance confidence, quality of life, physical activity, lower extremity physical performance, depressive symptoms, increase of  $\geq 50$  meters in distance walked in six minutes, cognitive status, and nutritional status.

Cost-effectiveness of the interventions. The economic value of the interventions will be determined by assessing the impact on QALYs, cost, and cost per QALY gained over the follow-up period. This RCT will provide critical information on whether the specific PUSH intervention can improve a hip fracture patient's ability to ambulate in the community in a cost-effective manner compared to the non-specific PULSE intervention. To address the economic value of trial interventions versus usual care, a model-based analysis that combines trial data with other data sources also will be undertaken.

## 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.<sup>10,11</sup> 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.<sup>12</sup> with a predicted increase to over 650,000 per year by 2040.<sup>13</sup> The estimated cost to hip fracture patients, their families and the

health care system is between \$14 and \$20 billion annually.<sup>14-19</sup> 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.<sup>20</sup>

### **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.<sup>21-25</sup> 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.<sup>26</sup> The SMWT has been used as a proxy for aerobic capacity and is considered an endurance measure in elderly, frail and severely compromised patients.<sup>27</sup> 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.<sup>28</sup> Mangione reported average SMWT distances of approximately 200 meters after usual care for hip fracture.<sup>29</sup> 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<sup>30</sup> or 350 meters reported for a sample of comparable age in the Cardiovascular Health Study.<sup>31</sup>

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.<sup>10,32</sup> 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.<sup>10</sup> Balance deficits remain at seven months<sup>33</sup> at a time when physical recovery is reported to approach a plateau.<sup>1,2</sup>

Walking Speed. The proportion of individuals achieving independence in ambulation one year post-fracture is between 30% and 83%, depending on the study.<sup>34-37</sup> 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.<sup>38</sup> 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.<sup>39-42</sup> 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.<sup>43,44</sup> 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%).<sup>2,45</sup> The majority of patients who



report independent ambulation also report they do not walk as well they did prior to fracture.<sup>1,46</sup> Even at one year, most hip fracture patients do not return to pre-fracture functional status.<sup>2,45,47-50</sup> They walk more unsteadily and more slowly for shorter distances.<sup>51,52</sup>

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,<sup>53</sup> 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.<sup>54</sup> 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<sup>20</sup> 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<sup>26,55-60</sup> 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.<sup>26,55,56</sup> 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.<sup>61</sup> 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.<sup>62</sup> 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.<sup>55,56</sup> Strength, gait speed, balance, and balance confidence improved in the experimental groups. The third trial,<sup>26</sup> which included aerobic conditioning during in-patient rehabilitation, demonstrated improved endurance (VO<sub>2</sub> 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.<sup>22,29,63-68</sup> 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.<sup>69</sup> 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.<sup>70</sup> 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.<sup>22,68</sup> 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 nationally to describe usual home care physical therapy following in-patient sub-acute care for hip fracture.<sup>53</sup> 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 study will compare the effect of two interventions that provide additional supervised exercise in the home following completion of post-acute rehabilitation. One intervention will be specific in delivering exercise focused on addressing the precursors of ambulation in the community (PUSH). The other intervention (PULSE) will be non-specific and will be similar to the joint-specific therapeutic exercises described in the Mangione et al. trial<sup>71</sup> and will add a modality for pain relief.<sup>72</sup> Since a systematic review indicates that the evidence is insufficient with respect to best practices in rehabilitating hip fracture in older adults, both interventions are plausible for improving mobility in patients after hip fracture.

PUSH. Older adults improve functional performance when engaging in high intensity multiple component interventions.<sup>73-79</sup> Despite disagreement about exercise type, intensity, frequency, duration, and mechanism, it is known that the older musculoskeletal system adapts to increased demand.<sup>80</sup> 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.<sup>22,77,78,81-85</sup> 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<sup>81,83</sup> 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.<sup>77,82</sup>

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.<sup>80,86-88</sup> 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.<sup>86</sup> 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.<sup>89,90</sup> 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.<sup>80,86</sup> 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.<sup>91-95</sup> 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.<sup>80</sup> The older person with hip fracture is more complex because of the significant newly acquired deconditioning, muscle atrophy, fracture healing, and other metabolic changes.

**PULSE.** The PULSE intervention emphasizes increased mobility through AROM exercises for the whole body. In addition, this intervention will be supervised by a physical therapist so that participants perform techniques correctly and proper breathing is ensured throughout. Following hip fracture, lower extremity muscle strength is reduced. Many factors have been cited to account for this impairment including inactivity, fear of moving the injured limb, and pain. Arthrogenic muscle response (AMR), defined as an ongoing reflex reaction of the musculature surrounding a joint after distension or damage to structures of that joint, is another reported consequence of joint injury.<sup>71</sup> AMR has been suggested to be the result of inhibition of a muscle's motoneuron pool excitability and appears to be independent of pain and swelling and may persist after the acute injury has resolved. A current hypothesis is that AMR occurs in response to distorted articular sensory receptors after joint injury. Although AMR has been studied in the knee, shoulder, elbow and ankle, this response may also occur in the hip muscle following hip fracture and surgical repair. One reason, therefore, that TENS will be applied to the gluteal, quadriceps, and gastroc-soleus muscles is to promote somatosensory input; the goal of this input is to induce changes in the excitability of the motor neurons and to somatosensory motor cortex to assist in activation of the motor neurons.<sup>96</sup>

The other reason that we are proposing the use of TENS is to assist in pain management. Herrick et al (2004) grouped persons with hip fracture as moderate/severe or mild/no pain.<sup>97</sup> Forty-two percent of the sample reported moderate/severe pain at baseline. The other benefit of TENS will be to reduce pain which may lead to an increased activity level. TENS has been demonstrated to be effective in managing both acute and chronic pain for a number of conditions. Cheing and Hui-Chan (2004), for example, reported that TENS alone applied to persons with chronic pain secondary to knee osteoarthritis resulted in an increase in knee ROM during walking and increased gait speed.<sup>98</sup> TENS was compared with a sham control after surgical repair of hip fracture. When TENS was applied after surgery, pain on movement was reduced and health-related quality of life improved.<sup>99</sup> Gorodetskyi (2007) compared the effect of electrical stimulation to a sham control in 60 older people during acute hospitalization following hip fracture repair.<sup>100</sup> Participants receiving electrical stimulation reported substantially and significantly less interference from pain on walking ability after each of the 10 sessions. Pain

scores, which decreased over the 10-day treatment period in both groups, were also markedly less in the electrical stimulation group. The two studies that have examined the use of TENS for pain alleviation have not, however, examined its effect on alleviation of the chronic pain reported by persons after hip fracture.

#### 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.<sup>101</sup> 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).<sup>102</sup> Although community ambulation is complex, covering a minimal distance within a specified period of time is a critical feature.<sup>103,104</sup>

The SMWT is a standardized test that examines both the distance and time components of community ambulation.<sup>105</sup> The Cardiovascular Health Study<sup>106</sup> concluded that the SMWT is safe for use in community samples to measure the impact of multiple comorbidities on endurance in older adults.<sup>31</sup> Harada et al<sup>107</sup> proposed that the SMWT is a useful integrated measure of mobility function taking into account any limitations imposed by major body systems.<sup>107</sup> Lord and Menz<sup>108</sup> 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.<sup>107</sup> Construct and predictive validity and responsiveness to change were established for the SMWT in a sample of 108 persons with hip fracture.<sup>109</sup> A high positive correlation was reported between pedometer-determined physical activity and the SMWT test suggesting that both are correlates of community ambulation.<sup>110</sup> 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.<sup>29,63,111</sup>

Distance. Some investigators use a 400 m threshold (2-3 city blocks) for the SMWT to identify community-dwelling elders at risk for developing a mobility disability.<sup>27,82,107,108,112-114</sup> This threshold appears valid to detect early decline in community dwelling elders.<sup>27,31,82,107,108</sup> Four hundred meters, however, is considered too high for this investigation where the goal is to assist participants, with a significant mobility disability due to recent hip fracture, to return to community ambulation. Several investigators support a 300 m threshold for community ambulation.<sup>102,107</sup> Reasons to adopt a 300 m distance threshold on the SMWT test include: 1) at six months post-fracture or post-stroke, average group performance is < 300 m<sup>29,63,72,109,115</sup>; 2) achieving < 300 m on the SMWT is a predictor of mortality;<sup>28</sup> 3) average distance from parking space in a supermarket parking lot to task completion in the supermarket in both urban and rural communities is 301 m.<sup>103</sup>

Time. Usual walking speed has been determined from observing walking speeds of urban pedestrians and from human performance laboratory investigations.<sup>116-120</sup> Functional walking categories have been developed to include the community walker (i.e., independent in all home and community activities). A reported gait speed of 0.8 m/s signifies the community walker.<sup>121,122</sup> One year post-hip fracture, usual gait speeds range from 0.44 to 0.97 m/s,<sup>29,33,56,57,64,72,123-125</sup> the average of which is below the community ambulation threshold. Others have reported that a speed threshold of 0.8 m/s is a useful and discriminative primary endpoint in clinical trials of exercise rehabilitation.<sup>125</sup>

Summary and Primary Endpoint: The SMWT is an assessment with excellent psychometric properties, and there is sound justification for a 300 m distance threshold on the SMWT (equivalent to walking at 0.8 m/s) to serve as an indicator for community ambulatory ability.

### 5.5 Economic Evaluation of Interventions to Reduce Post-fracture Disability

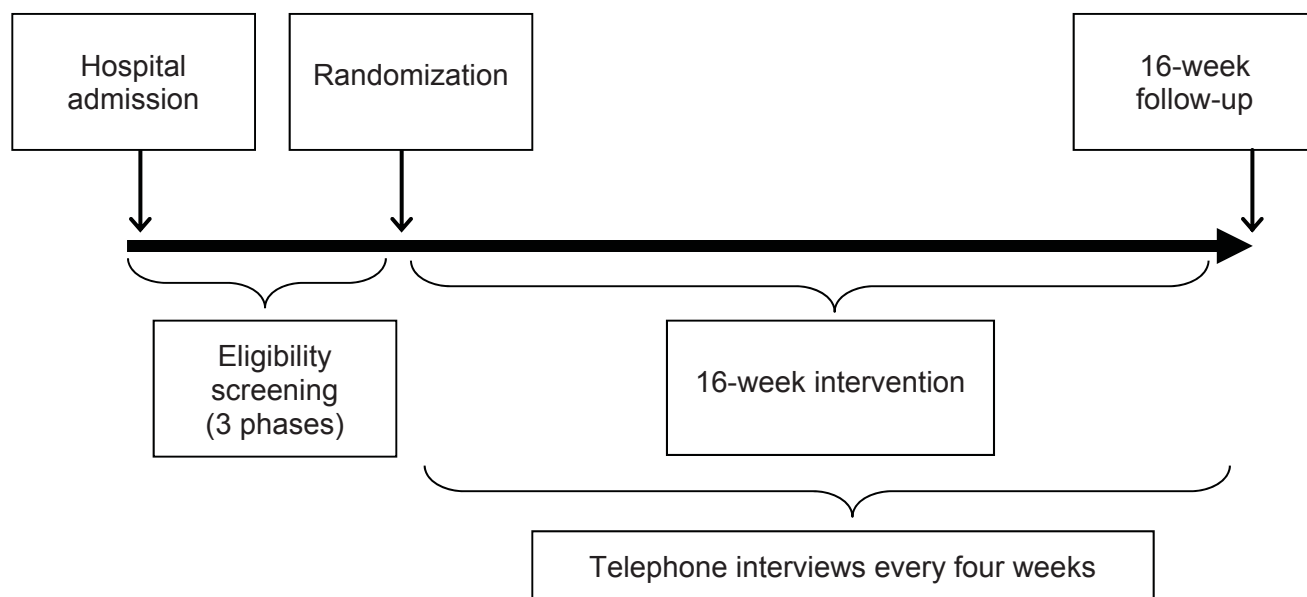
The economic consequences of hip fracture are substantial.<sup>17</sup> In a society with limited resources, each additional expenditure should produce a benefit that is worth the additional cost. Although a number of studies have addressed the cost-effectiveness of hip fracture prevention through pharmacological and hip-protector interventions,<sup>126-134</sup> the value of exercise interventions to reduce post-fracture disability has not been evaluated. Nonetheless, the role of post-fracture disability in overall economic costs is well-recognized as is the dearth of studies that have attempted to characterize indirect costs of fracture.<sup>135</sup> Therefore, a secondary aim of the study will be to assess the economic value of the interventions compared to each other as well as the interventions compared to usual care. This evaluation will estimate the cost per additional quality-adjusted life year (QALY) gained.<sup>136</sup>

## Section 6: Study Design

### 6.1 Overview of Study Design

A RCT of 210 older adults who have experienced a hip fracture will be carried out at three clinical sites (AU, UMB, and UCHC) with half of the subjects receiving a specific multi-component intervention (PUSH) and the other half receiving a non-specific multicomponent intervention (PULSE). Randomization of 210 participants meeting eligibility criteria will take place after post-acute rehabilitation ends, up to 26 weeks after admission to the hospital for hip fracture. The primary endpoint will be measured 16 weeks after randomization. Patients age 60 and older who have had surgical repair for hip fracture will be identified at the three clinical sites through a variety of recruitment sources and will be evaluated for eligibility. Following consent to participate, eligible participants will undergo a comprehensive baseline assessment and will then be randomized to one of the two treatment groups. The cohort will be measured again 16 weeks post-randomization. Figure 1 shows the sequence of participant contacts from the time of hospitalization until the final assessment approximately 16 weeks after randomization.

Figure 1. Timeline for screening, randomization, and follow-up



Within a week of randomization, participants will initiate the intervention with a PT in their place of residence and receive counseling with a registered dietician. The follow-up assessment will take place 16 weeks post-randomization. Telephone interviews will be conducted every four weeks, beginning four weeks post-randomization, 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.

For participants randomized prior to version 10.0 of the protocol, follow-up assessment visits occurred 16 weeks and 40 weeks from the date of randomization and telephone interviews were conducted every four weeks during the 40-week study period for a total of 10 telephone interviews.

## **6.2 Randomization**

Randomization will occur up to 26 weeks after admission to the hospital for a hip fracture. The randomization schedule for each clinical site will ensure that treatments are randomly assigned within blocks of 2, 4, 6, or 8, with equal numbers of participants assigned to each treatment within each block. Block sizes (two to eight participants per block) will be randomly selected with the probability of each block size specified by DCC staff.

To ensure that those performing evaluations remain blinded to treatment assignment, randomization will only be performed by appropriate unblinded study personnel who have received training and certification on randomization procedures. The clinical site PI, clinical site coordinator, or another unblinded designee will perform the randomization. Random treatment assignments will be obtained using a secure Web-based randomization system. Each member of the study staff who has permission to randomize participants will be assigned a unique, nontransferable user ID that will be required to obtain random treatment allocations. The study staff member will access the system by login on a secure (encrypted) Web site and receive the treatment assignment after responding to prompts confirming that the participant meets all inclusion and exclusion criteria and has given informed consent for enrollment. A printable report will be available as part of the Web system. Site staff will be instructed to print the report and retain it in the participant's binder. Access to the binders is limited to the clinical site PI and coordinator. The date of randomization will mark the start of follow-up for each participant; a computer record is maintained for each attempt to randomize a participant. The clinical site coordinator will inform participants of their group assignment and will tell them when their PT sessions will begin. The coordinator will also provide the name of the PT who will be contacting them. The coordinator will then alert the assigned PT who will contact the participant to schedule the first intervention visit.

