Using Color Doppler Ultrasound to Promote Exercise in Adults With Peripheral Artery Disease

Sarah Fittro
Yale Physician Associate Program, sarah.fittro@yale.edu

Follow this and additional works at: https://elischolar.library.yale.edu/ysmpa_theses

Recommended Citation
Fittro, Sarah, "Using Color Doppler Ultrasound to Promote Exercise in Adults With Peripheral Artery Disease" (2020). Yale School of Medicine Physician Associate Program Theses. 12.
https://elischolar.library.yale.edu/ysmpa_theses/12

This Open Access Thesis is brought to you for free and open access by the School of Medicine at EliScholar – A Digital Platform for Scholarly Publishing at Yale. It has been accepted for inclusion in Yale School of Medicine Physician Associate Program Theses by an authorized administrator of EliScholar – A Digital Platform for Scholarly Publishing at Yale. For more information, please contact elischolar@yale.edu.
USING COLOR DOPPLER ULTRASOUND TO PROMOTE EXERCISE IN
ADULTS WITH PERIPHERAL ARTERY DISEASE

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the Degree of
Master of Medical Science

August 2020

Sarah Fittro, PA-SII
Class of 2020
Yale Physician Associate Program

Catherine Weikart Yeckel, MS, Ph.D.
Assistant Professor of Clinical Public Health
YSPH
# Table of Contents

List of Figures ................................................................................................. v

Abstract ........................................................................................................ vi

Chapter 1 - Introduction ...................................................................................... 1
  1.1 Background ................................................................................................. 1
  1.2 Statement of the Problem ........................................................................... 6
  1.3 Goals and Objectives ................................................................................ 7
  1.4 Hypothesis .................................................................................................. 7
  1.5 Definitions .................................................................................................. 8
  1.6 Clinical Significance .................................................................................. 8

References ......................................................................................................... 9

Chapter 2 - Review of the Literature ................................................................. 11
  2.1 Introduction - Literature Search Criteria .................................................. 11
  2.2 How Exercise Reduces Claudication Pain ............................................... 12
  2.3 Supervised Exercise Training: Strengths and Limitations ....................... 13
  2.4 Home Exercise Programs: Strengths and Limitations ............................. 16
  2.5 Poor Health Literacy and Disease Understanding as a Barrier to Change ... 18
  2.6 Fear as a Barrier to Change ...................................................................... 19
  2.7 Increased perceived control leads to better outcomes ......................... 20
  2.8 Using Imagery to Increase Education and Motivate Treatment Adherence ... 21
  2.9. Review of Relevant Methodology ........................................................... 24
    2.9.1 Standard of Care ................................................................................ 24
    2.9.2 Level of Claudication Pain to Stop Walking ..................................... 25
    2.9.3 Length of Intervention ...................................................................... 27
    2.9.4 Transferring Near Infrared Spectroscopy Protocol to this Intervention ... 28
    2.9.5 Using a Graded Treadmill Test to Obtain the Primary Outcome ......... 29
    2.9.6 Inclusion and Exclusion Criteria ....................................................... 30
    2.9.7 Sample Size ....................................................................................... 32
  2.10 Possible confounding variables ............................................................... 33
  2.11 Conclusion ............................................................................................... 34

References ......................................................................................................... 36
Appendix G. Walking Impairment Questionnaire\(^6\) .............................................. 79
Appendix H. Fear-Avoidance Beliefs Questionnaire (FABQ)\(^7\) .................................. 81
Appendix I. Sample Size Calculation ........................................................................... 82
References .................................................................................................................... 83
Bibliography .................................................................................................................. 84
List of Figures

Figure 1. Experimental Protocol ................................................................. 46

Figure 2. Color Doppler Ultrasound Image of a Stenotic Popliteal Artery ................. 47
Abstract

Peripheral artery disease impacts greater than 200 million people worldwide and is the third leading cause of atherosclerotic vascular morbidity. The early stages of the disease are ideally treated behaviorally with exercise. However, there is poor exercise adherence due to fear of pain, poor perceived control over the disease, low motivation, and lack of education surrounding the diagnosis. Imaging has been used to change exercise behaviors among patients with other diseases, such as coronary artery disease. This study will test whether allowing participants to see ultrasound images of their vasculature in response to exercise-associated claudication pain will increase adherence to 12 weeks of at-home exercise. We hypothesize that using imaging to create a personalized pain-function scale during the clinical workup will improve patient exercise adherence and thus increase claudication onset time during exercise. If effective, this approach may prove to be instrumental to slowing the progression of peripheral artery disease.
Chapter 1 - Introduction

1.1 Background

Peripheral artery disease (PAD) is a condition where atherosclerosis, plaque buildup within arteries, reduces oxygenated blood flow through peripheral arteries and may even lead to thrombosis.\(^1\) PAD is classified into several categories based on symptoms and severity progression: asymptomatic, claudication (pain due to intermittent, restricted blood flow to the limb during exercise), critical limb ischemia, and acute limb ischemia.\(^2\) Once patients reach the point of critical limb ischemia, they typically need a surgical intervention.\(^2\) However, severe damage occurs before patients reach the stage of critical limb ischemia.\(^3\) For example, patients experience an increased risk for cardiovascular events beginning in the asymptomatic stage, including myocardial infarctions, ischemic strokes, heart failure, and vascular deaths.\(^4\) Therefore, it is crucial to control the disease in the early stages. Exercise is known to improve early stage PAD symptoms and outcomes, but exercise adherence rates are low.\(^1\) In attempt to prevent disease progression and improve symptoms, this research will focus on an exercise adherence strategy for patients with lower extremity intermittent claudication (IC) PAD.

*PAD Prevalence, Health Risks, and Economic Burden*

Around 202 million people worldwide have PAD, a 23.5% increase from 2000.\(^5\) This increase is due to our aging population and a rise in chronic disease risk factors.\(^5\) PAD has a widespread effect, with 140.8 million (70%) people from low- and middle-income countries and 61.3 million (30%) from high-income countries.\(^5\) In the U.S., there are 12 million people living with PAD.\(^5\) The large burden and widespread prevalence of PAD demonstrate the urgency to prevent, diagnose, and treat PAD.
The large number of people impacted by PAD is concerning due to the associated cardiovascular risks. Lower limb PAD is the third leading cause of atherosclerotic vascular morbidity behind coronary heart disease and stroke. Regardless of the stage of PAD, those with the disease have three times the chance of experiencing major cardiovascular events. These cardiovascular events have high mortality rates; up to 23% of people with PAD die from coronary or cerebrovascular disease. With its large impact on health, PAD has a significant economic burden. The rate of hospitalization for U.S. PAD patients in 2014 was 89.5/100,000 with a total annual cost of $6.31 billion. More than half of these patients are discharged to skilled nursing facilities or need home healthcare, bringing additional costs. Improved early treatment options are needed in order to decrease the significant health and cost burdens associated with PAD. This is especially pertinent due to the increasing prevalence of primary PAD risk factors such as diabetes, hypertension, and hyperlipidemia. IC PAD patients are the perfect population to work with to increase exercise adherence and take control of PAD outcomes early in the disease.

Intermittent Claudication PAD and Quality of Life

The prevalence of those experiencing PAD-associated IC is around 40 million worldwide. PAD with IC is described as fatigue, discomfort, or pain that arrives with exercise and dissipates with rest. During exercise, muscles have a higher oxygen demand that cannot be met due to atherosclerosis, leading to the described symptoms. IC is concerning because the symptoms lead to a decreased quality of life (QOL), and the physiology leads to significantly higher mortality rates. Patients with IC were shown to have an impaired QOL compared to asymptomatic PAD patients and
those without PAD. This study by Dumville et al. administered a health-related quality-of-life questionnaire which revealed that patients with IC had significantly lower physical functioning, higher physical limitations, higher emotional limitations, lower energy, higher pain, and lower general health perception compared to patients without claudication pain. Another study found that this poorer QOL was most strongly predicted by physical function rather than specific markers of disease severity. These findings support the need to improve claudication symptoms which, in turn, is predicted to improve QOL.

*Intermittent Claudication PAD Medical Management*

Medical therapy, exercise programs, and surgery are all used to treat patients with IC PAD. Some medical therapies target symptoms, while others are for secondary risk reduction. Even with significant research, only two medications are FDA approved to improve IC symptoms: cilostazol and pentoxifylline. While cilostazol, the more commonly prescribed medication, has been shown to improve walking performance, adherence is low. Less than 40% are adherent to the medication after 36 months because it comes with adverse effects such as headache, palpitations, and diarrhea. There is little quality data showing the benefits of pentoxifylline, so it has been given a class 3 recommendation, meaning it is not indicated or useful, for claudication symptoms. In conclusion, medical treatment options remain suboptimal in providing symptomatic relief or reversal of pathology without adverse effects that lower adherence.

Similarly, while aggressive medical therapies are effective in reducing the poor secondary outcomes of PAD such as myocardial infarctions and strokes, adherence rates
are low. Aggressive medical treatment includes antiplatelet agents, statins and lipid-lowering agents, and blood pressure control agents. Unfortunately, the observational National Health and Nutrition Survey showed that only 35.8% of PAD patients were taking aspirin, 30.5% were taking statins, and 24.9% were taking angiotensin converting enzyme inhibitors.

The last line of PAD medical treatment is revascularization and amputation surgeries, which come with a host of risks such as infection, atelectasis, pain, reactions to anesthesia, and blood clots. Since many PAD patients are not taking the medications needed to improve their outcomes and surgery comes with additional risk and cost burdens, we need to ensure patients are utilizing other strategies to keep their disease under control, such as exercise.

*Intermittent Claudication PAD Behavioral Management*

In direct contrast to the normal exercise advice given to the general public about using pain as a warning sign to stop exercise, the main behavioral treatment for IC is exercising to the point of moderate or severe claudication pain. With proper treatment, the progression to critical limb-threatening ischemia and amputation is <10% and <1%, respectively. Unfortunately, despite research showing that exercise helps with PAD symptoms, those with PAD walk less and at a slower pace compared to those without PAD. This leads to an impaired functional status and to a poorer QOL. Supervised exercise training (SET) is the gold standard to improve QOL, walking speed, walking distance, vascular function, and cardiovascular outcomes. Unfortunately, it is challenging to get patients to participate. A systematic review found that 75.8% of screened PAD patients were not able or willing to participate in SET; common barriers
were cost, travel time, and access.\textsuperscript{17} Therefore, we need to find a way to increase adherence to exercise while avoiding these barriers.

