PROTOCOL TITLE:	Low InTensity Exercise intervention in PAD: The LITE Trial
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1. Objectives

1.1 Purpose/Objectives.

Clinical practice guidelines recommend supervised, high-intensity, ischemic-pain inducing treadmill exercise to improve walking performance in people with lower extremity peripheral artery disease (PAD) (1,2). However, supervised exercise is not paid for by medical insurance. Furthermore, the ischemic leg pain induced by high intensity exercise is a barrier to exercise for patients with PAD. Thus, fewer than five percent of the more than eight million men and women with PAD in the United States participate in supervised exercise (3,4). This proposed study will determine whether an alternative exercise intervention that avoids continuous supervision and exercise-related ischemic pain improves functional performance at 52-week follow-up in people with PAD. Our intervention directly addresses two aspects of current practice guidelines that are major barriers to exercise for patients with PAD: 1) the recommendation for long-term supervised exercise and 2) the recommendation for high intensity ischemic-pain inducing walking exercise (1,2).

We will randomize 305 PAD participants to one of three parallel arms: Group 1: Low-intensity, self-paced walking exercise; Group 2: Standard high intensity, ischemic pain-inducing walking exercise; Group 3: Non-exercising attention control group. The low and high intensity exercise groups will attend center-based exercise sessions once per week for four weeks followed by transition to an entirely home-based exercise program for an additional 48 weeks (52 weeks total). The low and high intensity exercise interventions will use identical self-regulatory and support strategies. However, the low intensity exercise group will be instructed to exercise with minimal to no ischemic leg discomfort and the high intensity group will be instructed to exercise to maximal ischemic leg pain. These two distinct exercise prescriptions will be reinforced during 48 weeks of home-based exercise, using a well-validated behavioral coaching model that can be delivered by telephone once weekly. Our primary outcome is change in six-minute walk distance at 52-week follow-up. If our hypotheses are correct, millions of people with PAD will benefit from this alternative exercise regimen which will be accessible to most of the 8 million people in the U.S. who suffer from PAD.

1.2 Specific Aims/Hypotheses.

Primary Specific Aim. We will determine whether PAD participants randomized to a low intensity, self-paced home-based walking exercise intervention achieve greater improvement or less decline in six-minute walk performance at 52-week follow-up, compared to those randomized to a high-intensity, ischemic pain inducing home-based walking exercise intervention and as compared to the attention control group, respectively. We hypothesize that PAD participants randomized to low-intensity exercise will achieve greater increases or less decline in six-minute walk distance at 52-week follow-up compared to those randomized to high-intensity exercise and as compared to the attention control group, respectively.

Secondary Specific Aim #1. We will determine whether PAD participants randomized to a low intensity, self-paced walking exercise intervention achieve greater improvement or less decline in six-minute walk distance, physical activity, patient-perceived walking performance (measured by the Walking Impairment Questionnaire (WIQ)), and health-related quality of life (measured by the short-form 36 physical functioning (SF-36 PF)) score at 26-week follow-up, compared to PAD participants

randomized to the high-intensity exercise intervention and as compared to the attention control group, respectively. We hypothesize that PAD participants randomized to low intensity exercise will achieve greater increases or less decline in six-minute walk distance, physical activity, WIQ distance and speed scores, and the SF-36 PF Score at 26-week follow-up, compared to those randomized to high-intensity exercise and as compared to the attention control group, respectively.

Secondary Specific Aim #2. We will determine whether PAD participants randomized to a low intensity, self-paced walking exercise intervention achieve greater improvement or less decline in maximal treadmill walking time, physical activity, patient-perceived walking performance (measured by the Walking Impairment Questionnaire (WIQ) distance and speed scores), and health-related quality of life (measured by the short-form 36 physical functioning (SF-36 PF)) score at 52-week follow-up, compared to PAD participants randomized to the high-intensity exercise intervention and as compared to a control group, respectively. We hypothesize that PAD participants randomized to low intensity exercise will achieve greater increases or less decline in maximal treadmill walking time, physical activity, WIQ, and the SF-36 PF Score at 52-week follow-up, compared to those randomized to high-intensity exercise and as compared to the control group, respectively.

Secondary Specific Aim #3. We will determine whether participants randomized to low intensity exercise have greater adherence to the home-based exercise intervention compared to participants randomized to high intensity exercise. Adherence is defined as the proportion achieving at least 80% of the prescribed exercise frequency and duration during the final month of the intervention. Exercise frequency and duration will be measured objectively with the ActiGraph and by patient self-report. We hypothesize that participants randomized to low intensity exercise will have higher adherence to the prescribed exercise intervention than participants randomized to high intensity exercise.

Secondary Aims #4 and #5 were added in March 2020, before any outcome data were analyzed. These specific aims were added because randomized trials published since the LITE Study was designed, demonstrated no effect of a high intensity home-based walking exercise intervention on six-minute walk distance or other walking outcomes in people with PAD at 6 and at 9 month follow-up compared to a control group that did not exercise (5, 6). Since the LITE Trial studied the effect of a high intensity home-based walking exercise intervention on change in six minute walk distance at 6-month and 12-month follow-up, compared to an attention control group, Secondary Specific Aims #4 and #5 are particularly important.

Secondary Specific Aim #4. We will determine whether participants randomized to the high intensity exercise intervention have greater improvement or less decline in six-minute walk distance, physical activity, patient-perceived walking performance (measured by the WIQ distance and speed scores), and health-related quality of life measured by the SF-36 PF score at 26 week follow-up, compared to PAD participants randomized to the control group. We hypothesize that participants randomized to the high intensity exercise intervention will have greater improvement or less decline in each outcome at 26-week follow-up compared to the attention control group.

Secondary Specific Aim #5. We will determine whether participants randomized to the high intensity exercise intervention have greater improvement or less decline in six-minute walk distance, maximal treadmill walking time, physical activity, patient-perceived walking performance (measured by the WIQ distance score), and health-related quality of life measured by the SF-36 PF score at 52 week follow-up,

compared to PAD participants randomized to the control group. We hypothesize that participants randomized to the high intensity exercise intervention will have greater improvement or less decline in each outcome at 52-week follow-up, compared to the control group.

Secondary Specific Aim # 6.
Preliminary evidence suggests that ischemia-reperfusion, such as that experienced during high-intensity exercise in PAD, is associated with reduced muscle mitochondrial oxidative metabolism and increased oxidative stress (7-9). Therefore, in a randomly selected subset of participants, we will determine whether participants randomized to low intensity exercise (N=50) have greater improvement in calf muscle mitochondrial oxidative metabolism and lesser increases in calf muscle oxidative stress at 52-week follow-up, compared to the high-intensity intervention (N=50). We will also determine whether those randomized to low intensity exercise (N=50) and those randomized to high-intensity intervention (N=50), respectively, have greater improvement in calf muscle mitochondrial oxidative metabolism at 52-week follow-up, compared to the control group (N=50).

Exploratory Specific Aim 1. We will use qualitative methods to explore participants' perceptions of the exercise interventions in the high and low-intensity exercise groups, respectively, at 52-week follow-up.

Exploratory Specific Aim 2. In an exploratory specific aim, in up to 15 people with PAD and a body mass index > 28 kg/M^2 who previously participated in the LITE Study or who were evaluated for participation, we will test the feasibility and efficacy of a 16-week weight loss intervention combined with the LITE home-based exercise intervention. The primary goals will be to determine whether it is feasible and effective give to add a weight loss intervention to the LITE home-exercise intervention in people with PAD who are overweight. We will determine whether this modification of the LITE intervention (weight loss combined with the LITE home-based exercise intervention) can improve six-minute walk distance in people with PAD.

Exploratory Specific Aim 3. In an exploratory specific aim, in up to 30 people with PAD, we will determine whether, compared to placebo, nitrate-rich beetroot juice acutely improves six-minute walk distance or the short physical performance battery (SPPB), two-hours after nitrate-rich beetroot juice or placebo ingestion. We will also collect preliminary data to determine whether, as compared to placebo and as compared to nitrate-rich beetroot juice, far-red light (approximately 660 nm) alone and the combination of far-red light + nitrate-rich beetroot juice acutely increase plasma nitrite and improve six-minute walk distance, four meter walking velocity at usual or fast pace, or the SPPB, approximately two to three hours after far-red light treatment alone and the combination of far-red light treatment with nitrate-rich beetroot juice.

2.0 Background

2.1 Relevant experience.

A. **Our prior work supports the LITE Trial proposal.** Our multidisciplinary investigative team includes internationally renowned experts in PAD, behavioral change, exercise training, functional performance, and skeletal muscle metabolic function. Our observational work, funded by the NHLBI, established that people with PAD have greater functional impairment, faster functional decline, and greater mobility loss than individuals without PAD (11-15). These associations are present even in PAD patients who are asymptomatic or who do not have classic intermittent

claudication symptoms (11-15). We have completed two NHLBI-funded randomized trials of exercise in people with PAD. The Study to Improve Leg Circulation (SILC) (R01-HL073351) demonstrated that supervised treadmill exercise significantly improves six-minute walk in PAD participants both with and without claudication symptoms (55). However, the SILC trial's requirement for supervised exercise is burdensome. Furthermore, our SILC trial showed that once supervised exercise is removed, PAD participants stop adhering to exercise and lose gains in walking performance (see Table 2 below). Our Group Oriented Arterial Leg Study (GOALS) trial (R01-HL088589) demonstrated that a Group Mediated Cognitive Behavioral intervention significantly improved walking performance in patients with PAD (52). However, the GOALS intervention required weekly attendance at group sessions, which is impractical for many patients with PAD and is not covered by medical insurance. Furthermore, assembling a group of PAD participants can be difficult. The LITE Trial overcomes all of these limitations and employs remote monitoring to promote home exercise and avoid regular visits to the exercise center.

B. **Our SILC Trial showed that gains from a high intensity supervised treadmill exercise intervention are lost when supervision is no longer available.** In our SILC trial, PAD participants randomized to supervised treadmill exercise improved their six-minute walk at six-month follow-up by +20.6 meters, while the control group declined (-20.4 meters) (55). After completing supervised exercise, participants in the intervention were asked to continue high-intensity exercise at home and were telephoned at regular intervals for an additional six months. Although participants were encouraged to walk for exercise at least three times weekly, the mean frequency of home-based exercise was only 1.9 times per week and participants lost the gains they had achieved during supervised exercise as shown in Table 1.

Table 1. Changes in six-minute walk during the supervised and unsupervised phases of our SILC trial

	Supervised Exercise: Baseline to 6 month f/up			Unsupervised Exercise: 6 to 12 month f/up.		
	Treadmill Exercise Group (N=41)	Control Group (N=39)	P Value	Treadmill Exercise Group (N=41)	Control Group (N=39)	P Value
Change in 6-minute walk.	+ 20.6 Meters	-20.4 Meters	<0.001	-24.5 Meters	+3.34 Meters	0.031

2.2 Significance of the research.

A. **Lower extremity peripheral artery disease (PAD) affects eight million people in the United States (U.S.) (10).** PAD will be increasingly prevalent as the U.S. population survives longer with chronic disease. Men and women with PAD have greater functional impairment and more rapid functional decline than those without PAD (11-15). The functional limitations experienced by people with PAD are associated with increased rates of mobility loss, increased hospitalization rates, and poor quality of life (16-19).

B. **Clinical practice guidelines recommend high-intensity, ischemic-pain inducing supervised treadmill exercise to improve walking performance and prevent mobility loss in PAD (1,2).** This Class I, Level of Evidence A recommendation originates from a meta-analysis of 21 studies of exercise for PAD patients, published in JAMA in 1995 (20). In this meta-analysis, supervised treadmill exercise was associated with a 122% increase in maximal treadmill walking distance and a 179% increase in pain-free treadmill walking distance, compared to control. Participants who were

asked to walk to maximal ischemic leg pain achieved greater gains in treadmill walking distance than those who were asked to walk to onset of pain +(606.8 meters ± 426.6 vs. +195.5 meters ± 78.3, respectively, P=0.005). Yet, our data (section C3e), and that of others (21-23) show that exercise-related ischemic pain is a major deterrent to exercise in PAD. *Recent evidence from supervised exercise trials suggests that low-intensity exercise may be beneficial for people with PAD.*

C. **Three recent clinical trials of supervised low-intensity treadmill exercise suggest benefit for patients with PAD (24-26).** One trial demonstrated that low-intensity **supervised** exercise was more effective than a no-exercise control group in PAD (24). Two trials (25,26) demonstrated increases in treadmill walking performance as compared to baseline in PAD patients randomized to a **supervised low intensity** exercise intervention (see Table 2).

Table 2. Summary of three trials showing that SUPERVISED low-intensity exercise is effective in PAD

Author/year	*Study Design*	*Results*	*Limitations*
Mika P et al/2005 (24)	98 participants with PAD and claudication were randomized to 12 weeks of supervised treadmill exercise vs. control (no exercise).	Treadmill time to onset of claudication pain increased by 119% in the supervised low-intensity exercise group vs. 17% in the control group.	The study tested supervised exercise, which is not accessible to most PAD patients.
Gardner AW et al/2005 (25)	64 participants with claudication were randomized to 6 months of high-intensity supervised ischemic pain-inducing exercise vs. 6 months of low-intensity supervised exercise.	Compared to baseline, maximal treadmill walking distance increased by 63% in the high intensity group compared to baseline (P<0.01) and by 61% in the low-intensity group compared to baseline (P<0.01).	The study tested supervised treadmill exercise, which is not accessible to most PAD patients. There was no control group.
Mika P et al/2012 (26)	60 participants with claudication were randomized to 12 weeks of high-intensity supervised treadmill exercise vs. 12 weeks of low-intensity supervised exercise.	Maximal treadmill walking time increased by 98% in the low-intensity supervised group and by 100% in the high-intensity supervised group.	The study tested supervised exercise, which is not accessible to most PAD patients. There was no control group that did not exercise.

