PROTOCOL TITLE:

HOme-based moNitORed Exercise for PAD

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1.0 Objectives

1.1 Describe the purpose, specific aims, or objectives.

We will conduct a randomized controlled trial of 200 patients with PAD to determine whether a home-based walking exercise program significantly improves walking performance and other patient-centered outcomes at the nine-month follow-up, compared to usual care.

PAD patients selected the trial's outcome measures as those that best represent PAD patients' physical limitations. All outcomes are well-validated and accepted outcome measures. The primary outcome measure is the six-minute walk test, an objective measure of walking endurance. Secondary outcomes consist of the Walking Impairment Questionnaire and the PROMIS questionnaires that assess patient-perceived walking ability, mobility, pain, and social functioning. Additional secondary outcomes consist of Actigraph-measured physical activity and quality of life, measured by the SF-36 physical functioning questionnaire.

Feasibility Stage (Specific Aim #1): With input from PAD patients and healthcare providers, we will perform feasibility studies necessary to finalize our home-based exercise intervention.

Trial Stage (Specific Aim # 2): In 200 patients with PAD, we will conduct a randomized controlled trial to determine whether our PAD patient-centered home-based exercise program improves walking ability, mobility, pain, and social functioning, compared to a usual care group. Our primary outcome is the six-minute walk, an objective, well validated measure of mobility. Secondary outcomes are well-validated questionnaire measures consisting of the Walking Impairment Questionnaire (WIQ) the PROMIS measures of mobility, pain, and social functioning, the SF-36 physical functioning score, and the Actigraph measure of physical activity. Primary and secondary outcome measures will be measured at baseline, 4.5 month follow-up, and nine-month follow-up.

Exploratory Analysis. In an exploratory specific aim, in up to 20 people with PAD, we will test the feasibility of wearing a pneumatic compression device for two hours per day in addition to home-based walking exercise. We will also determine whether the combination of the pneumatic compression device + home-based walking exercise results in improved leg symptoms or walking performance in people with PAD.

1.2 State the hypotheses to be tested.

We will determine whether our PAD patient centered home-based exercise program improves walking ability, mobility, pain, and social functioning compared to a usual care group.

1.3 In an exploratory analysis, we will collect some preliminary data regarding the efficacy of wearing a pneumatic compression device for two hours per day combined with home-based walking exercise for improving walking performance in people with PAD.

2.0 Background

2.1 Relevant prior experience and gaps in current knowledge.

Lower extremity peripheral artery disease (PAD) is a chronic and disabling condition that is common in the United States (U.S.). Atherosclerosis, or cholesterol blockages, of the lower extremity arteries, also known as peripheral artery disease (PAD), affects 8 million men and women in the U.S and more than 200 million people world-wide (1,18). The prevalence of PAD is increasing world-wide and will continue to grow as the population lives longer with chronic disease (18).

Risk factors for PAD include diabetes mellitus, cigarette smoking, hyperlipidemia, and hypertension (1,18). PAD can be accurately and easily diagnosed with the ankle brachial index (ABI), a ratio of Doppler-recorded systolic blood pressures in the lower and upper extremities (19). An ABI < 0.90 is the accepted criterion for PAD (19). PAD is associated with a higher rate of death from heart disease and stroke compared to people without PAD (20,21). With improved medical therapy, rates of death from heart disease and stroke have declined (1). The result is that PAD patients are living longer with physical impairment and mobility loss (22).

People with PAD have greater functional impairment, increased mobility loss, and poorer quality of life than people without PAD (2-6,23). PAD patients have difficulty walking because the cholesterol blockages in their leg arteries prevent adequate oxygen supply to leg muscles during walking activity. Intermittent claudication is the most classic symptom of PAD and is characterized by pain in the calf muscle with walking activity, due to insufficient oxygen supply to leg muscles during walking (1,3,5). Most PAD patients slow their walking speed or reduce their activity level to avoid walking-related leg pain (2-4). This leads to functional impairment and poor quality of life (2,3,23). In addition, people with PAD have increased mobility loss and greater declines in walking ability over time, compared to people without PAD (5,6). In our Walking and Leg Circulation Study (WALCS), PAD patients with severe PAD at baseline were 12 times more likely to become unable to walk continuously for six minutes two years later, compared to those without PAD (5). PAD-related walking impairment has significant social and economic costs. People with walking difficulty, such as that experienced by persons with PAD, are less likely to remain independent in the community and have increased rates of hospitalization and mortality, compared to people without PAD (6,24-27).

Summary of the burden of PAD. PAD affects 8 million individuals in the U.S. and will be increasingly common as the population survives longer with chronic disease (1,18,22). People with PAD have greater walking impairment and increased rates of mobility loss compared to people without PAD (2-6). PAD-associated functional impairment affects daily activities such as crossing a busy street, stair climbing, and social functioning. The impairment experienced by people with PAD is associated with higher rates of

institutionalization and poorer quality of life (24-27). Effective interventions that are accessible to the majority of PAD patients are urgently needed to reduce the health burden cause by PAD.

2.2 Relevant Preliminary Data and Significance

Few therapies are available to improve functional impairment in PAD patients. Only two medications (pentoxifylline and cilostazol) are FDA-approved for treating PAD-associated walking impairment. Of these, recent data show that pentoxifylline is usually ineffective and benefits from cilostazol are modest (28-32). Many patients with PAD are unable to take cilostazol long-term because of side effects that include heart palpitations, diarrhea, and headache. Most people with PAD continue to have significant difficulty with walking endurance even on cilostazol therapy (31-32). Furthermore, most PAD patients are not candidates for lower extremity revascularization (13,14). Even among PAD patients who undergo lower extremity revascularization, 40% of lower extremity angioplasty/stent procedures fail within three years (14). **Effective and accessible therapies are urgently needed to prevent mobility loss and reduce the health burden caused by PAD.**

Published clinical guidelines for PAD recommend supervised treadmill walking exercise to improve walking limitations in patients with PAD (13,14). Supervised exercise significantly improves treadmill walking performance and six-minute walk performance in PAD patients (7-10). However, most PAD patients do not participate in supervised exercise programs (11,12). First, Medicare and other medical insurance companies do not pay for supervised exercise programs for patients with PAD. Lack of insurance coverage for supervised exercise is a major barrier to participation in supervised exercise programs. Most patients with PAD cannot afford to pay for supervised exercise. Second, traveling to the exercise center three times weekly, as recommended by clinical practice guidelines (14), is **burdensome** for PAD patients.

Current clinical practice guidelines state that there is insufficient evidence to support home-based exercise in PAD patients (13,14). Because most patients with PAD find supervised treadmill exercise too costly and burdensome, effective home-based exercise programs are needed for PAD patients. Yet PAD patients have difficulty exercising at home because of PAD-related leg pain that occurs with walking (see section 2.1). Learning to manage PAD-related pain during walking exercise is important in order for PAD patients to initiate and sustain a home-based exercise program. To our knowledge, no prior studies have engaged PAD patients to design a home-based exercise program. Similarly, prior studies have not adequately addressed leg symptoms experienced by PAD patients exercising at home. **An effective home-based exercise program that is designed by PAD patients and other stakeholders is needed to improve the physical impairment and prevent mobility loss that is associated with PAD**. Practice guidelines state that there is insufficient evidence to support home-based exercise for people with PAD (14).

PAD patients tell us they have difficulty adhering to home-based walking exercise. For the past ten months, we have worked directly with PAD patients and healthcare to develop an acceptable, accessible home-exercise program that overcomes barriers to exercise and meets the specific needs of PAD patients. We conducted multiple focus groups of PAD patients, completed a preliminary study of home-based exercise, carried out focus groups of healthcare providers, and engaged PAD patients to select outcome measures that best represent their PAD-related disability. We used information from these activities to develop our intervention.

We asked PAD patients were asked to identify and discuss the major barriers to home-based walking exercise activity. In six focus groups of 30 PAD patients, we obtained the following key messages.

Table 1. Key messages obtained from PAD patients regarding home-based exercise interventions.

What are the main barriers to regular walking exercise?
• "Exercise-related leg pain is a major barrier to walking exercise." • "Pain with walking is a big problem. I will think of any excuse not to walk. There is always a reason." • "I need something to motivate me." • "I need a "coach" that I am accountable to." • "I find it difficult to stick to a home-based exercise program, because I need some kind of skilled direction in the type of exercise I should do." • *Comment from a patient who indicated he did not know what exercise he should be doing for PAD:* "…the best I had gotten for advice was physical therapy and the programs they had were not beneficial to my condition, and these therapies did not restore my ability to walk comfortably"

The patient testimonials in Table 1 lead to these key conclusions from PAD patients:

- PAD patients find that leg pain during walking is a major barrier to walking exercise;
- PAD patients want a trainer or coach to be accountable to;
- PAD patients are not sure what type of exercise to engage in.