## **6.3 Interventions**

Over a 16-week period, participants in both groups will receive two visits per week, on non-consecutive days, for a total of 32 visits. Visits from a study PT will take place in participants' place of residence. The PUSH intervention group will be receiving a specific multi-component training intervention and the PULSE intervention group will receive a non-specific multi-component intervention that stimulates the same muscle groups as in the PUSH group. Participants in both intervention groups will receive 2000 IU of vitamin D3, 600 mg of calcium, and a multivitamin daily for the duration of the study and nutritional counseling to ensure weight stability and adequate nutrient intake inclusive of a healthy diet.

## **6.4 Blinding of Study Staff**

Given the nature of the interventions being tested in this study, it will not be possible to blind the participants or the PTs providing the interventions. To minimize “contamination” of the interventions, each PT will provide only one of the interventions and PTs will not have contact with participants in the other group or with PTs providing the intervention to the other group. The interventionists will be told that this is a study comparing a specific multi-component intervention and a non-specific multi-component intervention to increase mobility following hip fracture, but specific hypotheses or rationale of the study will not be discussed with them. The interventionists will be blinded to participants’ study outcomes.

Clinical site PIs and clinical site coordinators who are responsible for assigning work and/or assessing for treatment fidelity of PTs in both groups are unblinded. Unblinded study staff involved in randomization will not perform follow-up data collection.

Only those who will perform evaluations (clinical site visits and telephone interviews) after randomization and the Independent Safety Monitor (ISM) will be blinded to treatment assignment. Blinded study staff performing follow-up assessments or telephone interviews are instructed not to ask about treatment assignment when in contact with participants. Participants will be asked not to discuss their treatment experience (including the identity of the PT providing the intervention) during study visits and telephone calls conducted by blinded staff.

Only a small number of DCC staff members and members of the DSMB will see group-specific study results. In the event of inadvertent unblinding of study staff, a protocol deviation will be reported and a notation will be made in the participant binder specifying the circumstances of the unblinding event and a list of all persons unblinded.

## **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. Patients who are provisionally eligible based on medical chart review at phase 1 will be approached in the hospital (or soon after discharge) and told about the study. Interested patients (or their legally authorized representative) will be asked to provide permission to contact for additional screening. Phase 2, which will take place any time before the maximum timeframe for randomization (26 weeks post hospital admission) will involve contacting the participant to assess for medical, safety, and feasibility criteria.

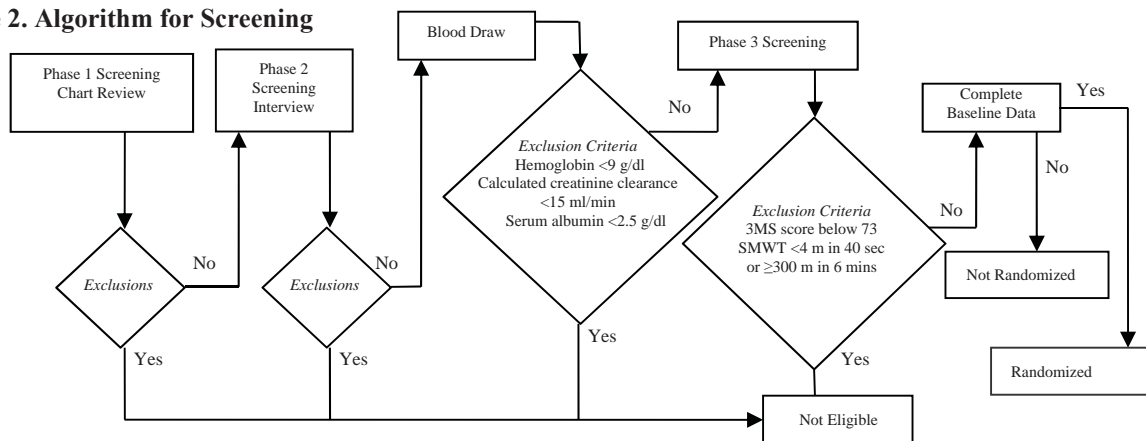
Blood will be collected and tested for hemoglobin (<9 g/dl), serum creatinine to calculate creatinine clearance (<15 ml/min), and serum albumin (<2.5 g/dl). The blood collection can occur anytime between phases 2 and 3 screening as long as it occurs after informed consent is obtained and no more than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

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. Prior to the phase 3 visit, the study coordinator will attempt to contact an appropriate medical professional (e.g., primary care physician, orthopaedic surgeon, etc.) who has had contact with the person since the hip fracture to review medical history and confirm safety for participation in the interventions. Phase 3 will include a review of all disqualifying medical

conditions, measurement of height and body weight to calculate body mass index (BMI), 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 clinical site study clinician must review all study eligibility documents and sign off on final eligibility for all potential participants prior to collection of baseline data. Those individuals for whom a medical provider was not consulted for clearance to participate in the study will be seen by the clinical site clinician.

Eligible individuals will receive the baseline assessment consisting of questionnaire items and testing of muscle, balance and functional performance. Participants with complete baseline data will be randomized to one of two treatment groups.

**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 randomization
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 randomization

## 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. Not randomized by 26 weeks post admission for hip fracture
  - 4.6. Final sign off from study clinician 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
    - 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 randomization
    - 5.9. Receiving PT for the hip fracture in the hospital or in an inpatient rehabilitation facility at time of randomization
- 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 randomization
    - 6.8. Denied medical clearance by appropriate medical provider
    - 6.9. Clinical site clinician thinks participant is not a good candidate for study (e.g., not likely to survive study period)
    - 6.10. Development of chest pain or substantial shortness of breath or ambulating with severe pain during baseline SMWT

#### **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, social media, 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, from each of the three clinical sites, and from each study

hospital.

Clinical site PIs will identify other method(s) of recruitment that are appropriate for their respective sites.

### **7.5 Participant Screening and Recruitment**

Participants will be evaluated for eligibility in three phases to be completed no later than 26 weeks after admission to the hospital for hip fracture. Information for phase 1 will be collected from the patient's medical chart. For those identified in acute care hospitals, study staff with adequate medical training and experience reviewing medical records will check the admitting records and operating room logs of study hospitals to identify potential hip fracture patients. A HIPAA Partial Privacy Waiver (for recruitment) or verbal consent to review the medical chart for eligibility will be obtained for patients identified at study hospitals. Patients who are provisionally eligible based on medical chart review at phase 1 will be approached in the hospital (or soon after discharge) and told about the study. Written permission from the patient will be obtained to allow future contact to collect additional eligibility information. Patients who are identified through means of recruitment other than screening in study hospitals will be asked to provide written authorization for release of medical records for review of phase 1 eligibility criteria. Clinical sites will address specific recruitment methods and content (e.g., customized landing pages for websites, print advertisements and flyers) in their local IRB applications.

Phase 2 will assess for additional safety and feasibility criteria prior to the baseline visit. Phase 3 will assess eligibility at the beginning of the baseline visit. This final phase, which will be performed at the clinical site, will include a review of new onset medical exclusions, measurement of height and weight for BMI, assessment of cognitive status with the 3MS, and assessment of ability to walk 300 meters in six minutes. At any point post-admission, potential participants and others identified by patients (e.g., caregiver or other family member) will be provided with additional information about what participation in the study entails.

### **7.6 Informed Consent**

Written informed consent and appropriate HIPAA authorizations and/or waivers will be obtained in compliance with procedures reviewed and approved by the clinical sites' 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 randomization to a treatment group. 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 a local IRB-approved method, such as 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 clinical site 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.

#### **7.6.1 Enrollment**

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

## **Section 8: Retention**

### **8.1 Retention Promotion Efforts**

At the time of randomization, 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.

Participants will be interviewed by telephone every four weeks after randomization for 16 weeks to collect information on expected AEs and RAEs. These regular phone contacts also help with retention. Participants will be reminded of the next phone call and follow-up assessment.

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.

Clinical sites will keep detailed records of rescheduled and missed study assessment visits, missed phone interviews, and missed intervention visits. Participant retention will be monitored, and efforts will be made to provide support and encouragement to participants who are at risk of being lost to follow-up.

## **8.2 Drop-out Prevention Efforts**

The following procedures will be implemented to minimize and monitor missed follow-up assessments, telephone interviews, and intervention visits:

- Providing pre-visit reminders (e.g., postcards and phone calls) for upcoming assessment visits. Also, reminders about the upcoming follow-up assessment will be provided during the four-week phone calls.
- Calling participants the night before a follow-up assessment to remind them of the visit and the time for transportation pick-up, if appropriate.
- Utilizing an Access study management database developed by the CCC to monitor participation and attendance within each clinical site, so that staff will be immediately alerted to a missed intervention or assessment visit.
- Contacting participants (or significant others) when they miss a visit.
- Rescheduling the visit within the same window, if possible.
- Rescheduling the visit during the out-of-window interval, if necessary.

Some randomized participants may not actively participate in the study, either by declining the intervention visits and/or by not attending follow-up assessments. 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 after randomization 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.

## **8.3 Monitoring Recruitment and Retention**

The CCC will monitor recruitment and retention with the help of a study management database (see Section 16:), which will be used to track all participant contacts, status of participants, activity of study staff members, form completion, and form submission. The CCC will track screening and recruitment yields against the number expected per site. The CCC will work closely with clinical site PIs and the Recruitment and Evaluation SOC to identify and reduce barriers to recruitment. 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.

### **8.3.1 Monitoring and Quality Control of Recruitment and Retention**

The DCC will collect data to monitor recruitment and retention activities, the number of potential participants screened at each site, the yield at the various screening phases, the percent who are eligible, and the percent who are randomized. Additionally, a study management database will be used by the clinical sites, the Recruitment and Evaluation SOC, and the CCC to monitor recruitment to determine if the study hospitals and other recruitment sources are providing the expected number of patients. This monitoring will allow early detection of issues and the clinical sites will implement procedures for additional recruitment methods, as appropriate. Reports from the study management database can also be generated according to individual study staff member to identify possible areas for retraining. Retention will be monitored through completion rates of follow-up assessment visits, intervention visits, and telephone interviews. Regular reports will be available to clinical sites and the CCC. Members of the CCC maintain regular phone contact with clinic staff to:

1. Review recruitment goals and yields for clinical sites,
2. Review the recruitment plan and progress in achieving the objectives outlined in the plan,
3. Share successful and unsuccessful recruitment methods, and
4. Review retention.

If clinical sites encounter difficulties in recruitment or retention, the CCC (or a subgroup it designates) will provide a graduated set of assistance responses that are based on the degree of recruitment or retention shortfall. Solutions will be developed that are based on site-specific issues.

## **Section 9: Study Interventions**

### **9.1 Overview**

Participants will be assigned to one of two treatment groups: 1) PUSH or 2) PULSE. The PUSH intervention group will receive a specific multi-component training intervention and the PULSE intervention group will receive a non-specific intervention that stimulates the same muscle groups as the PUSH intervention. Both groups will receive 32 visits of approximately 60 minutes duration from a study PT. Participants will receive two visits per week, on non-consecutive days, for 16 weeks. 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.

### **9.2 Nutritional Intervention**

Given the importance of ensuring adequate nutrition in both study groups, 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 randomization to assess nutritional risk using the Mini Nutritional Assessment-Short Form (MNA®-SF).<sup>6</sup> Those who score  $\leq 7$  (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 randomization. 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.<sup>7-9</sup> 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 randomization. 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  $\geq 12$  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 randomization 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 clinical site PI or clinical site clinician 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.

Participants randomized prior to version 10.0 of the protocol received vitamin D, calcium, and multivitamin supplements for a total of 40 weeks.

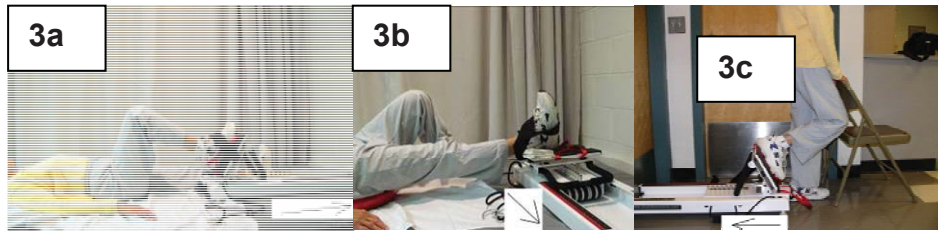
### 9.3 PUSH Intervention

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.<sup>137</sup>

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.<sup>138-140</sup> 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.<sup>141</sup> 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.<sup>139</sup> Plantar flexors will be strengthened in standing against body weight<sup>77</sup> because of their role in the push-off phase of gait and the strong association of plantar flexion power and walking speed.<sup>77,138-142</sup> 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<sup>143</sup> 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<sup>88</sup> yet is not so aggressive that it is associated with injuries.<sup>144,145</sup> This protocol has been used safely and effectively in elders<sup>21,73,74,77,140,146</sup> and specifically in persons post-hip fracture.<sup>29,70</sup> 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 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-

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



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.<sup>29</sup>

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.<sup>147-149</sup> 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.<sup>150</sup> 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.

#### **9.4 PULSE Intervention**

The PULSE intervention group will receive flexibility exercises, AROM for the upper and lower extremities, breathing exercises and TENS. During the AROM exercises, participants will be working to increase flexibility and range of motion in order to increase the motion the participant produces. The exercises will include the neck, shoulders, arms, trunk, hips, knees and ankles. During all of the AROM exercises, the participant will focus on deep breathing techniques. Progression will be gradual by beginning with three repetitions and slowly progressing to 10 reps. We will add a second set of exercises when necessary. This portion of the session will last approximately 20-30 minutes.

The second part of the session will use sensory level electrical stimulation to the lower extremity muscle groups. The TENS portion of intervention is intended to decrease pain and increase muscle recruitment thereby allowing greater ease of mobility. Conventional TENS uses low-level electrical current to stimulate superficial cutaneous nerve fibers through the skin. The amount of current for sensory level stimulation is the level which the participant detects as a "tingling" sensation and is not high enough to produce a visible muscle contraction (below motor threshold).<sup>5</sup> To achieve sensory level stimulation, we will use a frequency of 80 pulses per second, pulse duration 50 µsec, and amplitude which produces a comfortable paresthesia (tingling or 'pins and needles' sensation). Flexible carbonized, disposable electrodes coated with a self-adhesive conductive polymer will be applied to the skin. The electrodes will be placed bilaterally near the motor points on muscle bellies (the gluteal complex, the quadriceps, and the gastrocnemius) for seven minutes per muscle group. The muscle regions selected are important for function after hip fracture. Repetitions and duration of the AROM program, as well as TENS intensity will be recorded in the training log.

#### **9.5 Treatment Fidelity Plan**

Treatment fidelity<sup>151,152</sup> will be evaluated with regard to: (1) design, which focuses on whether the interventions are consistent with underlying theories, and whether the study is free of contamination such as treatment crossover or unintended motivational interventions; (2) training, which addresses skill acquisition and maintenance in PTs; (3) delivery, or the assessment that the two interventions were 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 interventions, 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 protocols which could threaten the study's ability to detect treatment differences.

##### **9.5.1 Initial Training for Procedural Reliability**

The Intervention Monitor (IM) will train PTs in either PUSH intervention or PULSE intervention procedures. In order to minimize crossover, the PTs will only be trained on one intervention. There will be separate training sessions for each intervention and the PTs will not know the details of the other intervention.

Knowledge of procedures will be tested by written examination and by psychomotor skills observation via video. The IM will document that PTs are "CAP certified PTs" 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.

### **9.5.2 Ensuring Ongoing Competency**

We will use a multi-faceted approach to ensure ongoing treatment fidelity. The approaches include direct observation of skills by the clinical site coordinators, mandatory monthly telephone calls with all active PTs, periodic review of PT log books, access to online discussion boards, and face-to-face meetings with the intervention team at least twice per year.