All three studies shown in Table 1 tested a SUPERVISED exercise intervention. However, most PAD patients do not have access to supervised exercise (see section A4). No studies have assessed whether an alternative home-based low intensity walking exercise intervention improves walking performance in PAD.

D. **The importance of establishing an exercise program that is accessible and acceptable to PAD patients.** Few people with PAD participate in supervised high intensity exercise programs that are recommended by practice guidelines (1,3,4,27). There are several reasons. First, medical insurance does not pay for supervised exercise. Second, transportation to a center three times weekly for supervised exercise is burdensome for people with PAD. Third, ischemic leg pain is a major barrier to walking exercise activity in people with PAD (21-23). Our proposed alternative exercise intervention that employs low-intensity, self-paced walking exercise carried out at home will be accessible to most PAD patients. An effective exercise intervention that is accessible and acceptable

to most patients with PAD is urgently needed to improve walking performance and prevent disability in the large and growing number of patients suffering from PAD.

E. **Clinical practice guidelines state that evidence is insufficient to recommend home-based walking exercise for PAD patients (1,27).** Three small trials of home-based walking exercise in PAD patients using telephone coaching yielded contradictory results (28-30). But sample sizes of these studies were small, ranging from N=16 to N=24 (26-28). Two of these studies showed that telephone coaching did not increase home-based walking exercise in PAD (28,29). The third trial randomized 21 patients with PAD to either a 24 week home-based walking exercise program or a 12 week supervised exercise program followed by a 12 week home-based walking exercise program (total of 24 weeks for each arm). At 24 week follow-up, both groups (24 continuous weeks of home based exercise vs. 12 weeks of supervised followed by 12 weeks of home exercise) significantly improved their treadmill walking time as compared to baseline. There was no significant difference between the two groups (30). However, there was not a non-exercising control group in this study. Treadmill walking distance, the study's primary outcome, is associated with a significant learning effect in people with PAD (28). None of these three studies (28-30) used proven behavioral techniques to promote home-based exercise (28-30). Clinical practice guidelines state that there is insufficient evidence to support home-based exercise in PAD patients (1,27). Most physicians do not recommend walking exercise for PAD patients (31,32). A definitive trial is needed to establish that a home-based walking exercise program that does not require regular visits to an exercise center improves walking performance in people with PAD.

F. **High intensity, ischemic pain-inducing walking exercise may adversely affect calf skeletal muscle in people with PAD.** Mitochondria are double membrane-enclosed organelles that generate adenosine triphosphate (ATP), the primary energy source for skeletal muscle cells (33). In patients with PAD, high-intensity exercise is associated with ischemia and subsequent reperfusion of calf skeletal muscle (7,38,39). Animal studies and preliminary human evidence show that re-perfusion of target tissue after ischemia increases oxidative stress, promotes mitochondrial dysfunction, and reduces ATP production (7-9,34-36). Preliminary human evidence suggests that high-intensity, ischemia-inducing walking exercise has harmful effects on calf skeletal muscle (36-39). We hypothesize that by avoiding the ischemia and re-perfusion associated with high intensity exercise, low-intensity exercise will promote more favorable calf muscle mitochondrial changes in PAD. We expect these favorable muscle changes will facilitate improved functional performance. Therefore, in our Secondary Aim #3, we will determine whether high-intensity, ischemic-pain inducing exercise increases calf muscle levels of oxidative stress and impairs calf muscle mitochondrial function, compared to low-intensity exercise. We will also determine whether low-intensity exercise improves mitochondrial function, compared to the control group. Because low intensity exercise is not associated with ischemia/reperfusion, we will not compare oxidative stress between the low intensity intervention and the control group.

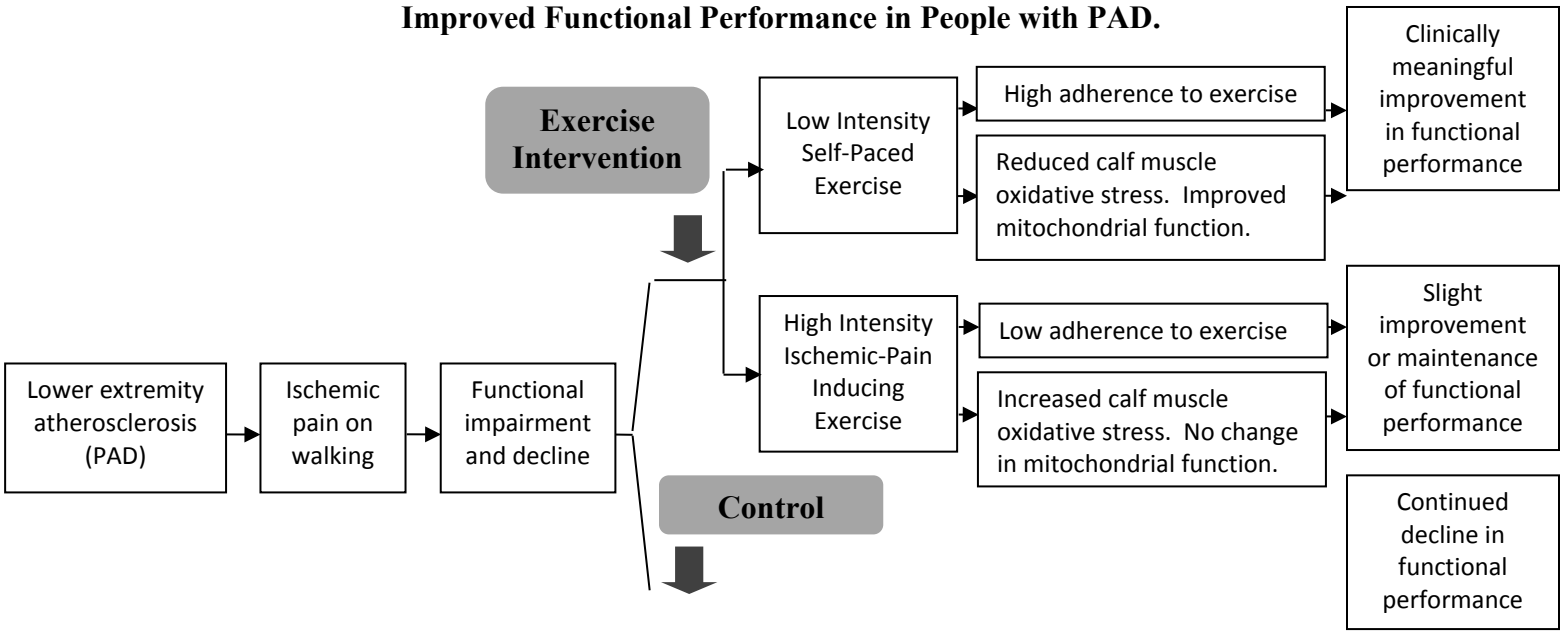
G. **Conceptual Model/Basis for our Study Design.** Walking-related leg pain is a major deterrent to exercise in PAD (21-23). This phenomenon is not surprising from a behavioral perspective. According to Social Cognitive Theory (40,41), people's self-efficacy (confidence) in their ability to perform a health behavior and the behavior's incentive (reward) value are major determinants of adherence to healthy behaviors (42). Aversive physical symptoms (i.e. pain) that are associated with a behavior (i.e. walking) diminish the behavior's reward value, result in avoidance of the behavior,

and undermine self-efficacy about the ability to perform the behavior (40,41). Consistent with this, we observed in patients with knee arthritis that more intense knee pain is related to poorer performance on measures of both self-reported and objective measures of physical function (43,44). In a trial of 439 participants with knee osteoarthritis (mean age 68.6± 6, 30% males), who were randomized to aerobic walking exercise, resistance training, or a control group, Rejeski and colleagues observed that improvement in knee pain in response to the intervention mediated the benefits of exercise on performance (45,46). Among participants randomized to aerobic exercise, knee pain was reduced in participants who exercised at a low intensity but not in participants who engaged in high/maximal intensity exercise. These findings in people with knee osteoarthritis are consistent with our hypothesis that self-paced walking exercise will be more acceptable and will achieve greater gains in walking performance compared to high-intensity ischemic-pain inducing exercise in people with PAD.

A patient's ability to cope with pain is an important predictor of physical disablement (47-49). Pain acceptance is the ability to accept and deal with pain (49). We recently modified McCracken and colleagues' measure of pain acceptance (49) for use with PAD patients. We found that PAD patients with higher (more favorable) scores for pain acceptance walked significantly further in the six-minute walk (48). Pain acceptance was inversely related to number of depressive symptoms (r = -0.53).These findings are consistent with our hypothesis that PAD patients who exercise at a low intensity with minimal pain will achieve greater gains than those randomized to the high intensity, ischemic pain inducing exercise intervention.

Prior studies of sedentary people without PAD demonstrate that a low-intensity exercise intervention improves physical activity levels and/or cardiopulmonary fitness (50,51). However, a home-based low-intensity exercise intervention has not been previously tested in people with PAD. We hypothesize that our low-intensity home-based walking exercise intervention will improve functional performance by encouraging adherence to a home-based walking exercise program and by improving calf muscle health (see Figure 1).

Figure 1. Theoretical Model for Association of a Low-intensity, Self-paced Exercise Intervention with Improved Functional Performance in People with PAD.



H. **Importance of the LITE Trial.** Few men and women with PAD participate in the high-intensity supervised exercise recommended by clinical practice guidelines (3,4). Our proposed alternative exercise intervention overcomes two **major** barriers to exercise for patients with PAD: 1) the recommendation for **supervised** exercise and 2) exercise-induced ischemic leg pain. If our hypotheses are correct, our results will have major implications for the 8.0 million men and women in the U.S. who suffer from PAD.

2.3 Innovation of the research.

A**. No prior studies have tested whether home-based low-intensity exercise improves functional performance in patients with PAD.** Three previous trials demonstrated that supervised low-intensity exercise improved treadmill walking in people with PAD (24-26). These supervised exercise trials support our hypotheses. However, home-based low-intensity exercise has never been studied in people with PAD. Determining whether a home-based low-intensity exercise intervention improves outcomes is important, because most PAD patients do not have access to supervised exercise (see section A4 above).

B**. No prior studies have used mobile devices to help PAD patients self-monitor exercise activity or intensity.** As mobile technology is increasingly accessible, it is an important tool to promote healthy behaviors in patients with chronic disease. In the LITE Trial, PAD participants randomized to exercise will use an ActiGraph accelerometer to monitor their walking exercise frequency, duration, and intensity. Uploaded data will be visible to participants and the study coach (see section C12c). Using a mobile device to help PAD participants monitor walking exercise behavior is a highly innovative feature of the LITE trial.

C. **No prior randomized trials have tested the ability of a 52-week home-based exercise intervention to improve outcomes in PAD.** Prior home-based exercise interventions in PAD have ranged from 12 weeks to six months duration (29-31,52-54). Home-based exercise interventions that are sustainable over the long term are essential for populations with chronic disease, such as those with PAD. No prior studies of PAD participants have employed a coach that remotely monitors exercise activity for 52 weeks.

D**. No prior studies have tested whether low-intensity exercise reduces calf muscle oxidative stress or increases calf muscle mitochondrial function compared to high intensity ischemia-inducing exercise.** During high intensity exercise in people with PAD, metabolic demands for oxygen exceed oxygen supply. Calf muscle reperfusion occurs during rest, when blood supply becomes sufficient to meet calf muscle oxygen requirements. However, animal data and preliminary human evidence suggest that re-perfusion after ischemia increases oxidative stress and impairs mitochondrial function (7-9,35-39). We hypothesize that an exercise intervention that avoids ischemia will protect calf muscle against oxidative stress and improve mitochondrial function. This hypothesis has never been tested in people with PAD.

3.0 Inclusion and Exclusion Criteria

3.1 Screening for eligibility.

Initial eligibility criteria will be assessed by telephone with a recruitment call script. Potential participants who remain eligible after the telephone screening will be scheduled for a baseline visit, where they will undergo additional testing to determine their eligibility for randomization.

A. **Recruitment**. We will randomize 305 PAD participants over 32-months, allowing for a 15% drop-out at 52-week follow-up. This drop-out rate is comparable to the 52-week drop-out rate in our GOALS and SILC trials (52,55). We will identify participants using 1) Northwestern's Enterprise Data Warehouse to identify patients with PAD; 2) radio and newspaper advertising; and 3) bulk mailed postcards to people age 55 and older living in the Chicago area. We have successfully used each method in our prior clinical trials. Based on our previous work involving participants with PAD, we anticipate that the average age will be approximately 70 years, that at least 33% of participants will be minorities, and that approximately 50% will be women. For example, in our recently completed SILC randomized controlled clinical trial of exercise in patients with PAD (55), participants were average age 70.6 $\pm$ 10.3 and the average ABI was 0.61 $\pm$ 0.17. In SILC, participants included 52% women and 45% African-Americans. In general, patients with PAD have a high prevalence of comorbid diseases, particularly coronary artery disease, cerebrovascular disease, and diabetes mellitus. Thus the patient population is likely to be of poorer health than that of similarly aged men and women without PAD in the general population.

B. **Our experience successfully enrolling PAD participants in NHLBI-funded studies:** Since 2004, we have randomized 661 PAD participants from the Chicago-area into NHLBI-funded clinical trials. Since 1998, we have enrolled more than 1,800 participants with PAD into our NHLBI-funded studies. Thus, we have the experience and expertise to successfully recruit the proposed 305 PAD participants for the LITE Trial.

C. **Randomization.** Participants will be randomized to one of three parallel arms using a SAS computer program. Block randomization will be implemented to ensure balance between the three groups. Randomization will be stratified by according to whether the participants are eligible for (and consented to) muscle biopsy.