One promising strategy is home exercise programs (HEPs), which could be implemented on a global level, irrespective of income level. HEPs are more convenient and low-cost because patients are able to walk at an easily accessible location instead of traveling to a supervised exercise center. Gardner et al. found that SET increased peak walking time by 192 seconds, while a structured HEP increased peak walking time by 110 seconds; both statistically significant improvements compared to the control group of light resistance training.\textsuperscript{18} The structured HEP utilized a step activity monitor and monthly meetings.\textsuperscript{18} Other techniques used in HEPs to increase adherence include goal setting, keeping an activity log, working with a psychologist, and interacting with a coach.\textsuperscript{19} While these motivation tools have been successful, they cost money and take additional time. There is still a gap in the literature on how to make home exercise more affordable and maximally time efficient. A potential solution is to motivate patients to adhere to home exercise prior to when they start, so they will not need lots of additional resources to keep them motivated throughout.

\textit{Novel Use of Imaging for Intermittent Claudication PAD Management}

Prior studies have utilized coaches, goal setting, activity logs, and activity monitors for HEP motivation, but no one has used imaging.\textsuperscript{18,19} Ultrasound is a commonly used tool that is noninvasive, fast, simple, and relatively inexpensive. Our plan is to use ultrasound imaging in order to break down known barriers to exercise among the PAD population including lack of education regarding the pathology associated with PAD, fear of claudication pain, lack of perceived control over the disease,
and lack of motivation. To do so, we will use ultrasound as a way for patients to visualize their disease state during different levels of exercise-associated pain, personalizing their pain and condition. If we are able to use imaging in order to increase exercise adherence among IC patients by allowing them to understand and target a useful level of pain for their condition this would be a great intervention to incorporate into the PAD diagnosis appointment. Creating this motivation to exercise prior to starting the home exercise regimen will help alleviate the need for expensive and timely motivation tools during HEPs. Overall, establishing this understanding and behavior early on is intended to slow down the progression of disease.

1.2 Statement of the Problem

Exercise is known to improve IC symptoms and PAD outcomes. Evidence supports SET as the primary treatment, but barriers such as cost, access, and convenience lead to low adherence rates. HEPs are shown to be effective and mitigate these barriers, but do not completely eliminate them. Effective HEPs have used coaches, frequent office visits, and psychologists, but these motivators for adherence still introduce barriers such as cost and time. In addition to these barriers, poor understanding of how walking helps alleviate symptoms, fear of claudication pain, and perceived lack of control over the disease also contribute to low HEP adherence rates. Therefore, an intervention that targets all of these barriers is needed in order to increase home exercise adherence rates. In other medical conditions, using images to improve patient attention to their diagnosis, comprehension of their disease, and adherence to their treatment has been effective. For example, imaging has been used with coronary artery disease (CAD) patients to positively change exercise behaviors. Therefore, we are proposing
the use of color Doppler ultrasonography imaging to show patients their personalized
pain scale during exercise-associated claudication in clinic. The intent is to have the
imaging increase home exercise adherence among the IC PAD population.

1.3 Goals and Objectives

The proposed study aims to determine the effect of color Doppler ultrasonography
on exercise-associated claudication onset time (COT) in adults with PAD after 12 weeks
of home exercise. More specifically, prior to 12 weeks of home exercise, we will allow
patients to view their vasculature obtained during different levels of exercise-associated
(during a treadmill test) claudication pain and establish a personalized pain scale.

The primary outcome will be COT, in seconds, during a graded treadmill test in
participants who saw their vasculature on ultrasound compared to participants who did
not see their color ultrasound images. Secondary outcomes will be mean walking
distance, in meters, to reach mild, moderate, and severe claudication pain during the
graded treadmill test, 6-minute walk test distance in meters, peak systolic velocity
(cm/second) through the popliteal artery, average steps per day during home exercise,
health-related quality of life score, fear of claudication pain and physical activity score,
and walking impairment score.

1.4 Hypothesis

Among adults with intermittent claudication peripheral artery disease, we
hypothesize that using color Doppler ultrasonography during an personalized pain-scale
walking assessment will increase adherence to standard of care home exercise for 12
weeks, thus improving their graded treadmill walking test claudication onset time, in
seconds, from baseline compared to those who did not see their vasculature on ultrasound.

1.5 Definitions

Color Doppler: An ultrasound setting that allows visualization of blood flow through a vessel and differentiation from the surrounding tissue.\(^{24}\)

1.6 Clinical Significance

It is well-established that exercise improves IC PAD outcomes but inducing behavior change is challenging. Exercise adherence is especially important right now in a time when PAD risk factors are increasing. Exercising through pain goes against everything people are told about exercise, but we believe that showing patients that their leg blood flow is present during pain should encourage them to push through the pain and reassure them in order to increase exercise adherence.

In the PAD diagnosis appointment at the Yale New Haven Hospital (YNHH) Heart and Vascular Center, patients undergo an ABI and pulsed volume recording (PVR) to confirm the diagnosis, show the location of the lesion, and determine the severity of the disease. For patients with a normal ABI/PVR at rest, but symptoms consistent with IC, technicians facilitate a graded treadmill test to induce claudication pain and then perform an ABI/PVR. The same technicians perform ABI/PVRs, treadmill tests, and ultrasonography. The fact that the equipment and technician knowledge for our study already exist at YNHH makes our proposed study feasible to incorporate into the PAD diagnosis appointment. If it is successful in improving exercise adherence rates and walking performances, adding a personalized pain-function imaging scale would offer a step forward to improving morbidity and mortality within this population.
References


Chapter 2 - Review of the Literature

2.1 Introduction - Literature Search Criteria

A review of the literature took place from July 2019 to May 2020 using Medline (used medical subject headings, MeSH), Pubmed, Scopus, ScienceDirect, and PyscINFO. The key terms used, independently and in combination, to find information regarding peripheral artery disease, prevalence, pathophysiology, exercise programs, barriers to treatment adherence, and the impact of imaging on treatment adherence were *peripheral artery disease* (*peripheral vascular disease, peripheral atherosclerosis, peripheral arterial occlusive disease, lower extremity arterial disease*), *prevalence* (*epidemiology*), *risk factors* (*associated disease*), *claudication* (*intermittent claudication, claudication pain, calf cramping*), *pathophysiology*, *supervised exercise training* (*supervised exercise programs*), *home exercise programs* (*home workouts, walking, exercise*), *change* (*modify, develop*), *adherence*, *behavior* (*habit*), *barrier* (*limitation, obstacle*), *fear* (*worry*), *avoidance*, *pain*, *picture* (*image, imagery*), *ultrasound* (*Doppler, ultrasonography, color mode*), *perceived control* (*control*), *health literacy* (*health understanding*), *education* (*knowledge*), and *motivation*. They were sorted by relevance or year of publication. Only articles written in English were used. Articles’ titles and abstracts were preliminarily used to determine whether an article would be relevant to this review. To find additional pertinent research, articles cited within studies found during the original search were used. Most of the articles are meta-analyses, literature reviews, randomized controlled trials (RCTs), observational, or prospective cohort studies.
2.2 How Exercise Reduces Claudication Pain

We have known for many years that exercise reduces claudication pain. In 1995, a meta-analysis with 21 studies showed that exercise training increased pain-free walking distance by 179% (125.9±57.3m to 351.2±188.7m; p<.001). More recently, a study looked at the underlying mechanisms of PAD. Arterial obstruction, endothelial damage, altered skeletal muscle phenotype, mitochondrial dysfunction, and inflammation were all factors involved in claudication pain that could be reduced with exercise.

Until recently, an imbalance in oxygen supply and demand during exercise was thought to be the only reason for claudication pain. Arterial stenosis, which accompanies PAD, does not allow for enough blood flow to properly oxygenate the muscles. While this is true, further research has shown that the physiological mechanism behind claudication pain is much more complicated.

Exercise helps alleviate claudication symptoms by promoting arteriogenesis and arterial dilation in hypoxic tissues. During exercise, there is increased laminar shear stress and tangential wall stress acting on the vessel walls which promote collateral vessel growth and an increase in lumen diameter. This leads to increased oxygenation of lower extremity muscles, which lowers ischemia and decreases future claudication pain. In a healthy artery, the endothelium releases vasoprotective factors, such as nitric oxide, to regulate arterial flow. With PAD, there is endothelial damage, so less nitric oxide is released. With ischemia, the muscle requires increased blood flow, but decreased nitric oxide production prevents a hyperemic flow response. Brendle et al. showed that SET increased endothelium-dependent flow-mediated dilation by 61% (0.18 ±0.03mm to
Exercise was shown to increase shear stress, which stimulated nitric oxide production and allowed for increased bloodflow.\(^4\)

In PAD, periodic ischemia combined with low physical activity levels reduces overall skeletal muscle area, decreases muscle density, and increases fat content within lower limb muscles.\(^6,11\) On a more microscopic level, there is increased muscle cell apoptosis, reduced type I muscle fibers, and reduced capillary density which lead to an accumulation of metabolites.\(^3,12\) These metabolites lead to mitochondrial dysfunction, which decreases oxygen utilization and accelerates endothelial damage. Exercise has been shown to reverse ischemic muscle changes and improve mitochondrial function.\(^12\)

IC PAD patients have chronic inflammation.\(^13\) In addition, a cross-sectional study by McDermott et al. showed that higher levels of inflammatory blood markers, C-reactive protein and interleukin-6, in PAD patients were associated with poorer 6-minute walk performance.\(^7\) These inflammatory markers increase with short periods of exercise, but decrease with long-term exercise training.\(^13\) Therefore, performing regular exercise is expected to decrease inflammation and increase walking distances.

There is strong evidence for many mechanisms by which exercise reduces claudication pain and improves function. This supports the need for adherence to long-term, regular exercise among PAD patients in order to improve symptoms and outcomes.