*Direct Observation:* Direct observations of PTs as they perform the interventions will be conducted by the clinical site coordinators who will be trained on both intervention protocols. The coordinators will document their observations using a structured checklist that addresses data completeness, physical performance, qualitative observations, and verbal and non-verbal communication. In the PUSH intervention group, 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. The checklist for the PULSE intervention group will document that the participants completed the AROM exercises, had electrodes placed appropriately, and received the TENS at the appropriate level and for the proper amount of time. 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 IM and clinical site 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. The Treatment Fidelity Manager will take minutes of the telephone meetings to document ongoing training. During these calls (which will be done separately for the PTs in the two groups), 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:* Clinical site coordinators will review PT intervention logs when the PTs come to the study office to pick up study medications or to submit completed forms. The coordinator will note if PTs are completing logs and if there are modifications to the intervention protocols. This information will be sent to the IM for discussion during the monthly phone calls.

*IM Site Visits:* The IM will visit each site semi-annually to meet with all the PTs, with separate meetings for each intervention group. This will be a team building visit emphasizing proper delivery of the intervention and discussing issues specific to the site.

### **9.5.3 Monitoring Physiologic Response**

As a measure of treatment fidelity, we will monitor physiologic response (heart rate) during the intervention sessions using Polar heart rate monitors. The monitors will be worn by all participants at all intervention sessions. The Polar monitor allows the operator to indicate the start and end of distinct time segments referred to as "laps" by the device's software system. Each intervention session will consist of four laps, defined as follows:

Lap	PUSH Intervention	PULSE Intervention
1	Greeting, health questions, BP, HR	Greeting, health questions, BP, HR
2	Strength training, BP, HR	AROM training, BP, HR
3	Endurance training	TENS
4	Wrap-up	Wrap-up

BP=blood pressure; HR=heart rate; AROM=active range of motion; TENS=transcutaneous electrical nerve stimulation.

The Polar monitoring will provide a dichotomous variable reflecting whether, during laps 2 and 3 of each intervention session, the participant's average HR was equal to or greater than his or her target heart rate ( $\pm 5$  beats). The target heart rate is defined as 50% of heart rate reserve and is calculated as follows:

Target HR= $((220-\text{age}) - \text{RHR}) * 0.5 + \text{RHR}$ , where RHR=resting heart rate.

In addition, the IM will perform ongoing qualitative reviews of the HR curves that are generated by the software. She will examine the duration of the laps as well as the pattern of activity within the laps (height of curve, duration of the rise in HR, number of times HR rises within a lap) and compare them to pre-specified criteria established for each intervention. If the pattern of HR curves deviates from the pre-established expectations, she will confer with the PT regarding the possible reasons and implement appropriate actions as necessary.

## 9.6 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 day of randomization = Day 0.
2. The schedule of intervention visits is anchored to the date of randomization 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.

For all randomized participants, Week 1 will begin on the day of the first intervention visit or on Day 7 post-randomization, 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 post-randomization (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 10: 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. This information will be used as part of the adjudication process, as described in section 11.5. Also, the four-week phone calls will be conducted with a proxy when the participant is not available.

In the description of measures below, we identify the measures that will not be collected for participants consented under protocol version 11.0 or later.

### 10.1 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 calculated BMI, the 3MS, and the SMWT. These components will be typically administered over three contacts, in-person or by telephone (phase 2). Those who qualify after phases 1 and 2 will be invited for the first clinic visit for phase 3 screening (see section 7.5).

#### 10.1.1 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 at each follow-up visit. Measured height and weight will be used to calculate BMI.

#### 10.1.2 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.<sup>153,154</sup> The 3MS will be used at the baseline visit to identify and exclude participants with cognitive impairment (3MS score <73).<sup>155</sup>

### 10.2 Primary Outcome Measure: Community Ambulation

The primary study outcome reflects the concept of a minimum distance a person needs to be able to walk to carry out usual activities in the community. This will be defined as achieving the threshold value of 300 meters or more on the SMWT.

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 ( $r = .95$ ).<sup>107</sup> Concurrent validity with  $\dot{V}O_2$  peak ( $r = .64$ ) and cycle ergometry ( $r = .58$ ) have been reported.<sup>105,156,157</sup>

## 10.3 Secondary Outcome Measures - Precursors to Community Ambulation

### 10.3.1 Endurance

To assess endurance, the SMWT (described above) will be used to obtain a continuous measure of total distance walked in six minutes.<sup>158</sup> 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.<sup>105,156,158</sup> It has been performed by elderly, frail and severely compromised participants who cannot perform standard maximal treadmill or cycle ergometry exercise tests.<sup>31,159</sup>

### 10.3.2 Balance

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).<sup>160</sup> 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.

### 10.3.3 Quadriceps Muscle Strength

Isometric force for bilateral knee extensors will be measured with a portable, hand-held dynamometer (Microfet2 Manual Muscle Tester). Participants will be seated on the strength testing chair, with hip flexion 90° and knee flexed to 70°, stabilization straps on the pelvis and thigh, and resistance applied just proximal to the ankle on the anterior surface of the leg.<sup>161</sup> Participants will be asked to push as hard and as fast as possible for five seconds. Three maximal effort trials, with a one-minute rest between trials, will be performed. The reported test-retest reliability with hand-held dynamometry is excellent ( $r > .90$ ) if tested in one session and in subjects with muscle weakness (intraclass correlation coefficient  $\geq .90$ ).<sup>162-164</sup> The peak force will be recorded for each of the three trials and the highest value will be used.

This measure will not be collected for participants consented under protocol version 11.0 or later.

### 10.3.4 Lower Extremity Function

A modified version of the Physical Performance Test (mPPT)<sup>165</sup> will be used to measure lower extremity function at baseline and follow-up. The modification, used by Binder et al., substitutes a chair-rise task and a balance task for writing and eating tasks, in order to emphasize lower extremity function.<sup>68</sup> The modified PPT includes nine standardized tasks that will be timed (e.g., picking up a penny from the floor, standing up five times from a 16-inch chair). The tasks are performed twice and the times from the two trials are averaged. The score for each item ranges from 0 to 4, with 36 representing a perfect score. Test-retest reliability for the modified PPT score is 0.96.<sup>22</sup> Because there is some overlap between the mPPT and SPPB items, we have integrated the two scales so that participant burden is minimized but it is still possible to obtain scores on each of the scales.

### **10.3.5 Fast Walking Speed**

Within the mPPT, participants are asked to walk a distance of 50 feet walking quickly but safely. The time required to walk 50 ft will be the measure of fast walking speed.

### **10.3.6 Cost Effectiveness: Health Care Utilization**

Resource utilization will be tracked every four weeks via telephone interview and unit costs will be assigned to each resource for which data are obtained. Resource use will reflect health care use (including both formal and informal care) since the last telephone interview. This interview will be patterned after that used in the NIH-sponsored Spine Patient Outcomes Research Trial (SPORT).<sup>166</sup> In addition to caregiver costs, the questionnaire will document other resource use including hospitalizations, other care facilities, health care visits, and diagnostic tests. As in SPORT, a health diary will be provided to each participant to assist them in accurately recording health care encounters and use of health services.

Effectiveness will be assessed in the QALY framework where health state values will be used to reflect the desirability for health outcomes on a scale from 0 (worst imaginable health state) to 1 (best imaginable health state). To estimate QALYs, health state values will be obtained using the SF-6D health state classification system,<sup>167</sup> which defines health states using participant responses to the SF-36 (described below). QALYs estimated using SF-6D are consistent with recommendations to use societal values in economic evaluations in health and medicine.<sup>136</sup> Although current SF-6D scoring uses preference weights from a UK population, use of the SF-6D will facilitate the planned model-based comparison between trial interventions and usual care, because several BHS investigations have utilized SF-36 in similar hip fracture populations.

Costs associated with participant-reported resource utilization will be estimated using the Resource-Based Relative Value Scale (RBRVS)<sup>168-170</sup>, which is used by the Center for Medicare and Medicaid Services (CMS) to reimburse physicians for their services. This approach has the advantage of reflecting national fee schedules and relating them to the RBRVS. To estimate costs of other health care services not consistently covered by Medicare, providers will be surveyed on charges for services at the geographic locations involved in this study. For each item, units of utilization will be multiplied by prevailing charges to estimate costs for each participant. To estimate indirect costs, information about informal caregivers' employment status and job class will be obtained at baseline. This will allow for estimation of the indirect economic costs associated with informal caregiving. Costs associated with providing the interventions will be estimated based on the amount of physical therapist time required to deliver the interventions as recorded during the trial.

This measure will not be collected for participants consented under protocol version 11.0 or later.

## **10.4 Tertiary Outcomes**

A series of outcomes that are relevant for the recovering hip fracture participant also will be evaluated. These were selected since: 1) all are affected by a hip fracture; and 2) all are important in understanding the degree to which hip fracture patients recover.

### **10.4.1 Activities of Daily Living (ADLs)**

We will measure ADLs using the Pepper Assessment Tool for Disability (PAT-D)<sup>171,172</sup> 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.<sup>173</sup> 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).

This measure will not be collected for participants consented under protocol version 11.0 or later.

#### **10.4.2 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).<sup>174</sup> The measure has been validated as a generic measure of quality of life in many different populations, including patient and non-patient samples.<sup>174, 68, 175, 176</sup>

This measure will not be collected for participants consented under protocol version 11.0 or later.

#### **10.4.3 Balance Confidence**

The Activities-specific Balance Confidence (ABC) scale<sup>177</sup> is a 16-item measure that asks respondents to rate their confidence in maintaining their balance while doing daily activities. Test-retest reliability, internal consistency, and concurrent validity with fall and physical activity are high.<sup>177, 178</sup> This measure has been used successfully in hip fracture patients.<sup>32, 179</sup>

This measure will not be collected for participants consented under protocol version 11.0 or later.

#### **10.4.4 Yale Physical Activity Survey (YPAS)**

This interviewer-administered questionnaire includes five categories of common activities related to work, exercise, and recreation performed during a typical week in the past month.<sup>180</sup> The YPAS increases the sensitivity of other physical activity surveys by describing a wider range of lower intensity activities that older adults often engage in. Participation in each activity (hrs/week) will be multiplied by an intensity code (kcal/min) and then summed over all activities to calculate a weekly energy expenditure summary. The measure has been validated against several physiological variables of habitual activity.<sup>180, 181</sup> The YPAS has been used to estimate change in older adults in an exercise intervention program.<sup>182</sup>

This measure will not be collected for participants consented under protocol version 11.0 or later.

#### **10.4.5 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.<sup>183, 184</sup>

#### **10.4.6 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.<sup>184-186</sup> 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.<sup>184,186</sup> 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.

*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.

#### **10.4.7 Depressive Symptoms**

Depressive symptoms will be measured using the 20-item Center for Epidemiologic Studies Depression (CES-D) scale,<sup>187</sup> which asks about depressive symptoms experienced in the previous week. There is evidence that recovery post-fracture is delayed in the presence of depression.<sup>188-191</sup> This scale ranges from 0-60 with higher scores indicating greater depression.

#### **10.4.8 Cognitive Status**

Cognitive status will be assessed at follow-up using the 3MS (see section 10.1.2).

This measure will not be collected for participants consented under protocol version 11.0 or later.

#### **10.4.9 Nutritional Status**

Nutritional status will be assessed using the Mini Nutritional Assessment-Short Form (MNA®-SF),<sup>6,192</sup> a validated and widely used malnutrition screening tool.<sup>192-195</sup> 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.<sup>6,192</sup>

This measure will not be collected at follow-up for participants consented under protocol version 12.0 or later.

### **10.5 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.

### **10.5.1 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.

### **10.5.2 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.<sup>196</sup>

### **10.5.3 Psychological Measures**

The following psychological measures will be administered at the baseline assessment to allow us to perform pre-specified subgroup analyses.

#### Life Orientation Test-Revised (LOT-R)

The LOT-R assesses self-reported optimism and pessimism. A total of six brief statements is read to the participant, and response categories range from strongly disagree to strongly agree on a 5-point Likert type scale; three items measure optimism and three items measure pessimism.<sup>197</sup>

#### Brief Resilience Scale

The Brief Resilience Scale assesses self-reported ability to bounce back after a stressful event. A total of six brief statements is read, and response categories range from strongly disagree to strongly agree on a 5-point Likert-type scale.<sup>198</sup>

## **10.6 Other Measures to be Monitored**

### **10.6.1 Adherence**

Adherence with PT interventions. 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. For the PUSH group, 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.

Additionally, at the end of each intervention visit, the PT will retrieve the average HRs for laps 2 and 3 from the Polar heart rate monitor receiver and record them in the logbook and on the appropriate data forms. The Polar heart rate monitoring will provide a dichotomous variable reflecting whether, during laps 2 and 3 of each intervention session, the participant's average HR was equal to or greater than his or her target heart rate ( $\pm 5$  beats). In addition, the IM will perform ongoing qualitative reviews of the HR curves to ensure that the pattern of activity is consistent with pre-specified criteria established for each intervention.

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 entire 16-week study period.



In protocol version 11.0, we will eliminate the collection of information on use of study-provided dietary supplements. However, procedures for drug accountability will remain unchanged (see section 3.2.3).

### **10.6.2 Weight Loss**

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

### **10.6.3 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. These events will be tracked in a separate database by the CCC. RAEs will be captured every four weeks during the telephone interviews using standardized questions on the Reportable Adverse Events Form. 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 13.4.1).

### **10.6.4 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); breathing problems or chest pain; skin irritations, rash, or skin tears; numbness or tingling; and falls (with and without injury).

## **Section 11: Study Procedures**

### **11.1 Baseline Assessments**

The baseline assessments will be performed immediately following screening for phase 3 criteria. The following measures will be assessed at the baseline visit.

- Baseline Weight, Height, and Body Mass Index\*
- Demographics and Blood Draw Information\*
- Modified Mini-Mental State Examination\*
- Six-Minute Walk Test\*
- Baseline Interview
- Activities-Specific Balance Confidence<sup>†</sup>
- Short Physical Performance Battery
- SF-36 Health Survey<sup>†</sup>
- Modified Physical Performance Test
- Yale Physical Activity Survey<sup>†</sup>
- Weight and Quadriceps Strength<sup>†</sup>
- Center for Epidemiologic Studies-Depression scale
- Pepper Assessment Tool for Disability<sup>†</sup>
- Mini Nutritional Assessment-Short Form
- Life Orientation Test-Revised
- Brief Resilience Scale

\* Collected as part of phase 3 screening

<sup>†</sup> Eliminated from baseline assessment in protocol version 11.0

## 11.2 Follow-up Assessment

The following measures will be obtained at 16 weeks post-randomization.

- Six-Minute Walk Test
- Modified Mini-Mental State Examination<sup>†</sup>
- Activities-specific Balance Confidence<sup>†</sup>
- Short Physical Performance Battery
- SF-36 Health Survey<sup>†</sup>
- Modified Physical Performance Test
- Yale Physical Activity Survey<sup>†</sup>
- Weight and Quadriceps Strength<sup>†</sup>
- Center for Epidemiologic Studies-Depression scale
- Pepper Assessment Tool for Disability<sup>†</sup>
- Mini Nutritional Assessment-Short Form<sup>^</sup>

<sup>†</sup> Eliminated from follow-up assessment in protocol version 11.0

<sup>^</sup> Eliminated from follow-up assessment in protocol version 12.0

Note: The subset of participants randomized prior to protocol version 10.0 received a second follow-up assessment at 40 weeks post-randomization using the complete list of measures above.