D. **Rationale for focus on walking exercise.** Walking exercise is the only form of exercise that consistently improves walking performance in PAD and is the only exercise currently recommended by practice guidelines for PAD (1,2,27,64).

3.2 Criteria.

Inclusion and exclusion criteria. All participants will have PAD. PAD will be defined as follows. First, an ABI $\leq$ 0.90 at the baseline study visit is a well-accepted standard for the diagnosis of PAD and will be an inclusion criterion (59-62). Second, people with an ABI of >0.90 and $\leq$1.00 who experience a 20% ankle systolic pressure drop after the heel-rise test will also be included. Third, potential participants with an ABI > 0.90 who have vascular lab evidence of PAD* or angiographic evidence of PAD** who have ischemic symptoms during the six-minute walk and/or treadmill exercise stress test will be eligible. In addition to meeting a criterion for PAD, all participants must be symptomatic, defined by one of the following criteria:; a) ischemic leg symptoms (primarily assessed with the San Diego Claudication

Questionnaire); b) report ischemic leg symptoms at the end of the six-minute walk; c) report ischemic leg symptoms at the end of the baseline treadmill stress test; d) walking impairment questionnaire results, e) interview with the potential participant about the presence and nature of leg symptoms during walking activity. Exclusion criteria are listed in Table 3.

* If the only criterion by which a participant is eligible to participate is a toe pressure, the toe pressure must be < 70 or the toe brachial index ratio must be < 0.60 if asymptomatic or < 0.70 if symptomatic.
** Angiographic criteria of PAD consist of a stenosis of 70% or greater in a lower extremity artery.

Table 3. Summary of exclusion criteria and justification for each criterion.

List of specific exclusion criteria	*Justification for exclusion criteria*
1. Above or below knee amputation, critical limb ischemia, wheelchair confinement, or foot ulcer.	*1. Inability to fully participate in the intervention.*
2. Individuals whose walking is limited by a condition other than PAD.	*2. The intervention is designed to improve PAD-related walking impairment.*
3. > Class II NYHA heart failure or angina. Increase in angina, angina at rest, or abnormal baseline treadmill stress test.	*3. Exercise may not be safe for these potential participants.*
4. Major surgery including lower extremity revascularization or orthopedic surgery during the prior three months or anticipated in the next twelve months.	*4. Surgery may influence change in functional performance, independent of study interventions.*
5. Major medical illness including renal disease requiring dialysis, lung disease requiring oxygen, or cancer (other than non-melanoma skin cancer) requiring treatment in the prior three years. Note: Potential participants may still qualify if they have had treatment for an early stage cancer in the past three years and the prognosis is excellent. Patients who use oxygen at night may still qualify.	*5. These conditions may interfere with the ability to fully participate and complete the study.*
6. Mini-mental status examination score <23 (63), dementia, or psychiatric illness including severe depression or anxiety. However, investigator discretion may be used to allow some people with an MMSE below this threshold to participate, if the investigator determines there is another reason for their lower score, including lack of sufficient familiarity with the English language or lack of sufficient education to achieve a score of 23 or higher. Note that the MMSE includes some spelling and English writing proficiency.	*6. May interfere with ability to fully engage in the study.*
7. Currently walking regularly for exercise at a level comparable to the amount of exercise prescribed in the intervention.	*7. The interventions may not further improve functioning.*
8. Currently enrolled in another clinical trial, exercise trial, or in cardiac rehabilitation. Currently enrolled in a clinical trial or participation in cardiac rehabilitation or a	*8. Interference with ability to determine whether study interventions are responsible for improved outcomes.*

trial of a therapeutic intervention within the past three months. For a clinical trial of a stem cell or gene therapy intervention, potential participants will be potentially eligible immediately after the final study visit for the clinical trial, so long as long as at least six months has passed since the participant received their final treatment in the stem cell or gene therapy intervention. For a clinical trial involving open-label therapy in which the treatment is not related to functional performance and will not change during the LITE Trial, participants may still qualify for the LITE Trial based on investigator discretion.	.
9. Individuals with PAD who have a history of lower extremity revascularization and currently have a normal ABI.	*9. We are seeking participants who currently have ischemia*
*10.Potential participants who are unable to walk for exercise at a sufficiently slow pace to avoid ischemic leg symptoms.**	*10. Participants randomized into the low intensity intervention must be able to walk slowly enough to avoid ischemic leg symptoms.*

*All *individuals who are unable to walk for three minutes during a modified Gardner protocol or for one minute on a Gardner protocol exercise stress test* will be interviewed by the study Principal Investigator (PI) or another physician investigator to determine whether they are able to walk sufficiently slowly to avoid ischemic leg symptoms during exercise activity.

3.3 Special Populations.

Vulnerable populations (fetuses, pregnant women, children, prisoners, and institutionalized persons) and adults unable to consent will not be included in this study.

4.0 Study-Wide Number of Subjects

NA

5.0 Study-Wide Recruitment Methods

NA

6.0 Multi-Site Research

To maximize recruitment rate for the LITE Trial, the University of Pittsburgh and the University of Minnesota will also serve as recruitment sites.

7.0 Study Timelines

7.1

- *The duration of an individual subject's participation in the study.*
  Each participant's part in this study will last approximately 52 weeks. During the first four weeks, participants will attend four weekly on-site visits to orient them to the intervention followed by transition to entirely home-based exercise, using identical behavioral techniques, for an additional 48 weeks.

- *The duration anticipated to enroll all study subjects.*
  We anticipate that we will enroll all study subjects over 32 months.

- *The estimated date for the investigators to complete this study (complete primary analyses).*
  We anticipate that we will complete data collection over 44 months. See study timeline below.

Study Timeline

Months	2	3	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	47	48
Start-up																										
Recruitment & enrollment																										
Intervention and follow-up measures																										
Data analyses & manuscript writing																										

8.0 Study Endpoints

8.1 Primary and secondary study endpoints.

We selected the Six-minute walk as the primary study endpoint because ability to walk long distances was the most common outcome that PAD patients wanted to improve. The six-minute walk is an objective and well-validated measure of walking endurance that is well accepted in the scientific community (3-8,11,17,46-48). Change in the six-minute walk has been linked to clinically meaningful outcomes, including mobility loss, mortality, and meaningful declines in quality of life (49,50). Therefore, the six-minute walk, an objective measure, is our primary outcome. We have substantial experience measuring the six minute walk (2-8,11,17). Most prior clinical trials of PAD patients used treadmill walking as their primary outcome measure. However, PAD patients in our focus groups report that treadmill walking is not a natural form of walking for them. Published studies from older patients confirm this, and demonstrate that treadmill walking is associated with balance problems and anxiety (51-53). The intra-class correlation coefficient for the test-retest reliability of the six-minute walk test among 156 PAD participants in our laboratory was 0.90 ($p<0.001$) when two six-minute walk tests were completed one to two weeks apart (46). For all of these reasons, the six-minute walk test will be our primary outcome measure.

Additional endpoints include a) treadmill walking performance; b) seven day physical activity levels; c) calf muscle biopsy measures; d) patient perceived walking ability (WIQ distance and speed scores); e) Health-related quality of life (SF-36 PF); f) adherence to exercise; g) qualitative interviews (exploratory). In addition, some participants may be asked questions about their interest in supervised

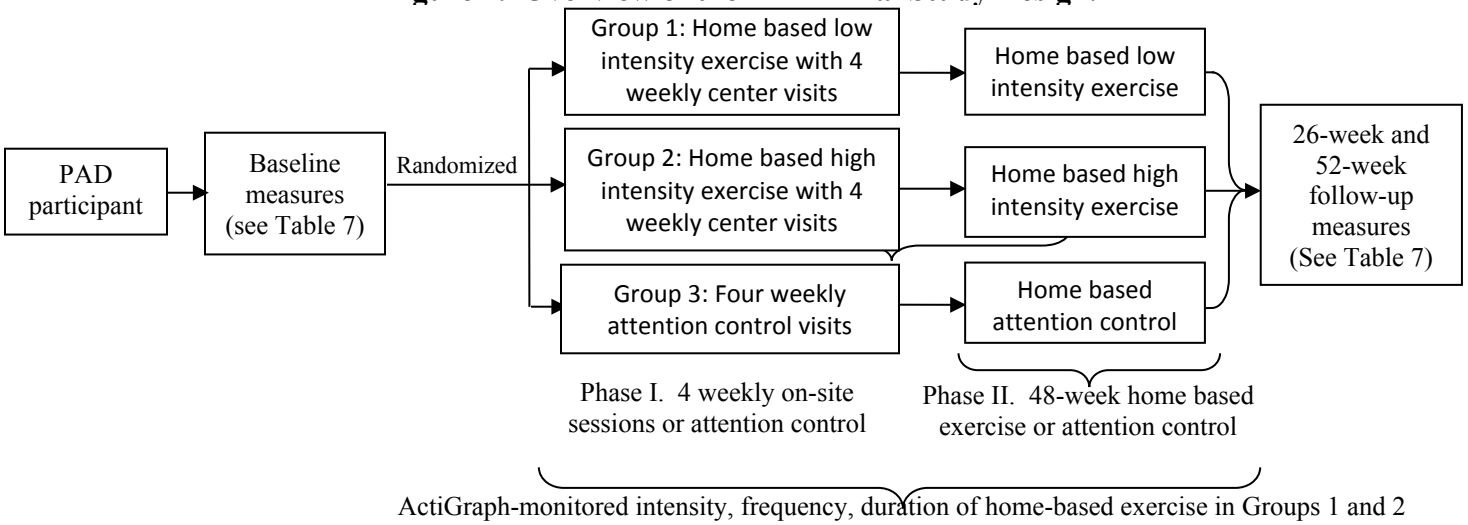
treadmill exercise programs, barriers to their participation in supervised exercise programs, and their ability to participate in supervised treadmill exercise programs. Blood samples will be collected for potential later analyses. The WIQ stair climbing score will also be measured.

9.0 Procedures Involved

9.1 Study design.

LITE TRIAL OVERVIEW. 305 participants with PAD will be randomized to one of three parallel arms: Group 1: low-intensity, self-paced walking exercise; Group 2: high intensity, ischemic pain-inducing walking exercise; Group 3: Non-exercising attention control group. Groups 1 and 2 will attend four weekly on-site sessions to orient them to the intervention followed by transition to entirely home-based exercise, using identical behavioral **techniques, for an additional 48 weeks (total duration= 52 weeks).**

Figure 2. Overview of the LITE Trial Study Design.



A. Data collection overview. Table 4 shows outcome measures planned at each time point.

Table 4. Data Collection Plan

Study Measure	*Baseline*	*26 week follow-up*	*52 week follow-up*
Six minute walk distance (Primary Outcome)	*X*	*X*	*X*
Treadmill walking performance	*X*		*X*
Blood collection	*X*		*X*
Seven day physical activity levels	*X*	*X*	*X*
Calf muscle biopsy measures	*X*		*X*
Patient perceived walking ability (WIQ scores)[2]	*X*	*X*	*X*
Health-related quality of life (SF-36 PF)	*X*	*X*	*X*
Adherence to exercise[1]	*0*	*X*	*X*
Qualitative interviews[1]	*0*		*X*

[1]These outcomes will be measured at 52-week follow-up in participants randomized to high or low intensity exercise.[2] The WIQ distance and speed scores are secondary outcomes. The WIQ stair climbing score is a pre-specified additional outcome.

In addition, some participants may be asked questions about their interest in supervised treadmill exercise programs, barriers to their participation in supervised exercise programs, and their ability to participate in supervised treadmill exercise programs. These additional questions will be collected as pilot data for a subsequent study and may be administered at any time point during the LITE Trial.

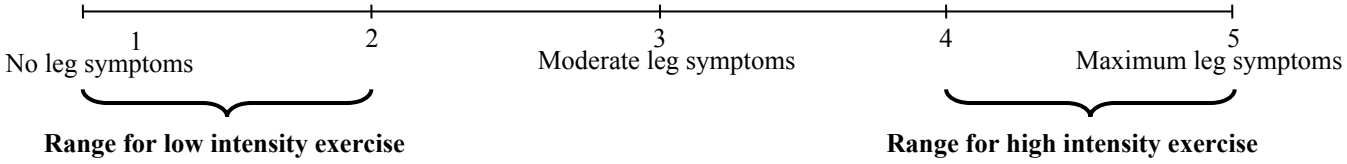
Following final follow-up testing, participants may be called and asked to complete a questionnaire about their current walking activities. The trial demonstrated an important and unanticipated finding, that walking exercise that induced ischemic leg symptoms significantly improved walking ability more than walking exercise that did not induce ischemic leg symptoms. Despite its benefits, it was more difficult for participants to engage in high intensity exercise in this trial. In order to determine the long term effects of the intervention, we will ask study participants who completed the trial about their current exercise activity. Specifically, we will telephone individuals who have completed the study and ask them approximately five to ten minutes of questions about their current mobility, exercise activity, and physical activity. In addition to providing additional information about the exercise intervention, this information may be used to support a grant application. We will administer a verbal consent form prior to completing the study questionnaire. Only participants who agree via verbal consent will be asked the questionnaire.

9.2 Research procedures.

A. **Exercise intervention overview.** Drs. Jack Rejeski and Bonnie Spring, internationally recognized experts in behavior change, will direct the exercise interventions in the LITE Trial. Their expertise is complementary. Dr. Rejeski has specific expertise promoting exercise for patients with chronic health conditions (43,44,65,66). Dr. Spring has specific expertise in telephone-delivered behavioral interventions for diet and activity change that incorporate mobile technology. She pioneered the use of mobile transmission of participants' behavioral data to telephone coaches in behavioral intervention trials (67). This connective approach to behavioral interventions enables the coach to offer responsive, highly tailored interventions efficiently and allows participants to feel supported but also held accountable and avoids the need for regular visits to the exercise center.