### 2.3 Supervised Exercise Training: Strengths and Limitations

Current AHA/ACC guidelines state that supervised exercise training (SET) is the first-line treatment for IC PAD patients.\(^14\) SET includes treadmill training to moderate or maximal ischemic leg symptoms three times a week for up to six months, with each
session lasting 30-60 minutes. The sessions are located at a hospital or an outpatient clinic and patients must be under direct supervision of a provider.

Significant research shows SET is effective in improving claudication symptoms and PAD outcomes. In the 1995 meta-analysis, those in exercise programs demonstrated a significantly greater increase in maximum walking distance (255.8m; p=.02) and pain-free walking distance (107.1m; p=.02) compared to controls. A limitation to this study is that only 3 of the 21 studies were RCTs. However, the results of the three RCTs were consistent with the results in the 18 nonrandomized, uncontrolled trials.

A more recent systematic review of 25 RCTs showed similar results where SET increased maximal walking distance by 180m (95% CI, 130-230m) and pain-free walking distance by 128m (95% CI, 92-165m) compared to controls given no exercise instructions. A strength of this review is it only included RCTs, but it did come with the limitation of all reviews: the results were limited by the quality of the original studies. The included studies utilized different treadmill protocols to assess walking distances and the SET protocols involved diverse training components in terms of duration, mode, and intensity. However, the two reviews show consistent results over a long period of time, supporting the idea that some form of SET is effective in improving PAD symptoms.

Despite the evidence of SET improving claudication symptoms, participation rates in these programs are low. A systematic review found that only 24.2% of IC PAD patients screened for SET were able or willing to participate. It is important to note that the review included 67 trials, but only 23 gave screening information; this limits the application of the results. Additionally, only 13 of the 23 studies gave specific reasons
for screening failure. However, it still allowed for the analysis of 1,820 subjects, which provides some evidence of participation rates and reasons for screening failure.

From the studies that reported the reason for screening failure, 30.6% of patients were not interested or refused to participate, 16.2% had comorbidities affecting their ability to exercise, 11.7% of patients were unable to attend SET classes due to distance or timing, and .2% did not participate due to inadequate insurance coverage. Participation rates were expected to rise in 2017 when Medicare and Medicaid started covering SET, but this systematic review was performed in 2016, so even prior to insurance changes, coverage was the least common reason for nonadherence.

The SET adherence review included all 67 articles. Of the 4,012 subjects who agreed and participated in SET, 3,015 (75.1%) adhered to and completed the regimen. The most common reason for drop out of the SET was lack of motivation (29.2%). Other reasons were patient choice (16.7%), lack of results (8.2%), travel problems (3.8%), and time or family/work commitments (2.8%). The main limitation to these results is that none of the articles defined the number of sessions needed for SET completion, so it may have meant attending all sessions or just a few. Additionally, those who agreed to participate likely had a higher baseline level of motivation, which may have introduced selection bias. This is hard to avoid in exercise trial studies, but it impacts the external validity of the study. While the results of this review were limited by the methods of the included studies, it still gave a current picture of SET adherence rates and is one of the few studies that has directly analyzed adherence. These results show that there are significant barriers to SET participation and adherence, indicating that a more appealing, motivating, and convenient solution is needed for patients.
2.4 Home Exercise Programs: Strengths and Limitations

AHA/ACC guidelines give home exercise programs (HEPs) a class IIA recommendation, meaning the treatment is reasonable and has been found useful based on evidence from RCTs.\textsuperscript{14} The appeal of HEPs is they are low-cost, accessible, and efficient compared to SET programs. A recent meta-analysis showed that HEPs were effective in increasing walking distances, but it is important to look at the details of how these programs achieved positive results.\textsuperscript{17} Evidence indicates that increasing walking distances via HEPs requires more than simply telling patients to go home and exercise.

In 2011, Gardner et al. compared the efficacy of a HEP versus SET to increase claudication onset time (COT) and peak walking time (PWT) in participants with IC.\textsuperscript{18} HEP and SET participants walked to near-maximal claudication pain three days a week for 12 weeks.\textsuperscript{18} The HEP group wore a step activity monitor during exercise and had an in-person meeting with an exercise physiologist every two weeks to discuss their progress and plan.\textsuperscript{18} HEP and SET both significantly increased COT (HEP 204s to 337s, \(p<0.001\); SET 196s to 361s, \(p<0.001\)) and PWT (HEP 402s to 526s, \(p<0.01\); SET 325s to 540s, \(p<0.01\)) compared to the control group (COT 225s to 209; PWT 505s to 494s) who was told to exercise more than usual.\textsuperscript{18} HEP and SET results were not significantly different from each other (\(P>0.05\)).\textsuperscript{18} While this study suggests that HEP, with proper motivational tools, can be just as effective as SET in producing statistically significant results, it did not discuss whether the difference in mean change from baseline between SET and HEP groups (31s higher in SET for COT, 91s higher in SET for PWT) was \textit{clinically} significant.\textsuperscript{18} Clinical significance is important because the goal is to stop the progression of the disease and make a meaningful change in participants’ daily life.
A recent RCT showed that HEPs make positive changes within the vasculature, similar to those of SET discussed in the prior section. The study found that HEPs significantly decreased endothelial cell apoptosis (1.11 arbitrary units, AU to .77 AU; p = .016), increased circulating HORAC (an antioxidant; .95 AU to 1.19 AU; p = .005), increased VEGF-A (26 pg/mL to 35 pg/mL; p = .003), decreased E-selectin (36 pg/mL to 35.5 pg/mL; p = .04), and decreased blood glucose (100 mg/L to 90 mg/L; p = .041). These changes increase antioxidants, induce angiogenesis, decrease inflammation, and lower blood glucose values. A limitation to note is the study did not follow the participants after trial completion to determine whether the changes altered the long-term progression of PAD. However, the results suggest that if participants continue to exercise, they will continue to reverse vascular damage.

The benefits of HEPs stated above required motivational techniques, such as meeting with a coach, motivational interviewer, or an exercise physiologist which comes with time, cost, and convenience barriers. A more recent trial studied whether HEPs could significantly increase walking distances without in-person visits. In 2018, McDermott et al. studied whether a HEP utilizing a wearable activity monitor and telephone coaching could significantly increase walking distances among PAD participants. The results showed no significant difference (p = .31) between HEP participants (5.5 m mean change from baseline) and controls (14.4 m mean change from baseline) at 9 months during a 6-minute walk test (MWT). However, this intervention was missing several components that may have limited the results. Participants did not receive immediate coaching feedback after uploading exercise data. While this may have led to significant results, it creates a more challenging intervention to conduct and
would be less feasible in the general population. Additionally, the adherence rate (79%) to coaching phone calls within the exercise intervention group may not have been sufficient for significant results; this represents the realistic challenge of adherence with this type of intervention.\textsuperscript{20} However, 79% is still relatively high for exercise programs, suggesting there may be another factor responsible for insignificant results, such as insufficient patient understanding of appropriate exercise intensity. These findings suggest that telephone coaching for a HEP is not effective, demonstrating the continued need to find a way to increase walking distances without regular in-person visits.

2.5 Poor Health Literacy and Disease Understanding as a Barrier to Change

In 2003 The National Assessment of Adult Literacy found that 35% of the population had basic or below basic health literacy as measured by clinical, prevention, and navigation of the health care system domains.\textsuperscript{21} Healthcare is full of its own vocabulary and complex topics making it difficult to understand. Americans struggle to understand medication instructions, appointment reminders, discharge instructions, and health education materials, leading to a lack of adherence to treatment and poor management of diagnoses.\textsuperscript{22} Consistent with this, an observational study showed that PAD patients are often not aware of the risk factors contributing to their disease.\textsuperscript{23} Only 31% of the diabetic PAD patients knew that diabetes was a risk factor for PAD.\textsuperscript{23} The results were similar for smoking, hypercholesterolemia, and hypertension patients where only 58%, 25%, and 10% of PAD patients knew these were risk factors for their PAD.\textsuperscript{23}

In a more recent qualitative study, IC PAD patients underwent focus group discussions about experiences living with PAD, attitudes and beliefs about PAD, and opinions for behavior change interventions.\textsuperscript{24} Most patients could define PAD, but were
unable to define claudication.\textsuperscript{24} Patients thought diagnostic appointments are too short and lack follow-up, leading to confusion about the disease.\textsuperscript{24} Most patients knew that exercise was suggested, but were unclear on how much and whether it works.\textsuperscript{24} The most common barriers to physical activity were pain, fear of leg damage by walking a lot, and lack of motivation.\textsuperscript{24} Patients stated that if they were convinced that walking would help prevent progression of their disease, and if they were able to see improvement, they would be more motivated.\textsuperscript{24} Given the nature of qualitative studies, this study was limited by a small sample size and potential biases that come with compiling individual responses into conclusive statements.\textsuperscript{24} However, bias was minimized by having three researchers review the responses and agree upon identified themes and trends.\textsuperscript{24}

Taken together, these studies reflect the need for better patient education. It appears that PAD patients would be more motivated to make changes if they understood the risk factors, pathophysiology, and logic behind the treatment plan for their disease. Integrating patient education into the diagnostic appointment through a personalized image-guided exercise test may be an opportunity to increase PAD patient exercise adherence. Patients would see blood flow in their leg both with and without pain but would be able to see it is limited. This would give patients a better understanding of their disease etiology and the need for collateral vessels and increased vessel diameter in order to increase blood flow and therefore increase function and reduce pain during exercise.

2.6 Fear as a Barrier to Change

There is an association between pain beliefs and treatment adherence, supported by the fear-avoidance model.\textsuperscript{25} This model states that negative beliefs and misunderstanding regarding an activity can lead to fear and avoidance of that
activity. To examine fear in the context of PAD, Sharath et al. performed a pilot study with 19 participants. Participants had underlying fear and misunderstanding regarding their pain. Sixty-three percent of participants thought the primary etiology of their leg pain was walking (and not due to atherosclerosis), 56% thought physical activity would harm their legs, 30% thought they should not perform physical activity because it will make their pain worse, and 30% thought they could not perform physical activity because it will make their pain worse. Authors stated they found “a significant association between fear-avoidance beliefs and expected benefit from exercise (p=.01)”.

While the study suggests that people who have less fear about walking expect a greater benefit from walking, the small sample size did not allow the study to account for confounders; this threatens the internal validity of the study. Based on this limited information, fear appears to play a role in PAD exercise adherence, but more studies are necessary to understand the potential confounding variables.