## 11.3 Telephone Interviews

Structured telephone interviews with blinded assessors will be conducted every four weeks for 16 weeks post-randomization starting four weeks after the date of randomization. Participants will be given a health diary at the baseline visit to assist with recall during the telephone interviews. The following measures will be administered:

- Reportable Adverse Events (RAE) Form
- Health Care Utilization questionnaire<sup>†</sup>
- Expected Adverse Events (AE) Form
- Self-report of study medication adherence<sup>†</sup>

<sup>†</sup> Eliminated from telephone interview in protocol version 11.0

Note: The subset of participants enrolled prior to protocol version 10.0 received telephone calls every four weeks for 40 weeks post-randomization using all the measures listed above.

## 11.4 Timing of Study Procedures

The target date for completion of the pre-randomization (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 of randomization (see Table 1).

**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
Randomization	As early as possible following admission	Up to 26 weeks post-admission
Dietitian consult	1 week post-randomization	+1 week
First intervention visit	1 week post-randomization	+16 weeks
First telephone interview	4 weeks post-randomization	-1 week, +3 weeks
Subsequent telephone interviews	At 4-week intervals from date of randomization	-1 week, +3 weeks
First follow-up assessment	16 weeks post-randomization	+2 weeks
Out-of-window assessment	16 weeks post-randomization	0-16 weeks and 18-38 weeks post-randomization

### 11.5 Primary Outcome Classification

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. All cases for which, despite intensive efforts, administration of the SMWT is not possible will be submitted for adjudication. See Figure 4.

Although there is an absence of highly sensitive and specific surrogate measures for the ability to walk  $\geq 300$  m in six minutes, prior studies suggest that there are factors that are highly predictive of the *inability* to walk at that speed. Therefore, the purpose of the adjudication will be to reduce the number of participants with missing outcomes by identifying treatment failures in cases where the SMWT could not be administered. Based on the adjudication, participants who meet one or more of the following criteria at the follow-up assessment will be classified as treatment failures in the primary analysis for the given follow-up time:

- 1) Participant died
- 2) Participant was too sick, based on adjudicators' review of source documentation, to walk 300 m or more in six minutes
- 3) Gait speed based on SPPB four-meter walk was less than 0.6 m/s (very slow speed incompatible with ability to walk 300 m in six minutes)
- 4) Participant or proxy reports (a) participant limitation in walking several blocks or (b) in walking across a small room without help from another person

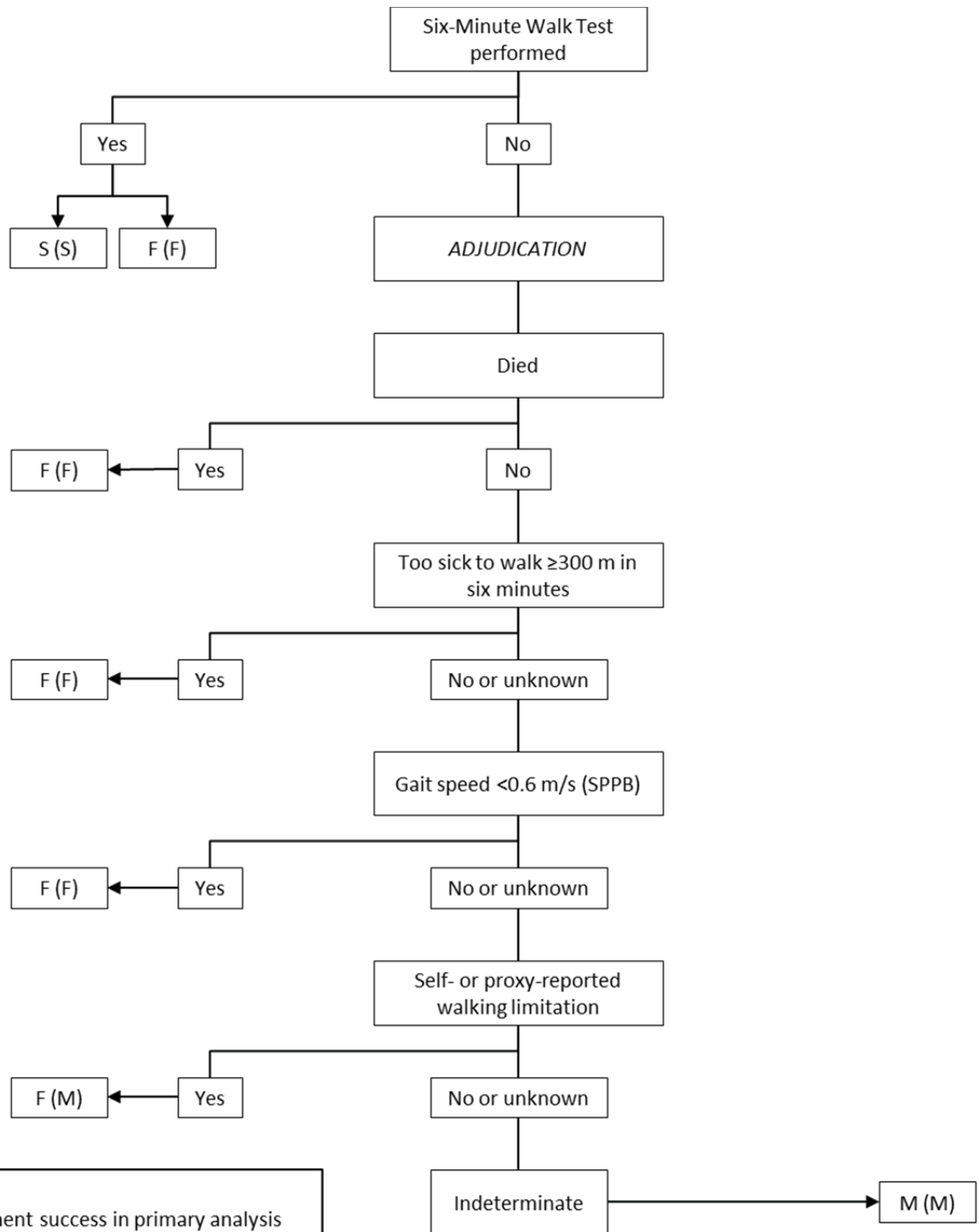
Criterion 4a is an item from the Activity Limitations section of the SF-36 and was chosen because, in a previous hip fracture study performed by our group, 100% of 27 participants meeting the criterion were unable to walk 300 m or more in six minutes (unpublished data). Also, in that study, 85% of 26 participants who had a missing SMWT reported this level of walking limitation, suggesting that use of this item will allow us to assign a classification to a large proportion of those who were not tested on the SMWT. Criterion 4b is an item from the Pepper Assessment Tool for Disability and was chosen because it has high face validity for predicting treatment failure. To improve our ability to classify the outcome status of participants whose SMWT was not administered, we will make intensive efforts to obtain self- or proxy-

reported information on these two items in person or by telephone, even when other data cannot be collected at the given follow-up time.

There will be three adjudicators, all experts in mobility assessment and the clinical management of older persons. Each adjudication case will be randomly assigned to two of the adjudicators who will independently review all the relevant documents and classify participants as treatment failures or indeterminate. If the two adjudicators disagree on the classification, the case will be discussed in a meeting with the two adjudicators. If there is no consensus after discussion between the two assigned adjudicators, the case will be discussed in a meeting with all three adjudicators. Discrepancies will be resolved by a vote if the three adjudicators cannot reach a consensus. To monitor the adjudication process, an unblinded statistician will calculate, among the cases submitted for adjudication, the outcome of adjudication (proportion classified as failure and indeterminate), by treatment group. The incorporation of adjudication results into the analysis plan is described in Section 15.1.

Cases where the SMWT was administered but not according to protocol (e.g., using a walking course of less than 10 m) will also be submitted for adjudication. The adjudicators will review the description of the circumstances and outcome of the testing as recorded by the evaluator and will judge whether the participant's classification (treatment success or treatment failure) based on the distance walked is valid. If not, the participant will be classified as 'indeterminate'. For simplicity, this part of the process is not depicted in Figure 4.

**Figure 4. Classification and Analysis of Primary Outcome**



**Legend:**  
 S Treatment success in primary analysis  
 (S) Treatment success in secondary analysis  
 F Treatment failure in primary analysis  
 (F) Treatment failure in secondary analysis  
 M Missing in primary analysis  
 (M) Missing in secondary analysis  
 SPPB Short Physical Performance Battery

Note: This flow chart applies only to follow-up assessments. At baseline, all participants will be tested with the Six-Minute Walk Test.

## **Section 12: Safety Assessments**

### **12.1 Participant Safety Parameters: Methods and Timing**

#### **12.1.1 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 clinical site study clinician and PI will be responsible for giving permission for potential participants to be randomized, 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.<sup>199</sup>

#### **12.1.2 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, the SPPB, or the mPPT, 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. 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 clinician.
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 clinician and follow up as needed.
Resting pulse Rate > 120 or < 40 beats/min	Qualified staff will consult with the study clinician and follow up as needed.
Chest pain, dizziness, significant shortness of breath, or severe musculoskeletal pain during the intervention or study assessment.	Qualified staff will consult with the study clinician and follow up as needed.
CES-D Score $\geq$ 27	Qualified staff will talk to the participant and provide a referral for additional follow-up and/or medical evaluation for depression.
Weight loss $\geq$ 2% in four weeks during intervention period	Participant will be referred to the registered dietician for follow-up by telephone.
Weight not obtained at the final PT intervention visit and there is weight loss $\geq$ 5% between baseline and follow-up.	Clinical site PI or clinical site clinician will review participant's weight trajectory, baseline BMI, baseline MNA®-SF score and registered dietician's documentation and, if warranted, will refer the participant to a dietician or medical provider for follow-up of possible poor nutritional status.
Participant expresses desire to commit suicide	Call primary care provider and report findings. Report to clinical site coordinator/study clinician for follow-up and clearance.

**12.1.3 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.<sup>200</sup> No significant cardiac events were reported after performing 1-RM testing for over 6600 healthy subjects.<sup>201</sup> 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.<sup>202,203</sup> 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.<sup>199</sup> 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.<sup>204</sup> 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 clinician 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.

#### **12.1.4 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.

#### **12.1.5 Safety Considerations for the PULSE Intervention**

TENS is generally considered safe. However, electrical current that is too intense or that is used incorrectly can burn or irritate the skin. The electrodes should not be placed over the eyes, heart, brain, or front of the throat. Electrodes should not be placed over the chest of persons with demand-inhibited synchronous pace makers. People with allergies to adhesives may react to the electrode pads. If the participant is allergic to adhesives, carbon electrodes with gel and non-allergenic skin tape will be used. Skin tears may occur when removing the pads.



Participants may experience tingling or numbness that only lasts when the electrodes are delivering current. Those with implanted pacemakers, defibrillators, infusion pumps, and other such devices should not have current passing over the body areas where these devices are located. This should not be a problem in this study since the electrode placements are not on the upper body and are restricted to targeted muscle groups on the lower extremities. Please see Table 3 for a summary of alerts and appropriate action during the PT intervention visits.

**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	<ol style="list-style-type: none"> <li>1. If initial BP check is high (systolic &gt; 170; diastolic &gt;100), have participant sit for 5 minutes and rest then check BP again. This may be done twice.</li> <li>2. If three BP readings are greater than 170/100, then individual should not exercise.</li> <li>3. The PCP, clinical site coordinator, and study clinician should be called before exercise is initiated.</li> <li>4. If initial BP is low for that person (systolic&lt;90; diastolic&lt;50) follow same protocol.</li> </ol>
New chest pain	Call 911.
Reported chest pain that occurred between visits	<ol style="list-style-type: none"> <li>1. Cancel treatment and call PCP.</li> <li>2. Report to clinical site coordinator and study clinician to follow-up until cleared.</li> </ol>
Acute shortness of breath	<ol style="list-style-type: none"> <li>1. Have participant stop exercising and rest.</li> <li>2. Take vital signs.</li> <li>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.</li> <li>4. Report to PCP, clinical site coordinator, and study clinician.</li> </ol>
Fall	<ol style="list-style-type: none"> <li>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.</li> <li>2. Report all falls to clinical site coordinator.</li> <li>3. Complete an incident report.</li> </ol>
Stroke symptoms	Call 911 immediately.

ALERT	ACTION
Dizziness during exercise	<ol style="list-style-type: none"> <li>1. Stop exercise and have person sit or lie down.</li> <li>2. If sitting is not sufficient to resolve dizziness, then check vital signs.</li> <li>3. Call 911 if clinically unstable.</li> <li>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 &gt; 160/100 or systolic &lt;90.</li> <li>5. Report event to clinical site coordinator and study clinician.</li> </ol>
Resting pulse Rate > 120 or < 40 beats/min	<ol style="list-style-type: none"> <li>1. PT will stop delivery of the intervention.</li> <li>2. Qualified staff will consult with the study clinician and follow up as needed.</li> <li>3. PT will resume delivery of the intervention only after the participant receives medical clearance.</li> </ol>
New irregular heart rate with complaint of heart palpitations	<ol style="list-style-type: none"> <li>1. Do not exercise and call PCP.</li> <li>2. Report to clinical site coordinator and study clinician for follow-up.</li> <li>3. Wait for medical clearance to resume exercise.</li> </ol>
New acute musculoskeletal pain during exercise (pain > 5 on VAS)	<ol style="list-style-type: none"> <li>1. Have the participant stop the exercise and rest.</li> <li>2. Attempt to alter position of participant to reduce pain. If pain persists, do not continue specific exercise. Attempt to do other exercises.</li> <li>3. If pain does not resolve, refer to PCP or orthopedist and study clinician.</li> </ol>
New, acute, non-musculoskeletal pain (pain > 5 on VAS)	<ol style="list-style-type: none"> <li>1. Do not exercise.</li> <li>2. Take pain history and call PCP.</li> <li>3. Report to clinical site coordinator and study clinician for follow-up and clearance.</li> </ol>
Acute change in mental status	<ol style="list-style-type: none"> <li>1. Do not exercise.</li> <li>2. Call PCP or if unavailable, call 911.</li> <li>3. Report to clinical site coordinator and study clinician for follow-up and clearance.</li> </ol>
Participant expresses desire to commit suicide	<ol style="list-style-type: none"> <li>1. Call PCP and report findings.</li> <li>2. Report to clinical site coordinator and study clinician for follow-up and clearance.</li> </ol>

### 12.1.6 Safety Measures for the PULSE Intervention

The intervention visits 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

PULSE sessions and will be CPR certified. Also, community EMS services will be activated if needed.

In order to maximize safety, participants will be taught the proper method of performing the AROM exercises and the importance of following the proper method. Participants will be supervised at all times and instructed on technique on all activities during the session. Participants will be instructed to talk with the PTs about any muscle soreness, discomfort, tingling or numbness.

Every effort will be made to prevent AEs including stopping intervention activity when the participant reports discomfort. Precautions for TENS use include not placing the electrodes in the thoracic region in the presence of demand-inhibited synchronous pacemakers, checking for skin irritation from the electrodes, and keeping the current path outside of open wounds. 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. 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. The level of sensory stimulation provided during the intervention will be at a level that should not cause pain or muscle contraction.

#### **12.1.7 Safety Considerations for the Nutritional Intervention**

Individuals who have sustained a hip fracture are frequently at risk for protein and calorie malnutrition and have low calcium and vitamin D intake.<sup>205</sup> 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 <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.

#### **12.1.8 Safety Measures for the Nutritional Intervention**

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. 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 clinical site PI or clinical site clinician 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.

## **12.2 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.

## **12.3 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 CAP study.

# **Section 13: Reportable Adverse Events (RAEs) and Expected Adverse Events (AEs)**

## **13.1 Overview**

In this study we will capture study-defined expected adverse events (AEs) through structured telephone interviews with blinded assessors 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 13.4. The timely and complete account of RAEs will be a critical requirement for the protection of human subjects in the CAP trial.