Participants randomized to low-intensity exercise will be advised to walk at a low, self-paced intensity that feels comfortable, maintaining a pain level of ≤ 2 on the 1-5 Likert claudication pain scale, where '1' indicates no pain and '5' indicates maximum, severe pain (Figure 3). Participants randomized to low-intensity exercise are told that the important goal is total time exercised at a comfortable, self-selected pace. Participants randomized to high-intensity exercise will be asked to maintain a pain level of 4-5 on the 1-5 Likert pain scale (Figure 3). These participants are told that to benefit from exercise training they must exercise at a level inducing moderate to high levels of ischemic pain (1,2).

Figure 3. Claudication symptom severity for the low intensity and high intensity exercise



B. **Phase I of the intervention (weeks 1-4):** In Phase I, participants randomized to either one of the two exercise groups will be asked to attend a total of four weekly visits to the exercise center over a four week period. If the sessions cannot be completed at weekly intervals over four weeks, the participant will have eight weeks to complete all four sessions to allow for make-up sessions. At the first session, participants will be asked to begin walking for exercise at home at least five days weekly. Our exercise facility has a 1/8 mile indoor track that participants will use to help them "get started" on a regular walking exercise regimen. During Phase I, participants will learn to use the ActiGraph to collect and upload data regarding their walking exercise activity. They will be taught to distinguish between high and low intensity exercise, using the ActiGraph to define activity counts corresponding to their low and high intensity exercise, respectively. They will meet and bond with the coach. Based on our pilot studies, the four weekly exercise center visits will be sufficient to teach participants to use the ActiGraph to monitor their exercise and get started on home-based walking exercise. Limiting Phase I to four weeks (four visits) will ensure that Phase I is not burdensome or difficult for participants. Phase I is less demanding, for example, than a typical course of physical therapy prescribed for a patient suffering from low back pain (68).

C. **Phase II of the intervention (weeks 5-52).** Phase II will consist of entirely home-based exercise. Participants will be asked to wear the ActiGraph while they are exercising. The ActiGraph records duration, frequency, and intensity of exercise. The ActiGraph Bluetooth mechanism, available in the ActiGraph model that we will use in the LITE Trial, automatically uploads data to the study website, whenever participants walk within 15 feet of their home computer/tablet. Participants without a home computer suitable for uploading ActiGraph data will be provided with a computerized tablet with wireless internet access for the duration of the study. Our pilot data, collected in 150 consecutive PAD participants in our ongoing studies, show that 65% own a home computer and that 50% have home internet access. Dr. Spring's technology team will build the user-friendly website that participants and the coach will access to remotely monitor all aspects of home-based walking exercise. Because we successfully taught 10 consecutive PAD patients to upload ActiGraph data on their home computer during one visit to our exercise center, we anticipate no difficulty teaching participants this method in the LITE Trial.

D. **Monitoring intensity of home-based walking exercise.** We will use the ActiGraph to objectively monitor fidelity to group assignments of high or low intensity exercise. We selected the ActiGraph because data output is in raw form without proprietary equations, it has become the standard among researchers for physical activity measures, and it has accumulated a wealth of excellent validation data documenting its sensitivity to movement speeds and intensity (56-58). As in our pilot study (section C3b), we will use the ActiGraph to establish individualized definitions of high vs. low intensity exercise for each participant at home. We will define ActiGraph measured activity counts for high and low intensity exercise at home, because the environment in which participants exercise can influence their activity counts during high and low intensity exercise. In addition, defining intensity in the home environment avoids visits to the exercise center. To define activity counts for high intensity exercise at home, the coach will read this script over the telephone while the participant is in their home exercise setting wearing the ActiGraph, "I would like you to walk for five minutes at a high intensity pace so that you are experiencing moderate to severe discomfort. Once you reach moderate to severe discomfort, please continue walking for as long as you can. If you must rest, please begin walking again as soon as you are able." Participants will then put down their telephone and walk at a high intensity for approximately five minutes while the ActiGraph

records activity counts corresponding to high intensity exercise. For low intensity exercise, the coach will read this script over the telephone while the participant is in their home exercise setting, "I would like you to walk for five minutes at a comfortable pace, so that you are not experiencing any pain or discomfort. If you begin to experience pain or discomfort, please slow your pace so that it becomes comfortable again." Participants will then put down their telephone and walk at a low intensity for approximately five minutes while the ActiGraph records activity data corresponding to low intensity exercise. ActiGraph-recorded activity count values for high vs. low intensity exercise will be used to determine whether the participant is adhering to their assigned intensity level. We successfully used these methods in our pilot study. Table 5 shows two theoretical participants and how their ActiGraph-measured walking intensity would be used to ensure fidelity to their assigned group.

Table 5. Examples of how the ActiGraph will be used to ensure fidelity to the assigned exercise intensity.

Theoretical participants	Mean and range of defined low intensity exercise	Mean and range of defined high intensity exercise	Actual mean exercise intensity
Participant #1- assigned to low intensity.	2,900 activity counts (range 2,000-3,500)	5,000 activity counts (range 4,500-5,500)	2,700 activity counts
Participant #2- assigned to high intensity.	2,000 activity counts (range 1,500 to 2,500)	4,500 activity counts (range 4,000-5,000)	3,500 activity counts

For the theoretical participants in Table 9, the coach will counsel Participant #1 that they are exercising within their target (low intensity) and encourage them to continue. The coach will counsel Participant #2 that they are exercising below their target intensity range and will push them to increase their walking exercise intensity. We did not add ecological momentary assessment to the ActiGraph measure because of concern that wearing two devices combined with regular prompting for the ecological momentary assessment measures may be overly burdensome for PAD participants.

E. **Re-measuring high and low- intensity definitions during the intervention.** Exercise intensity definitions for an individual may change over time. Therefore, we will repeat the ActiGraph defined walking intensity measures at specified intervals during the study. In supervised walking exercise interventions for PAD participants, the greatest improvements in walking performance occur during the first 8-12 weeks of the intervention (70). Therefore, ActiGraph intensity definitions will be performed at baseline, and after one month, three months, six months, and nine months of the exercise intervention. We will also define the ActiGraph intensity definitions after hospitalizations or inter-current illnesses. Since the exercise definitions will be carried out at home, with the coach reading the study script by telephone, these calibrations will not be burdensome.

F. **Weekly telephone coaching.** The coach will contact participants randomized to an exercise intervention by telephone once weekly for a five to fifteen minute coaching session. Both the coach and participant will have access to the website showing the participant's exercise duration, frequency, and intensity. Each coaching contact will have a structured format. Adherence to this format (treatment fidelity) will be monitored by the coach using a check-list (see Table 10). Either a subset or all telephone coaching calls will be audiotaped, enabling additional monitoring by an independent rater who is blinded to the intervention condition (see section C12f). The components of each session, recorded on the check-list, are as follows: **a) Checking in:** Review ActiGraph data, including the frequency, duration, and intensity of home-based exercise. This will be reviewed in the context of the participant's assigned group (high vs. low intensity) and walking exercise goals

established during the prior weekly telephone contact with the coach; **b) Ensuring adherence to assigned low vs. high intensity exercise.** The coach will review the participant's actual exercise intensity, based on ActiGraph recordings and provide feedback on intensity, using the established ActiGraph definitions of high and low intensity exercise for each participant. **c) Discussion of challenges encountered during the past week and strategies for overcoming them.** Potential challenges we may encounter, based on our experience, include adverse weather affecting outdoor walking, difficulty finding time to exercise, and inter-current illness. **d) Discuss My Action Plan (MAP) for the coming week.** Participants will be asked to set exercise goals for the coming week. Goals will be written down and serve as a reference for the next weekly contact; **e) Wrap-up/questions-** mindful reflection with focus on successes and challenges.

G. **Intervention checklist.** The coach will use a checklist to guide each call. A ten to fifteen percent subsample of audiotaped calls will be reviewed each quarter by investigators Drs. Spring, and Rejeski to ensure fidelity to the intervention. Particular attention will be paid to fidelity to the exercise intensity the participant was randomized to receive. No mention of high-intensity exercise will be permitted for participants in the low-intensity group. No mention of low-intensity exercise will be permitted for participants randomized to high intensity exercise. When the coach deviates from the protocol, the coach will be re-trained and certified.

Table 6. Study Checklist Components for Monitoring Fidelity to the Study Intervention.

Component	Low intensity,	High intensity
Checking in-adherence to transmitting exercise frequency/duration	X	X
encouragement of self-paced, low-intensity walking exercise	X	0
Encouragement of high-intensity, ischemic pain inducing exercise	0	X
Discuss challenges encountered with solutions to overcome them	X	X
Discussion of My Action Plan (MAP)	X	X
Wrap-up, conclusion	X	X

H. **Interventionist training and certification.** Prior to beginning the study, the coach will undergo formal training in cognitive behavioral interventions by Dr. Rejeski. Our coach, Mr. Al Rego, is an exercise physiologist who has served as an interventionist for our successful GOALS Study and for the LIFE Study at the Northwestern Field Center. Training will include an overview of social cognitive theory, the conceptual background for the intervention, and an overview of PAD-related ischemic leg pain and optimal exercise programs for PAD. Mr. Rego will role-play telephone coaching sessions, and receive feedback. Management of "difficult" participants and challenging scenarios will be reviewed. Once training is complete, the coach will perform telephone counseling calls with five mock participants. A certification checklist will be used to ensure that the interventionist follows the protocol. Once certified, Drs. Rejeski, Spring, and McDermott will hold monthly telephone calls with the coach to discuss problem participants or challenging issues that arise in the delivery of the intervention. A back-up coach is available if needed during the study.

I. **Attention control group.** Our attention control group controls for the possibility that regular contact with the study team may improve outcomes in participants randomized to the intervention. Participants randomized to the control group will attend weekly one-hour educational sessions at Northwestern University for the first four weeks of the intervention (Phase I). If the sessions cannot be completed at weekly intervals, the participant will have eight weeks to complete all four sessions. These sessions are on topics of interest to the typical PAD patient and are led by physicians and other health care workers. Topics include Medicare Part D, nutritional supplements, and cancer screening. During Phase II (weeks 5-52), the attention control group will receive weekly telephone calls, lasting 5-15 minutes, with information on a health-related topic. We have substantial experience delivering these sessions in our prior randomized trials (52,55).

J. **Six-minute walk test.** The primary outcome is change in six-minute walk distance between baseline and 52-week follow-up. We have selected the six-minute walk as our primary outcome for several reasons. First, the six-minute walk is a well validated measure of walking endurance that better represents walking during daily life than treadmill walking performance in older people (15,71-76). Second, our prior work demonstrates that poorer six-minute walk performance is associated with higher rates of mortality and mobility loss in people with PAD (15,71). Third, treadmill walking performance is associated with a significant learning effect (77-80). However, the six-minute walk does not have this limitation (72,80). In the six-minute walk, participants walk back and forth along a 100-ft hallway for six minutes after standardized instructions to complete as many laps as possible (15,52,55,71,72). Distance covered in six minutes is recorded. The intra-class correlation coefficient for the test-retest reliability of the six-minute walk test among 156 PAD participants in our laboratory was 0.90 ($p<0.001$) when two six-minute walks were completed one week apart (55,72).

K. **Four-Meter Walk.** Participants are timed walking a four-meter distance in a corridor at their usual and fastest pace. Each walk is performed twice, and the fastest walk in each pair is used in analyses.

L. **Short Physical Performance Battery (SPPB).** *Repeated chair rises:* Participants sit in a straight-backed chair with arms folded across their chest and are timed standing from the seated position five times consecutively as quickly as possible. Timing begins with the word, "go", and ends when the participant stands upright for the fifth time. *Standing balance*: This measure is also a component of the summary performance score. Participants are asked to hold three increasingly difficult standing positions for ten seconds each: standing with both feet together side-by-side and parallel (side-by-side stand), standing feet parallel with the toes of one foot adjacent to and touching the heel of the opposite foot (semi-tandem stand), and standing with one foot directly in front of the other (tandem stand).

M. **Maximal treadmill walking time and treadmill time to onset of leg symptoms.** The Gardner graded treadmill exercise test is the standard, accepted protocol for measuring change in maximal treadmill walking time in response to interventions in PAD (77-78). Maximal treadmill walking time and treadmill time to onset of leg symptoms are secondary outcomes in the LITE Trial. In the Gardner protocol, speed is maintained at 2.0 miles per hour (mph) and treadmill grade increases by 2.0% every two minutes (77-79). If patients cannot walk at 2.0 mph, treadmill speed is started at

0.50 mph and increased by 0.50 mph every 2 minutes until the participant reaches 2.0 mph, after which the treadmill grade is increased every 2 minutes.

N. **Blood collection and long-term storage.** At each study visit, participants will have 45 mls of blood drawn for processing and long-term storage at -70 degrees Celsius. Approximated 10% of participants selected by chance will have an additional set of blood drawn for quality assurance, for a total of 90 mL at each visit. Blood obtained will be collected in serum, plasma EDTA, and plasma citrate tubes. Stored blood will await later analyses for inflammatory biomarkers and other emerging blood markers that may change in response to the intervention. Genetic testing may also be performed on stored blood samples.

O. **Health Related Quality of** Life will be assessed with the Short Form-36 physical functioning domain (SF-36 PF) (81). Perceived walking ability will be measured with the Walking Impairment Questionnaire (WIQ) (82-87). These measures document changes in quality of life, health status, and perceptions of walking in response to our intervention. We have substantial experience with them (52,55,85). The WIQ distance and speed scores are secondary outcomes. The WIQ stair climbing score is a pre-specified additional outcome.

P. **COVID-19 Questionnaire.** Currently enrolled and past participants may be called to see if they are willing to complete a questionnaire related to the COVID-19 pandemic. The questionnaire will be completed over the telephone and will help investigators determine how the pandemic is affecting older adults with PAD and how physical activity levels are affected during this time.