In conclusion, this study suggests that PAD patients misunderstand the etiology and fear their pain, they do not understand the benefit of walking, and those with worsened symptoms have a higher fear-avoidance score. These results, in combination with those from the prior section, emphasize the importance of improving education among PAD patients about their disease to increase adherence to exercise treatment.

2.7 Increased perceived control leads to better outcomes

Perceived control refers to one’s belief about the ability to influence future life outcomes. Those with higher levels of perceived control over their health have healthier behaviors. While there has not been extensive research on perceived control and PAD specifically, a cross-sectional study in 2014 suggests that perceived control is
an important indicator of functional health and cardio-metabolic risk. They used a scale of 1 to 6 to rank patients’ level of perceived control. For each one point increase on the scale, grip strength increased by 0.95 kg, hemoglobin A1c decreased by 0.04%, HDL-C levels increased by 0.92 mg/dL, pulse rate decreased by 0.62 beats per minute, and weight circumference decreased by 0.24 inches. Higher perceived control led to significantly more physical activity when compared with lower perceived control. Physical activity was a mediator between perceived control and markers of functional health and cardio-metabolic risk. Therefore, increased perceived control increased physical activity, which improved functional health and lowered cardio-metabolic risk. Perceived control in PAD patients was prospectively examined with statements such as “I am in control of my ability to walk for exercise”. Rejeski et al. found patients with low control ratings had significantly lower 6-MWT distances (1.41, 1.62, and 1.78 were the perceived control scores among participants who had low (≤976 ft), middle (between 976 and 1,285 ft), and high (≥1286 ft) 6-MWT distances; \( p = 0.0179 \)). This latter study is one of a few studies that has analyzed perceived control in the area of PAD, so the results need to be further studied in a RCT.

Our goal is to increase the perceived control patients have over their exercise behavior and disease by allowing them to see the exercise response of their own vasculature, personalizing their pain-scale, and showing them improvement overtime with exercise. This increased perceived control should increase exercise adherence.

2.8 Using Imagery to Increase Education and Motivate Treatment Adherence

Appointments are short, medical terms are confusing, there is a lot of information provided in a single appointment, and patients are afraid to ask questions with the fear of
appearing uneducated. These challenges are not likely to change, so we must find another way to educate patients. Using imaging seems to be a promising next step.

Findings from a RCT demonstrated that patients who were shown a picture with text about their disease, instead of just text, had improved attention to, comprehension of, recall of, and adherence to health information. Patients who presented to the emergency department (ED) with a laceration were given a pamphlet for wound care with either pictures and text or just text. Three days later they were asked if they had read the pamphlet (attention), particular questions about the information (comprehension), and if they had performed wound care (adherence). Ninety-eight percent in the picture group read the instructions, 46% answered the comprehension questions correctly, and 77% adhered to wound care, which were all significantly better proportions compared to 79%, 6%, and 54% in the text-only group. This study had 400 eligible patients, but only 234 were included in the analysis because the rest were unavailable by telephone for follow-up. However, those who were unavailable were not significantly different in demographics, time present in the ED, or level of treating physician, so it is less likely to have impacted the external validity. Another limitation is the data relied on self-reported information; this potentially allowed for bias because the patients may have felt pressured to tell the interviewers what they wanted to hear. However, it was a RCT with interviewers blinded to which group the patients were in, lowering the risk of bias. Overall, this study supports the use of images for diagnosis and treatment information.

A prospective cohort study analyzed the best way to present information via pictures. They found using prompts helped participants interpret the picture correctly. For example, circling the most important part of the image increased comprehension.
because it helped the patient focus. Next, having an underlying understanding of what the picture was showing led to the best improvement in understanding; pictures enhanced understanding instead of creating an understanding. Pictures helped show changes over time, how medicine affected the body, and how behavior affected health. Lastly, simple drawings using lines and color allowed for better patient understanding compared to complex images in black and white. These concepts will be utilized in this study as we use color Doppler ultrasonography to provide a simple image to participants in order to link exercise-associated leg pain (or not) with blood flow (color) in their own leg, increase disease attention and comprehension, show how behavior impacts health, and show vascular changes overtime.

Ultrasound imaging has been used previously among the smoking population to see if visualizing atherosclerosis increased smoking cessation rates. Seventy-nine smokers did not see their ultrasound imaging and only received smoking cessation counseling, 20 smokers saw their imaging and did not have atherosclerosis, and 54 smokers saw their imaging and had at least one atherosclerotic plaque; six months later, 6.5%, 5.0%, and 22.2% of each group, respectively, had quit smoking. Those who saw their plaque had significantly higher quit rates (p = .003). A limitation of this study is they relied on self-report for smoking cessation which comes with the risk of recall bias or stating answers to please the interviewers. However, the risk of bias should be similar among intervention groups, so it should not significantly change cessation rates among groups. Additionally, their six-month follow-up does not guarantee that smoking behaviors would not resume, but prior research states this timeline is sufficient for cessation studies. While our outcome of interest is different, both exercise and
smoking behaviors are challenging to change. Their success of creating behavior change using ultrasound to reveal atherosclerosis is extremely promising for our proposed study.

More recently, a study using more advanced diagnostic imaging modalities helped patients better understand their disease state, as well as helped increase exercise adherence.\textsuperscript{38} Electron beam computed tomography (EBCT) was used to detect coronary artery disease (CAD) and predict cardiovascular risk.\textsuperscript{38} EBCT allowed patients to visualize calcium within their coronary arteries, which initiated behavior change.\textsuperscript{38} Patients saw the calcium in their coronary arteries and were told whether it was mild, moderate, or severe atherosclerosis.\textsuperscript{38} Those with atherosclerosis were significantly more likely to have aspirin initiation (2.98 OR, CI 1.83-4.83), diet changes (2.66 OR, CI 1.63-4.32), and increased exercise (2.03 OR, CI 1.26-3.27) compared to those without atherosclerosis.\textsuperscript{38} These results are replicated in other CAD studies, supporting the idea that showing patients their vasculature promotes exercise adherence and other risk-reducing behaviors.\textsuperscript{39} Together, these studies support the use of imaging as a promising next step to increase PAD patients’ disease understanding and exercise adherence.

2.9. Review of Relevant Methodology

2.9.1 Standard of Care

Current AHA/ACC guidelines state SET is the first-line treatment for IC PAD patients, but SET prescription and adherence rates are low.\textsuperscript{14,17} For this reason, SET is the gold standard management, but not the standard of care. A systematic review of 25 RCTs looked at SET among IC PAD patients and found that most of the control groups were told to walk as much as possible at home, but were not given any specific instructions.\textsuperscript{15} Similarly, within a meta-analysis of 11 RCTs that examined the benefits
of HEPs, control groups were told to walk at home, but were not given specific instructions. While the exact wording may vary, this is the type of advice that patients receive during follow-up vascular appointments. Since our study will take place at YNHH Heart and Vascular Center, home exercise instructions given to the participants within this study will be similar to the standard of care exercise instructions given by their providers. We expect this to be similar to the advice given in prior studies.

It is important to note that the standard of care does not typically include any motivational components to encourage exercise. As previously mentioned, McDermott et al. sought to determine whether a wearable activity monitor combined with telephone coaching would increase walking distances. They found no significant difference in 6-minute walking distances among experimental and control groups. We will provide an activity monitor to all participants in our study to record home walking distances. Given the data from McDermott et al., we do not anticipate this significantly impacting the exercise outcomes of either group; if it does, it should be similar among groups.

2.9.2 Level of Claudication Pain to Stop Walking

There is mixed evidence on the necessary pain level threshold that people with IC PAD must reach to improve outcomes. The 1995 meta-analysis looked at 21 studies where 15 had participants exercise to claudication onset or slightly beyond, and 6 studies had participants exercise to near-maximal claudication pain. The post-intervention claudication onset distance was significantly higher when participants walked to near-maximal claudication pain compared to onset of pain, 350.2m (±246.2m) and 104.7m (±91.2m) respectively (p=.007). This suggests that people should be encouraged to
exercise to near-maximal claudication pain to best improve symptoms. Again, it is important to keep in mind that only 3 of the studies within this meta-analysis were RCTs.

More recent data reveals conflicting evidence. A systematic review in 2011 looked at 36 RCTs and showed that pain-free exercise significantly increased walking distances (ranging from 45-71% with relative effect size of 1.54 to 2.91) as did walking to mild, moderate, or maximum pain (ranging from 52-189% with relative effect size of .93 to 3.53). None of the reviewed studies directly compared pain-free walking versus walking to mild, moderate, or maximal pain, but these results suggest that exercising to any level of pain increases walking distances.

The most recent study exploring what level of claudication pain is best to stop exercising was performed by Novaković et al. in 2019. This RCT found that both moderate-pain and pain-free groups improved claudication onset distance (moderate-pain: 50m to 107m, p = .005; pain-free: 53m to 128m, p = .003) and absolute walking distance (moderate-pain: 85m to 194m, p = .005; pain-free: 92m to 163m, p = .003), but only the moderate-pain group had significantly improved vascular function. Vascular function was represented by flow-mediated dilation (FMD; 4.4% to 8%; p = .002) and pulse-wave velocity (PWV; 6.6 m/s to 6.1 m/s; p = .013). On a 5 point pain scale, with 3-4 consistent with moderate to severe pain. This is a subjective way to measure pain and it hard to replicate from day to day; this is a limitation we hope to address in this proposed study. Another limitation was the small sample size, 29 patients, which created an underpowered study to detect differences in secondary variables such as FMD and PWV. However, small sample sizes are common in PAD exercise trials because motivation is low. Overall, this is a novel study that provides information on the most
appropriate pain level to stop exercise to improve exercise distances and improve vascular function.

Given the conflicting data and the fact that many of these studies were analyzing SET, it is challenging to come to a conclusion on what level of pain we should include in the standard of care exercise instructions for the participants in this study. This inconclusive data also suggests that providers are most likely giving different pieces of advice to their patients. We will instruct patients to exercise to near-maximal claudication pain in our study to increase the chance of improving vascular function.