The CAP DSMB will review and approve study-defined expected AEs and will be involved in regular monitoring of the RAE reporting system. Study-wide reporting of expected AEs to the CCC, the DSMB, the NIA, and the clinical site IRBs will be mediated through a central database. RAEs will be monitored and tracked separately by the CCC and reviewed by the DSMB and the NIA as outlined in section 13.8.

Clinical site staff will have responsibility for reporting RAEs to their own local IRB according to local policies.

## 13.2 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.

### 13.2.1 Severity

The following guidelines will be used 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.

### 13.2.2 Expectedness

AEs will be assessed 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 13.3). Expected AEs are captured in a standardized way by blinded personnel.

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 13.4.2). Unexpected AEs are reportable.

### 13.2.3 Relatedness

An independent safety monitor (ISM) who is blinded to treatment assignment will determine the degree to which RAEs are related to CAP study procedures or to procedures conducted as part of an ancillary study to CAP using the criteria shown below.

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).

### 13.3 Expected AEs

Expected AEs will be captured through telephone interviews every four weeks by blinded personnel, 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
- breathing problems
- chest pain or discomfort
- skin tears, rash, or skin irritations
- numbness or tingling
- fall (with or without injury)

### 13.4 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 clinical site clinician and clinical site PI to determine if they should be reported.

#### 13.4.1 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 captured through telephone interviews every four weeks by blinded personnel, using the Reportable Adverse Events Form. SAEs will also be assessed at the beginning of each PT visit and clinical site follow-up visit, and by any study staff who learns of a serious event.

#### **13.4.2 Unexpected Adverse Event**

Unexpected AEs will be defined as medical events that occur during study participation, but do not commonly occur in the CAP study population and which are not listed in the ICF or study protocol (section 13.3). 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 clinical site study office where they will be logged in the participant binder and then reported to the CCC and the Independent Safety Monitor (ISM).

A reportable unexpected AE will be one that meets all 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 clinical site clinician and the clinical site 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.

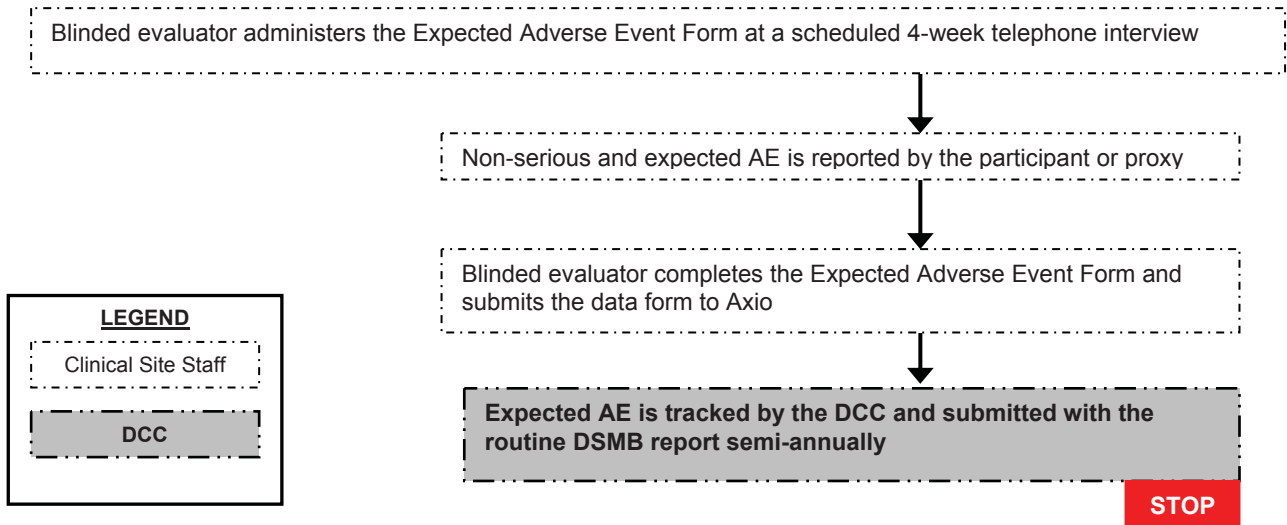
#### **13.4.3 Injury that Occurs while Under the Supervision of Study Related Personnel**

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 during the conduct of an ancillary study to CAP) 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.

### **13.5 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 post-randomization. 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**

Blinded evaluator administers the Reportable Adverse Events Form at a scheduled 4-week telephone interview

Event is identified by the participant or proxy & meets the criteria for an RAE

Blinded evaluator completes a Reportable Adverse Event Record for each event and submits documentation to the clinical site coordinator

YES  
Clinical site coordinator records RAE ID#, marks as duplicate, and files in participant binder

Has the RAE been previously reported?

NO

Clinical site coordinator notifies clinical site PI and clinical site clinician immediately

Clinical site coordinator assigns new RAE ID#, and records event on the RAE Log in the participant binder

Clinical site PI (or designee) redacts documents to conceal treatment assignment and notifies the CCC in writing (by fax or email) within 24 hours of the event being reported to the PI

CCC NOTIFIES DSMB AND NIA IN WRITING (BY FAX OR EMAIL) WITHIN 24 HOURS OF THE EVENT BEING REPORTED TO THE CCC

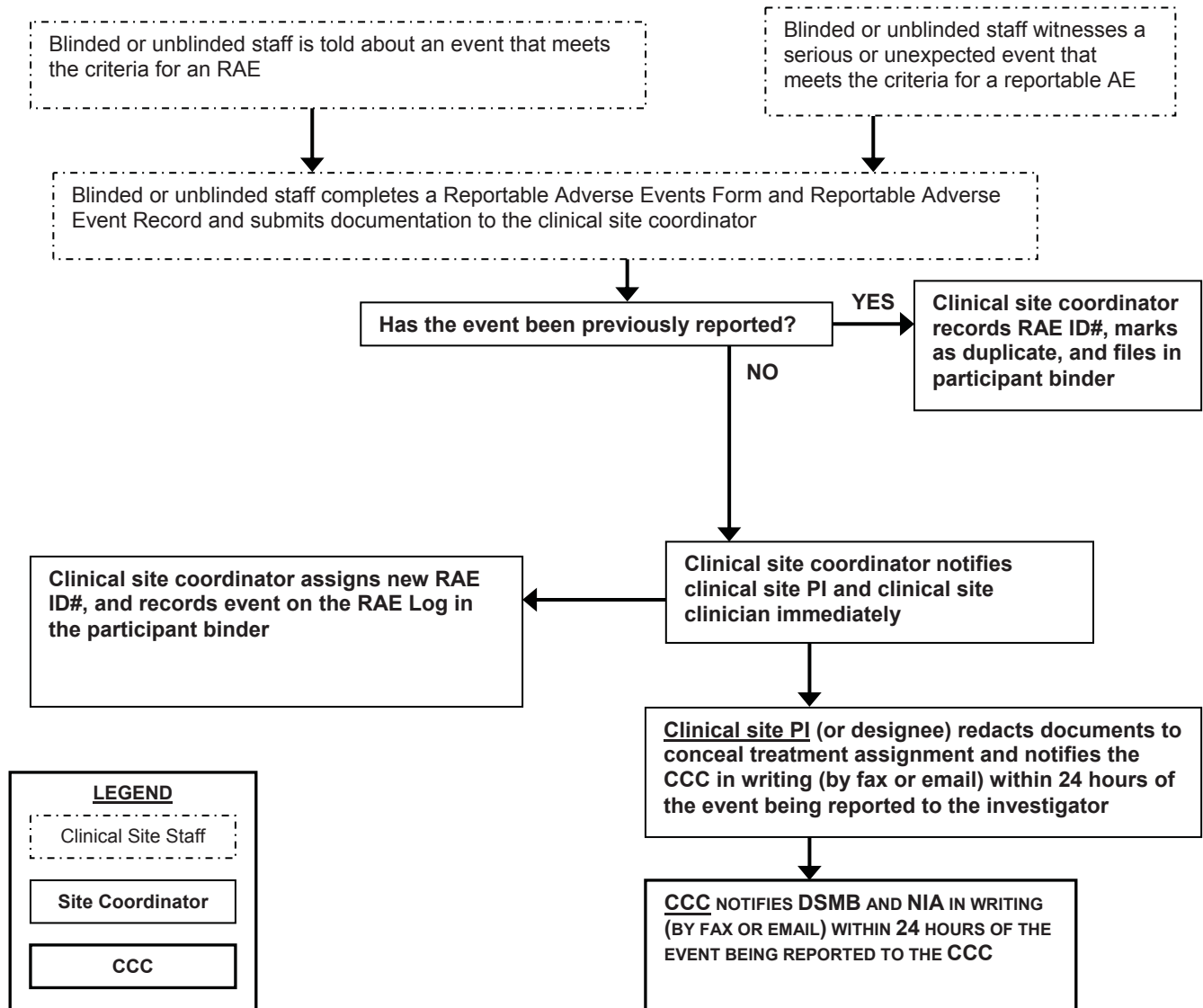
**LEGEND**

Clinical Site Staff

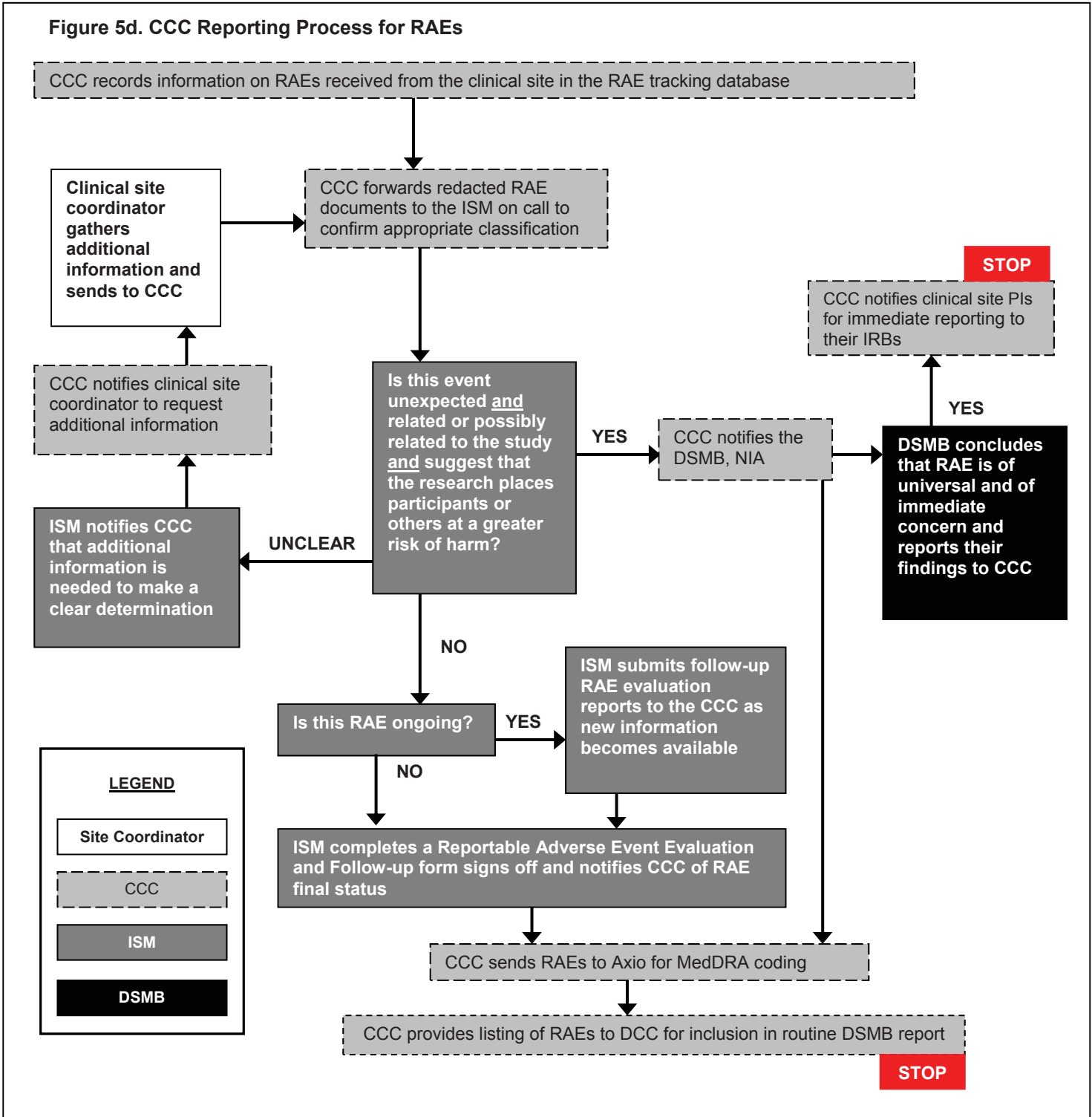
Site Coordinator

CCC

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



**Figure 5d. CCC Reporting Process for RAEs**



### Timeline for Reporting Events

The RAE reporting schedule is shown below:

1. RAEs will be reported to the clinical site PI and clinical site clinician as soon as the event is known.
2. The clinical site PI (or designee) will redact documents to conceal treatment assignment and report all RAEs to the CCC in writing (by fax or email) within 24 hours of the event being reported to the investigator.
3. The CCC will report all RAEs to the DSMB and NIA in writing (by fax or email) within 24 hours of being notified.
4. The DSMB and NIA will receive notification about all RAEs within 48 hours of when the event is known and reported by study staff.

### **13.6 Evaluation and Follow-up of RAEs**

All RAEs submitted to the CCC will be forwarded to a blinded ISM for adjudication and follow-up. The ISM may contact the clinical site 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 contact the clinical site PI who 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 clinical site clinician and/or clinical site 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 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.
2. If there are follow-ups to an event (and the event is ongoing), the ISM will use the Reportable Event Evaluation and Follow-up Form to record the event follow-up and submit to the CCC.
3. Once the event is no longer ongoing and a final status for the event has been determined, the ISM will record the final status, enter the closed date, and sign and date the Reportable Adverse Event Evaluation and Follow-up Form that will be submitted to the CCC.

The CCC will be responsible for reporting RAEs to the DSMB, NIA, and clinical sites, as needed. Clinical sites will be responsible for reporting RAEs to their respective IRBs according to local requirements.

#### **13.6.1 Action Taken**

The clinical site PI, in consultation with the study clinician and the ISM, will decide whether or not an RAE requires that the participant be removed from the study intervention and will forward the decision to the CCC. The DSMB will be notified of the recommended course of action by the CCC. 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

### **13.7 Responsibilities**

Clinical site PIs have primary responsibility for the safety of participants as it relates to the study protocol. Clinical site coordinators will be responsible for reviewing RAEs and assuring accurate and timely reporting of RAEs. Clinical site clinicians will be responsible for reviewing RAEs before they are sent to the CCC. Blinded ISMs will evaluate and classify RAEs and provide follow-up for events until they are resolved. The DSMB will be responsible for reviewing monitoring data for evidence of harm attributable to participation in CAP.

#### **13.7.1 Clinical Site Clinician**

The clinical site clinician 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 sites. In addition, the clinical site clinician will be responsible for reviewing and RAEs requiring immediate notification of the IRB and CCC and for being “on call” for study-related emergencies. The clinical site clinician may delegate responsibilities related to immediate notification to a “covering” clinician.