Q. **Measuring physical activity.** Physical activity will be measured in all participants over 10 days at baseline and follow-up, using the ActiGraph accelerometer (56-58). Participants are asked to wear the ActiGraph on the right side of their beltline for 10 days, removing it only for bathing or sleeping. After 10 days, participants mail the accelerometer back in a stamped, pre-addressed envelope provided to them at their study visit. We also contact participants by telephone to ensure monitors are returned. Although activity data will be collected over 10 days, the first seven days of data will be used in analyses. In addition, a consecutive subset of up to 50 LITE Trial participants and up to 50 participants excluded from the LITE because of absence of PAD will wear an additional Actigraph strapped to their thigh for 10 days in order to measure the number of times that they stand up and sit down during the 10 day period. Again, our interest will primarily be in the first seven days of data collection.

R. **Measuring adherence to the exercise intervention.** For patients randomized to high or low intensity exercise, we will use the ActiGraph to objectively measure exercise adherence. As delineated above (see section C12c), the ActiGraph is an extremely well validated and well accepted measure of physical activity (56-58). Adherence will be defined as achieving at least 80% of the prescribed exercise frequency and duration during the final month of the intervention. Exercise frequency and duration will be measured based on the ActiGraph data combined with patient self-report. Specifically, participant report is used to estimate daily exercise, which is confirmed with ActiGraph data. However, participant report is used for people who do not wear the ActiGraph for an exercise bout or to resolve discrepancies between ActiGraph and participant reported data.

S. **Calf muscle biopsy measures.** Muscle biopsies will be obtained on consecutive participants who provide informed consent for muscle biopsies until the required number of muscle biopsies is completed. Muscle biopsies may be obtained in up to 30 participants who are found to have a normal ABI consistent with the absence of PAD at their baseline visit. Muscle biopsies will be performed by co-investigator Robert Sufit MD, a neurologist with > 30 years of experience performing muscle biopsies. Dr. Sufit completed all muscle biopsies for our pilot study (Section C3f). The biopsy will be performed in the medial head of the gastrocnemius muscle, at the point that is 67% of the distance between the medial malleolus and the medial aspect of the proximal tibia. This site represents greatest calf muscle diameter in >95% of individuals (88). Anesthesia is achieved with subcutaneous lidocaine. Subcutaneous and adipose tissue are dissected until muscle is identified. Approximately 250 mgs of muscle tissue is removed and immediately frozen at -70 degrees Celsius. The fascia is closed with absorbable suture. The wound is closed with subcuticular sutures and steri-strips. Participants return for a wound check one week later. At 52-week follow-up, we will repeat the measurement using identical techniques, at the site adjacent to the baseline incision. In the open biopsy, muscle tissue is directly visualized, ensuring an optimal muscle tissue sample and providing substantial advantages over the blind needle biopsy. If a participant refuses the open biopsy at either baseline or follow up, a Bergstrom needle biopsy will be offered, which involves using a Bergstrom needle to remove muscle. The Bergstrom needle biopsy method requires a small skin incision. Lidocaine is injected into the skin and subcutaneous tissue. A small incision of the diameter of the needle (5 mm) is made through the skin and superficial fascia of the muscle. The Bergstrom needle is a side-cut tool with a sharp end that includes an inner needle that obtains the muscle specimen. After the Bergstrom needle is advanced directly into the muscle, the inner needle is first withdrawn and then reinserted cutting the muscle that has pushed through the side cut of the outer needle. The entire apparatus is then removed and the specimen is examined. If that tissue is of insufficient size the technique can be repeated. The wound is closed with steri-strips. The biopsy will be performed at the same site as the planned open biopsy. This method avoids the long incision and need for sutures, but has the disadvantage of obtaining a smaller quantity of muscle tissue and has the disadvantage that the physician cannot directly see what tissue he/she is obtaining during the biopsy. Multiple passes with the Bergstrom needle will be required to obtain the amount of tissue usually obtained through the open technique. Specimens are shipped to the Univ. of Florida for measuring 3-nitrotyrosine with Western Blot (89) mitochondrial content (mtDNA copy number) measured by RT-PCR (90) and cytochrome c oxidase (COX) and citrate synthase activities using established methods (91-93). Muscle specimens may be sent to the Universities of Florida and University of Kentucky for analyses that include inflammatory biomarkers, markers of oxidative stress, measures of mitochondrial function and quantity, and muscle myofiber typing. Analyses may also be tested for protein measures of mitochondrial function, macrophages, satellite cells, and PCR/gene expression. Other measures related to skeletal muscle quality and function may also be performed.

In addition, in a subset of participants we will obtain a muscle biopsy on the left and the right legs, respectively. These bilateral biopsies could be obtained at baseline, at 12-month follow-up, or both time points. The first biopsy will be performed as per our current procedures. The second biopsy will be performed seven days later when the participant returns for their incision site checks. It will be necessary for these individuals to remain off of their anti-platelet therapy for 14 days. Physician approval will be required. If the participant prefers to schedule the second biopsy at a later date (i.e. more than seven days after the initial biopsy), that will also be acceptable. In this case, anti-platelet

therapy will be held seven days prior to the contra-lateral biopsy. Participants will receive $100 for their time and effort for each biopsy performed.

T. **Qualitative measures.** To achieve our Exploratory Aim, we will perform digitally recorded qualitative interviews among participants in the low and high exercise intensity interventions, respectively. We will assess participants overall perceptions of the exercise intervention and participant-identified facilitators and barriers to exercise behavior that is consistent with the study goals. Interviews will be performed under the direction of Dr. Kenzie Cameron, a nationally-recognized expert in qualitative research. Prior work shows that theoretical saturation, or the point of redundancy at which no new themes emerge, often occurs in interview studies within the first 12 interviews; basic elements for themes may be present as early as six interviews (94). We will interview 15-20 randomly selected participants in each of the low- and high-intensity groups. Following transcription, responses to these open-ended items will be independently coded by the qualitative interviewers and Dr. Cameron using content and constant comparative analysis (95-97).

U. **Other measures.** As in our previous trials, patient report will be used to document comorbidities. Patient report is highly correlated with comorbid disease measured with medical record review (98-101). Participants are asked to bring their medication bottles to each visit to assess medication use.

V. **Quality control of outcome measures.** Health interviewers are trained by senior health interviewers and certified by Dr. McDermott in all aspects of data collection including the ABI, patient interviewing, and six-minute walk. Health interviewers are re-certified every six months. For quality control of calf muscle measures, a commercially available standard muscle specimen, with known characteristics, is included in each set of analysis, to monitor the quality of each protein measurement. Dr. Cameron will train selected assessment staff and monitor the fidelity of the qualitative assessments.

W. **Weight Loss + LITE Exercise Intervention in PAD.** We will obtain informed consent from up to 15 participants with PAD who have body mass index (BMI) > 28 Kg/M^2 for a study of weight loss combined with home-based exercise. This study will be conducted in people who completed the LITE Trial or in people who were evaluated for the LITE Trial, but who were not able to participate in the LITE Trial (for example if they were not willing to commit to a 12-month study for example). This component of the LITE Trial addresses the Exploratory Aim #3 of the LITE Trial and will last for up to 16 weeks. This phase of the LITE study is similar to the LITE exercise intervention but will include a weight loss intervention and is limited to people with a BMI > 28 Kg/M^2.

Participants will be asked to attend weekly group sessions at Northwestern Medical Center, meeting with other participants with PAD, a Registered Dietician, the LITE exercise coach, and a behavioral change expert. These on-site sessions will last approximately 60 to 90 minutes. These on-site sessions will be similar to the LITE exercise sessions and will include some walking exercise activity, discussion of walking exercise goals, and behavioral change strategies to meet the exercise goals. In addition, during these sessions, participants will be helped to adopt healthy lifestyle behavior changes to achieve weight loss, by receiving instruction about dietary change and healthy eating. Participants will receive instruction about behavioral techniques (such as goal setting and self-monitoring) to help them achieve weight loss while they participate in regular walking exercise activity. Participants will also be helped to develop behavioral change strategies to help them engage in regular walking exercise at home. These methods consist of those described elsewhere in this protocol for the LITE

Trial intervention. The group on-site sessions may be audio recorded and reviewed by study investigators to monitor the quality of the intervention. Participants will be asked to walk for exercise approximately five days/week for up to 50 minutes per session. Only people who have completed an exercise stress test in the past year that shows no evidence of coronary ischemia will be eligible. Potential participants who have not completed an exercise stress test in the past year will have one as part of their study participation, using the methods described elsewhere in this protocol. Potential participants with exertional chest pain that has recently increased will not be eligible for this phase of the study.

To assist with weight loss, participants will be asked to use a weight loss APP to monitor their food intake. If necessary, they will be lent an iPAD for the duration of this phase of the LITE Trial. Participants will also receive a wireless scale for monitoring their daily weight. Participants will receive a FitBit activity monitor to help monitor their walking exercise activity. Information from the FitBit and wireless scale will automatically be uploaded (with Bluetooth) onto the participant's computer device or telephone and the data will be visible to both the study participant and the study coaches. Information about the participant's eating behavior, weight, exercise activity, and goals will be discussed by the coach with the participant at the weekly meetings during a brief individual encounter outside of the group interaction. The coaches will also telephone the participant during the week to assist them with their exercise and weight loss goals.

The six-minute walk, physical activity level for up to 14 days, and the short physical performance battery will be measured prior to the start of this pilot study and these measures will be repeated at the end of this phase of the LITE Trial. Pain-free and maximal treadmill walking time may be measured before and after this weight loss + exercise intervention phase of the LITE Trial. Participants will be invited to return to the medical center to meet in a group with other participants and provide feedback to study investigators about their experience in this study. All participants from the pilot will be contacted over the phone and invited to participate in the focus group. The additional group visit will take approximately 60 to 90 minutes.

X. **Potential problems and solutions.** First, we recognize that a subset of PAD patients do not own computers or have home-internet capability. We have budgeted for the costs of a home computer tablet and internet capability for participants who require these. Additionally, low cost items that may help participants better adhere to study procedures may be purchased. Examples include chargers for telephones or computers, which will allow participants to communicate with the study coach. In no instance will the cost exceed $50 per participant. Participants who provide a reason for poor adherence to study protocol (i.e. "I cannot take the study coaching telephone calls because I do not have a charger for my telephone") and if on further questioning the participant indicates that they cannot afford to purchase a charger, then study staff will potentially pay for this. With increasing availability of computer technology and internet access, we anticipate that our intervention will be accessible to the majority of PAD patients in the near future. *Second, we recognize that some PAD participants will change medication or undergo revascularization procedures during the LITE Trial. As in our previously completed randomized trials in PAD participants, we will systematically collect data on changes in medications and new revascularization procedures throughout the study. If there is imbalance regarding medication changes or revascularization procedures across the three study groups, we will repeat our analyses, adjusting for these changes. In our prior trials, medication changes and revascularization procedures have not meaningfully influenced our results.*

Some or all study measures may need to be repeated at baseline or follow-up testing for data quality purposes. In some cases, it may be necessary to take an additional, unscheduled blood pressure measurement. For instance, if a participant has high blood pressure during the ABI

and investigators would like to double check their arm pressure measurement before performing the six-minute walk either at the same visit or at a subsequent visit. Determinations about blood pressure checks will be made on a case-by-case basis in consultation with Dr. McDermott or Dr. Lloyd-Jones or other qualified personnel.

Y. Pilot Data Collection. *Some participants may be asked to complete a short questionnaire to allow investigators to better understand whether and how people with peripheral artery disease prefer to carry out walking exercise, and to collect data on whether weight loss is an important goal for people with peripheral artery disease.*

Z. Pilot Data Collection 2. To understand how people completing the LITE Trial metabolize nitrates, we will perform a preliminary study in which people who have completed follow-up testing are asked to drink one serving of "Beet It", an all-natural beet root juice. This product is available for purchase on Amazon (*https://www.beet-it.com/product/beet-it-sport-shot/).* It contains 98% concentrated beet root juice and 2% lemon juice. Nutritional ingredients consist of 97 Kcal, 20 grams of carbohydrates, four grams protein, and 0.2 grams of total fat. Participants will be asked to attend a visit at the medical center after data collection for LITE is completed (this may often be an additional visit) and will be asked to drink one serving of the beet root juice (70 mL, 2.4 ounces). A blood draw will be performed prior to drinking the beet root juice and 2-3 hours after the participant consumes the beet root juice, for measurement of nitrates and nitrites. The amount of blood collected will be 16 ml total before and after consuming the beet root juice. Our goal is to determine the proportion of participants who achieve a concentration of nitrates of 400 nM after consuming the single serving of beet root juice. Variability has been demonstrated in metabolism of nitrate containing products, and we aim to determine inter-individual variability in metabolism in participants who have completed the LITE Trial.