Our home-based exercise intervention was designed to respond to these key messages from PAD patients.

Healthcare providers tell us they have insufficient tools available to them to help PAD patients adhere to home exercise. We conducted focus groups of healthcare providers for PAD patients, including vascular surgeons, general internists, and nurse practitioners caring for PAD patients. Healthcare providers report that few therapies are available to patients with PAD and that they have difficulty helping PAD patients adhere to home-based exercise. Table 2 shows key messages from focus groups of healthcare providers.

Table 2. Key messages reported by healthcare providers about the care of PAD patients.

What are the barriers to treating PAD patients?
• "Getting PAD patients to walk for exercise is difficult because walking is painful for PAD patients". • "Getting PAD patients to exercise regularly is like any health behavior change: Difficult to achieve." • "I would like to know exactly what characteristics of a walking exercise program are best. How many times should patients walk per week, for example, and how long should they walk per session." • "A hand out or written prescription that I could hand to the patient would be very helpful."

The healthcare provider feedback shown in Table 2 leads to these key conclusions: Health care providers report that a) healthcare providers need tools to help PAD patients adhere to home-based exercise; b) healthcare providers would like a "prescription"- similar to a physical therapy prescription- that they could provide to PAD to get them started in a home-based exercise program. Therefore, Phase I of our intervention (see section C below) will help PAD patients develop the habit of home-base exercise and acquire the skills needed to adhere to a home-based exercise program. We anticipate that healthcare providers will prescribe Phase I of our intervention to PAD patients, just as they might prescribe a physical therapy program for patients with chronic low back pain. In Phase II of our intervention, PAD patients will continue their home based exercise with the assistance of a Fitbit for self-monitoring and a remote coach.

Summary of the significance of this proposal. PAD patients experience significant physical impairment and disability (2-6). Few therapies are available that improve the disability caused by PAD. Although supervised treadmill exercise improves walking ability, PAD patients do not have access to supervised exercise. Current clinical practice guidelines state that there is insufficient evidence to support home-based exercise for patients with PAD (13,14). Our proposed study addresses a critical gap in the care of PAD patients. Our home-based exercise intervention was designed to be accessible and acceptable to the vast majority of PAD patients. **We expect that our home-based exercise intervention will improve functioning and prevent mobility loss in the large and growing number of people with PAD.**

3.0 Inclusion and Exclusion Criteria

3.1 Screening for eligibility.

Recruitment. We will randomize 200 PAD participants over 16 months. Based on our prior clinical trials of PAD patients, we anticipate an 10% drop-out at 9-month follow-up (9,15). As in our prior clinical trials, we will identify potential PAD participants using Northwestern's Enterprise Data Warehouse and we will contact all patients with PAD cared for at Northwestern. We will also use radio and newspaper advertising and we will mail informational postcards to age-eligible men and women living in the Chicago area. We have substantial experience successfully using each method. Since 2004, we have randomized 620 PAD participants from the Chicago-area into NIH-funded clinical trials (9,15,38). We have the experience and expertise to successfully recruit the proposed 200 PAD participants for this proposed trial.

3.2 Criteria.

Inclusion Criteria. An ABI $\leq$ 0.90 at the baseline study visit is a well-accepted standard for presence of PAD and will be our inclusion criterion (39-42). In addition, participants with an ABI > 0.90 but $\leq$ 1.00 who experience a 20% drop in ABI after the heel-rise exercise will be eligible. Participants with an ABI > 0.90 who have medical record evidence of prior lower extremity revascularization for PAD will also be eligible. Finally participants with an ABI > 0.90 who have medical record evidence of PAD based on non-invasive vascular laboratory testing or based on angiographic findings will be eligible. Note that screening via Lifeline Screening is not sufficient for inclusion in the study. Non-invasive vascular laboratory evidence of PAD must be obtained from a vascular laboratory.

Exclusion Criteria. Exclusion criteria and justification for each criterion follow.

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, inability to walk without a walker, wheelchair confinement, foot ulcer, non-English speaking, significant visual impairment that interferes with walking activity, hearing impairment that interferes with full study participation, unable to return to the medical center or fitness center at the expected visit frequency, or unwilling to use technology required for the intervention.	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, abnormal baseline 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 nine months.**	4. Surgery may influence change in functional performance, independent of study interventions.
5. Major medical illness including lung disease requiring oxygen, Parkinson's Disease that impairs walking ability,	5. These conditions may interfere with the ability to fully participate and complete the study.

or cancer requiring treatment in the prior two years. (Note: Potential participants may still qualify if they were diagnosed with non-melanoma skin cancer in the past two years or if they have had treatment for an early stage cancer in the past two years and the prognosis is excellent. Patients who only use oxygen at night may still qualify.) **	
6. Heart attack, stroke, or coronary artery bypass surgery in the last 3 months.**	6. Recovery from these conditions may improve study outcomes independently of study interventions.
7. Mini-mental status examination score < 23 (43), dementia, or psychiatric illness.	7. May interfere with ability to fully engage in the study.
8. Currently walking regularly for exercise at a level comparable to the amount of exercise prescribed in the intervention.**	8. The intervention may not further improve functioning.
9. Currently enrolled in another clinical trial, exercise trial, or in cardiac rehabilitation. Currently enrolled in a clinical trial or current participation in cardiac rehabilitation or a 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 s at least six months has passed since the participant received their final treatment in the stem cell or gene therapy study.	9. These interventions may alter outcome measures, independently of other study interventions.
10. Deemed a poor candidate for the study or poorly suited for the intervention (at PI discretion).	10. May not be well suited for the program

*Consistent with current practice guidelines, potential participants will be asked to complete a baseline exercise stress test. Participants who have had a recent cardiac stress test separate from the HONOR study showing no evidence of ischemia may be eligible to participate without undergoing the HONOR baseline stress test. Specifically, participants with a normal cardiac stress test within the past six months who have no chest discomfort on exertion may decline to undergo a cardiac stress test as part of the HONOR Study and still be eligible to participate. Participants with an abnormal baseline stress test may be eligible if they have had a recent cardiac stress test with imaging or an angiogram showing no evidence of ischemia. They may also be eligible if their recent cardiac stress test with imaging or angiogram shows mild to moderate coronary artery disease so long as the following are all true: a) their physician states that it is safe for them to exercise in the HONOR study; b) the HONOR Study's medical safety officer states that it is safe for them to exercise in the HONOR study; c) ischemic leg symptoms are the primary reason for their walking limitations.

** These participants may be eligible at a later date. For example, people currently exercising too much may become eligible at a later date if they stop regular exercise. =

Participant Subgroups. We will we acknowledge that these analyses are post-hoc, and we will check for baseline imbalances in the two study groups and we will adjust for any imbalances. Next, we will stratify participants according to the following variables and determine whether the intervention is more effective in groups defined by these variables: socioeconomic status (education level and zip code are very reasonable ways to measure), age > 65 vs. < 65, presence of exertional leg pain at baseline, prior revascularization vs. no prior revascularization, African-American vs. not African-American, sex (male vs. female), baseline six-minute walk performance, and baseline ABI < 0.50 vs. 0.50 to < 0.90.