2.9.3 Length of Intervention

A meta-analysis of PAD HEPs showed great variability in the lengths of study interventions, from 6 to 36 weeks. There is not a known relationship between program length and effectiveness, and there has not been a study comparing the length of the program for HEPs like there has been for SET. For SET, a meta-analysis showed a significant increase in MWDs for short (4-11 weeks), medium (12-26 weeks), and long (>26 weeks) interventions compared to the standard of care. However, medium-length interventions increased MWD from baseline (223m; SD 149-298m) significantly more than short-term (123m; 41-204m) and long-term (145m; 27-263m) interventions. These results were not confirmed by meta-regression analysis and thus need to be studied in a RCT, but they suggest that a medium length intervention is best to create significant results. However, the long-term intervention results question whether changes made in medium length interventions will be sustained after intervention completion; we hope to create change that can be seen quickly within 12 weeks, but also changes patients’ mindset about their disease to change their long-term lifestyle. To do so, we will have
participants return after 12 weeks to see their improvements which should help reinforce the level of motivation and create long-term behavior change.

As previously discussed, Gardner et al. performed a 12-week study, within this medium length category, comparing a HEP, SET, and usual care.\textsuperscript{18} They found that both the HEP and SET significantly increased COT and PWT compared to the control group.\textsuperscript{18} HEP and SET results were not significantly different from each other.\textsuperscript{18} This indicates that exercising 3 times a week for 12 weeks is long enough to show significant change among not only SET, but also HEPs. While previous studies have not specifically explored HEP intervention length, 12 weeks seems to be the standard for SET and enough time to see improvement with HEPs. The proposed study home exercise component will be different than structured HEPs because it will not be using a form of motivation \textit{during} the 12-week course, it will have the motivational piece prior to home exercise. However, we hope to induce exercise changes similar to structured HEPs, so exercising 3 times a week for 12 weeks should still be a sufficient amount of time to see exercise adherence changes if the motivational piece is effective.

\textbf{2.9.4 Transferring Near Infrared Spectroscopy Protocol to this Intervention}

In 2019, Murrow et al. used near infrared spectroscopy (NIRS) to determine whether using tissue hypoxia levels as an endpoint for exercise training is better than using pain levels for PAD patients.\textsuperscript{42} NIRS is a non-invasive method that uses the absorption of reflected light to measure oxygen levels within an active muscle.\textsuperscript{42} This study is relevant to our methods because the authors fastened the NIRS device to the participants’ legs to obtain data in real time.\textsuperscript{42} This is very similar to how we will be fastening an ultrasound probe to participants’ legs to get continuous imaging. In order to
limit the motion artifact in the NIRS signal during a graded treadmill test (GTT), the
NIRS optode was secured to the calf using Velcro straps and bioadhesive tape. Our
study will use the same techniques to fasten the ultrasound probe to participants’ legs
during a GTT in order to obtain continual data; it is encouraging that another study was
able to perform a similar setup and obtain quality results. The proposal here is novel for
performing graded-exercise in PAD with pain-scaling and continuous ultrasonography.

2.9.5 Using a Graded Treadmill Test to Obtain the Primary Outcome

The primary outcome in most HEP trials is walking performance assessed by a
treadmill (constant-load or graded) or a corridor-walking test (6-MTW). There has
been great controversy in cardiovascular medicine about whether the 6-MWT or
treadmill test is a better functional test for PAD patients.

McDermott et al. performed a RCT where they used a 6-MWT and a treadmill
test to evaluate an exercise intervention; the between-group change comparisons of the
exercise and control groups were statistically significant for both the 6-MWT and
treadmill test. However, the estimated effect size of the 6-MWT was .70, while the
treadmill test was 1.01. This implies that the treadmill test would need fewer patients
than the 6-MWT to show statistically significant results. Another benefit of the treadmill
test over the 6-MWT is it is able to show submaximal and maximal performance as the
grade increases, while the 6-MWT only shows submaximal walking endurance. Lastly,
the 6-MWT is self-paced, so it is not as standardized. The treadmill test will allow for a
direct pre- and post-intervention comparison of speed and grade for specific pain levels,
performance, and ultrasonography measures which is not possible when using the 6-
MWT. For these reasons, this study will use treadmill walking over corridor walking as the primary testing format, but also collect 6-MWT results per standard clinic testing.

There are constant-load (constant speed and grade) and GTTs (constant speed with increasing grade). The most common GTT starts at 2mph, 0% grade and increases by 2% every 2 minutes. The problem with the constant-load test is the inability to assess the wide range of PAD patient functionality. This protocol may be too challenging for those with severe PAD, or it may take too long to reach claudication pain in those with earlier stages of PAD. The GTT is able to test a range of PAD patients because it starts at an easy level and increases to a challenging level in a standardized, but relatively short period of time. This GTT construct lends itself well to the intent of this proposed study: to establish a personalized exercise-associated pain-scale.

There have been questions regarding whether a treadmill test performance correlates with non-treadmill ambulatory function and QOL. Research shows that GTT performance is correlated with Walking Impairment Questionnaire (WIQ) results. The WIQ provides information regarding walking distances and speeds and severity of calf IC pain during walking. A study showed that a change in 0.1 on the WIQ score corresponded to a 345-meter change in treadmill walking distance with exercise training. This correlation between patient-reported outcomes and treadmill test results shows that the treadmill is a good marker of the patients’ function off the treadmill. For these reasons, this study will use a GTT to obtain the primary outcome, COT.

2.9.6 Inclusion and Exclusion Criteria

The main inclusion criterion for IC PAD studies is typical claudication pain: exertional calf pain that begins with walking and resolves within 10 minutes of rest.
Studies have used different ways to define claudication pain. One way is to use the Rutherford Classification System, which uses only patient-reported symptoms.\textsuperscript{17} Gardner et al. used symptoms and diagnostics: history of any type of exertional leg pain, ambulation limited by leg pain consistent with IC, and an ABI $\leq .90$ at rest or $\leq .73$ after exercise.\textsuperscript{18} We will use this more objective approach to ensure the pain has a vascular, not neurogenic, origin. Additionally, participants must have stenosis within the popliteal artery, confirmed by ultrasound. This has not been included in other studies, but ensuring the location of the stenosis is just upstream of the calf is important for patients to connect their calf pain to their vasculature imaging.

PAD exercise trials consistently excluded patients with physical impairments other than PAD because they prevent the study from measuring how effective the intervention is in improving claudication symptoms.\textsuperscript{47,48} These physical impairments include leg amputations, confinement to a wheelchair, and critical limb ischemia or a foot ulcer.\textsuperscript{47,48} Cardiovascular risks such as unstable angina, severe CAD, myocardial infarction, transient ischemic attack, or stroke within 3 months of screening are common exclusion criteria because the exercise regimen could induce a cardiovascular event.\textsuperscript{47,48} Participants who started cilostazol or pentoxifylline within 3 months of the trial start are typically excluded because these drugs may be responsible for a change in claudication symptoms instead of the exercise protocol.\textsuperscript{47,48} Those with serious medical conditions such as active cancer, class III or IV heart failure, renal failure, liver failure, or blindness are commonly excluded because participants may be too sick to complete the trial.\textsuperscript{47,48} Lastly, those with uncontrolled type 2 diabetes mellitus, defined as a hemoglobin A1c (HbA1c) level greater than 8\%, will be excluded from the study.\textsuperscript{49} This has not been a
typical exclusion criterion in other studies, but since diabetes is associated with vascular abnormalities such as vascular inflammation and endothelial cell dysfunction, uncontrolled diabetes may inhibit the vasculature from making changes with exercise and thus inhibiting improvement in symptoms. While this list of exclusion criteria limits the external validity of the results, it also decreases confounders and increases the chance of seeing an effect from the exercise protocol.

2.9.7 Sample Size

The sample sizes among the reviewed PAD exercise training trials are variable, but the majority of them have small sample sizes (n= 20-50). Obtaining large sample sizes for exercise training studies among the PAD population is challenging, mainly because motivation is low. This study will likely face the same challenge because the motivational piece is after the patients have agreed to participate. In addition to large sample sizes, low attrition rates are also hard to obtain. The Gardner et al. study had an attrition rate of 23% where 80% of these participants dropped out due to disinterest and lack of motivation; the rates are similar among other studies. However, we expect the nature of this proposed study to reduce these rates, so we will only be accounting for a 10% drop out rate.

The average of other studies that strived to improve COT increased it by 99s to 132s. However, a study most closely resembling our proposal was conducted by Duscha et al. and included 20 participants. They used a mobile health intervention and increased the COT by 205s. This study will be used to base our sample size calculations.
2.10 Possible confounding variables

Thirty percent of PAD patients have type 2 diabetes mellitus (T2DM); it is the most common risk factor.\textsuperscript{51} Therefore, we expect many participants in this proposed study to have T2DM. Since this is a RCT, participants with T2DM are expected to be balanced between groups. However, a controlled diabetic with a HbA1c of 6% has different vasculature than a diabetic with a HbA1c of 8%. This is especially true for those who have had diabetes for many years. It will be challenging to equally distribute participants based on HbA1c levels and years since diabetes diagnosis. For example, one may have a HbA1c of 6%, but from 20 years ago to 6 months ago, when one decided to get it under control, the HbA1c may have been 12%. For those who have had poor control for a long period of time, it will be difficult to reverse vascular damage and therefore improve symptoms. We will be measuring HbA1c levels during the screening appointment and we can use this information for randomization, but this will only represent the past 3 months. For this reason, glucose control and years since diabetes diagnosis may be confounders in this study. Since such a large portion of PAD patients have T2DM, it will not be part of the exclusion criteria; this would extremely limit the external validity. However, those with uncontrolled T2DM, HbA1c of >8%, will be excluded because they will be less likely to produce positive outcomes. Additionally, those with debilitating peripheral neuropathy will be excluded because this may limit their walking ability instead of claudication pain.

The type and amount of terrain available for exercise is known to be a barrier to exercise in PAD patients.\textsuperscript{52} We will be excluding participants who do not have any place to exercise, but for those included, the terrain type may vary. Those who have more
available green space may be more motivated to exercise and for longer periods of time. Additionally, including hills in home exercise may improve GTT performance. Lastly, if the study occurs in the winter, those who do not have access to a gym may be less motivated to exercise outside in the cold. For these reasons, the amount of space available for exercise and the terrain type during home exercise may be confounders for this study.