AA. In follow-up to the above, and for exploratory aim #3, we will assess the acute effects of nitrate-rich beetroot juice, compared to placebo, on change in six-minute walk distance, four-meter walking velocity at usual pace, four-meter walking velocity at fast pace, and the SPPB. Participants who sign written informed consent will be assigned to either nitrate- rich beetroot juice, described above, a matching placebo that is made by the same company that does not include the nitrate-rich beetroot juice, or 10 minutes of light therapy with a 660 nm light. They will be asked to perform a six-minute walk, four meter walking velocity at usual and fastest pace, and the SPPB without consuming any beverage at the first visit for this substudy. Approximately 1-5 weeks later, they will return for repeat measures. However, prior to the repeat measures, performed approximately 1-5 weeks after the initial measure, they will either consume one drink of nitrate-rich beetroot juice, consume the matching placebo, or receive light therapy. Blood will be obtained prior to the intervention (drink or light therapy) and at approximately 2.5 hours after ingesting the drink or 10 minutes after the light therapy. The blood will be obtained for measurement of nitrate and nitrite and potentially other blood measures for research. Participants assigned to light therapy will receive up to 10 minutes of light therapy with a 660 nm light (https://mitoredlight.com/products/mitomid) prior to the second blood draw at the second visit. The six-minute walk, the four-meter walk at usual and fastest pace, and the SPPB will be performed immediately after the blood draw. Participants may be asked to return for a third visit, in which they receive both nitrate-rich beetroot juice and the light therapy. At this third visit, participants will undergo a blood draw. They will then receive the nitrate-rich beetroot juice. Approximately 2.5 hours later, they will receive the 10 minutes of light therapy. Immediately after the light therapy they will have plasma measured for nitrite and they will undergo

functional performance measures (six-minute walk, four meter walks, and SPPB) immediately after the blood draw. In statistical analyses, the degree of change in each outcome (six-minute walk distance, four-meter walking velocity at usual pace, four-meter walking velocity at fastest pace, or the SPPB) between the initial measure and the measure obtained approximately 1-5 weeks later after consumption of the study drink and/or the light therapy, will be assessed and compared with those who received placebo. We will also analyze the association between the combination of the therapies (nitrate-rich beetroot juice + light therapy) and the individual therapies for the outcomes of increases in plasma nitrite and the degree of improvement in the functional measurements. Specimens may be shipped to Wake Forest University for measurement of nitrates and nitrites, for participants who agreed to the optional beetroot juice portion of the study.

Procedures performed to lessen the probability or magnitude of risks.

A. **Adequacy of protection against risks and methods to minimize potential risks.** *Overview of protection against risks*. Prior to beginning data collection, all study coordinators undergo training and are certified by Dr. McDermott using a detailed checklist for each data collection element (see Appendix C). Research coordinators are certified in each element of the study visit including obtaining informed consent, administering questionnaires, protecting confidentiality of collected data, performing the six-minute walk, and performing the ankle brachial index. Dr. McDermott re-certifies coordinators every six months to ensure continued adherence to protocol. Those not adhering to all aspects of the protocol undergo additional training followed by re-certification.

   All research staff members have completed human subjects training required by Northwestern's institutional review board (IRB). This training includes education about the importance of maintaining confidentiality of personal health information. The study principal investigator or a co-investigator is available to answer questions that arise during the informed consent process as needed.

   Participants are asked to sign a study consent form at each on-site visit. The research coordinator reviews study procedures, including risks and benefits associated with study participation. The research coordinator answers participants' questions. Dr. McDermott and other study investigators are available to answer participants' questions. Both the participant and the individual administering the consent form will sign the consent form. Dr. McDermott's pager, direct telephone line, and home telephone number are provided to participants.

B. **Minimizing risks related to exercise.** According to current clinical practice guidelines (1), all participants will undergo baseline exercise stress testing prior to randomization. Potential participants with an abnormal baseline exercise stress test will be excluded. A safety manual will be developed prior to beginning the exercise intervention and will be reviewed and approved by the Data Safety Monitoring Board (DSMB) before implementation. In addition, participants will be monitored during supervised exercise for development of chest discomfort, new dyspnea, or new fatigue during exertion. Dr. McDermott will be promptly notified when this occurs (by pager). Our exercise physiologists have significant experience working with populations of participants with PAD and have been trained in CPR, ACLS, and use of the automatic external defibrillator. During transition to the home-based exercise program, participants are educated on important symptoms to watch for during exercise, such as chest discomfort or dyspnea. Participants are instructed to

immediately contact their physician should these symptoms occur. During their first on-site exercise session, the coach discusses information regarding safety during exercise. Dr. McDermott's cellular telephone number, pager, and direct line are provided in the informed consent form so that they can reach Dr. McDermott easily with any questions or concerns.

C. **Minimizing risks related to muscle biopsy.** The muscle biopsy procedure will be performed by Dr. Robert Sufit who has more than 30 years of experience performing these muscle biopsies, primarily as part of his clinical practice as a Board-Certified Neurologist. As in our pilot study, completed in preparation for this proposal, the muscle biopsy procedures will be performed under sterile conditions using sterile technique. Local anesthesia will be obtained using subcutaneous lidocaine. All participants will be provided with written and verbal instructions about wound care and will be advised to contact Dr. McDermott immediately if any signs of wound infection occur. All participants will return for a one-week follow-up check of their incision site.

   Many PAD participants take anti-platelet therapy to prevent cardiac and cerebrovascular events. If potential participants are taking anti-platelet therapy, they will be asked to either hold their anti-platelet therapy (if they are taking 81 mgs of aspirin or less per day) or switch to a low dose (81 mgs) of aspirin therapy (if they are taking clopidogrel or an equivalent medication or > 81 mgs of daily aspirin at study entry) during the seven days leading up to the muscle biopsy procedure. Participants who are taking warfarin or other anti-coagulant therapy will be excluded from the muscle biopsy procedure.

D. **Minimizing risk related to baseline and follow-up testing.** All study coordinators undergo baseline training and are certified by Dr. McDermott before beginning data collection. Training and certification involves ensuring that coordinators are trained in methods to help minimize falls. Dr. McDermott re-certifies coordinators every six months to ensure continued adherence to study protocol. Those who are not adhering to protocol undergo additional training followed by re-certification.

E. **Minimizing risk related to loss of confidentiality.** The following methods will be employed to maintain confidentiality of participants. First, study recruitment letters will be mailed, using IRB-approved methods, only after receiving written permission from the participant's physician. The personal physician of each study participant will have the option of **not** allowing investigators to contact the potential participant. Lists of potentially eligible participants will be obtained by individuals who normally have access to these lists as part of their daily work requirements. Recruitment letters for potential participants identified from hospital and outpatient lists are prepared by research staff members whose job is to assist study investigators with recruitment. These research staff members have completed training in the ethical conduct of human subject research, including maintaining participant confidentiality. Recruitment letters to potential participants identified from medical center lists are mailed in sealed envelopes and addressed to the potential participant. All potential participants who receive mailed information about the study after the approval from their physician will have the opportunity to call a voice-mail system to ask NOT to be further contacted about this study. Secondly, only study investigators and key research staff will have access to the study database. Third, participants will be assigned a unique study identifier. Individual names will ultimately be removed from the study database and only the unique study identifier will be used to distinguish participants in the database. Fourth, collected data will be

maintained in locked computer files and file cabinets to which only study investigators have access. Collected data will be used only for research purposes. Any published data will not contain any individual identifiers.

F. **Minimizing risk related to loss of confidentiality during qualitative interviews.** Participation includes a risk of loss of confidentiality regarding personal health information. However, all research staff have undergone formal human subjects training. They are trained to protect the privacy of research subject participants. *Each qualitative interview will be digitally recorded to reduce the need for note taking and to facilitate analysis. When participants consent to the study, we will use a staged consent to ask permission to record the qualitative portion of the interviews to better capture qualitative data. If a participant does not give permission for audio-recording, s/he can still participate in the study. In those cases, the designated interviewer will enter as much of the participant's responses as possible. Digital recordings of the interviews will be permanently erased from the server five years following the end of the data collection period. We will retain de-identified transcripts of participant responses.*

G. **Minimizing risk related to the weight loss intervention.** Individuals who lose > 1.36 kilograms per week for three weeks in a row will be contacted by study staff. Calorie goals will be increased and Dr. McDermott will interview the participant to determine whether additional medical evaluation is warranted. Second, to avoid dehydration, participants will be advised early on in the trial of the importance of maintaining adequate hydration. Participants will be reminded regularly of the importance of adequate hydration.

H. **Data and Safety Monitoring Board (DSMB).** As per NHLBI guidelines, the DSMB will be appointed by the NHLBI. The DSMB will meet at least every six months during the study. The DSMB will meet to review and approve the protocol prior to beginning data collection. They will decide on specific stopping criteria for the study. The biostatisticians and data manager will work closely with the DSMB to perform interim analyses. Adverse events and hospitalizations will be monitored monthly via telephone call and will be reported to the DSMB and IRB in a timely manner according to pre-specified requirements. Analyses will be done according to the requests of the DSMB. In addition, for each major adverse event, the group assignment of the patient will be provided. In this way the DSMB can determine whether the event is intervention related. Adverse event rates and interim study results will be reviewed and discussed by the DSMB at the DSMB meetings. At least four categories of adverse events will be defined: a) Death; b) cardiovascular events (myocardial infarction, stroke, and coronary arrhythmias) c) musculoskeletal outcomes (muscle soreness, foot ulcer, joint aches and pains). We will also include adverse events for the muscle biopsy, including a) infection and b) bleeding requiring a visit to a healthcare provider. We will report all hospitalizations to the DSMB in a timely fashion. We will use a designated data collection form to record these events and they will be reported immediately to the Institutional Review Board and DSMB. Note that to date, however, exercise programs have been demonstrated to be safe in patients with PAD (1,52,55).

- *All drugs and devices used in the research.*

Participants will be asked to wear the ActiGraph while they are exercising. The ActiGraph records duration, frequency, and intensity of exercise. The ActiGraph Bluetooth mechanism, available in the ActiGraph model that we will use in the LITE Trial, automatically uploads data to the study website, whenever participants walk within 15 feet of their home computer/tablet. Participants without a home computer suitable for uploading ActiGraph data will be provided with a computerized tablet with wireless internet access for the duration of the study.

- *Source records that will be used.*

Sources of material. Primary and secondary outcome measures that will be collected for this study are shown in Table 7 and include the six-minute walk test, treadmill walking performance, physical activity measured by the ActiGraph accelerometer, calf muscle biopsy measures, quality of life questionnaire data (SF-36 PF score), and patient-perceived walking ability (WIQ scores). In addition, adherence to the prescribed exercise intervention will be measured during the final four weeks of the intervention in the two exercise groups using the ActiGraph. Qualitative interviewing will be conducted to obtain information about participants' perceptions of their walking exercise experience. We will also administer questionnaires to participants at baseline and at each follow-up visit to assess their medical history, including presence of comorbidities, medication use, smoking status, and other health characteristics. Data collection will not make use of existing records or data. The prevalence of comorbid disease will be measured using patient report, based on previous study (98-101).

9.3 Data collected.

Please see section 9.2 above.

10.0 Data and Specimen Banking

10.1 Storage of specimens.

Blood specimens for long-term storage will be stored in a freezer belonging to Dr. McDermott's research program at Northwestern University, in the freezer farm in the basement of Olson Pavilion.

Specimens will be stored for up to 70 years, after which they will be destroyed.

10.2 Data to be stored or associated with each specimen.

Specimens will be coded; meaning that a key will exist that can link the codes back to the direct subject identifiers. Each participant will be assigned a unique study ID number that can be traced back to the study participant. The blood samples that are maintained in long-term storage will be labeled with this unique identifier and the date and time of the blood collection.

10.3 Procedures to release data or specimens.

Only Dr. McDermott has control over release of study data or specimens. Any investigators seeking to analyze blood specimens must contact Dr. McDermott for permission. Each request, if it occurs, will be considered on a case-by-case basis. Dr. McDermott will obtain IRB approval prior to releasing any blood specimens for analysis, other than those tests specifically named in this application.

11.0 Data and Specimen Management

11.1 Data analysis plan.

A. **Data management.** We will use data management methods in place for our ongoing NHBLI-funded PAD studies. Data from baseline and follow-up study visits are acquired on paper forms and processed using the Teleform system by Cardiff Software. We have successfully used this system for over 8,000 patient visits in our previous and ongoing studies. Data are backed-up on multiple hard drives and copied to CDROM for secure off-site storage.

B. **Data Safety Monitoring Board (DSMB).** We have identified nationally recognized experts to serve on the DSMB.

Statistical Analyses. Analyses will be performed according to the intention to treat principle. Data will be analyzed according to each participant's originally assigned group, irrespective of whether the participant adheres to his/her assignment. Prior to analyses, the distributions of the variables (changes) will be examined and necessary transformations will be performed. The balance of socio-demographic factors and prognostic factors (such as age, sex, race, ABI, comorbidities, and relevant medication use) will be compared between the three groups using ANOVA or chi-square tests. If there is any indication of major imbalance, proper analysis of covariance adjustments will be performed in data analyses.

NOTE: The original plan to use two sample two-tailed t-tests was changed to a mixed model for repeated measures analysis on 8/27/2020 prior to analyzing any data. This change was made because as of 8/27/202, investigators are projecting an approximately 16% loss to follow-up rate at 52 week follow-up. The mixed model for repeated measures will be used to adjust for missing data.

For our Primary Aim, we will use mixed model for repeated measures (MMRM) analysis to compare changes in six-minute walk performance at 52-week follow-up between the low vs. the high-intensity exercise group and between the low-intensity exercise group vs. the control group, respectively. To this end, the 26-week and 52-week changes of six-minute walk from baseline are treated as correlated outcomes, and independent variables include visit (26-week and 52 week), treatment (low-intensity, high-intensity, control), visit/treatment interactions and baseline six-minute walk performance. Unstructured variance-covariance matrix will be used to model the within-person correlations. In addition, we will also adjust for potentially imbalanced baseline confounders such as age, sex and baseline six-minute walk performance. When there is evidence that the normality assumption for the distribution of measures of interest is severely violated, we will perform Wilcoxon rank-sum test for the comparison. The nonparametric adjustment for the imbalance in mean difference of baseline covariates will be employed, when needed.

For Secondary Aim #1, we will use MMRM analysis to compare changes in six-minute walk, physical activity, and SF-36 PF and WIQ distance and speed scores at 26-week follow-up between the low- and high-intensity exercise groups and between the low-intensity exercise and control group, respectively.

For our Secondary Aim #2, we will use MMRM analysis to compare changes in maximal treadmill walking time, physical activity, and SF-36 PF and WIQ distance and speed scores at 52-week follow-up between the low- and high-intensity exercise groups and between the low-intensity exercise and control groups, respectively.