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

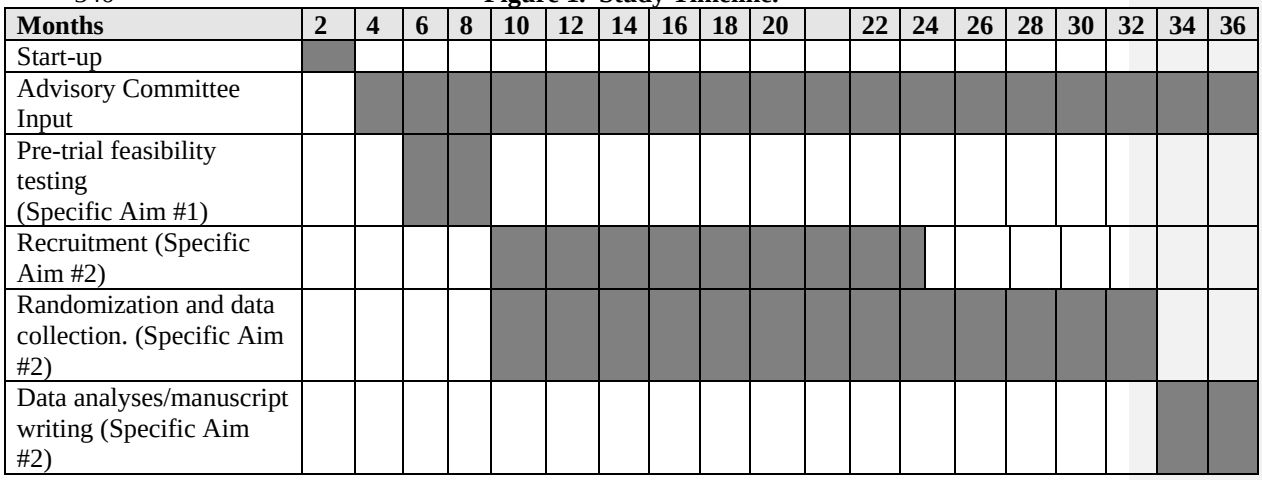
To accommodate the recruitment rate for this study, we will use additional study sites at New York University (NYU) Langone Medical Center and University of Minnesota (UM) Medical Center. Dr. Jeffrey Berger will serve as the site investigator for the HONOR study at NYU. The NYU HONOR team will randomize approximately 50 of the 200 participants into the study. Participants will be consented and assessed and complete on-site intervention at NYU medical centers. Dr. Diane Treat-Jacobson will serve as the site investigator for the HONOR study at UM. The UM HONOR team will randomize approximately 20 of the 200 participants into the study. Participants will be consented and assessed and complete on-site intervention at UM medical centers. Participants at NYU and UM will interact with Northwestern staff for their monthly phone and regular coaching calls.

7.0 Study Timelines

Overview of the timeline for this proposed study. Figure 1 shows the study timeline. Substantial input has already been obtained from PAD patients, healthcare providers, and other stakeholders. This has greatly improved the efficiency of our proposal and enabled us to begin with a patient-centered home-based exercise intervention that is largely complete. Between months 1-8 we will complete pre-trial feasibility testing of our intervention. Between months 9-32 we will conduct a definitive randomized controlled

trial of 200 PAD participants, to determine whether our home-based exercise intervention significantly improves patient-centered outcomes, compared to usual care. Our timeline is shown in Figure 1.

Figure 1. Study Timeline.



As shown in Figure 1, study manuals will be written between months 0-2, based on the home-based exercise intervention we have developed to date with PAD patient, healthcare provider, and other stakeholder input. These manuals will be reviewed by our Advisory Committee. An on-site meeting of our Advisory Committee will take place between months 3-4, during which our Advisory Committee will provide feedback to study investigators. The intervention will be modified based on the Advisory Committee's input. Final pre-trial feasibility testing of our intervention will take place between months 5-8 (Specific Aim #1). Results of our pre-trial feasibility testing will be shared with our Advisory Committee in month 8. Their feedback will be used to finalize our intervention. The randomized controlled trial, to definitively test our patient-centered home-based exercise intervention, will take place between months 9-32. Data analyses and manuscript writing will take place between months 33-36.

8.0 Study Endpoints

8.1 Primary and secondary study endpoints.

All primary and secondary outcomes (study endpoints) will be obtained at baseline, 4.5 month follow-up, and nine-month follow-up. Each outcome is described below.

Table 4. Study Outcomes and timing of measurement

Outcome measure	Baseline	4.5 month follow-up	Nine-month follow-up
Six-minute walk (primary outcome)	**X**	**X**	**X**
Walking Impairment Questionnaire distance and speed and stair climbing scores	**X**	**X**	**X**
Mobility Questionnaire (PROMIS)	**X**	**X**	**X**

Global Health Questionnaire (PROMIS)*	**X**	**X**	**X**
Pain Questionnaire (PROMIS)	**X**	**X**	**X**
Social role questionnaire (PROMIS)	**X**	**X**	**X**
Short-Form 36 (SF-36) physical functioning score	**X**	**X**	**X**
Actigraph	**X**	**X**	**X**

*Questionnaires with an asterix will be completed on a computer. All other questionnaires will be paper forms.

Primary Outcome: Change in six-minute walk distance at nine-month follow-up. The six-minute walk is an objective and well-validated measure of walking endurance that is well accepted in the scientific community (3-6,9,15,44-46). Change in the six-minute walk has been linked to clinically meaningful outcomes, including mobility loss, mortality, and meaningful declines in quality of life (47,48). Therefore, the six-minute walk, an objective measure, is our primary outcome. We have substantial experience measuring the six minute walk (2-6,9,15). 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 (49-51). 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 (44). For all of these reasons, the six-minute walk test will be our primary outcome measure.

Walking Impairment Questionnaire (WIQ). Change in WIQ distance and speed and stair-climbing scores between baseline and nine-month follow-up are secondary outcomes. The WIQ is a well validated questionnaire that measures patient-reported walking limitations in distance and speed (52-54). The WIQ scores correlate with PAD severity and improve in response to therapeutic interventions in PAD patients, such as supervised exercise (9,15,55). PAD patients rank their degree of difficulty walking increasingly greater distances and increasingly faster speeds (52). The patient rating for each question is multiplied by a factor corresponding to the magnitude of the distance and speed for each question. This score is divided by the maximum possible score to obtain a percent score, ranging from zero to 100, where zero represents the inability to walk the shortest distance and slowest speed, respectively, and 100 indicates no difficulty walking the greatest distance or fastest speed, respectively. Separate scores are calculated for walking distance and speed.

Patient-Reported Outcomes Measurement Information System (PROMIS) Questionnaires (www.nihpromis.org).

Validity of PROMIS measures. PROMIS instruments use modern measurement theory to assess patient-reported health status for physical, mental, and social well-being to reliably and validly measure patient-reported outcomes (PROs) for clinical research and practice (61-62). PROMIS has constructed item banks (a collection of questions that can be administered in short forms or adaptively through computerized adaptive testing). Short forms consist of 4-10 items; computerized adaptive testing (CAT) consist of 3-7

items. Administration by CAT yields more precise estimates of each construct, with fewer items, compared to a short form. The CAT selects the most appropriate items for each person, based on her/his ability. CAT also produces better measurement at the extremes (very high or very low) of the score range. Numerous studies have demonstrated high reliability and validity for the PROMIS instruments. Specifically, reliability is 0.90 or greater across most of the score distribution (58,60,61). Patterns of correlations with "legacy" (widely-used) instruments support construct validity. Specifically, correlations between PROMIS Physical Function (which includes Mobility) and the Health Assessment Questionnaire and SF-36 were -0.80 and -0.88, respectively; correlations between PROMIS Pain Interference and the Brief Pain Inventory interference subscale were 0.85 to 0.90 (62,65); correlations between PROMIS Ability to Participate in Social Roles and Activities and the FACT-GP Functional Well-being subscale was 0.66 (60). Several longitudinal validation studies were recently completed with PROMIS and demonstrated responsiveness to change (Hahn, personal communication).

Short-Form 36 (SF-36) physical functioning score. The SF-36 physical functioning score is a well-validated quality of life measure frequently used to assess changes in response to therapeutic interventions in patients with PAD.

Actigraph. The Actigraph will be used to measure physical activity at baseline and follow-up. Participants will be asked to wear the Actigraph for up to 20 consecutive days. At baseline and 4.5 month follow-up we will use the first seven days of high quality physical activity in analyses. At the final follow-up visit, participants will be asked to wear the Actigraph for up to 20 days in order to obtain a total of 14 days of activity data. This will allow us to collect seven days of physical activity data before the intervention is completed and seven days of physical activity data after the intervention is completed. These data will be obtained in both the intervention and usual care groups.

Additional Measures. A four-meter walk test will be administered at usual and fastest pace at the baseline and follow-up visits. Participants will be asked to perform the usual paced four-meter walk at usual pace and the "fast paced" four meter walk at their fastest pace. Each of these short walks will be performed twice. Blood will also be drawn at both visits to be stored and used for further research, for analysis of genetic factors and blood factors which may be associated with an increased risk of heart disease and stroke or with other important outcomes related to exercise. Participants will be asked to complete a series of standing and balance exercises, including chair stands.

8.2 Primary or secondary safety endpoints.

None.

9.0 Procedures Involved

9.1 Study design.

In our preliminary study, the Fitbit activity monitor and a telephone coach successfully helped patients with PAD adhere to a home-based exercise program. Based on information we obtained from PAD patients and healthcare providers, we designed and successfully completed a four-week pilot study of home-based walking exercise in patients with PAD. In this preliminary study, PAD participants were given a Fitbit activity monitor to help them monitor their walking exercise and worked with a remote coach, who telephoned the PAD participants once weekly, using behavioral techniques to help the PAD participants adhere to a home-based walking exercise program. The Fitbit activity monitor is a 3x axial accelerometer that is worn discreetly on clothing and records activity every two minutes. We selected the Fitbit because PAD patients previously indicated to us that an activity monitor motivates them to walk for exercise and because recent literature shows that activity monitors can successfully help patients without PAD achieve behavioral change (33,34). The Fitbit, shown in Figure 2a, is easy to use and uses Bluetooth technology to automatically upload physical activity onto a home computer when the participant walks within 10 feet of their computer. Uploaded data are displayed graphically and are visible to the participant and the remote telephone coach, allowing the participant and the coach to continuously monitor progress throughout the study.