#### **13.7.2 Independent Safety Monitor (ISM)**

Physicians serving on the Clinical Direction SOC and who are not affiliated with a clinical site will serve as ISMs to review RAEs reported to the CCC on a rotating basis. Other members on the Clinical Direction SOC will also serve as an ISM when necessary, but cannot review events from their clinical site. When a RAE is identified by a clinical site the information will be redacted to conceal treatment assignment, reported to the CCC, 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;
- Making a determination about relatedness of the RAE;
- Requesting additional information as needed in order to make a determination;
- Providing the CCC with follow-up reports for ongoing RAEs as new information becomes available; and
- Notifying the CCC of the final status for the event once it has been determined.

### **13.8 Reporting Expected AEs and RAEs to the DSMB**

The 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 CCC will forward the individual Reportable Adverse Event Records, including a narrative for each event, as well as a table showing all RAEs to the DSMB and NIA semi-annually. The DSMB will review all RAEs that are temporally related to the interventions in aggregate form at its scheduled meetings.

All RAEs that relate to hazards of the study interventions or are cause for urgent concern will be reported to the CCC and the CCC will report these to the DSMB chairman, NIA, and the UMB IRB immediately after recognition of their importance. If the DSMB chairman concludes that an RAE is of universal and immediate concern, the CCC will notify local clinical sites at once. The DSMB chairman may recommend convening the DSMB to review participant safety based on any individual report or accumulating evidence, including evidence according to treatment assignments.

## Section 14: 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 clinical site clinician and the primary care provider (if participant has one) agree that it is appropriate. For mild problems that require temporary cessation of intervention, the clinical site investigator, in consultation with the clinical site clinician and participant, may agree to reintroduce the participant to the study intervention.

At any time, the 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 15: Data Analyses

Analyses for all aims will be performed according to the intention-to-treat (ITT) paradigm. Prior to confirmatory analysis, exploratory data analyses will be performed. These exploratory analyses will consist of histograms for continuous outcomes to examine whether a transformation is needed to meet modeling assumptions and frequencies for categorical data to assess whether the data are sparse. With the exception of the statistical test of the primary hypothesis, all statistical tests will be two-sided and will not be adjusted for multiple comparisons. As described in greater detail below, the test of the primary hypothesis (comparing the groups with respect to proportion who are community ambulators at 16 weeks) will be based on a one-sided 0.025-level hypothesis test performed at five time points throughout the trial.

### 15.1 Primary Aim

The primary aim is to determine if a 16-week intervention based on aerobic conditioning, specificity of training, and muscle overload for strengthening (the PUSH intervention) is more successful in producing community ambulation at 16 weeks post-randomization than an intervention of transcutaneous electrical nerve stimulation, flexibility, and AROM exercises (the PULSE intervention). Therefore, the one-sided null hypothesis that the PUSH intervention does not result in a higher proportion of community ambulators 16 weeks post-randomization will be tested. This hypothesis will be tested at five time points based on a Z-statistic (which is equivalent to the square root of the Pearson chi-square statistic). The critical values for each time point were chosen to preserve an overall type-1 error rate of 0.025.<sup>206</sup> If the exploratory analyses reveal data sparseness (expected frequency less than 5 for at least one combination of treatment group and community ambulation status), Fisher's exact test will be performed instead of using the chi-square statistic. The difference in proportions with a 95% confidence interval will also be reported.

The binary outcome variable will be ability to walk at least 300 meters in six minutes (yes/no). This variable will take the value of 'yes' if the participant was tested with the SMWT and walked 300 m or more in six minutes. This variable will take the value of 'no' if 1) the participant was tested with the SMWT and walked less than 300 m in six minutes or 2) the participant was not tested with the SMWT (or the participant was tested but not according to protocol) and adjudication resulted in the participant's being classified as a treatment failure (see 11.5 for description of the adjudication procedure). Participants whose adjudication result is 'indeterminate' will be excluded from the primary analysis.

In a secondary analysis, an alternative outcome variable will be created to represent the participant's community ambulation status at 16-week follow-up. This secondary variable will take the value of 'yes' if the participant was tested with the SMWT and walked 300 m or more in six minutes. The secondary variable will take the value of 'no' if 1) the participant was tested with the SMWT and walked less than 300 m in six minutes, 2) the participant was not tested with the SMWT and adjudication resulted in the participant's being classified as a treatment failure because of death, sickness, or gait speed < 0.6 m/s, or 3) the participant was tested with the SMWT but not according to protocol and adjudication resulted in the participant's being classified as a treatment failure, whatever the reason. The secondary variable will take the value of 'missing' if 1) the participant was not tested with the SMWT and adjudication resulted in the participant's being classified as a treatment failure based only on self- or proxy-reported walking limitation or 2) the participant was not tested with the SMWT (or the participant was tested but not according to protocol) and adjudication resulted in the participant's being classified as 'indeterminate'. All participants, including those with a missing value for the alternative outcome variable, will be included in the secondary analysis. To be consistent with the principle of ITT, weighted estimated equations (described below) will be used for this analysis.

Study site will be investigated as a modifier of the effect of the intervention by testing a site-by-intervention interaction term. If study site is an effect modifier, we will report 1) site-specific treatment effects and 2) a summary measure of treatment effect using standardization. Standardization will be accomplished using inverse probability of treatment weighting (as a function of study site) in a marginal structural model.<sup>207</sup>

In the fall of 2014, a decision was made to modify the frequency of intervention visits during the first 8 weeks from 3 per week to 2 per week. The number of sessions per week in the first 8 weeks will also be assessed as a potential effect modifier, using the methods described in the previous paragraph. If we find strong evidence that the number of sessions per week modifies the comparison of the intervention groups, we will report treatment effects separately for the period when there were two sessions per week and the period when there were three sessions per week.

This change in number of sessions also affords us an opportunity to assess the impact of visit frequency on the intervention outcomes as a secondary analysis. To do so, assuming no significant interaction between site and intervention group, we will assess the statistical significance of the effect of number of sessions. If there is significant interaction between number of sessions and intervention group, then we will compare the outcomes obtained during the period with two sessions per week in the first 8 weeks to those obtained during the period with three sessions per week in the first 8 weeks separately in each intervention group.

In addition, a series of analyses will be performed to examine the differential impact of the PUSH intervention relative to the PULSE intervention in subgroups defined by participant

characteristics. To do this, a variable-by-intervention interaction term will be tested for each of the following variables:

1. Gender
2. Age at baseline ( $\geq 85$  years versus 60-84 years)
3. Baseline depression (CES-D score  $\geq 16$  versus CES-D score  $< 16$ )
4. Baseline balance confidence (with median Activities-Specific Balance Confidence scale score as the cutpoint to define the subgroups)
5. Baseline nutritional status (MNA<sup>®</sup>-SF score  $< 8$  versus MNA<sup>®</sup>-SF score  $\geq 8$ )
6. Baseline cognitive status (3MS score  $< 91$  versus 3MS score  $\geq 91$ )

If the interaction term for any of these subgroup variables is significant, results will be presented separately in strata of the subgroup variable.

## 15.2 Secondary Objectives

### 15.2.1 Delayed and Sustained Effects

Generalized estimating equations (GEEs)<sup>208</sup> will be used to examine whether the proportion of community ambulators differs between the PUSH and PULSE interventions at 40 weeks post-randomization and, for the subset of participants who were followed for 40 weeks, whether the difference in proportions at 40 weeks changed from the difference in proportions at 16 weeks. GEE will be used for this analysis because the data are longitudinal and, unlike in likelihood-based methods, the estimates are robust to misspecification of the working model (e.g., binomial, normal, etc.). This approach accounts for intra-participant correlation between repeated measures. With the use of GEEs we will be able to relate outcomes, at specific time points, to treatment group. For all analyses using GEE, the empirical variance estimate will be used because it is robust to model misspecification. The longitudinal model for this aim will be fit using a binomial working model and is expressed by the equation:

$$\text{Logit}(p) = a + b_1 X + b_2 t_{40} + b_3 X t_{40}, \quad (\text{Eq. 1})$$

where  $p$  is the probability of a particular outcome,  $\text{Logit}(p) = \ln(p/(1-p))$ ,  $X$  is the intervention indicator (1/0) variable;  $b_1$  is the treatment effect at 16 weeks;  $t_{40}$  is the 40-week follow-up time post-randomization indicator (0=16 weeks; 1=40 weeks); and  $X t_{40}$  is the intervention-by-time interaction variable. The fitted coefficients in Eq.1 provide estimates of the proportion of community ambulators in the PUSH vs PULSE interventions at 16 and 40 weeks post-randomization. To test the null hypothesis of equal proportion of community ambulators in both groups at 40 weeks post-randomization, we will test the null hypothesis  $H_0: (b_1+b_3)=0$  using a two-sided test with type I error of 0.05. This test will be performed regardless of results from the primary aim. However, the interpretation of results from this test will depend on those from the primary aim. If there is evidence for a difference in proportion of community ambulators at 16 weeks, then rejecting this hypothesis can be interpreted as evidence for a sustained effect of the PUSH intervention on community ambulation at 40 weeks; if there is no evidence for a difference in proportion of community ambulators at 16 weeks, then rejecting this hypothesis can be interpreted as evidence for a delayed effect of the PUSH intervention on community ambulation at 40 weeks. We are also interested in describing the trends in community ambulation from 16 to 40 weeks post-randomization in both groups. To assess the null hypothesis of no change in the between-group difference of proportion of community ambulators between 16 and 40 weeks post-randomization, we will test the null hypothesis  $H_0: b_3=0$  using a Wald chi-square test with type I error of 0.05. All treatment effects will be reported with their respective 95% confidence intervals.

A similar approach will be used to examine delayed and sustained effects for the secondary and



tertiary outcomes described below.

### 15.2.2 Secondary and Tertiary Outcomes

Secondary outcomes include five variables (endurance, dynamic balance, walking speed, quadriceps strength, and lower extremity function) that are hypothesized to be precursors to community ambulation. In addition, we will examine the difference between the treatments with respect to the following tertiary outcomes: ADLs, balance confidence, quality of life, physical activity, lower extremity physical performance, depressive symptoms, increase of  $\geq 50$  meters in distance walked in six minutes, cognitive status, and nutritional status. GEE will be used to compare the PUSH and PULSE interventions at 16 and 40 weeks post-randomization. Increase of  $\geq 50$  m in distance walked, a dichotomous outcome, will be analyzed using the same method as the primary outcome. All of the other secondary and tertiary outcomes are continuous; therefore, a normal working model will be used to estimate the parameters in the following equation:

$$\mu = a + b_1 X + b_2 t_{16} + b_3 t_{40} + b_4 X t_{16} + b_5 X t_{40}, \quad (\text{Eq. 2})$$

where  $\mu$  is the mean of a particular outcome,  $X$  is the intervention indicator (1/0) variable;  $t_{16}$  and  $t_{40}$  are the 16- and 40-week follow-up time post-randomization indicators, respectively; and  $X t_{16}$  and  $X t_{40}$  are the intervention-by-time interaction variables. This model accounts for outcomes at three time points: baseline, 16 weeks, and 40 weeks post-randomization. By treating the baseline value as an outcome, we quantify mean changes in the outcome relative to baseline levels. Differences between the two groups in changes from baseline to 16 and 40 weeks post-randomization will be compared using Eq. 2 by testing  $H_0: b_4=b_5=0$  using a Wald chi-square test with type-I error of 0.05. All treatment effects will be reported with their respective 95% confidence intervals.

### 15.2.3 Cost-Effectiveness of Interventions

To assess the cost-effectiveness of study interventions, the EEC will conduct analyses of within-trial comparisons for the economic endpoints (resource utilization/costs and SF-6D/QALYs) and will also undertake a model-based analysis that allows the economic value of both study interventions to be assessed relative to usual care. Longitudinal modeling appropriate for repeated measures data will be used to make inferences on the overall differences in cost and QALYs associated with the study interventions. The basic statistical analyses of cost and QALYs will be similar to the approach described for other study endpoints, but will be undertaken in the EEC in close collaboration with the DCC.

Statistical analyses of SF-6D will produce an estimate of the incremental QALYs associated with the PUSH intervention at each time point where SF-36 is measured. The estimated difference in QALYs attributable to the PUSH intervention will be estimated by taking a time-weighted average of the time-specific intervention effects. Statistical analyses of cost data, which will be adjusted to a constant dollar year (e.g., 2012 US dollars), will produce an estimate of the incremental costs associated with the PUSH vs. PULSE intervention.

The incremental cost-effectiveness ratio (ICER), which is defined as the net change in cost divided by the net change in effectiveness (QALYs) when interventions are ranked in order of increasing cost, is the focus of the economic analysis. When estimated as added cost per QALY gained, the ICER allows the value of interventions in hip fracture to be compared with interventions in other diseases. ICERs will be estimated using both the statistical analysis of cost and QALY data (i.e., trial-based ICER) and a model-based analysis that combines trial results with other existing data (i.e., model-based ICER). The trial-based ICER addresses the economic value of the PUSH intervention relative to the PULSE, while the model-based ICER

estimates the economic value of the study interventions relative to usual care (as described below).

The second objective of the cost-effectiveness analysis is to develop and implement a decision-analytic modeling framework that will incorporate within-trial findings regarding costs and QALYs for the purpose of evaluating the cost-effectiveness of the PUSH intervention and PULSE relative to usual care. Model-based analyses are commonly employed to extend or augment clinical trials because the cost of trials precludes study of all interventions of interest and because it is often desirable to consider the value of interventions over a longer time horizon than what is observed in the trial. To make inferences about the economic value of the study interventions relative to usual care, a Markov state-transition modeling framework that incorporates trial results will be developed and utilized. Estimates of the cost of the study interventions will be derived from time estimates recorded in the field over the course of the study. Estimates of the QALY impact of usual care will be derived from existing hip fracture cohorts (control arms of other trials). Estimates of changes in SF-6D for similar patient groups are available from the control arms of BHS RCTs. Because these studies have tracked resource utilization with few questions and follow up measures, extensive sensitivity analyses that vary the impact of the interventions on resource utilization will be undertaken to characterize the magnitude of change in costs that would be required to qualitatively affect the conclusions of the economic analysis.

The model-based ICER for the study interventions relative to usual care will be compared qualitatively with the costs per additional QALY estimates of other commonly accepted medical interventions. Uncertainty in the model-based analysis will include estimation of cost-effectiveness acceptability curves, which represent the probability that a particular cost-effectiveness threshold (e.g., \$100,000 per QALY gained) is achieved when variability in cost and QALYs is considered in probabilistic sensitivity analyses.

### **15.3 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.<sup>209</sup> 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.

### **15.4 Nonadherence**

In the presence of nonadherence, ITT analyses have the benefit of conservatively estimating effects. However, ITT analyses may miss true effects because their results are biased toward the null. To address this issue, we will examine adherence (defined as proportion of intervention visits completed) in both intervention groups. If adherence is less than 80% in either group, we will perform a secondary analysis adapting marginal structural modeling to address noncompliance. In this case, the weight will be the inverse probability of treatment received as a function of treatment assignment and factors that may affect treatment compliance. This method has the benefit of accounting for intermediary factors that may impact compliance without

distorting the randomization by conditioning on these factors (i.e., a marginal analysis rather than a conditional analysis). Precedents for this approach are available in the literature by Cook.<sup>210</sup>

## 15.5 Interim Analyses

Interim analyses will be conducted by an alpha and lower bound spending design. At the time of this update, we have already performed an interim analysis based on the first 28.6% of the data. We plan to perform three additional interim analyses (based on the first 40%, 60%, and 80% of data available), where the boundary values for early stopping will be evaluated using the Hwang-Shih-Decani spending function approximation to the O'Brien-Fleming alpha-spending function [ $\gamma = -4$  for lower-bound alpha spending (inefficacy/harm), and  $\gamma = 4$  for upper-bound alpha spending (efficacy)].<sup>211,212</sup> The upper and lower bounds will be computed for a test of efficacy with one-sided nominal  $\alpha = 0.025$ . For example, when testing for efficacy ( $\delta > 0$ ) at the first interim analysis,  $Z > 3.09$  would denote efficacy, and  $Z < -1.76$  would denote inefficacy/harm. Table 4 shows the anticipated proportion of the sample accrued at each of the remaining interim analyses along with the corresponding critical values for declaring significance (or lack thereof) at each time point. The critical values are subject to change if the actual information available at the time of the analysis differs from the expected information available. These critical values were calculated using the gsDesign package in R version 2.10.1.