For our Secondary Aim #3, we will use normal approximation for binomial distribution to compare the proportion of participants who achieve adherence (as defined in section C18) between the low vs. high intensity exercise groups. We will also use logistic regression to compare the adherence rate between these two groups, adjusting for potentially imbalanced baseline confounders such as age, sex, and baseline six-minute walk performance. We will also use two sample two-tailed t-tests to compare adherence to the exercise intervention overall and at the prescribed intensity between the high vs. low intensity groups at 52-week follow-up.

For our Secondary Aim #4, we will use MMRM analysis to compare changes in six-minute walk distance, physical activity, and SF-36 PF and WIQ distance and speed scores at 26-week follow-up between the high-intensity exercise and control groups.

For our Secondary Aim #5, we will use MMRM analysis to compare changes in six-minute walk distance, maximum treadmill walking time, physical activity, and SF-36 PF and WIQ distance and speed scores at 52 week follow up between high intensity exercise and control groups.

For our Secondary Aim #6, we will use two sample two-tailed t-tests to compare changes in COX, citrate synthase, and mitochondrial DNA at 52-week follow-up between the low intensity vs. the high-intensity exercise group and between the low-intensity exercise and control groups. We will also compare change in nitrotyrosine muscle measurements between the high-intensity exercise and the control groups. We will repeat these comparisons for the participants who adhere to their prescribed exercise intensity, measured by the ActiGraph.

For our Exploratory Aim #1, we will use two sample two-tailed test compare patients' perception to exercise at 52-week follow-up between high and low-intensity groups. For our Exploratory Aim #2, we will evaluate the effect of modified combo intervention (weight loss + LITE home-based exercise) on six-minute walk distance at approximately 12 week follow-up. This pilot study was completed in 2018.

The significance level for the Primary Aim will be 0.05/2 to adjust for two comparisons between low-intensity and high-intensity arms and between low-intensity and control arms.

The significance level will be 0.05 for all secondary aims. Furthermore, Secondary Aims #4 and #5 were pre-specified but added after the LITE Trial was underway in response to two negative trials of home-based exercise in patients with PAD demonstrating that a high-intensity walking exercise program did not improve six-minute walk or other outcomes in people with PAD (5, 6).

Missing data occur when participants are lost to follow-up. First, we will make every effort to ensure that participants return for the 52-week follow-up. We will use proxies to help us locate participants we are unable to reach and we will mail reminder letters when participants are not responsive to telephone calls. We will encourage participants who do not adhere to their assigned groups to return for the 52-week follow-up by providing transportation and monetary incentives. Thus, we anticipate that the proportion of participants without 52-week follow-up data will be small. Second, MMRM analysis is valid under the missing at random assumption. In case the proportion of missing data at 52-week follow-up is not small (>25%), we will additionally employ the multiple imputation approach to account for missing data as sensitivity analysis. If there is evidence for the possibility of missing not at random, we will perform additional analyses using pattern-mixture and shared-parameter models (105).

11.2 Power analysis.

Power estimates. For all primary and secondary aims, we anticipate a 15% drop-out rate at 52-week follow-up, based on 12-month follow-up rates in our GOALS and SILC trials (52,55). We will randomize 305 participants. Of these, 120 will be randomized to the low-intensity intervention, 120 will be randomized to the high-intensity exercise intervention, and 65 will be randomized to the control group. We will enroll more participants in each exercise group than the attention control group because we anticipate that the effect size of the low vs. high intensity exercise comparison will be lower than the effect size of the low intensity vs. the control group. For our Primary Specific Aim, we will have 80% power to detect a minimum difference of 0.43 standard deviations (SD) between the low intensity vs. high intensity exercise groups and a difference of 0.52 SD between the low-intensity and the attention control groups, in change of six-minute walk distance at 52-week follow-up, using two-sided two-sample t-tests **with a significance of 0.025 to adjust for the two comparisons.** Low intensity exercise will be considered effective if either comparison (i.e. with high intensity exercise or with the attention control group) is statistically significant. The SD of the change in six-minute walk in our GOALS and SILC trials was approximately 60 meters. Therefore, our sample size allows us to detect a difference in change in six-minute walk of 26 meters and 31 meters, respectively, between the low vs. high intensity groups and between the low intensity and control groups. Prior studies have defined clinically meaningful changes in the six-minute walk as 30 meters (small meaningful change) and 50 meters (large meaningful change) (102,103). Thus, our power should be adequate to detect a clinically meaningful difference. For our Secondary Aim #1, we will have 80% power to detect a difference of 0.39 SD between the high vs. low intensity exercise interventions and a difference of 0.47 SD between the low-intensity intervention vs. control group, respectively, in changes of six-minute walk, physical activity, WIQ scores, and SF-36 scores at 26 –week follow-up using two-sided two-sample t-tests with a significance of 0.05. For our Secondary Aim #2, we will have 80% power to detect a difference of 0.39 SD between the high vs. low intensity exercise interventions and a difference of 0.47 SD between the low-intensity intervention vs. control group, respectively, in changes of maximal treadmill walking time, physical activity, and WIQ and SF-36 scores at 52-week follow-up, using two-sided two-sample t-tests with a significance level of 0.05. In our SILC trial, the observed differences between the intervention and control groups are 0.61 SD, 0.59 SD and 0.61 SD in changes of maximal treadmill walking time, WIQ distance, and SF-36 physical functioning scores, respectively (52). In a study by Gardner et al of supervised exercise in participants with PAD (73), the observed improvement in physical activity

level as measured by accelerometer in the exercise group was more than 0.86 SD greater than that for the control group. Thus we should have adequate power to detect similar effect sizes. For our Secondary Aim #3, we will compare rates of ActiGraph-measured adherence to the prescribed exercise intervention (five exercise sessions per week for 45 minutes of walking exercise per session) between the low vs. high intensity exercise groups. Adherence will be defined as achieving at least 80% of the prescribed exercise intervention (see section C18). Based on the home-based component of our SILC trial, we expect the adherence rate in the high intensity exercise group will be about 30%. Our sample size provides 80% power to detect a minimum difference of 19% in the proportion of adherence between the low intensity and high intensity groups, based on the two-sided Z test with pooled variance using normal approximation for binomial distribution with a significance level of 0.05. For our Secondary Aims #4 and #5, we will have 80% power to detect a difference of 0.52 SD between the high-intensity intervention vs. control groups, in changes of six-minute walk distance, physical activity, and WIQ and SF-36 scores at 26-week and at 52-week follow-up, and in change of maximal treadmill walking time at 52-week follow-up, using two-sided two-sample t-tests with a **significance level of 0.05**. Therefore, we have adequate power for detecting differences similar to those observed in SILC trial. For our Secondary Aim #6, we will randomly select 50 participants from each of the three study groups. We will have 80% power to detect a difference of 0.61 SD between the low vs. high intensity exercise interventions, between the low-intensity exercise intervention and the control group, and between the high-intensity exercise intervention group vs. control group, respectively, in changes of citrate synthase, COX, and mitochondrial DNA at 52-week follow-up, using two-sided two-sample t-tests with a significance level of 0.05. In a randomized trial, Timmers et al reported observed differences in citrate synthase, COX, and mitochondrial DNA of 3.17 SD, 2.12 SD, and 0.75 SD, respectively, between a treatment and control group (104). Thus we should have adequate power.

11.3 Steps to secure data to maintain confidentiality during storage, use, and transmission.

First, all research assistants must complete training in protection of subject privacy and prevention of disclosure of identifying information.

Second, all data collection forms are maintained in a secure office space.

Third, our study databases are maintained in locked computer files or on secure hard-drives that are password protected; to which only authorized staff have access. Dr. McDermott or a study manager must provide permission for programmers and research assistants to access study databases.

Fourth, a study identification number will be assigned to each participant. This identification number will be used to label blood specimens, for example. In addition, most pages of our data collection forms will have only the study identification number listed (and not the participant's name, for example).

11.4 Describe any procedures that will be used for quality control of collected data.

Quality Control. As in our prior studies, health interviewers will be trained by a senior coordinator and certified by Dr. McDermott in each component of data collection, using a

detailed checklist developed for this trial. Health interviewers are rigorously evaluated for adherence to protocol, prior to beginning data collection and every six months after initial certification.

12.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

Serious adverse events will be reported to the DSMB within seven days of each serious adverse event. Adverse event data will be reported to the DSMB every six months during the study, and/or as requested by the DSMB. The DSMB will have the ability to stop the study at any time if there are concerns about safety.

13.0 Withdrawal of Subjects*

Subjects may withdraw from the research at any time. If they decide to leave the research, they should contact the investigator, Dr. Mary McDermott.

If they stop being in the research, already collected data may not be removed from the study database. They will be asked whether the investigator can collect data from their routine medical care. If the subject agrees, this data will be handled the same as research data.

14.0 Risks to Subjects*

14.1 Foreseeable risks.

A. **Risks associated with the exercise program.** First, the exercise program might be associated with an increased risk of heart attack, arrhythmia, or death. In addition, patients may develop ischemic chest pains during exercise. If participants develop chest pain while at a study visit, Dr. McDermott or Dr. Lloyd-Jones will be notified immediately. Dr. McDermott will oversee arrangement of appropriate follow-up (including immediate transport to the emergency room if appropriate). The exercise physiologist is certified in Cardiopulmonary Resuscitation (CPR) and use of an Automatic External Defibrillator (AED). As recommended by clinical practice guidelines (1), all potential participants will undergo a baseline exercise stress test. Those with an abnormal baseline exercise stress test will be excluded from participation and will be asked to follow-up with their physician. These tests on the heart may lead to the need for procedures to improve the blood flow to your heart or hospitalization if the result on the exercise stress test shows a particularly worrisome result. A treadmill exercise stress test may also be associated with an irregular heartbeat or a heart attack. In addition, those randomized to one of the two home-exercise programs will be educated regarding symptoms to watch for during exercise that should be reported immediately to their physician. Safety manuals and protocols will be developed prior to beginning the intervention. Dr. McDermott's direct line, pager, and cellular telephone number will be provided to all participants.

Second, chest pain during exercise may result in additional cardiac work-up that may lead to procedures to improve coronary blood flow. As indicated above, subjects will be screened for active heart problems with a baseline exercise treadmill test prior to enrollment, according to currently recommended standards of screening PAD patients for coronary artery disease prior to their beginning an exercise program (1). These exercise stress tests will be performed as part of our protocol and interpreted by board-certified cardiologist and co-investigator Dr. Lloyd-Jones.

Participants must have a normal 12-lead exercise stress test to be eligible. Abnormal baseline exercise stress tests may also lead to additional cardiac work-up by the participant's physician that may lead to coronary angiography or coronary revascularization.

Third, exercise may be associated with muscle fatigue or soreness. This typically resolves with rest.

Fourth, it is possible that walking may contribute to foot sores when shoes are poorly fitting. Additionally, walking may worsen or slow healing of foot sores or ulcers in PAD.

Fifth, risks associated with baseline and follow-up testing include loss of balance and falling during the walking tests, chair rises, and standing balance testing. However, the research assistant who will collect these data has been trained to prevent falling. The risk of falling is less than 1 in 200. Falling during these tests may be associated with fracture. The risk of a fracture secondary to a fall during the walking tests is less than 1 in 5,000.

B. **Risks associated with the muscle biopsy.** The muscle biopsy is associated with several potential risks. These include discomfort during the muscle biopsy procedure, scarring from the muscle biopsy skin incision, bleeding, and infection. Potential participants who are asked to hold or reduce their anti-platelet therapy or anti-coagulation therapy during the week leading up to the muscle biopsy procedure may experience a cardiovascular event related to the temporary reduction or discontinuation of the anti-platelet or anti-coagulant therapy.

   To minimize risk, all participants undergoing muscle biopsy will receive a written hand-out regarding signs to watch for of wound infection after the muscle biopsy. They will also be verbally instructed in this. The participant will be instructed to call Dr. McDermott immediately if any signs of infection occur. In addition, permission from the participant's primary care physician will be required before switching participants on anti-coagulant therapy to low-dose aspirin therapy for the seven days prior to the procedure. If the potential participant's primary care physician does not provide permission for switching to low-dose aspirin for patients taking anti-coagulant therapy, the potential participant will not be eligible for the study. However, based on our pilot study, we anticipate that the number of these exclusions will be very small.

C. **Six-minute walk test.** The six-minute walk test may be associated with the risk of falling or coronary ischemia or dyspnea due to heart failure or lung disease. Rarely, falling during the six-minute walk test may result in a fracture. However, the research assistant who will collect these data has been trained to prevent falling. The risk of a fracture secondary to a fall during the six-minute walk test is less than 1 in 5,000.

D. **Risks associated with ABI measurement.** The ankle brachial index measurement consists of measuring systolic blood pressure in each extremity using a hand-held Doppler. The ABI is non-invasive, safe and does not have any known lasting side effects. During the ankle brachial index test, participants may experience discomfort from the inflated blood pressure cuff. However, this discomfort resolves immediately when the cuff is released.

E. **Risks associated with drawing blood:** The potential risks of drawing blood include a bruise at the site of vein puncture, inflammation of the vein, and infection. Care will be taken to avoid these complications.

F. **Risks associated with questionnaire administration and qualitative interviewing.** Participation includes a risk of loss of confidentiality regarding personal health information. However, all research staff have undergone formal human subjects training. They are trained to protect the privacy of research subject participants. *Each qualitative interview will be digitally recorded to reduce the need for note taking and to facilitate analysis. When participants consent to the study, we will use a staged consent to ask permission to record the qualitative portion of the interviews to better capture qualitative data. If a participant does not give permission for audio-recording, s/he can still participate in the study. In those cases, the designated interviewer will enter as much of the participant's responses as possible.*

G. Risks associated with exposing the legs to far-red light for approximately 10 minutes. There are no known risks associated with the light exposure. The light is bright and can be uncomfortable if the participant looks directly into the light. The light will be directed away from the eyes and the participant will be provided with goggles to wear during the light treatment

14.2 If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable.

Either exercise intervention may have risks that are currently not foreseeable.