Figure 2a. Fitbit shown next to quarter from PAD participant

Figure 2b. Uploaded Fitbit data

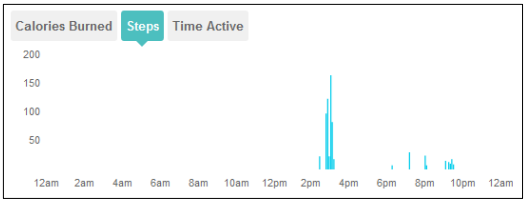


Figure 2 Legend. Figure 2a shows the Fitbit adjacent to a quarter. Figure 2b shows uploaded data from a PAD participant in our pilot study. As shown in Figure 2b, the y axis shows number of steps and the x-axis shows time. As shown in Figure 2b, this PAD participant was extremely inactive when he was not exercising.

We enrolled fifteen patients with PAD who were not exercising in this preliminary study. At baseline, all participants met at our exercise facility with the study telephone coach. The coach instructed participants on use of the Fitbit activity monitor and showed them how to upload Fitbit data on a computer. All participants successfully learned to link their Fitbit to a computer during their one on-site visit to the medical center. Please note that in our proposed study, those without a home computer will receive a computer tablet for the duration of the study, with which they can upload their Fitbit data. During the first week of the preliminary study, participants were instructed by the coach to walk for exercise at least five days per week for at least 15 minutes per session. Participants were instructed to increase their walking activity per session during each week of the four-week intervention until they achieved 40-60 minutes of walking per session. Participants were asked to monitor their activity using the Fitbit. Participants were contacted by telephone each week by the coach, who remotely reviewed their Fitbit data and discussed

their exercise activity. Using the Fitbit monitor combined with this weekly telephone coaching, sedentary PAD participants in our pilot study increased their exercise from 154.6 minutes per week in week one to 185.4 minutes per week in week four. These pilot study results demonstrate that the Fitbit activity monitor combined with a remote telephone coach helped PAD patients substantially increase their walking exercise over a relatively short time period.

We obtained feedback from the 15 PAD patients who participated in our preliminary home-based exercise study. A summary of their feedback is shown in Table 5. PAD participants were uniformly enthusiastic about the Fitbit activity monitor as a motivating device.

Table 5. Feedback from PAD patients in our pilot study of home-based walking exercise.

Representative feedback from PAD patients regarding the pilot home-exercise study.
• "I loved monitoring with the Fitbit. It was easy to use. I could track my progress." • "The Fitbit made me realize how sedentary I am. Even walking to the bathroom in my apartment made a big "blip" on my Fitbit. So the Fitbit motivated me to walk more." • "If I saw that I was close to a threshold value, I walked further in order to break the threshold value." • "Four weeks was too short for using the Fitbit. I did not want to return it." • "The coach helped me stay on track."

Based on these results, and feedback from healthcare providers and PAD patients (see section 2.2 and Tables 1-2 above), our proposed home-based exercise intervention will use the Fitbit monitor and a telephone coach to encourage PAD patients to adhere to a home-based walking exercise intervention.

Pre-trial Feasibility Testing Stage. During the pre-trial feasibility testing stage we will ask participants to take part in meetings or studies to fine-tune the home-based walking exercise intervention.

Home Exercise Feasibility Study. Up to 12 participants with PAD will participate in a feasibility study that will last for up to five weeks. This feasibility study will include an initial visit at the walking exercise facility at Northwestern Memorial Hospital's Cardiac Rehab Center or at the Northwestern Memorial Hospital. At this visit, participants in the feasibility study will learn how to use a Fitbit activity monitor to self-monitor their walking exercise activity. They will be helped to set goals for walking exercise frequency and duration for each week of the home exercise study. Fitbit activity data will be uploaded onto the participant's home computer. Study investigators will help the participants adapt their home computer to receive the Fitbit data, which can be viewed online by study participants and by the study coach. If a participant does not have a home computer, they will be provided with an iPad to allow them to upload their Fitbit data. The iPad will be loaned for the duration of the feasibility study only. After the

initial visit, participants will be telephoned each week by the study coach who will review their walking activity progress and provide feedback. Participants may be asked to return to the exercise study for additional instruction during the feasibility study. If necessary to help get their device set up to receive Fitbit data, the coach may travel to the participant's home to help them with their home computer. Participants will be asked to track their walking exercise goals and their walking exercise activity both on paper and on the study website during the feasibility study. The purpose of this pilot testing is to ensure that the Fitbit records the exercise activity recorded by participants on paper and to evaluate the participants' perceptions of using the website to record their walking exercise activity.

Pilot testing of group telephone calls. During the home exercise feasibility study, participants will be asked to participate in a group telephone conference call with other participants in the home exercise feasibility study. The study coach will also participate in these group telephone calls. We may also ask one of our PAD advisors to help lead the group telephone calls. These telephone calls will take place once per week during the feasibility pilot study. Topics discussed will include techniques to help the participants adhere to their home-based walking exercise, including goal setting, self-monitoring, managing ischemic leg pain during activity, and finding a location for home-based exercise. PAD participants on the telephone call will be asked to share their experiences participating in the home exercise feasibility study. These group telephone calls will last approximately one hour.

Pilot testing of website. During the home exercise feasibility study, participants will be asked to use the study's website. One of the main purposes of this website is to allow PAD participants in the feasibility study to communicate with one another. The website will provide an opportunity for PAD participants to post comments about their experience in the home exercise feasibility study including challenges and successes that they encounter. Study staff members will view the material from study participants and edit as needed before posting to ensure that only appropriate material appears on the website. The study website will also include individual participant exercise and Fitbit data, but this information will only be visible to the individual participants.

Focus Groups. The purpose of the home exercise feasibility study is to gather information from participants about what helped best motivate them to adhere to home-based walking exercise. Therefore, at the conclusion of the home exercise feasibility study, participants will be asked to participate in up to two focus groups to discuss their experiences recording their exercise data, viewing the Fitbit information, participating in the group telephone calls, and using the website. We will hold as many focus groups as needed to allow all of the participants to attend at least one session. Detailed notes will be taken and used to modify our protocol as needed to ensure the intervention is as efficacious as possible.

Overview of our proposed home-based walking exercise intervention. Our home-based exercise intervention focuses on walking exercise and consists of two phases. Phase I (weeks 1-4) consists of four on-site visits to an exercise facility over an

approximately four week period, where participants will meet the telephone coach, learn to use the Fitbit activity monitor, learn behavioral skills necessary for long-term adherence to home-based exercise, and get started on their exercise program. Phase II (weeks 5-36) is entirely home-based and includes a) use of the Fitbit for self-monitoring; and b) regularly scheduled telephone calls from the study telephone coach to monitor and support participants' home exercise activity. Participants in the intervention group will be contacted by telephone once per month to inquire about serious adverse events, such as hospitalizations for example.

Randomization. We will develop a specific SAS computer program for randomization. Participants will be randomized to one of two parallel arms: home-based exercise intervention vs. usual care. Only participants who complete all baseline measures and meet eligibility criteria will be randomized. Block randomization will be implemented, using randomly selected block sizes of four, six, or eight. Only subjects willing to be assigned to either condition will be randomized.

Phase I of the intervention (weeks 1-4 of our intervention). Based on our prior investigations combined with PAD patient and healthcare provider feedback, our home-based exercise intervention begins with four on-site visits to an exercise facility. During these on-site visits, the coach will teach PAD patients to use the Fitbit to self-monitor their exercise activity. The coach will help PAD patients learn behavioral skills including goal-setting, self-monitoring, and managing exertional leg pain during walking exercise. PAD patients will establish a relationship with the coach, who will begin contacting them weekly by telephone during Phase I (in addition to the on-site visits) and who will remain in contact with them via regularly scheduled telephone calls during Phase II. PAD participants will be scheduled in groups of about four participants for the on-site sessions in Phase I. This provides PAD patients an opportunity to meet and bond with other PAD patients.