**Table 4. Anticipated Critical Values for Each Planned Analysis**

Analysis	Expected % of information available	Critical z-value for upper-bound alpha spending (for efficacy)	Critical z-value for lower bound alpha spending (for inefficacy/harm)
First interim analysis	28.6%	3.09	-1.76
Second interim analysis	40%	3.03	-1.57
Third interim analysis	60%	2.69	-0.97
Fourth interim analysis	80%	2.37	-0.21
Final analysis	100%	2.03	2.03

The spending function applies specifically to analysis of the primary outcome (community ambulation at 16 weeks post-randomization). However, at each interim analysis, study performance and secondary and tertiary outcomes will be examined to aid in the interpretation of the primary outcome results.

## 15.6 Sample Size Adequacy

### 15.6.1 Primary Aim

The original power calculations for this study were based on the assumption of a 10% loss to follow-up and a 10% rate of nonadherence. However, based on data on the first 88 study participants, the estimated rate of loss to follow-up was 6.8% and the rate of nonadherence was 12.2%. These estimates were used to revise the power calculations using a new total sample size of 210.

The threshold defined for the primary outcome, the ability to walk 300 meters or more in six minutes, was exceeded by approximately 9% of subjects in the BHS 4 cohort at six months post-fracture (which corresponds approximately to the 16-week post-randomization follow-up in the proposed trial). Furthermore, 23% of controls in the pilot study for the current project surpassed the 300 meter threshold. The midpoint of this range (9% to 23%) is 16% and this was

used as the basis for power calculations for the primary outcome, using the R version 2.10.1.<sup>213</sup> Binder et al,<sup>68</sup> using a comparable intervention, reported an effect size of approximately 0.6 SD on a continuous measure of physical performance. The 0.6 SD effect size corresponds to a difference in six-minute walk distances of about 50 meters for hip fracture patients; a 50-meter difference has been determined by Perera et al.<sup>183</sup> to be clinically meaningful. Assuming normal distributions for the SMWT, and with 16% surpassing the 300 meter threshold in the PULSE group at 16 weeks, a 0.6 SD effect size projects to a 19 percentage point difference in the proportion of community ambulators between the PUSH group and the PULSE group. A difference of 20 percentage points or more in the proportion of participants achieving community ambulation is thus considered an achievable and clinically meaningful goal.

Using a group sequential design with four interim analyses (see Section 15.5), and assuming an overall loss to follow-up of 6.8% and treatment non-compliance of 12.2%, a total sample of 210 enrolled patients (105 patients per group) is sufficient to achieve over 80% power for the detection of a 20 percentage point difference between the groups, with 16% achieving the 300 m threshold of the SMWT in the PULSE group vs 36% in the PUSH group, using a one-sided 0.025 significance level. The power specified is for the detection of a time-specific difference at the 16-week follow-up. This calculation accounts for the sample size inflation of 2.4% needed to account for the group sequential design<sup>211,212</sup> and for the impact of noncompliance on the variance of treatment differences under the assumption that non-compliers assigned to the PUSH group have an equal 16-week proportion achieving community ambulation as participants assigned to the PULSE group.<sup>214,215</sup>

Table 5 shows the power to detect various between-group differences in proportions of community ambulators using a one-tailed test of the difference in proportions at the 2.5% significance level. The table indicates that the study has adequate power for detecting differences down to 20 percentage points.

**Table 5. Power to Detect Difference in Proportions**

True Difference in Proportion Achieving Community Ambulation at 16 Weeks	Power (%)
23 percentage points	89
22 percentage points	87
21 percentage points	84
20 percentage points	80
19 percentage points	76
18 percentage points	72
17 percentage points	68

### 15.6.2 Secondary Aims

Delayed and Sustained Effects. Follow-up will end at 16 weeks post-randomization for those consented under version 10.0 of the protocol. We estimate that there will be approximately 150 participants (not the full 210) for whom the 40-week measure of community ambulation will be available. In addition, based on our experience to date, we estimate that the community ambulation outcome will be indeterminate for 10% of the participants at the 40-week assessment. If we assume a sample size of 150 then there is 64% power for detecting a difference of 20 percentage points at alpha = 0.05 using a two-tailed test.

Effect on Secondary and Tertiary Outcomes. Using a two-sided test with alpha=0.05, a sample of 210 patients with 6.8% loss to follow-up and 12.2% treatment noncompliance will provide

80% power to detect effect sizes of 0.46 SD at 16 weeks, which are considered moderate in size, under the assumption that noncompliers assigned to the PUSH group have an equal mean and standard deviation as patients assigned to the PULSE group. Collection of some outcome measures will end after implementation of protocol version 11.0 (see Section 11:). For these measures, we estimate that there will be approximately 160 participants (not the full 210) for whom the 16-week measure will be available. Under the same assumptions, a sample of 160 will provide 80% power to detect an effect size of 0.53 SD.

Economic Evaluation. Follow-up will end at 16 weeks post-randomization for those consented under version 10.0 of the protocol. We estimate that there will be approximately 150 participants for whom the full 40-week follow-up will be available. Assuming a mean SF-6D score of 0.62 in the PULSE group and between-subject standard deviation of 0.10 (based on unpublished data from the fourth BHS cohort study), and assuming that non-compliers assigned to the PUSH group have an equal mean and standard deviation as patients assigned to the PULSE group, a sample size of 75 per group will allow us to detect a between-group difference in means of 0.055 with 80% power and using a two-sided 0.05-level test.

Costs will be used in conjunction with information on patient quality of life to make treatment outcome comparisons in terms of cost per QALY associated with treatment effects. The primary interest in the economic evaluation is to assess the impact of variability in cost and QALYs on the ICER. To address power for the economic evaluation, we computed the minimum detectable incremental net benefits (INB) for the planned study size.<sup>216</sup> To complete this calculation, a threshold ICER,  $\lambda$ , must be specified, which is the maximum one is willing to pay per QALY gained. INB is then defined as a function of changes ( $\Delta$ ) in QALY and costs as follows:  $\lambda \cdot \Delta \text{QALY} - \Delta \text{Cost}$ . We utilized ICER thresholds ( $\lambda$ ) of \$25,000, \$50,000, and \$100,000 in these computations with  $\alpha=0.05$  (two-sided) and 80% power, and utilized variances and covariances between QALYs (estimated by SF-6D) and cumulative costs from the observational, non-operative treatment arms of the Spine Patient Outcomes Research Trial. Although these subjects differ from hip fracture patients, they have similar ongoing musculoskeletal concerns and variation in QALYs. For  $\lambda$ 's of \$25,000, \$50,000, and \$100,000, minimal detectable INBs are \$2,638, \$4,079, and \$7,234, respectively.

## **Section 16: Data Capture, Data Management, and Quality Assurance**

### **16.1 Overview**

Data management will be provided under subcontract with Axio Research, LLC, Seattle, WA. Axio is a contract research organization with over 30 years of experience providing biostatistical and data management support for clinical trials sponsored by the NIH and industry. Axio operates under a set of Standard Operating Procedures (SOPs) designed to comply with NIH and FDA requirements.

A hybrid system will be employed in which some of the data forms are completed on paper and others using a Web form. All data will be stored and cleaned using Clintrial (Oracle/Phase Forward, Waltham, MA), a commercial clinical data management system in wide use. Data collected during intervention visits and telephone interviews will be entered using a Web system developed and validated by Axio. Some forms will be completed on paper and forwarded in batches to Axio for processing. This model was chosen to minimize costs and to provide maximum flexibility for each of the different types of data collection (clinical assessment, intervention visit, telephone interview). All systems used in this study will be validated according to Axio's SOPs prior to being put into production.

Axio will draft and maintain a Data Management Plan (DMP) for this study. This plan outlines the study data management processes including detailed descriptions of the data entry systems, the study database, data standards, data edit rules, query processing procedures (both automated and manual), and coding procedures. The database annotated data forms and details of the edit checks will be included as appendices in the DMP. Minor changes may be made to the DMP during the course of the study as appropriate.

## **16.2 Data Capture**

Data capture will utilize a hybrid system; some of the forms will be completed on paper and forwarded to Axio for entry and verification. Others, in particular forms completed at intervention visits and during telephone interviews, will be completed online (Web data entry) using a validated Web data collection tool. The original of all paper forms submitted will be filed in the participant binder and kept at the clinical site. Forms entered using the Web tool will be printed from the Web site and filed in the participant binder. It will be the clinical sites' responsibility to ensure that all forms are complete and submitted within the required time frame. For paper forms, the person who collected the data will sign and date the form attesting to its accuracy and completeness. For the Web-based forms, the person who entered the data will print the form after completion and will sign and date the form attesting to its accuracy and completeness. If the person who entered the data is not the person who collected the data, the latter will review the form and sign and date it to affirm its accuracy and completeness. Source documents and other study paperwork will be turned into the office on a regular basis by study staff.

## **16.3 Data Management**

### **16.3.1 Processing of Paper Data Forms**

Paper data forms will be completed by clinical site staff, scanned and emailed to Axio for entry, verification and cleaning. The database will be established using Clintrial (version 4.7). This clinical data management system is widely used in the pharmaceutical industry. This database will reside on the Oracle Database Server, located at Axio. Using Clintrial, Axio will set up a logging and tracking system to make sure that each form page received is processed in a timely manner. Each table in the database will be carefully checked to ensure that all the variables specified on the form have been appropriately entered into the database in the proper format (e.g. integer, date/time). Before implementing the data entry system and database, a sampling of data will be entered and loaded into the database. The resulting data from each data table will be tested to make sure that the entire process results in a database as expected.

Axio staff will program the data entry screens for the study using Clintrial. A screen may correspond to a paper data form page or to some portion thereof. The screens are programmed to require that numeric fields be re-keyed by a second data entry technician (double-data entry) for quality control.

Axio will define a data cleaning system comprised of: 1) computerized data validation rules to check for legitimate/expected values, completeness of data forms, and logical consistency; and 2) manual screening checks. The DCC will review and approve the data edit query definitions before Axio begins programming them. A complete list of the data edits will be maintained as an appendix to the DMP.

Upon receipt of paper CRF data, the data management staff will log receipt into the study management database and will review the data form prior to data entry. Potential problems with

the data (e.g., missing or illegible identification data) will be identified by this screening process and entered into Clintrial as “ad hoc” data queries, distributed and tracked for resolution. A data technician will enter the data from each data form page received. A separate data technician will verify the first entry by entering the data a second time (blinded double entry-verification). Text fields will be visually verified during this second pass.

Data edit checks will be run as each batch of data is entered and verified. Axio’s data coordinator will review the resulting list of problems, determine which problems should be sent as queries, and interact with the clinical site staff to clarify issues and answer questions. Queries will be printed to PDF and delivered to the sites via email by the data coordinator. Data edit queries will be distributed within one week of receipt of the data forms. Shorter turn-around will be provided in advance of DSMB meetings and towards the end of the study in order to freeze or close the database.

Using the query tracking reports, the data coordinator will make sure that all queries are promptly and completely addressed, following up on data problems and initiating communication when necessary to make sure that data problems are promptly addressed.

Clinical site staff and DCC staff may submit “ad hoc” queries that are tracked and processed in the same way as the programmed queries. Clinical site staff may also initiate ad hoc corrections.

Clintrial provides a complete 21CFR11-compliant electronic audit trail of all changes made to the database. The audit trail includes the name of the person making the change, the date/time of the change and the reason for the change.

### **16.3.2 Processing of Web-Entry Data**

Axio will design, program and validate a password-protected Web-based system for data entry of certain of the data forms. The Web system will allow the user to select the participant from a list of participants randomized at the user’s site. Entry of the letter code by site staff will be used to confirm that the proper participant has been selected. The application will display the assessment times and allow the user to select the assessment time and form for entry. Edit checks will be included for within-form logical, completeness and value/range checks. Once a form has been entered and submitted, the link will be disabled. At that point, the application will generate a print/readable PDF image of the data form that can be downloaded or printed.

On a daily basis, data from the Web system will be downloaded to the Clintrial (Oracle) database. Further edits will be applied to the data in Clintrial. Queries and updates to data entered over the Web will be handled as data from paper data forms, as described above.

The Web system is based on a “Survey Tool” that has been in use at Axio for over 5 years. The tool has been reliably implemented for a wide range of studies including some involving participant reported outcomes.

### **16.3.3 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 Clintrial database.

### **16.3.4 Extraction of Data for Analysis and Reporting**

Data will be extracted 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. Testing will be performed by an independent statistician/SAS programmer per Axio's SOPs.

## **16.4 Protection of Data**

### **16.4.1 Physical Security and Backup**

#### Axio

Axio's offices remain locked at all times. Access is controlled by individually-assigned PIN codes. Visitors are required to sign in and be accompanied at all times by an Axio staff member. Axio maintains a dedicated, access-controlled server room within its facility. The server room is supported by three uninterruptable power supplies, a dedicated heating, ventilation and air conditioning (HVAC) system, a temperature and humidity monitor and a facility fire detection system.

All corporate data and resources including users and computers are administered and secured in a Windows domain type network environment using Microsoft's Active Directory services. Access to the data and the programs on the network is secured using group based privileges. Passwords are required to be changed every 90 days and the strength and length of the passwords are set according to rules specified by the Director of Information Technology (IT).

Internet access is provided by two high-speed connections, a dedicated Ethernet line and a Comcast business class connection. The Axio phone system is supported by a separate, dedicated T-1 line. The Axio network is isolated from the Internet on each independent provider by a router and then subsequently by a Cisco Integrated Services router. The Cisco router includes a Cisco IOS Firewall and intrusion prevention, onboard encryption and additional security features.

Remote access to the corporate network is provided using the virtual private network services supported by the Cisco Integrated Services router. Access to the corporate network is controlled by the Microsoft's Active Directory services in the Axio domain.

Clintrial resides on an Oracle server located inside Axio's corporate firewall and on a server located within Axio's dedicated access-controlled server room, described above. Access to the Clintrial database is controlled by a security model imposed by the software, which requires login with an individually assigned user name and password. A role-based security model assures that staff are allowed to perform only those functions which are appropriate for their role (e.g., data entry/verification only, managing data queries, etc.). Backups are performed as described below.

The Axio collocation facility is located at the AdHost data center in Seattle, WA. The AdHost facility is access-controlled, monitored by both interior and perimeter security and all servers are located in locked cabinets. The server hardware at AdHost is monitored 24 hours/day, 365 days/year, by AdHost staff at their network operations center, located on site. The AdHost facility is supported by power from four physically diverse locations: (1) a diesel generation backup with rooftop helicopter delivery of fuel, (2) uninterruptable power supplies for each bank of cabinets, (3) a carrier neutral environment with nine separate ISPs, and (4) a fully redundant HVAC system. The AdHost facility meets or exceeds the California seismic zone 4 standards.

All Axio systems are managed by the Director of IT, a System Administrator and backup System Administrator. The System Administrator duties include configuration and daily monitoring of all networks including system performance and intrusion detection, daily monitoring of server



systems including server performance and logs, backup and restore, system validation, internal user support, software support and network security configuration including permissions and network access. The Axio backup plan defines the servers, folders and files that are included in the backup. Full backups are performed weekly and differential backups are performed daily. All backup tapes are retained onsite for one week and then sent to a hardened, secure offsite storage facility, Datasite Northwest.