15.0 Potential Benefits to Subjects

15.1 The potential benefits that individual subjects may experience from taking part in the research.

A. **Potential benefits of the proposed research.** Lower extremity peripheral artery disease (PAD) affects eight million people in the United States (U.S.) (10). PAD will be increasingly prevalent as the U.S. population survives longer with chronic disease. We previously demonstrated that men and women with PAD have greater functional impairment and more rapid functional decline than those without PAD (11-15). The functional impairment experienced by people with PAD is associated with loss of independence, increased hospitalization rates and poor quality of life (16-19). Yet few therapies exist for improving functional performance and preventing mobility loss in people with PAD.

B. Clinical practice guidelines recommend supervised, high-intensity, ischemic-pain inducing treadmill exercise to improve walking performance in people with lower extremity peripheral artery disease (PAD) (1,2). However, supervised exercise is not paid for by medical insurance. Furthermore, the ischemic leg pain induced by high intensity walking exercise is a barrier to exercise in patients with PAD. Fewer than five percent of the more than eight million men and women with PAD in the United States participate in supervised exercise (3,4). This proposed study will determine whether an **alternative** exercise intervention that employs remote monitoring, avoids continuous supervision, and avoids ischemic-pain improves functional performance at 52-week follow-up in people with PAD. Our intervention directly addresses two aspects of current practice guidelines that are major

barriers to exercise for patients with PAD: 1) the recommendation for long-term **supervised** exercise and 2) the recommendation for **ischemic-pain inducing** walking exercise (1,2). If our hypotheses are correct, millions of people with PAD will benefit from our proposed **alternative exercise regimen** which will be accessible to most of the eight million people in the U.S. who suffer from PAD.

C. **Importance of knowledge to be gained.** Lower extremity peripheral arterial disease (PAD) is common. Currently 8 million men and women in the United States (U.S.) have PAD (10). The number of individuals with PAD is expected to increase as the U.S. population lives to older ages with chronic disease. Our prior work and that of others shows that patients with PAD have greater functional impairment, increased rates of functional decline, and increased mobility loss compared to persons without PAD (11-15). Older patients with functional impairment are less likely to remain independent in the community, have higher rates of hospitalization, and have poorer quality of life than those without functional impairment (16-19). Yet few therapies have been identified that improve lower extremity functioning or prevent functional decline or mobility loss in persons with PAD. Only two FDA-approved medications improve functional performance in patients with PAD. Although supervised treadmill exercise is recommended by clinical practice guidelines to improve functional performance in PAD, fewer than five percent of PAD participants are actively engaged in supervised treadmill exercise (3,4). If our hypotheses are correct, millions of people with PAD will benefit from our proposed **alternative exercise regimen** which will be accessible to most of the eight million people in the U.S. who suffer from PAD. Remote monitoring is a highly innovative feature of our proposed trial that has not been tested previously in people with PAD and is expected to facilitate adherence to home-based walking exercise.

16.0 Vulnerable Populations

NA

17.0 Community-Based Participatory Research

NA

18.0 Sharing of Results with Subjects

Participants will receive results of their ankle brachial index (ABI) test results immediately after this testing is completed. They will be provided with a "result letter" at the end of their baseline visit. They will not be provided with other study results.

19.0 Setting

The research will be conducted at Northwestern Memorial Hospital, 680 North Lake Shore Drive, and 750 North Lake Shore Drive. If a participant is unable or unwilling to come back to our site for a follow-up visit or if they are unable or unwilling to come to the medical center for an intervention visit, we may go to their home to collect follow-up data or carry out the intervention visit.

Exercise intervention sessions will be conducted at either L.A. Fitness (355 E. Grand Ave. or 55 E. Randolph St.) or at 680 N. Lake Shore Drive. Heath education sessions will take place at 750

N. Lake Shore Drive.

20.0 Resources Available

20.1 Qualifications of staff.

Collaborating sites. Dr. Christiaan Leeuwenburgh is an internationally recognized expert in skeletal muscle biology and mitochondrial function. Dr. Leeuwenburgh's laboratory will measure mitochondrial oxidative metabolism measures and oxidative stress proteins in muscle biopsy samples obtained in the LITE Trial. Dr. Leeuwenburgh's laboratory performed all of the measures from our muscle biopsy pilot study. Dr. Leeuwenburgh's laboratory has demonstrated success measuring respirometry. Dr. Walter Jack Rejeski of Wake Forest is an internationally recognized leader in behavior change interventions in patients with chronic disease. Dr. Rejeski led the successful group mediated cognitive behavioral intervention for our GOALS Trial (52). Drs. Michael H. Criqui (University of California at San Diego), Jack M. Guralnik (University of Maryland), and Luigi Ferrucci (National Institute on Aging) have worked with Dr. McDermott on PAD studies of functional impairment for over eleven years and bring expertise in functional assessment, PAD, and clinical trials to the study team.

21.0 Prior Approvals

NA

22.0 Recruitment Methods

22.1 When, where, and how potential subjects will be recruited.

PAD participants will be identified from among consecutive patients diagnosed with PAD in the non-invasive vascular laboratory of Northwestern Memorial Hospital (NMH). Study co-investigator, Dr. Mark Eskandari, is medical director of the non-invasive vascular laboratory at NMH and will assist with identifying potential participants from the non-invasive vascular laboratory. As director of the vascular laboratory at NMH, Dr. Eskandari formally reads many of the non-invasive vascular laboratory tests. He maintains all non-invasive vascular test results in his vascular laboratory. As director of the vascular laboratory, Dr. Eskandari could conceivably contact the patients whose test results are maintained in his laboratory. However, Dr. Eskandari prefers that the contact of potential participants in studies come from the physicians referring him for testing. Lists of patients who have undergone lower extremity arterial testing in the non-invasive vascular laboratory are generated monthly and e-mailed by Dr. David Leibovitz from Northwestern Memorial Hospital to Dr. McDermott using an encrypted file. Dr. Leibovitz is the Director of Clinical Information Systems at Northwestern Memorial Hospital and he is Chief Medical Information Officer at Northwestern Medical Faculty Foundation. A research assistant, working on behalf of Dr. Eskandari, will contact referring physicians of potential participants identified from the vascular laboratory via fax, phone, page, or e-mail, to ask for permission to contact their patient about the study. Physicians will be advised that if they do not contact us to tell us to advised us NOT to contact their patient, we will send their patient a study recruitment letter from Dr. McDermott on behalf of the patient's

physician. We have substantial experience with our proposed recruitment methods, which are IRB approved for our previous or ongoing studies.

We also propose to obtain lists of consecutive patients with a diagnosis of lower extremity peripheral arterial disease who are seen in our vascular surgery practice, cardiology practice, and general internal medicine practice in the Northwestern Medical Faculty Foundation (NMFF). Co-investigator Dr. Mark Eskandari is a member of the vascular surgery practice at NMFF. Co-investigator Dr. Lloyd-Jones is a member of the cardiology division at NMFF. Dr. McDermott is a member of the general internal medicine practice at NMFF. We also propose to obtain lists of consecutive patients with a diagnosis of lower extremity peripheral arterial disease who are patients in our vascular surgery, cardiology, geriatrics, and general internal medicine practices at NMFF. Again, similar methods will be used as those described above, in which the patient's physician will be contacted to obtain permission to send a recruitment letter to their potentially eligible patient from Dr. McDermott on behalf of the patient's physician. We will contact the physicians and if after the physician does not advise us NOT to contact their patient within three weeks of sending the letter, three weeks, we will contact their patients.

Up to four recruitment letters will be mailed, three weeks apart. We may also contact by telephone (after three weeks) those who do not respond to the first mailing within three weeks. Lists of patients at NMFF will be obtained using the EDW system. These lists will be obtained by an individual who is employed by the Division of General Internal Medicine who has received training and permission to obtain the lists from the EDW.

In the recruitment letters, recipients are asked to call our voice mail line if they are interested in participation or if they do not want to be contacted. Potential participants who do not call us within three weeks of the first mailed recruitment letter may be telephoned by study staff and invited to participate.

In addition, we may use internet advertising, public transportation advertising, newspaper advertising, and radio advertising to identify potential participants for this study. A draft newspaper ad and a radio advertising script are included in this IRB submission. We will also use brochures/flyers that we will post in relevant office practices.

The EDW will be used to identify patients with peripheral arterial disease and other conditions which put them at risk for PAD (diabetes, coronary artery disease) using diagnosis codes. The patient will be contacted via a previously IRB approved recruitment letter signed by the principal investigator on behalf of the patient's physician.

On February 21, 2017, IRB approval was obtained at the Jesse Brown VA Medical Center. Dr. William Pearce, a vascular surgeon at the Jesse Brown VA Medical Center and a study co-investigator will provide lists of patients who have undergoing lower extremity arterial testing for PAD and lists of PAD patients seen in the vascular surgery clinic using IRB approved methods. A research coordinator from Northwestern University who has obtained Without Compensation status at Jesse Brown VA Medical Center (JBVAMC) will mail recruitment letters to patients with PAD identified at the Jesse Brown VA Medical Center. Letter recipients who do not telephone the investigators to indicate whether or not they are interested in study participation may be

telephoned by the study coordinator who will describe the study, assess the patient's interest, and perform initial telephone eligibility screening at the Jesse Brown VA Medical Center. Patients interested in participating who are deemed potentially eligible using telephone screening will attend a baseline visit at the Jesse Brown VA Medical Center, where they will sign a VA consent document and will undergo initial study testing. If the participant remains eligible after this initial testing, they will be scheduled for subsequent testing and interventions at Northwestern University. Eligible participants will be asked to sign the Northwestern University consent form at the start of their visit at Northwestern University.

22.2 Describe the source of subjects.

Please see details regarding "source of subjects" in section 22.0 and 22.1.

22.3 Describe the methods that will be used to identify potential subjects.

Please see details regarding methods used to identify potential subjects in sections 22.0 and 22.1.

22.4 Amount, timing, and method of any payments to subjects.

If the participant agrees to a muscle biopsy and is randomly selected to undergo a biopsy, s/he will receive $100 cash for each muscle biopsy that s/he undergoes. If the participant participates in two muscle biopsies, the total s/he could receive for study participation is $200. If the participant withdraws from the study, s/he may still retain payment for the portions of the study that s/he completed. Study payments are considered taxable income and reportable to the IRS. A Form 1099 will be sent to the participant if total payments from Northwestern University are $600 or more in a calendar year. We will pay up to $110.00 to reimburse participants for travel per study visit.

23.0 Local Number of Subjects

Recruitment. We will randomize 305 PAD participants over 32-months, allowing for a 15% drop-out at 52-week follow-up. We will identify participants using 1) Northwestern's Enterprise Data Warehouse to identify patients with PAD; 2) radio and newspaper advertising; 3) bulk mailed postcards to people age 55 and older living in the Chicago area; and 4) the CAPriCORN network, which is PCORI-funded network of medical centers in the Chicago area designed to assist investigators with recruitment for clinical trials. CAPriCORN has its own IRB (CHAIRb). The LITE Study has CHAIRb IRB approval for recruitment from individual sites that are part of CAPriCORN. Patients with PAD identified at these medical centers receive a recruitment letter that describes the LITE trial and invites the PAD patients to participate.

24.0 Confidentiality

NA

25.0 Provisions to Protect the Privacy Interests of Subjects

25.1 Steps that will be taken to protect subjects' privacy interests and to make the subjects feel at ease with the research situation.

Questionnaires will be administered in an enclosed space by a trained and certified research assistant. Dr. McDermott personally certifies study participants in data collection to help ensure that participants are treated with the highest level of professionalism.

25.2 Indicate how the research team is permitted to access any sources of information about the subjects.

All research staff undergo training (human subjects training) in the protection of participant confidentiality and privacy. Research staff have access to medical records only for the purpose of conducting research that is approved by the IRB.

26.0 Compensation for Research-Related Injury

26.1 If the research involves more than Minimal Risk to subjects, describe the available compensation in the event of research-related injury.

If the subject needs medical care because of taking part in this research study, they should contact the investigator and medical care will be made available. Generally, this care will be billed to the subject, their insurance, or other third party. Northwestern University has no program to pay for medical care for research-related injury.

27.0 Economic Burden to Subjects

NA

28.0 Consent Process

The "SOP: Informed Consent Process for Research (HRP-090)" will be followed. Participants will be consented by a research assistant who has been trained and certified by Dr. McDermott in obtaining informed consent. Prior to attending their first study visit, a research assistant will explain the study to potential participants by telephone. When a potential participant arrives to the medical center for study participation, the research assistant will explain the full details of the research study, including risks and benefits. The informed consent process will take place first at initial study visits. Data will be collected on the 11th floor of Galter in a private area. The research assistant will be collecting the signed consent form.

Potential participants will be provided plenty of time to read the consent form. The research assistant will answer study questions. However, if the participant would like more time to discuss the research study with their physician or family member, they will be allowed to do so. In this case, the study visit will not proceed. Dr. McDermott or another study investigator at Northwestern is also available to answer any questions that participants may have about the research.

Non-English Speaking Subjects

Potential participants who do not speak English will not be eligible for study participation.

Subjects who are not yet adults (infants, children, teenagers)

Children will not be involved in this research.

Cognitively Impaired Adults

Participants who are cognitively impaired will not be eligible.

Adults Unable to Consent

Written consent will be required from all study participants. Participants who cannot provide informed consent are not eligible for participation.

29.0 Process to Document Consent in Writing

The "SOP: Written Documentation of Consent (HRP-091): will be followed.

30.0 Drugs or Devices

30.1 Plans to store, handle, and administer drugs or devices.

Actigraphs. Participants will be asked to wear the ActiGraph while they are exercising. We will provide the ActiGraph for the participant to use.

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