Phase II of the intervention (weeks 5 to 36). After Phase I, participants will transition to Phase II of the intervention. Phase II does not involve on-site visits to the medical center. PAD participants will continue using the Fitbit to track their home-based exercise, and they will communicate by telephone with the coach. Between weeks 5-9, the coach will call PAD participants once per week. Between weeks 10-17, the study coach will call PAD participants every other week. Between weeks 18-36, the study coach will call PAD participants once per month. However, PAD participants who are not adhering to regular walking exercise activity will be telephoned by the coach more frequently as needed, so that the coach can offer additional help and ensure adherence to the home-based exercise program. Thus, remote coaching via regular telephone calls will be individualized. PAD patients will continue to use the Fitbit throughout Phase II. Output from the Fitbit monitor will be visible to both the coach and the patient throughout Phase II.

Our home-based exercise intervention focuses on walking. Our exercise intervention focuses on walking exercise for several reasons. First, our focus groups of PAD patients informed us that walking exercise is preferred by most people with PAD. PAD patients

consistently told us that walking exercise is easily accessible because they can walk outdoors, in the hall corridors of their apartment buildings, or even around the perimeter of their home basement. Second, PAD patients told us that walking exercise allows them to specifically focus on improving their walking. PAD patients believe that walking exercise will specifically help them overcome their walking difficulty. Third, supervised walking exercise is known to improve walking performance in PAD patients and is the only form of exercise currently recommended by practice guidelines for patients with PAD (7-10,13,14). Table 6 summarizes feedback from PAD patients and healthcare providers that justifies our plan to have our exercise intervention focused on walking.

Table 6. Feedback from PAD patients and healthcare providers about walking exercise.

Summary of key messages about walking exercise from PAD patients
• Walking exercise allows patients with PAD to practice and improve upon their walking difficulties • Walking exercise is accessible: patients can walk outside their home and start walking. • PAD patients know that walking is good for them.
Summary of key messages about walking exercise from healthcare providers.
• Healthcare providers are aware of practice guidelines recommending walking exercise for PAD patients. • Healthcare providers, based on available evidence, believe that walking exercise is the best type of exercise for PAD patients, but want help getting PAD patients to exercise.

Using the Fitbit to motivate PAD patients to adhere to home-based exercise. Our preliminary data collected for this proposal shows that PAD patients find the Fitbit highly motivating. A description of the Fitbit is provided in section 9.1 (see Figure 2). The Bluetooth mechanism automatically uploads Fitbit data on a home computer or tablet when the participant walks within 10 feet of the device. Each individual's activity data are visible on-line to both the PAD participant and the coach. The study coach will view each participant's exercise data once weekly. During the regularly scheduled telephone calls with study participants, the coach will use the uploaded Fitbit data to provide feedback to each participant. If participants do not have access to a Fitbit compatible computer or tablet or related equipment (such as a charger for their device) we will provide them with the necessary equipment. All borrowed devices will be returned at the end of the study.

Telephone calls from the coach. Each contact of the coach with each participant in the intervention will have a structured format. Adherence to this format (treatment fidelity) will be monitored by the coach using a check-list, completed at the end of each formal participant contact. In addition, for quality control purposes, all telephone coaching session will be audiotaped and a subset will be reviewed by an independent rater. The components of each session, recorded on the check-list, are as follows: a) *Checking in:* Review exercise data uploaded on the Fitbit web site. This information will include the total number of exercise sessions and the time spent engaged in exercise per session.

This will be reviewed in the context of the walking exercise goals established during the prior contact with the coach; *b)* D*iscussion of challenges encountered with exercise adherence and strategies for overcoming them;* The coach will discuss with the participant any barriers encountered to walking exercise activity and strategies to overcome them. Potential barriers we may encounter, based on our experience, include leg pain and discomfort during exercise, adverse weather affecting the ability to walk outdoors, and inter-current illness that interferes with exercise behavior. c*) Discuss MAPs (My Action Plan) for the coming week*; Participants will be asked to discuss with the coach their goals for the coming week(s). These goals will be written down by the participant and by the coach and will serve as a reference for the next telephone contact; d) *Wrap-up/questions*- mindful reflection and wrap-up/conclusion with focus on successes and challenges. We successfully used this method with PAD patients during in-person visits in our completed GOALS trial (15).

Coach training and certification. Prior to beginning the intervention, the coach will receive training by co-investigators and behavioral experts, Drs. Rejeski and Spring. Our study coach, Mr. Al Rego, is an exercise physiologist who has served as an interventionist for our successful GOALS Study and for our ongoing LIFE Study. Dr. Rejeski will travel to Northwestern for 1.5 days to lead the training sessions along with Dr. Spring. The study coach will read the study intervention manuals prior to training. Training will include an overview of the conceptual background for the intervention. Dr. McDermott will present information about PAD-related ischemic leg pain, and optimal exercise programs for PAD. The coach will role-play telephone counseling sessions, receiving immediate feedback. Management of "difficult" participants and challenging scenarios will be reviewed. After completing training, the interventionist will perform telephone counseling calls with five mock participants. A certification checklist will be used to ensure that the interventionist adheres to the study protocol (see Table 7).

Monitoring the coach's fidelity to the study intervention. The coach will use a checklist (shown in Table 7) to guide each telephone coaching call. All telephone contacts with participants will be audiotaped. A ten percent subsample will be reviewed each quarter by study investigators (Drs. McDermott/Spring/Rejeski) to ensure fidelity to the intervention. Feedback will be provided to the coach. When the coach deviates from the protocol, the coach will be re-trained and certified.

Table 7. Study Checklist Components for Monitoring Fidelity to the Study Intervention.

Component	Checklist
Checking in- adherence to transmittal of exercise frequency and duration.	**X**
Adherence to transmitting Fitbit data.	**X**
Discuss use of the website.	
Discuss group telephone calls (if applicable)	
Discuss challenges encountered with solutions to overcome them.	**X**
Discussion of My Action Plan (MAP)	**X**
Wrap-up, conclusion.	**X**

Group telephone calls with other PAD patients. Some PAD patients have told us that interactions with other PAD patients are supportive and motivating. Therefore, we will hold two telephone conference calls each month, led by the study coach, during which PAD patients will have opportunity to interact with other PAD participants via the group telephone call. The two conference calls each month will cover the same general topic. However, they will be held on different days to maximize the number of participants who are available to participate. Although we originally planned to hold these calls weekly, we reduced the frequency to monthly because patients with PAD were generally only moderately enthusiastic about these calls during our feasibility testing. All participants randomized to the intervention will be provided with a dial-in number that they can dial into if they choose. The coach will present a topic of interest related to PAD and/or exercise during each group telephone calls. Topics will include walking in extreme weather conditions, novel patient-centered methods to manage walking related leg pain, goal-setting, self-monitoring, and other topics that are likely to help PAD participants adhere to their home-based walking exercise program. PAD participants will have opportunity to share successes and challenges regarding exercise.

Focus Groups. At the conclusion of the home exercise study, participants may be asked to participate in up to three focus groups to discuss their experiences in the exercise intervention. They will be asked to complete an end-of-study questionnaire to obtain feedback on their experiences in the exercise intervention. Detailed notes will be taken and the information will be used to design subsequent research studies.

Intervention summary. Table 8 provides a summary of the components of our intervention.

Table 8. Summary of our home-based walking exercise intervention.

Intervention components	Phase I (on-site visits, weeks 1-4)	Phase II (entirely home-based, weeks 5-36).
Coaching	Participants will meet and bond with the coach during on-site meetings.	Participants will communicate with the coach remotely via telephone.
Fitbit self-monitoring	Participants will learn to use the Fitbit to track their exercise. They will learn to upload the data for on-line viewing.	Participants will use the Fitbit for self-monitoring of their exercise activity.
Goal setting	Participants will be taught to record walking exercise goals, reviewing them in person with the coach each week.	Participants will continue to set goals and these will be communicated to the coach by telephone and on the Fitbit web site.
Group support from other PAD patients	PAD participants will have opportunity to meet and bond with other PAD participants.	We will hold optional bi-weekly group telephone calls for PAD patients, led by the coach.

Each intervention component in Table 8 was selected because of feedback we received from PAD patients. *a) Justification for coaching (see Section 2.2).* PAD participants have indicated that they need a coach to be accountable to. They need to know that someone is checking on them (see Table 1); *b) Justification for Fitbit self-monitoring.* PAD patients were overwhelmingly enthusiastic about the Fitbit as a motivational tool to promote home-based exercise; *c) Goal-setting.* It is well-

documented that goal setting helps people achieve behavior change (35-37). In addition, PAD patients tell us that they needed accountability to adhere to regular exercise. Goal setting combined with coaching will help ensure that patients achieve this accountability; *d) group support*. Some PAD patients tell us that they find interactions and support from other PAD patients motivating. Therefore, PAD patients will have opportunity to meet and bond with other PAD patients during the on-site visits in Phase I. PAD participants will have opportunity to network with other PAD patients in the group telephone session in Phase II.