This study relies on taking the clearest images possible during claudication pain in order to show the participants afterwards. The ability to do so depends on the capability of the technicians and the patient anatomy; for this reason, these are confounders. Additionally, since this is a motivational study, the tone of voice of the researcher when explaining the ultrasound images may impact how the participant feels. For example, an encouraging tone may reassure the patient about what they are seeing and may impact their motivation to exercise at home. These types of variables when showing participants their images are potential confounders that will be addressed by only having the primary researcher explain the images and by having a script to say to patients.

2.11 Conclusion

The data presented strongly supports the idea that exercise improves claudication symptoms and PAD outcomes through many different mechanisms. SET is the gold standard treatment, but adherence rates are extremely low. HEPs have been used to try to find ways to increase adherence by alleviating some of the exercise barriers. Unfortunately, the HEPs that have been effective use motivational components that increase cost, decrease accessibility, and decrease efficiency. In addition to these barriers it is clear that fear of pain, lack of knowledge, and lack of perceived control over the disease are also contributing to low exercise adherence. As PAD prevalence
rising, we must find a way to increase exercise rates among the PAD population. While changing behavior is extremely difficult, there is data to suggest that using imaging may be a good solution.

Images have improved attention to, comprehension of, and recall of health information. This increased understanding will likely increase perceived control and decrease fear-avoidance behaviors, thus targeting several barriers of exercise adherence. Furthermore, imaging has already been found to increase exercise adherence among CAD patients. For these reasons, using imaging to increase patients’ understanding about their disease and exercise adherence among PAD patients is a promising next step.

The proposed study will use simple, color Doppler ultrasound images to enhance patients’ understanding of their PAD by showing how it impacts their affected leg during a personalized, exercise-associated graded pain scale test. If successful, increased understanding will alleviate fears regarding their pain and motivate them to increase their exercise adherence to appropriate levels of pain during 12 weeks of exercise typically instructed by providers as a starting point. This would allow for the motivational component to be given early on in during the diagnosis appointment, therefore helping to prevent disease progression.


30. Gerstorf D, Rocke C, Lachman ME. Antecedent-consequent relations of perceived control to health and social support: longitudinal evidence for between-


Chapter 3 - Study Methods

3.1 Study Design

We will use a single blinded randomized controlled clinical trial where participants will be randomized either to the experimental or to the control group using verified computer software. The experimental group will meet with the researcher to look at their color Doppler ultrasound images taken during a graded treadmill test (GTT) at different levels of pain. In contrast, the control group will perform the GTT without the benefit of seeing their images afterwards. Both groups will undergo 12 weeks of at-home exercise before reevaluation of their PAD. The ultrasound technicians will be blinded, but the participants and principal investigators will not be given the nature of the intervention. Due to the novelty of the intervention, three participants will undergo the treadmill component of the study prior to the rest of the participants starting the study in order to ensure protocol feasibility.

3.2 Study Population and Sampling

The study population will include English-speaking adults between 45 and 70 years old with IC PAD. The claudication pain must be in the calf, the most common location of pain, and the disease burden must be in the popliteal artery, a common place of atherosclerosis. The standard ABI/PVR diagnostic test performed at YNHH Heart and Vascular (H&V) Center will be used to diagnose and locate the disease. The results will be confirmed with an ultrasound image of the popliteal artery.

The YNHH H&V Center and New Haven area primary care clinics will be given study details and asked to refer patients during a 16-month timeframe. Prior to randomization, there will be a screening visit to determine whether patients meet
inclusion and exclusion criteria. The screening visit will include a consent form (Appendix A), an ABI/PVR, an ultrasound to confirm the disease burden in the popliteal artery, the San Diego Claudication Questionnaire to confirm true intermittent claudication symptoms (Appendix C), a history and physical exam to determine height, weight, BMI, HbA1c, comorbid conditions, smoking status, number of medications, number of diabetic medications, medication use of cilostazol or pentoxifylline, age, race, and gender, and 6-minute walking distance (in meters) test to assess walking safety.¹

### 3.3 Inclusion Criteria

The following criteria will be obtained at the screening appointment. Participants must be PAD patients with disease burden in the popliteal artery and classic intermittent claudication symptoms in the calf. PAD is defined as either an ABI <.90 at rest or <.73 after exercise. Intermittent claudication is pain that starts with exercise and diminishes after rest. Patients must be able to ambulate safely during a 6-minute walking test (6-MWT) and their distance must be limited by their claudication pain. Due to the importance of sight in this protocol, participants must have intact vision, including the ability to see color.

### 3.4 Exclusion Criteria

Patients without PAD (ABI >.90 at rest or >.73 after exercise), those unable to provide an accurate ABI recording, and those who do not have disease burden in the popliteal artery with associated calf pain will be excluded. Patients with no leg pain, resting leg pain, critical limb ischemia, or acute limb ischemia will be excluded. Patients with impairments that prevent walking on a treadmill, those without access to a safe walking location, and those with exercise ability limited by factors other than
claudication leg pain will be excluded. Participants who started cilostazol or
pentoxifylline within 3 months of the trial start are excluded. Patients with major
medical diseases such as chronic obstructive pulmonary disease, asthma, class III or IV
heart failure, angina, abnormal baseline stress test, active cancer, stroke or TIA in the past
3 months, liver failure, or renal failure will be excluded. Patients with uncontrolled
T2DM, defined as HbA1c >8%, will be excluded. Patients with an allergy to bioadhesive
tape will be excluded because this is needed for attaching the ultrasound probe to the leg.

3.5 Subject Protection and Confidentiality

Prior to recruitment, we will seek approval for the study from the Yale Human
Investigation Committee (HIC) Institutional Review Board (IRB). All participants must
provide written, informed consent prior to participating in the study. There are seven
components in our consent form: the purpose and procedures of the study, potential risks
or discomforts, potential benefits that can be expected from the research, alternatives that
may benefit the participant, a statement regarding confidentiality of information, contact
information in the event of questions, and a statement that research participation is
voluntary. Participants may drop out at any time and this will not impact their current or
future medical care.

The Yale 400 IRB Policy and Confidentiality of Human Health Research
Information document will be used to ensure protection of patient information. The study
will comply with current HIPAA regulations and only gather information that is needed
in order to accomplish the goal of the experiment. Participants must know who will
know about their participation in the study, how the data will be used, who will have
access to the data, how their information will be protected from those who should not
have access, and how long the data will be retained. All information will be deidentified as soon as possible and kept confidential within password-protected, encrypted servers. Everyone involved with the study will complete the Human Subjects Protection Training and HIPAA privacy training. No one involved in the study will have any financial relationship with any component of the study that may create a conflict of interest.

Lastly, since our study takes place in New Haven, it is likely that some of the eligible participants will be employees of YNHH. This eligible group of participants will be informed that participation is not required, and it will not impact their employment or performance evaluation. If the employee chooses to participate, the employee will not experience any coercion and their privacy will be respected. All parts of the study will be done out of sight of employees not directly involved in the study. If the employee chooses not to participate, their supervisor will not be informed under any circumstance.

3.6 Recruitment

The YNHH H&V Center and New Haven area primary care clinics will be given information about the study and flyers (Appendix D) to distribute to eligible participants. Interested patients will be referred to the study. Additionally, the flyers will be mailed to patients between 45 and 70 years old in the New Haven area and participants in prior PAD studies. This study will not include financial compensation because we want to limit the use of additional motivational tools in order attribute any effect to the imaging intervention. Participants will be able to keep the Fitbit activity monitor given to them during the study as compensation for their participation.
3.7 Experimental Protocol

Participants who meet criteria during the screening visit and sign the informed consent to participate will be randomized to either the experimental or control arm of the study. Three participants who meet criteria will undergo a trial of the GTT at the end of the screening visit to ensure the feasibility of strapping the ultrasound probe to participants’ legs for continuous imaging. After, all participants will be invited to the YNHH H&V Center for the baseline visit. They perform the GTT and to fill out several surveys. Prior to starting the treadmill test, ultrasound will be used to locate the stenosis within the popliteal artery. Using Velcro straps and bioadhesive tape, the ultrasound probe will be taped in place over the stenosis allowing for a continuous recording during the test. The GTT will start at 2 mph and 0% grade and increase by 2% every two minutes. At rest, mild, moderate, and severe claudication pain, the ultrasound technician will record the peak systolic velocity (PSV) and take a color Doppler image of flow through the popliteal artery. The treadmill grade and distances to mild, moderate, and severe claudication pain will be measured in both groups. Claudication onset time will also be measured. All distances will be measured in meters and all times in seconds. For safety, a pulse oximetry device will be used to measure heart rate and oxygen saturation throughout the treadmill test and periodic blood pressure recordings will be taken.

After the treadmill test, the principal researcher will show the experimental group their color Doppler image recordings at rest and mild, moderate, and severe pain. The researcher will explain that seeing color within the vasculature means there is blood flow. More color means more blood flow, while less color means less blood flow, which is what is contributing to their symptoms. Participants will be shown two sample images of
what a healthy versus atherosclerotic vessel looks like (Appendix E) and be able to compare them to their own imaging. Participants will be able to ask the researcher any questions regarding their pain and associated imaging at this time.

Both experimental and control groups will meet with the researcher after the treadmill test to get the standard of care instructions for the next 12 weeks and to ask any questions that they have. All participants will be strongly encouraged to exercise to near-maximal claudication pain three days a week for 45 minutes to start, but with increasing frequency in the number of days overtime. Both groups will be given a Fitbit to wear only during their walking exercise sessions and instructions on how to use it. The number of steps during exercise each day will be recorded by the participant either by writing it down or connecting it to an application on their phone.