Axio maintains a disaster recovery plan that addresses all aspects of business activities. The technical portion of the plan includes processes for recovery of critical systems, e-mail, data and support services under a variety of scenarios. Axio maintains a collocation facility that is capable of hosting all critical functions in the event of a disaster. The disaster recovery plan is reviewed yearly and major technical portions of the plan are exercised quarterly.

#### Data Coordinating Center at University of Maryland, Baltimore

All files, including programs used for data management functions, are fully archived once every week with an incremental backup (one in which only records containing new or modified data are archived) as well. The backup system is designed to permit the restoration of the system with a minimum expenditure of time and money should any file be destroyed. Every four weeks, the backup devices are copied and stored off site. Prior to any major change in the operating system, backup devices of the main database are created and saved for as long as needed.

#### Economic Evaluation Core at Dartmouth University

The Economic Evaluation Core (EEC) has offices located at Dartmouth-Hitchcock Medical Center (DHMC) with computing support provided by The Dartmouth Institute for Health Policy and Clinical Practice (TDI) computing services and Geisel School of Medicine Computing. All computers operating on the DHMC campus are fully encrypted. TDI provides 7-day, 24-hour access to its own Dell PowerEdge 6650 servers, running Red Hat Enterprise Linux. These servers contain four parallel processors, 12 GB of RAM, and 7.2 terabytes of hard disk, along with several more terabytes of online tape archives. Data are protected by the use of Decru Dataforts, which provide on-the-fly 256-bit level encryption. All connections to this server are secured by Secure Shell which encrypts all communications to and from the work stations on an isolated firewalled network. Authorized users may access the system only via VPN, or locally through the firewalled intranet, using Red Hat Linux workstations.

Current research is supported by a cluster of 2 Dell 2950 servers using the VMWare virtualization suite, which allows multiple “virtual machines” to run simultaneously on each physical machine. Physical machines communicate together in a cluster to automatically share resource load and to assume the work of physical machines that experience hardware failure, minimizing possible down-time. Each of the two VMWare servers is configured with two dual-core 3.2 GHz Pentium processors, dual-power supplies, and 8 GB of memory. The dual processors and internal power-supplies prevent shutdown from a single component failure. For storage, we have two fault tolerant (RAID-5) Network Attached Disk arrays. The RAID (Redundant Array of Independent Disks) configuration prevents a single disk failure from affecting data integrity or resulting in data loss. For backup an 80/160 GB tape and another 400/800 GB tape backup drive are used. Additionally, two external APC 3000 and one 1500 universal power supply along with PowerChute software minimizes short-term power loss and allows for graceful shutdown during extended power outages to prevent corrupted data. In addition to the clustered VMWare servers, the Research Computing Service has Dell PowerEdge 2600 and 750 systems. Each has its own RAID-5-based internal disk storage and the 2600 has dual-CPU's and dual-power supplies for additional fault-tolerance.

Databases are implemented through Microsoft SQL-Server relational database management system. Data on the research workstations is protected through a "near disk" online backup strategy along with a tape facility for long-term, off-site storage. All workstations in the CAP EEC's domain are backed up in real time to the server disks to provide short-term file and disk recovery using Symantec Backup Exec software. These workstation backups along with all server changes are then backed up nightly to tape for long-term and off-site storage. Additionally, file copies can be synchronized in real time between laptops and workstations using the Symantec Desktop-Laptop Option.

#### **16.4.2 Software Systems Security**

##### Randomization and Web Data Entry Systems

The randomization and web data entry systems will be implemented by Axio as a SSL Web application on the AdHost collocation facility described above. Access to these systems will be accessible only through successful login using an individually assigned user ID and password. Passwords will be required to adhere to specific rules to ensure strong security and will be reset every 180 days. The application will encrypt all transactions (https:// web site). Data will reside on a SQL/Server protected from the internet by firewall. Separate passwords will protect the SQL/Server databases. All transactions will be logged, recording the user ID of the person performing the transaction and the server and local date/time of the transaction.

##### Analysis Data

Data for statistical analysis and reporting will be downloaded from the Web systems described above and from Clintrial. All files will be stored to a file server located at Axio.

Access to the directories where study data will be retained will be controlled by a security group model, allowing only those Axio staff working on this trial to have access to the files and data. Access to unblinded randomization assignment data will be further restricted to those specifically designated by the Director of the DCC to have access to the randomization codes.

#### **16.5 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 for the clinical sites to track time-sensitive study activities throughout the study and for the CCC to track activities across all three clinical sites. Each clinical site will house the study management database on a password-protected computer drive that will be automatically backed up daily. Access to the database will be restricted to the PI and study coordinator and, if necessary, one other study staff member who has no participant contact. There will be several standard reports available in the database for the clinical sites 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.

#### **16.6 Quality Assurance (QA)**

Quality assurance (QA) will be a shared responsibility of all investigators. 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 and providing regular reports to the DSMB, NIA, and IRBs. Study monitoring will be based on early implementation of reviews of accumulating data with rapid feedback to the clinical sites regarding problem areas. The Steering Committee will regularly review progress.

### **16.6.1 Training**

Staff from each clinical site will be trained at the initial central training session(s). Certification and recertification will be required in order to assure that clinic staff have a clear understanding of the CAP Protocol and Manual of Procedures (MOP). Separate training sessions will be provided for staff conducting study assessments, telephone interviewers, PTs providing the PUSH intervention, PTs providing the PULSE intervention, staff conducting screening and informed consent procedures, and the registered dietitians. The clinical site 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; randomization; capturing and reporting expected AEs and RAEs; administering the interventions; performing diet consults; and using the paper-based and web-based data entry systems.

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, training in consent, enrollment, and assessment procedures will be provided by the CCC director, while training in randomization and forms completion will be provided by the DCC director. 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.

Local recertification sessions will be held annually for all staff groups. In addition to refresher training on all study procedures, these sessions will focus on current issues facing the staff, new components implemented in the clinical sites, and problem areas. Recertification procedures improve compliance with the protocol and the maintenance of study skills over the course of the trial. The clinical site coordinator will be responsible for documenting that certification and recertification training has been completed and forwarding that information to the CCC.

### **16.6.2 Quality Assurance Oversight**

QA will be a major activity of the CCC and DCC throughout the study. Annual visits to each clinical site will be carried out by the directors of the DCC and CCC, accompanied by other DCC and CCC staff, and the outcome of QA visits will be reported to the study chair and the Steering Committee. Clinical site investigators will be actively engaged in project oversight on an ongoing basis via regular meetings of the Recruitment and Evaluation SOC. Conference calls will be used to review study progress, exchange information, and engage in joint problem solving. Recruitment, follow-up contact and participant retention, adherence to the interventions, protocol deviations and AEs will all be monitored. Please refer to the Treatment Fidelity Plan (section 9.5) for QA related to the interventions.

### **16.6.3 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 interventions, or that undermine fundamental premises of the study, such as failure to provide the assigned intervention according to protocol or randomizing an ineligible participant. Minor deviations will be those that

impede the progress of the study, such as not submitting data in a timely fashion. After the first major deviation, a clinical site will be asked to submit a proposal outlining how recurrence will be prevented. If remedial efforts fail to correct a problem, access to the randomization system will be suspended and the situation will be reviewed by the SC, DSMB, and/or NIA, depending on the nature of the deviations. This review could result either in more aggressive remedial efforts or in termination of the clinical site. The DCC will document minor deviations in performance reports, as well as notifying the clinical sites of them. Repeated minor deviations that are not corrected may result in suspension of the clinical site. Such a clinical site can only resume study activities once a corrective action plan has been submitted and approved by the Steering Committee. Clinical sites with enrolled participants will be required to complete data collection for those participants even if randomization is suspended. Prior to separation of a clinical site from the study, the directors of the DCC and CCC will visit the clinical site and provide a site visit report to the DSMB for recommendation on final action.

Major deviations will be reported promptly by the clinical site to its IRB and to the CCC and will be tracked at each site using a protocol deviation log, which will then be stored in a study-wide cumulative report in the CCC. The following classifications of protocol deviations will be captured, documented, and reviewed:

- 1) Enrollment, consent, and randomization deviations
  - a. Randomization 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. Wrong intervention administered to participant
  - b. Required aspects of intervention not administered (e.g., dietician referral)

## **16.7 Monitoring**

Ongoing QA monitoring will be performed by the DCC and the CCC. The DCC will check study forms to confirm that certified staff are performing study procedures and will perform exploratory statistical investigations of aggregate data to identify unusual patterns and distributions. Regular reports will be generated showing the site-specific frequency of missing data, delinquent forms, and other study performance parameters. These reports will be reviewed by CCC staff who will promptly initiate action to remedy any problems, and will perform follow-up evaluations of actions taken, if necessary.

Each clinical site will be visited before study start-up to ensure readiness for enrollment and data collection activities. Each site will then be visited at least once a year during the enrollment and follow-up period, and again for a close-out visit six months after the completion of data collection. If problems are identified, the CCC will develop a corrective action plan for the clinical site with clearly defined tasks and timelines. The CCC will track the implementation of the plan and assure that all tasks are completed within the defined timeframe.

Site visitors will discuss any difficulties clinical site staff are having and will work cooperatively to try to resolve them. Additional visits will be made to clinical sites experiencing difficulty in meeting their goals for recruitment or in delivering the study intervention, and recommendations

for improvement will be made to them. Additional visits will also be made if there are concerns about data quality or protocol adherence. Following each visit, a report will be sent to the SC. The SC will review site deficiencies and protocol deviations; remedial action and/or site suspension will be recommended based on severity and frequency of occurrence.

The purposes of the monitoring visits will be to:

- assure the rights and safety of participants
- assure that informed consent has been obtained and documented in accordance with the protocol and NIH regulations
- verify adherence to the protocol and examine staff knowledge via interviews and formal testing
- observe staff performing screening, informed consent, evaluations and interventions to confirm that study conduct follows the guidelines of Good Clinical Practice
- observe office space and procedures to assure secure maintenance of required documents
- observe location for the storage of study medications and review temperature logs
- review drug accountability logs
- review files for documentation of informed consent and to monitor the quality of data collected
- review participant binders for completeness
- assure the information recorded on the forms is complete and accurate
- assure there are no omissions in the reports of specific data elements
- assure participant status at study exit is accurately recorded
- assure accurate reporting and documentation of all AEs

Clinical site investigators must provide the QC monitors access to all requested study documents, including ICFs, drug accountability records, and source documents. During these visits, a spot-check of the accuracy of selected participant records will be carried out based on data already submitted to the DCC.

Additional QA monitoring will be conducted by audiotaping all four-week telephone calls. A random sample of the recordings will be reviewed centrally to confirm the date, time, and length of call; completeness and accuracy of administration of the questions; and completeness and accuracy of the responses recorded on the data collection form.

## **Section 17: Participant Rights and Confidentiality**

### **17.1 Institutional Review Board (IRB)**

The study protocol for scientific oversight and management will be reviewed by the UMB IRB as the umbrella protocol (excluding aspects specific to human subjects that will be addressed by the clinical sites' IRBs). Subsequent modifications to the umbrella protocol must be approved by UMB IRB before submission to the IRBs at the clinical sites and IRBS at respective study hospitals.

The study chair will be responsible for sending DSMB recommendations to individual clinical site PIs, who in turn will be required to distribute the report to their local IRBs.

## **17.2 Informed Consent Forms (ICF)**

It will be the sole responsibility of each clinical site PI to ensure that informed consent was properly obtained for every participant who entered into the study at her/his site. 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 randomization to a treatment group. Written informed consent will be obtained according to procedures reviewed and approved by the clinical sites' IRBs. 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 clinical site's IRB approved consent form and/or the HIPAA Authorization Form. However, clinical site IRBs and local hospital IRBs may require that language be added to the consent form to correspond to local requirements. The clinical sites will be responsible for ensuring that the correct version of the ICF is used at their site.

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 7.6.

### **17.2.1 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 clinical site 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.

### **17.2.2 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.

## **17.3 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.

Information may be entered by prospective participants through social media (e.g., Facebook) or other online communications. These web-based tools must meet HIPAA guidelines to ensure that protected health information is kept private and secure and use of these technologies will be subject to approval by the clinical sites' IRBs.

To ensure confidentiality of study data, completed questionnaires and study forms will be kept in participant binders stored in locked offices at each clinical site, 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 and letter code. Clinical sites will record names, contact information, and other direct identifiers to enable them to maintain contact with participants. Logs accessible only to the local clinical site investigators 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. The participant's letter code and a study status date (e.g., date of randomization) will be used as a second level of check. Names and addresses of participants corresponding to each identification number will be kept in secure files at the clinical sites. 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.

In the final year of award, after the completion of a final data edit, DCC staff will prepare a data file in SAS containing all study variables intended for use in publications; identifying information and administrative data (e.g., edit trail) will not be included in this data file. A de-identified data set will be created which merges all the essential data from all time points of the study. Documentation (including abstracts of published works and calculated variable definitions) and form images will be included with the data file. The data file will be provided to the NIA/NIH after the end of the period of funding for sharing with other investigators according to NIH policy.

## **Section 18: 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) CAP publications will be of the

highest scientific quality; 2) CAP 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 from CAP will be overseen by the Publications and Ancillary Studies Committee (PASC). In addition to committee co-chairs, the PASC will have at least one representative from the DCC, CCC, EEC, and each clinical site. The PASC will make recommendations to the SC.

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

## **Section 19: Ancillary Studies Policies**

An ancillary study will be defined as a study that (1) uses supplementary data that will be collected on participants who are recruited in CAP, over and above the data collection required by the CAP protocol, (2) collects biological specimens (e.g., blood) or performs diagnostic tests (e.g., bone density scans); and/or (3) collects data on subjects not enrolled in CAP but who may be compared to CAP subjects (e.g., participants who receive an alternate intervention). Ancillary studies will be distinct from databank studies, which use data previously collected on participants who are enrolled in CAP.

Ancillary studies will be reviewed and approved by the PASC and ratified by the SC prior to initiation to ensure that they do not conflict with the main study protocol. All approved ancillary studies will also be reviewed by the DSMB and NIA prior to initiation. If approved, the ancillary study PI will report to the DSMB on the same schedule as the main study. Review by the PASC (and approval by the SC) will also be required for presentation or publication of ancillary study results.

CAP investigators will be encouraged to consider ancillary studies and to involve other investigators, within and outside of CAP personnel. Participation in an ancillary study will be subject to the approval of the CAP PASC, SC, and DSMB. The following factors will be considered in determining approval of a proposed ancillary study:

1. Participant burden
  - a. The proposed study must be acceptable to the participants (e.g. in terms of time, discomfort, privacy).
  - b. The proposed study must not reduce enrollment or hamper continued participation in the main study.
2. Study interference
  - a. The proposed study must not interfere with other parts of the main study.
  - b. The proposed study must put no additional demand on CAP resources.
3. The proposed study must be of the highest scientific merit.
4. The investigators must have adequate resources to effectively complete the ancillary study, including:
  - a. Sufficient budget (including enough to offset any costs to CAP).
  - b. Staff having the requisite expertise to meet the objectives of the project.

### **19.1 Concurrent Studies**

Study investigators agree not to conduct studies which would compete with or have a detrimental effect on the conduct of CAP during the period of recruitment and follow-up.



However, it is understood that each clinical site has the right to conduct concurrent studies with participants who do not meet criteria for enrollment into CAP. Concurrent studies of patients who meet eligibility criteria for CAP but are not enrolled in CAP must be disclosed and reviewed by the CAP SC.

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## Section 21: References

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