Intervention Comparison: Usual care group. PAD participants randomized to usual care will not receive any study interventions. Rather, they will receive usual care from their own physicians. The usual care group represents typical practice currently available to patients with PAD. To minimize loss to follow-up and to allow meaningful comparisons between the intervention and usual care group in this randomized trial, participants in the usual care group will be contacted by telephone once per month to inquire about serious adverse events, such as hospitalizations for example. Participants randomized to usual care will return for follow-up testing at nine-month follow-up. An incentive of $25.00 has been budgeted to help maximize follow-up rates for all participants, including those randomized to usual care and the intervention.

9.2 Describe all research procedures.

Some or all study measures may need to be repeated at baseline or follow-up testing for data quality purposes for example if too much time has passed since baseline measures were completed or if results were not valid.

Ankle Brachial Index (ABI). We have extensive experience measuring the ABI (4-9,50-52). After the participant rests supine for five minutes, the right brachial, dorsalis pedis (DP), posterior tibial (PT) and left DP, PT, and brachial artery pressures are measured using a hand-held Doppler probe. Pressures are measured twice. The ABI is calculated for each leg by dividing the average of the DP and PT pressures by the average brachial pressure.

Questionnaire Administration. Participants will be administered study questionnaires by a trained and certified health interviewer.

Height and Weight. Participants will have their height and weight measured by a trained study coordinator.

Six-minute walk. Participants will be asked to walk back and forth along a 100-foot hallway for six minutes. They will be instructed that the purpose of the six-minute walk test is to measure how long a distance they can walk in six-minutes. A script will be read to describe the study procedure. Participants will be asked whether they feel the test is safe to try and whether they have any questions. The six-minute walk is a well validated measure of walking endurance that predicts mobility loss and mortality in PAD populations (5,8,63,64) and improves in response to therapeutic interventions in older people with PAD (50,52,63-65). The intra-class correlation coefficient for the test-retest

reliability of the six-minute walk test among 156 PAD participants in our SILC exercise trial was 0.90 ($p<0.001$) when two six-minute walks were completed 1-2 weeks apart (50,62).

Four-Meter Walk. Participants are timed walking a four-meter distance in a corridor at their usual and fastest pace. Because of a learning effect, the four-meter walk is performed twice, and the fastest walk in each set is used in analyses. Participants are read a script by the study coordinator, describing the test. The test is demonstrated for the participant by the study coordinator- both at usual and at fastest pace.

Treadmill Stress Test. The Gardner graded treadmill exercise test is the standard, accepted treadmill protocol for assessing the presence of coronary ischemia at baseline, as recommended by clinical practice guidelines for patients with PAD. In the Gardner exercise protocol, speed is maintained at 2.0 miles per hour (mph) and treadmill grade increases by 2.0% every two minutes (82-84). 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 two minutes.

Feasibility Study of Pneumatic Compression Devices. We will ask up to 20 participants to participate in a pilot study of pneumatic compression device treatment for up to twelve weeks. Participants will be asked to wear pneumatic compression devices, which inflate briefly several times per minute, for two to four hours daily at home (http://acimedical.com/artassist). Up to half of participants may be assigned to use a low level of compression (i.e. approximately 20 – 30 mmHg) while remaining participants will use a higher level of compression (i.e. 120 mmHg). The lower systolic pressure intervention will serve as a 'sham' control. Participants may have the pneumatic compression devices mailed directly to their home by the company. Investigators or United Postal Service may come to pick up the device when the study is over to return them to the company. Participants will be asked to keep track of how many hours per day they are wearing the devices on a paper form provided to them by investigators. They will be asked to bring in their log each to study investigators at their follow up visits at Northwestern medical center. If participants forget to bring in their log to their visit, they will be provided with a stamped and addressed envelope to return the log by mail or be asked to bring it with them to their next visit. They will be asked to wear the pneumatic compression device for two hours each day. They will be provided with a log to record the number of minutes that they wore the pneumatic compression device each day. The study coach will speak to them about their adherence to the pneumatic compression device during weekly or bi-weekly telephone calls. Participants will also be telephoned each week by study investigators, who will inquire about their adherence to the pneumatic compression device therapy. Participants who are having difficulty with the device that cannot be resolved by telephone may be asked to return to the medical center for assistance or may be visited in their home by study coordinators. Participants will be asked by a study coach to engage in home-based walking exercise during the time period (up to 12 weeks) that they are wearing the pneumatic compression device. Walking exercise will be tailored to individual ability, but participants will be asked to walk up to

50 minutes for approximately five days per week. They will be asked to set walking exercise goals each week, record the number of minutes that they walk for exercise each week, and they will be telephoned weekly by the study coach to encourage and support their walking exercise. Only people who have completed an exercise stress test in the past year showing no evidence of ischemia will be eligible. However, people without an exercise stress test in the past year may still be allowed to participate if their physician indicates that it is safe for them to exercise. Potential participants with exertional chest pain that has recently increased will not be eligible for this phase of the study. We will measure the six-minute walk, physical activity level for up to 14 days, and the short physical performance battery. We may measure pain-free and maximal treadmill walking time using the Gardner or modified Gardner protocol before and after the pneumatic compression device therapy. These additional measures may be performed before and after the participant wears the pneumatic compression device and will require additional visits before and after the pneumatic compression device therapy.

9.3 Protection against risks.

The source records, including medical or educational records, that will be used to collect data about subjects. (Attach all surveys, scripts, and data collection forms.) **Adequacy of protection against risks and methods to minimize potential risks.** *Overview of protection against risks.* Prior to beginning data collection and study interventions, all study coordinators undergo training and are certified by Dr. McDermott using a detailed checklist for each data collection element. 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 measuring the ABI. 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. Dr. McDermott 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 prior to data collection. 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.

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.

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.

Data Safety Monitoring Board (DSMB). To ensure complete participation of PAD patients in all aspects of this study, our (DSMB) will include a PAD patient. The PAD patient member will be a voting member of the DSMB. Other DSMB members will be a statistician, an exercise expert, and a PAD expert.

- *Source records that will be used.*

We will use standardized questionnaires to collect data about each study participant. Please see attached data collection forms. We may use medical records to determine whether the patient was diagnosed with PAD prior to study enrollment.

9.4 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.

Data Management. Data from baseline and follow-up visits are collected using REDCap. Some data are collected on paper forms and then entered into REDCap. Only authorized study personnel will have access to the study data. All paper forms are stored in locked filing cabinets.

Data Safety Monitoring Board (DSMB). To ensure complete participation of PAD patients in all aspects of this study, our (DSMB) will include a PAD patient, who will participate in DSMB discussions and be a voting member of the DSMB. Other DSMB members will be a statistician, an exercise expert, and a PAD expert.

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 assigned group. We will use two sample two-tailed t-tests to compare changes in primary and secondary outcomes at 9-month follow-up between the intervention and usual care groups. When there is evidence that the normality assumption for the distribution of changes in the primary and secondary outcomes of interest is violated, we will either apply appropriate transformation before conducting t-tests or performing Wilcoxon rank-sum test for the comparisons. We will also check

for imbalance of baseline characteristics (i.e. age, sex, race, ABI, BMI, smoking status) between the two groups using t-test for continuous factors and chi-square test for discrete factors. If there is any indication of major imbalance in these factors, we will perform multivariate linear regression analysis with the change in each outcome as the response variable, adjusting for imbalanced baseline factors as potential confounders. Missing data may occur when some participants are lost to follow-up. First, we will make every effort to ensure that participants return for the 9-month follow-up. We will use proxies to help us locate participants we are unable to reach. We will mail appointment reminders when participants are not responsive to our telephone contacts. We will encourage participants who do not adhere to their assigned groups to return for 9-month follow-up. We will provide transportation and monetary incentives. Thus, we anticipate that the proportion of participants without outcome data at 9-month follow-up will be small. Second, we will record the reason for dropout for each participant. If dropout occurs completely at random, then the aforementioned analyses based on available data provide valid statistical inferences. When dropout is not completely at random, we will perform several sensitivity analyses. Specifically, we will employ the multiple imputation approach to account for missing data at 9-month follow-up under the assumption of missing at random (65). We will perform additional sensitivity analyses to guard against the possibility of missing not at random using pattern-mixture models and shared-parameter models (65).