During the clinic visit, the principal investigators will administer three questionnaires to all participants. Health-related quality of life will be measured using the 36-Item Short Form Survey Instrument (SF-36; Appendix F). The subcategories within this survey are physical functioning, role limitations due to physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to personal or emotional problems, and mental health. The survey is scored from 0 to 100 with higher numbers representing a more favorable health state. The second survey, the Walking Impairment Questionnaire (WIQ; Appendix G), assesses walking distance, stair-climbing, and walking speed. Participants will rate how difficult certain tasks are within these categories from 0 (unable to perform activity) to 4 (no difficulty with activity). Questions within each category are weighted based on difficulty in order to calculate a final score. Scores range from 0 to 100, with 0 being the
most impaired. Lastly, the Fear-Avoidance Belief Questionnaire (FABQ; Appendix H) will measure participants’ fear of their claudication pain and physical activity.\textsuperscript{4} The FABQ determines how much physical activity and normal work impacts their leg pain. Scores range from 0 to 96 with 96 corresponding to the highest level of fear-avoidance beliefs. After completion of the treadmill test and questionnaires, participants will be given a follow-up appointment for 12 weeks after.

At the follow-up visit, the GTT, questionnaires, and 6-MWT will be administered again, but both groups will be shown their images after the treadmill test. They will also be notified of any improvements in, distance to varying levels of claudication pain, PSV through the popliteal artery, 6-MWT distances, and quality of life, fear beliefs, and walking impairment scores. Participants will keep the Fitbit as compensation for participating in the study. Figure 1 outlines the experimental protocol.

\textit{Figure 1. Experimental Protocol}

<table>
<thead>
<tr>
<th>Screening Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Read/ask questions/sign consent form</td>
</tr>
<tr>
<td>• ABI/PVR, Ultrasound</td>
</tr>
<tr>
<td>• San Diego Claudication Questionnaire</td>
</tr>
<tr>
<td>• History and Physical Exam</td>
</tr>
<tr>
<td>• 3 participants will trial the graded treadmill test</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Initial Visit After Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Graded treadmill test</td>
</tr>
<tr>
<td>• Health-related quality of life questionnaire</td>
</tr>
<tr>
<td>• Walking impairment questionnaire</td>
</tr>
<tr>
<td>• Fear-avoidance questionnaire</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-up Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Graded treadmill test showing all participants their vasculature</td>
</tr>
<tr>
<td>• Repeat 3 questionnaires</td>
</tr>
<tr>
<td>• Information on the changes over time</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Home Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Told to exercise to near-maximal pain 3 times a week for 45 minutes (with increasing frequency overtime)</td>
</tr>
<tr>
<td>• Use a FitBit only during exercise sessions to monitor steps/day</td>
</tr>
</tbody>
</table>

12 weeks
3.8 Study Variables and Measures

The intervention will be visualizing color Doppler ultrasound imaging of the popliteal artery taken during mild, moderate, and severe claudication pain. Color Doppler mode is a setting on the ultrasound device that allows for visualization of blood flow through a vessel. It gives information regarding the presence of blood flow, the direction of flow, and speed of flow. Figure 2 is an example of a color Doppler ultrasound recording.

The patients in the control group will not visualize the popliteal artery on ultrasound, but images will still be obtained. The primary dependent variable will be claudication onset time (COT), in seconds, during the standard Yale GTT. Secondary dependent variables include mean walking distances (MWD; in meters) to mild, moderate, and severe claudication pain, 6-MWT distance (meters), peak systolic velocity through the popliteal artery, average steps per day during the 12-week home exercise component, health-related quality of life score, walking impairment score, and the fear-avoidance score. All of these dependent variables will be measured at baseline and follow-up except for average steps per day which will be measured throughout the intervention.

Figure 2: Color Doppler Ultrasound Image of a Stenotic Popliteal Artery. There is blood flow towards and away from the probe, as shown by the red and blue colors. Since the lumen is not full of color, this shows there is an atherosclerotic occlusion.
3.9 Blinding

The participants and the principal investigators will not be blinded to the intervention, but the ultrasound technicians will be. The investigators need to know which participants are in each group in order to show and explain the images, or not. Similarly, the participants will not be blinded during the intervention because it will be clear whether they are seeing their imaging or not. In fact, the study is centered on the experimental group seeing their imaging. The ultrasound technicians are blinded because they will take images of all of the participants during the GTT.

3.10 Assignment of Intervention

Assignment of participants to the experimental or control group will be randomized by a computer program (SAS programming software). We will be using stratified permuted block randomization. We will be stratifying based on HbA1c levels since this is the largest potential confounder. Block randomization will be used to ensure a balance in group sizes since the sample size is relatively small.

3.11 Adherence

The Fitbit will help monitor adherence to home exercise, as it will record daily walking distances. Additionally, post-intervention graded treadmill walking performance will indicate adherence to the home walking protocol. If participants are adherent to exercising at home, the COT and other outcomes are expected to improve. Lastly, this study requires relatively little time from the participants which should increase adherence. It only requires three office visits which should all be less than an hour and a half long. While it will take time for participants to exercise three times a week (or more frequently overtime), this is something that should be incorporated into their daily life.
regardless of the study. All participants will receive free parking and the Fitbit for compensation; this will be advertised on the flyer.

3.12 Monitoring of Adverse Events

In order to mitigate adverse events, only those who have a steady gait during the 6-MWT in the screening visit will be able to participate in the study. During the GTTs, the participant will be told to notify the technician if they are experiencing any chest pain, shortness of breath, lightheadedness, dizziness, or other symptoms that are new for them. Pulse oximetry recordings will be taken continuously throughout the test to observe for any hypoxemia or abnormally elevated/depressed heart rate. Blood pressure recordings will be taken at baseline and periodically during the test to monitor for extreme hypotension or hypertension. Showing participants their imaging after completion of the treadmill test, instead of during it when they are experiencing the pain, will mitigate risks during the treadmill test. If chest pain, shortness of breath, vision changes, hypoxemia, extreme tachycardia or bradycardia, or concerning changes to blood pressure occurs, the test will be stopped. While exercising at home, participants will be encouraged to call the research assistant or medical provider if they experience any new or concerning symptoms.

3.13 Data Collection

The screening appointment clinical and survey data will be collected by the principal investigators and technicians will perform the ABI/PVR and ultrasound. The technicians will also be responsible for all data collection during the treadmill test as well as monitoring the patients’ vitals. We will attempt to limit the number of different technicians administering the tests to avoid administration variability. The principal
investigators will be responsible for explaining the standard at-home exercise protocol to all participants. In addition, the principal investigator will show and explain the imaging to the experimental group after the treadmill test (and to both groups at the follow-up appointment). The investigator will distribute the three questionnaires during the initial and follow-up visits and score them for feedback. This investigator will also obtain the step logs or information from the participants’ phone applications at the follow-up appointment. Having the principal investigator explain the ultrasound images, instead of the ultrasound technicians, will allow for less variability in the explanations and for the technicians to stay within their normal scope of practice. Participants will be responsible for remembering to put on the Fitbit during their home exercise sessions.

3.14 Sample Size Calculation

We based our sample size calculation (Appendix I) on the difference in mean claudication onset time (COT; in seconds) between the experimental and control groups after a mobile health motivational exercise program among PAD patients in the Duscha et al. trial. The experimental group experienced a 205 second increase in COT after the intervention, which is well above the average of 99-132 seconds’ improvement in SET. We strive to create improvement that matches highly successful prior interventions. To see a difference in COT of 205 seconds with a standard deviation of 256 seconds, assuming an alpha of .05 and power of 80% with a 2-tailed hypothesis, we calculated a required sample size of 44. Adjusting for a 10% expected drop-out rate and ensuring an even number, we will recruit 50 participants to be randomized within our study.
3.15 Analysis

The descriptive characteristics include age (years), weight (kg), height (inches), BMI (kg/m²), number of medications, number of diabetic medications, HbA1c, 6-MWT distance, and ABI with mean and standard deviation and gender, race, smoking status, presence of hypertension, medication use of cilostazol or pentoxifylline in the past, and presence of diabetes using relative frequencies. We will perform intention to treat analysis. We will use a significance level of P<0.05 to look for differences among the baseline characteristics. All of the primary and secondary outcomes are continuous variables and will be presented as means with standard deviations. An independent sample Student’s t test will be performed to determine if post-intervention changes from baseline in primary and secondary outcomes are different between groups. ANCOVA will be used to analyze mean changes in primary and secondary outcomes from baseline within each group and adjust for confounders. Statistical significance is defined as P<0.05.

3.16 Timeline and Resources

The recruitment process and experimental protocol will take two years. Prior to recruitment, we expect the Human Investigation Committee (HIC) approval to take 2-3 months. After approval, the next 16 months will be used for a rolling recruitment and study protocol until the target sample size is met. The first 3 eligible participants will test the feasibility of continuous ultrasound recordings during the GTT. This feasibility test will be a shortened version of the treadmill test during the screening appointment, just long enough to ensure the probes will stay in place to obtain quality recordings. They will need to sign an additional consent form (Appendix B). After the probe technique has
been optimized to produce high quality images, other eligible participants will begin the experimental protocol. The number of appointments per day and week will be limited by technician availability. All of the initial appointments must be completed by 16 months into the study to allow for 12 weeks of home exercise and the post-intervention appointment. Upon completion of the study, we expect data analysis to take an additional 3 months; the HIC approval and data analysis are not included in the 2-year time frame.

The Principal Investigator (PI) will be Catherine Yeckel, PhD and the co-PI will be Sarah Fittro, PA-SII. They will present the study to YNHH and Yale University School of Medicine for approval and approach the YNHH H&V Center and local primary care offices to hand out flyers. Sarah Fittro will be responsible for obtaining the descriptive characteristic data during the screening appointment, showing the experimental group their ultrasound images after the treadmill test, explaining the standard of care exercise training to both groups, and administering the questionnaires. Ultrasound technicians at the YNHH H&V Center will perform the ABI/PVR, find the disease within the popliteal artery, administer the GTT, and operate the ultrasound device. Two ultrasound technicians will be needed for each participant appointment to allow for the responsibilities to be split up and increase accuracy. For example, one technician will operate the treadmill and monitor vitals while the other technician operates the ultrasound device. Currently, it is common for at least two ultrasound technicians to be on-site at the YNHH H&V Center. There is already a treadmill within the suite where technicians record an ABI after exercise, so no additional resources are needed for this experiment. The technicians will just need to be trained on how to secure the ultrasound probe during exercise.
References


Chapter 4 - Conclusion

IC PAD is a common debilitating disease worldwide. Exercise is known to improve IC symptoms and PAD outcomes, but adherence is low due to fear of pain, lack of disease knowledge, and poor perceived control over the disease. Adherence to SET and HEPs is low due to cost and accessibility. Finding a way to increase adherence to home exercise by mitigating these barriers is highly desirable. Imaging has been used among other populations to increase exercise adherence. Whether an imaging strategy offers a solution to increase exercise adherence in PAD patients is unknown. The proposed study will use simple, color Doppler ultrasound images to enhance patients’ understanding of their PAD by showing how it impacts their affected leg during a personalized, exercise-associated graded pain scale test. If successful, increased understanding will alleviate fears regarding their pain and motivate them to exercise more and to a higher pain level. This would allow for the motivational component to be given early on during the diagnosis appointment and prevent disease progression.