Sensitivity Analyses to determine the impact of key assumptions. We will determine whether people who drop out of the intervention have poorer outcomes than those who do not drop out. Second, we will determine whether people who log on more frequently to the Fitbit website have better outcomes than those who log on less frequently. Third, we will determine whether people who view their data on the HONOR website more frequently have better outcomes than those who view their data less frequently. Fourth, we will determine whether people who wear their Fitbit more regularly have better outcomes than those who wear their Fitbit less regularly. Finally, we will determine whether people who participate in group calls/website interactions have better outcome than those who do not participate in group calls/website interactions.

In addition, we will perform a sensitivity analysis to determine whether results differ when participants with a history of lower extremity revascularization prior to enrollment and a normal baseline ABI are excluded. We will perform a sensitivity analysis to determine whether exclusion of participants who stopped the treadmill test for a primary reason other than ischemic leg symptoms affects the results.

11.2 Power analysis.

Power Calculations. For the randomized controlled trial in our Specific Aim 2, we will determine whether our home-based exercise intervention significantly improves study outcomes at nine month follow-up, compared to usual care. Study outcomes are listed in Table 4 and include the six-minute walk, WIQ distance and

speed scores, and PROMIS measures. Our primary outcome is change in six-minute walk. Remaining outcomes are secondary. Based on our GOALS and SILC trials in PAD participants (9,15), we anticipate a 10% drop-out rate at 9-month follow-up. A total of 200 recruited participants will provide 80% power to detect a minimum difference of 0.42 standard deviations (SD) between our home exercise intervention and usual care in changes of six-minute walk performance and each of the secondary outcomes, using a two-sided two-sample t-test with a significance level of 0.05 and taking into account the anticipated 10% drop-out rate at 9-month follow-up. In our GOALS trial, the observed differences in changes of six-minute walk performance, WIQ distance score, and WIQ speed score at 9-month follow-up between the intervention and control groups were 0.78 SD, 0.46 SD, and 0.44 SD, respectively (15). Thus we should have adequate power for these outcomes. For the PROMIS outcomes, prior studies have shown that physical function can be improved by 0.72 SD by a 3-month intervention for patients with chronic heart failure (63), pain is reduced by 0.54 SD by a 3-month intervention for patients with back pain (64), and that social functioning differs by 0.94 SD between people with and without comorbidities (60). The global health questionnaire measure is an overall measure of physical and mental health. Thus we should have adequate power to detect similar effect sizes for the PROMIS outcomes.

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 Quality Control Measures

Quality Control and blinding during outcome measurement. Health interviewers who collect baseline and follow-up data are trained by senior staff members and certified by Dr. McDermott in all aspects of data collection. Certification is required before health interviewers can begin collecting data. A checklist is used to certify health interviewers. When

deficiencies are identified, health interviewers undergo re-training and their certification attempt is repeated. Health interviewers are re-certified every six months. Health interviewers are distinct from those administering the intervention and will be unaware of participant's group assignment. Participants are advised not to inform health interviewers of their group assignment. If a health interviewer is notified of a participant's group, another health interviewer is paged or telephoned and continues the study visit.

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*

Potential Risks.

Risks associated with the exercise and the exercise program. Exercise may be associated with muscle fatigue or soreness. The exercise program may be associated with an increased risk of heart attack, arrhythmia, or death. In addition, patients may develop ischemic chest pains during exercise. Chest pain symptoms during exercise may result in additional cardiac work-up that may lead to medical procedures to improve coronary blood flow, such as coronary revascularization with angioplasty and stenting or even coronary artery bypass surgery. Abnormal baseline exercise stress tests may also lead to additional cardiac workup by the participant's physician that may result in coronary angiography or coronary revascularization.

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. The risk of falling is less than 1 in 1,000. 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 7,000.

Risks associated with ankle brachial index (ABI) measurement. The ABI 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 ABI test, participants may experience discomfort from the inflated blood pressure cuff. However, this discomfort resolves immediately when the cuff is released.

Risks associated with blood draws: The potential risks of drawing blood include a bruise at the site of vein puncture, inflammation of the vein, and infection. Participants may experience lightheadedness or dizziness or fainting after injections. Care will be taken to avoid these complications.

Risks associated with questionnaire administration. Participation includes a risk of loss of confidentiality regarding personal health information. However, all research staff has undergone formal human subjects training. They are trained to protect the privacy of research subject participants.

Risks associated with treadmill stress tests. The treadmill stress test can potentially precipitate coronary ischemia, potentially resulting in an arrhythmia or symptoms that require immediate treatment and/or hospitalization. The treadmill stress test is conducted in the coronary stress laboratory at Northwestern Memorial Hospital. Cardiologists are present in the stress laboratory. Exercise physiologists conducting the stress tests have been trained to treat any acute coronary ischemic events in response to the treadmill stress test.

Risks associated with pneumatic compression. The pneumatic compression device is commercially available and associated with few risks. Although the device is not painful and is worn while the participant is sitting comfortably, participants may find the compression device irritating, since it compresses the lower legs three times per minute. Participants will have the option of discontinuing the device if they find it irritating or uncomfortable.

15.0 Potential Benefits to Subjects

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

Potential benefits of the proposed research. Participants have the opportunity to benefit from study interventions, including an increase in the distance they can walk, improved quality of life, and a reduction in leg pain associated with walking. Our home-based exercise intervention using the Fitbit is provided without charge to study participants. Transportation to study visits is also provided. Our prior work demonstrates that a supervised treadmill exercise program significantly improves walking endurance and prevents mobility loss in people with PAD. However, supervised exercise is not paid for by medical insurance and regular travel to an exercise center for exercise is burdensome for people with PAD. An 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. Our proposed patient-centered, home-based intervention does not require regular travel to the exercise center and combines components of prior successful interventions with innovative technology allowing for remote monitoring and remote group support.

Importance of knowledge to be gained. Exercise has repeatedly been demonstrated to be beneficial for many groups of patients, including those with peripheral artery disease. We are taking steps, outlined above, to minimize risk for potential participants. Based on information we obtained from PAD patients and healthcare providers, we designed and successfully completed a four-week pilot study of home-based walking exercise in patients with PAD. The pilot study results demonstrated that the Fitbit activity monitor combined with a remote telephone coach helped PAD patients substantially increase their walking exercise over a relatively short time period. 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.

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.

The Bluetooth mechanism automatically uploads Fitbit data on a home computer or tablet when the participant walks within 10 feet of the device. Each individual's activity data are visible on-line to both the PAD participant and the coach. The study coach will view each participant's exercise data once weekly. During the regularly scheduled telephone calls with study participants, the coach will use the uploaded Fitbit data to provide feedback to each participant.

Treadmill Stress Test. Results of the baseline treadmill stress test will be mailed to the participant's designated physician.

19.0 Setting

The research will be conducted at Northwestern Memorial Hospital and at 680 N Lake Shore Drive. Participants may also be asked to come to Northwestern University at 750 N. Lake Shore Dr. or to L.A. Fitness at 355 E. Grand Ave. while participating in the study. Please see section 22.0 for more details.

20.0 Resources Available

20.1 Qualifications of staff.

Overview. Patients with PAD and other stakeholders have been involved in all aspects of developing this proposal. PAD patients are members of our investigative team (see section F1). Our Data Safety Monitoring Board includes a PAD patient member. Our Advisory Committee, which will provide study oversight, includes five patients with PAD and four healthcare providers for PAD patients from across the United States.

We engaged PAD patients, healthcare providers, and other stakeholders to develop this proposal. Our investigative team has more than fifteen years of experience working with PAD patients in clinical investigations, including exercise intervention studies, all of which required at least one visit per week to the medical center (9,15). This is the first time that we have actively engaged PAD patients or healthcare providers to develop an exercise intervention for PAD patients. This is the first time we have designed an exercise intervention that does not require ongoing medical center visits. In preparation for this proposed study, we conducted multiple focus groups of PAD patients and healthcare providers and completed a preliminary study of home-based exercise in PAD patients. **We used information from all of these sources to develop a patient-centered home-based exercise intervention**. Below we present results of the preliminary studies completed in preparation for this proposal. These preliminary results were used to design the exercise intervention proposed here, thereby greatly increasing the efficiency of this proposed study.

Our Advisory Committee consists of PAD patients and A Multi-disciplinary Team of Healthcare Providers for PAD Patients. Our advisory committee is already

assembled and includes both PAD patients and a multi-disciplinary team of representative healthcare providers for PAD patients. Members of our Advisory Committee have reviewed this grant application and provided feedback prior to submission. The healthcare providers were identified from multiple regions of the U.S. and represent vascular medicine, cardiology, vascular surgery, and vascular nursing disciplines (see Table 9).

Table 9. Members of our Advisory Committee

Name	Description
Advisory Committee members who are PAD patients	
A. Sommers	74-year-old female with PAD diagnosed about 10 years ago.
W. Vartan	81-year-old male retired pilot diagnosed with PAD about eight years ago. Loves travel, but avoids vacations due to PAD-related walking difficulty.
B. Sullivan	66-year-old female attorney diagnosed with PAD about three years ago.
J. Sullivan	73-year-old male diagnosed with PAD about five years ago. He does not exercise.
S. Quesada	75-year-old male diagnosed with PAD about 15 years ago. He does not exercise.
Advisory Committee members who are healthcare providers for patients with PAD	
Michael Conte, MD	Practicing vascular surgeon at the University of California at San Francisco. Chair of the Peripheral Vascular Disease Council for the American Heart Association.
Mark Creager, MD	Practicing cardiologist and vascular medicine specialist at Harvard Medical School. Member of American Heart Association's Board of Directors.
Heather Gornik, MD	Practicing cardiologist and vascular medicine specialist at Cleveland Clinic. Editor of Vascular Medicine. Member of the Society of Vascular Medicine Board of Directors.
Diane Treat-Jacobson, RN, PhD	Practicing Vascular Nurse Specialist at the University of Minnesota. Member of the Leadership committee for the Society of Vascular Nursing.

Our Data Safety Monitoring Board (DSMB) will include a PAD Patient Representative. To ensure complete participation of PAD patients in all aspects of this study, our (DSMB) will include a PAD patient. The PAD patient will be a voting member of the DSMB.Other DSMB members will be a statistician, an exercise expert, and a PAD expert.

Additional stakeholders who are committed to assisting us and improving care of patients with PAD. We have secured letters of support from four organizations who are major stakeholders in the care of PAD patients. These stakeholders have agreed to support our trial. These stakeholders are dedicated to improving the health of PAD patients and include: The Society of Vascular Surgery, the American Heart Association, the Society of Vascular Nursing, and the American College of Cardiology. If our intervention is successful, all of these stakeholders have agreed to assist us with disseminating our findings to healthcare practitioners for PAD patients.

How PAD patients and Stakeholders were identified for participation in this research study. We identified PAD patients involved in this project (i.e. the PAD

patient investigators and PAD patient Advisory Committee members) using recruitment methods that we use for our research studies, including newspaper and radio advertising. We also contacted PAD patients from lists of consecutive patients diagnosed with PAD from Chicago-area medical centers. In summary, the PAD patients involved as investigators and in our Advisory Committee come from the larger Chicago area and represent a diverse group of PAD patients, including some who have exercised successfully and some who do not exercise at all. We identified healthcare providers for our Advisory Committee by selecting leading, active clinicians who care for PAD patients from across the United States. The healthcare providers on our Advisory Committee represent different disciplines in the care of PAD patients (vascular medicine, vascular surgery, and vascular nursing). All have leadership positions in stakeholder organizations including the American Heart Association, the American College of Cardiology, and the Society of Vascular Surgery and the Society of Vascular Medicine. In summary, the healthcare providers on our Advisory Committee are uniquely positioned to contribute to the study and assist with dissemination of our findings.

PAD patients, healthcare providers, and other stakeholders have contributed to all aspects of this proposal and will remain integrally involved in all aspects of our proposed study throughout its duration. Table 10 summarizes how PAD patients and healthcare providers for PAD patients have contributed to this proposal and will continue to contribute to this study through its duration. In addition to the data shown in Table 10, we have obtained letters of support from stakeholder organizations, who have agreed to assist with dissemination of our findings, if our exercise intervention is successful.

Table 10. Contributions of PAD Patients, Healthcare Providers, and Stakeholders to this Proposal

	PAD Patients	Healthcare Providers for PAD Patients
Proposal Development	• PAD patient focus groups; • Pilot studies of PAD patients; • We solicited feedback from PAD patients about the pilot study; • PAD patients selected study outcomes.	• Healthcare provider focus groups. • Reviewed and provided feedback of our intervention.
During the funding period.	• PAD patients are study investigators. • PAD patients are members of our Advisory Committee. • A PAD patient will serve on our DSMB	• Healthcare providers are members of our Advisory Committee. • Healthcare providers will serve as members of our DSMB.
After the study is complete.	• PAD patients will assist with disseminating results to healthcare providers and patients.	• Healthcare providers will assist with disseminating results.

In summary, PAD patients, healthcare providers for PAD patients, and other stakeholders committed to the care of PAD patients will be involved in all aspects of this study.

21.0 Prior Approvals

21.1 Approvals that will be obtained prior to commencing the research.

The study is being funded by the Patient-Centered Outcomes Research Institute (PCORI).

22.0 Recruitment Methods

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

PAD participants will be identified from among individuals with PAD who have participated previously in research conducted by Dr. McDermott and/or who have expressed an interest in participating in future studies conducted by Dr. McDermott.

In addition, some PAD participants may be identified from among consecutive patients diagnosed with PAD in the non-invasive vascular laboratory of Northwestern Memorial Hospital (NMH). 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. If we do not hear back from the physician within three weeks, we will contact the patient. Up to five letters are mailed from Dr. McDermott on behalf of the patient's physician about the research study. 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 and individuals at high risk for peripheral arterial disease who are patients in our vascular surgery, cardiology, geriatrics, and general internal medicine practices at NMG. Co-investigator Dr. Mark Eskandari is a member of the vascular surgery practice at NMG. Co-investigator Dr. Lloyd-Jones is a member of

the cardiology division at NMG. Dr. McDermott is a member of the general internal medicine practice at NMG. 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. The notice to the physician will indicate that if the physician does not respond within three weeks, the potential participant will receive a recruitment letter.

Up to five 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 NMG 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 newspaper advertising, public transportation advertising, internet 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.

We will obtain a list of patients who may be in an eligible age range for the study and live in the Chicago area from a mass mailing company. Using this, we will send postcards to those individuals on the list. The postcards will instruct people to call a study number if they are interested.

Furthermore, we will use the Illinois Women's Health Registry as a recruitment source. We will provide inclusion and exclusion criteria to the registry, who will mail out letters to the women registered in the registry. If they express interest, we will receive the women's contact information.

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.

Participants who have participated in previous studies and indicated interest in future studies will be contacted for either stage of the study. Participants who we screen for ongoing studies who may have PAD but are ineligible for that study and interested participating in a study may be screened for either stage of this study.

We will also use the PCOR-NET for recruitment. PCOR-NET is a PCORI-funded network of institutions in the Chicago area. The purpose of the PCOR-NET is to assist investigators with recruitment for clinical trials. PCOR-NET has its own IRB (University

of Illinois at Chicago). We have obtained PCOR-NET CHAIRb (Chicago Area IRB) IRB approval for the HONOR study. PCOR-NET uses ICD-9 codes and the electronic health record to identify potential participants who have PAD. We will follow similar recruitment methods to those we use with the EDW at Northwestern at the PCOR-NET sites following the CHAIRb approved protocol.

22.2 Source of subjects.

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

22.3 Methods that will be used to identify potential subjects.

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

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

Participants will receive up to $25.00 for taking part in this research study. Participants will be paid in cash at the time of the final study visit (i.e at nine month follow-up).

Participants will be given assistance and/or reimbursement for expenses related to travel such as parking, bus/train fare, taxi fare, and mileage, if requested. A receipt will be required for taxi fare reimbursement. Participants will be provided up to $85 per visit for travel reimbursement. If they require the use of our taxi service, we will estimate the fare on www.taxifarefinder.com. A one-way fare estimate must be less than or equal to $42.50 (i.e. round trip of $85) in order for the study to provide round trip taxi service.

23.0 Local Number of Subjects

Recruitment. We will randomize 200 PAD participants over 18 months. Based on our prior clinical trials of PAD patients, we anticipate an 10% drop-out at 9-month follow-up (9,15). As in our prior clinical trials, we will identify potential PAD participants using Northwestern's Enterprise Data Warehouse and we will contact all patients with PAD cared for at Northwestern. We will also use radio and newspaper advertising and we will mail informational postcards to age-eligible men and women living in the Chicago area. We have substantial experience successfully using each method. Since 2004, we have randomized 620 PAD participants from the Chicago-area into NIH-funded clinical trials (9,15,38). We have the experience and expertise to successfully recruit the proposed 200 PAD participants for this proposed trial.

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. The phlebotomy will also take place in an examination room with the door closed to ensure optimal privacy.

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

NA

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 visit at Northwestern. 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 (i.e. Dr. Lloyd-Jones, Dr. Spring, Dr. Liu) 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. Specifically, coordinators will record that they reviewed the consent with the participant and whether the participant had any questions regarding the consent. Coordinators will also record that they gave a copy of the consent to the participant. Consent documentation will be recorded in REDCap.

30.0 Drugs or Devices

NA

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