4.1 Advantages and Disadvantages

The main advantage of the proposed study is its novelty: using imaging to increase exercise adherence breaks into a new realm of techniques to support PAD patients. The data in using imaging to increase exercise adherence among the CAD population is very promising and warrants investigation of imaging use among other populations, such as PAD. The proposed study is advantageous compared to other PAD exercise adherence studies because it addresses at least six reasons for lack of adherence: cost, accessibility, efficiency, fear of claudication pain, lack of health understanding, and lack of perceived control; other studies aimed to increase adherence have not been able to
touch on all of these through one intervention. This intervention provides a feasible, noninvasive, relatively inexpensive way for patients to actually visualize the impact of disease on their body in order to motivate behavior changes early on in the disease process. It also allows patients to visualize the resulting positive impact of their exercise efforts at the subsequent vascular appointment. If effective, this intervention could be used worldwide to decrease economic and health burdens.

While the novelty of this proposed study is an advantage, it also could be a disadvantage. As with any new idea, it may come with unexpected challenges requiring modification of the procedure. Additionally, ideally, we would have a double-blinded study, but it is impossible to blind the participants or the investigators. The study is centered on the experimental group seeing their ultrasound images. Next, the recruitment process is on a volunteer basis, which means those who sign up may be more motivated than the general population; it is hard to predict how this will impact the results. This may even bias the results towards the null, making it more challenging to see a difference; this would mean if the results are significant, they may be even stronger in the general population. Lastly, it may be challenging to motivate exercise in the winter months, especially among those who are low-income and do not belong to exercise facilities. This is a reality of HEPs and requires a broader community solution.

4.2 Feasibility

One of the biggest advantages to this proposal is most of the needed resources already exist at the YNHH Heart and Vascular Center. The ultrasound technicians are already trained in ABI/PVRs, color Doppler ultrasonography, and graded treadmill tests and all of the needed equipment is already there. The only training the technicians will need is
how to strap the ultrasound probe to participants’ legs. Other studies have already attached a device to participants’ legs in the same location, so we should be able to replicate this in our design. As for cost, the study requires a Fitbit and several additional appointments using ultrasound, ABI/PVR, and treadmill equipment. A Fitbit that monitors activity is around $50. Spending relatively little upfront to control the disease will decrease the need for money spent on medications and surgeries in the future. As for timing, it may be challenging to recruit 50 participants who meet all of the criteria in less than two years. This study is unique in that disease burden must be within the popliteal artery due to proximity to the calf. While most of PAD burden is within the popliteal artery, this does limit the population we can recruit from. However, we do not envision this inhibiting recruitment completion because there is a large PAD burden within the New Haven area. Lastly, this study does not require an extensive time commitment from participants; it involves less than 5 hours of appointment time and daily home exercise. While daily exercise will most likely be an adjustment for participants, this is important for their health regardless of the study.

4.3 Clinical Significance

The medical community has not been successful in increasing exercise adherence among PAD patients and the prevalence continues to rise due to increasing incidence in risk factors such as diabetes. Due to the sedentary, high-calorie, and busy American lifestyle, the prevalence of PAD is expected to remain high. Therefore, we need to identify ways to better treat these patients early on in their disease, which the proposed study is well-positioned to do. The IC PAD population is the perfect group of patients to target because this stage is early on in the disease where behavioral changes can still
make a difference. If this study is successful, it will decrease poor outcomes and the need for more costly interventions such as surgery. It would be an easy intervention to incorporate into the diagnostic appointment worldwide because it is simple, noninvasive, and relatively low cost. This intervention offers a different route to obtain the same end goal, improved symptoms and quality of life, that other studies have been trying to achieve. It could be a way to not only produce change during the study, but also sustained behavioral changes after the study.

4.4 Future Directions

This study has the potential to develop an innovative approach to increase exercise adherence among PAD patients. A future direction that could take place after the proposed study is, we could perform the study among those with atherosclerotic burden within any lower extremity artery; eliminating this exclusion criterion would allow for a larger sample size and easier recruitment. This future study would highlight whether the proximity of the popliteal artery to the calf is a necessary component for motivation. Moreover, patients with poorly controlled type 2 diabetes were excluded from our initial trial. These patients would be a good target group for future focus. Most importantly, this study will inform clinicians on how to best increase exercise adherence among PAD patients, which is crucial right now as the prevalence is rising.

In conclusion, using ultrasound to show how PAD impacts the affected leg during a personalized, exercise-associated graded pain scale test is a promising next step to enhance adherence to exercise interventions. The results of the study will demonstrate a means to achieve the extremely challenging task of inducing behavior change to improve PAD outcomes and quality of life.
References

Appendices

Appendix A. Sample HIC Full Consent form
Created using 200 FR.1 HIC Consent For Participation in a Research Project Template

CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT
200 FR.1 (2016-2)

YALE UNIVERSITY SCHOOL OF MEDICINE-YALE-NEW HAVEN HOSPITAL

Study Title: Using Color Doppler Ultrasound to Promote Exercise in Adults with Peripheral Artery Disease
Principal Investigator: Catherine Yeckel, MS, Ph.D.,
Co-Principal Investigator: Sarah Fitro PA-SII
Funding Source: [Insert name of company or agency]

Invitation to Participate and Description of Project

We are inviting you to participate in a research study designed to look at how color Doppler ultrasound can be used to promote exercise among adults with peripheral artery disease. You have been asked to participate because you are an adult with peripheral artery disease and intermittent calf claudication pain and have expressed interest to your primary care or cardiovascular provider. This will be a study with 50 participants. Preliminarily, we will need several participants to trial the treadmill portion of the study. This is the novel component of the study, so we need to ensure the feasibility prior to initiating the complete trial. If you are willing to volunteer for this, please let us know; it will add about 20-30 minutes at the end of your screening appointment.

In order to decide whether or not you wish to be a participant in this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, possible benefits, and possible alternative treatments. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

Screening Appointment: Located at Yale New Haven Hospital Heart and Vascular Center
• An ABI/PVR and ultrasound will be performed to confirm your disease burden is within your popliteal artery; neither of these tests should induce any pain, they are simple diagnostic tests using blood pressure cuffs and an ultrasound device to take images of your blood vessels.
• You will fill out the San Diego Claudication Questionnaire to confirm your symptoms are typically considered intermittent claudication symptoms.
• You will perform a 6-minute walking distance test to assess walking safety and functional ability.
• A provider will perform a basic history and physical exam to determine height, weight, BMI, hemoglobin A1C level, other health conditions, smoking status, medications, age, race, and gender.

**Initial Visit After Screening:** Located at Yale New Haven Hospital Heart and Vascular Center

• Each participant will perform a treadmill test where the incline gradually increases while you walk. Using ultrasound, the place where the blood vessel in your calf is not allowing enough blood flow will be marked with a marker. Velcro and bioadhesive tape will be used to attach the ultrasound probe over this spot to obtain continuous images and blood flow information during the test. The treadmill test starts very slowly, at 2mph, 0% incline and will increase by 2% grade every two minutes. You will be asked to tell the ultrasound technician when you are experiencing mild, moderate, and severe calf pain. Some participants will see their color Doppler ultrasound image at these points and others will not; computer randomization will determine which group you are in. Blood pressure, heart rate, and oxygen saturation will be measured throughout the test for safety.
• Those participants who will see their ultrasound image will be educated on the very basics of what they will be seeing and the meaning of it prior to the graded treadmill test.
• The ultrasound technicians will know which participants are in each group, but the investigators will be blind to this information.
• You will be asked to fill out a health related quality of life survey with 36 questions that will look at your physical functioning, limitations due to health problems, pain, health perceptions, vitality, social functioning, limitations due to personal or emotional problems, and mental health.
• You will be asked to fill out the 22 question Walking Impairment Questionnaire that assesses walking distance, stair-climbing, and walking speed.
• You will be asked to fill out the 16 question Fear-Avoidance Belief Questionnaire (FABQ) which measures your fear of your claudication pain and physical activity.
• You will be given a FitBit and instructions on how to use it while exercising at home.
Home Exercise:

- You will be told to exercise at home 3 times a week (or more overtime) for 45 minutes for 12 weeks. If you reach maximal claudication pain during exercise, you may stop temporarily until pain dissipates.
- You will wear the provided FitBit only during exercise to monitor your steps/day.
- You will record your number of steps/day by writing it down or connecting the FitBit to a phone application to automatically collect the data.

Follow-Up Visit: Located at Yale New Haven Hospital Heart and Vascular Center

- You will perform the same treadmill test and 6-minute walk test again. You will also fill out the same three questionnaires again.
- During this treadmill test everyone will be shown their vasculature on ultrasound and will be notified of any changes in how long they can walk until they experience different levels of pain.
- You will be notified of any change in distance walked during the 6-minute walk test.
- You will be notified of any changes to your quality of life, fear beliefs, and walking impairment scores.

Overall:

- The study consists of three appointments at YNHH, ranging from about 1-2 hours long, where you will undergo diagnostic tests, fill out questionnaires, perform a 6-minute walk test, and perform a graded treadmill test. You will be instructed to exercise at home to near-maximal claudication pain for 12 weeks prior to coming back in for follow-up tests.
- After screening is complete, the entire protocol will span over 5-6 months.
- A computer randomization program will determine whether participants will see their vasculature on ultrasound with their claudication pain during the graded treadmill test or not.

A description of this clinical trial will be available on [http://www.ClinicalTrials.gov](http://www.ClinicalTrials.gov), as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

You will be told of any significant new findings that are developed during the course of your participation in this study that may affect your willingness to continue to participate.

Risks and Inconveniences

- Exercising on the treadmill and at home comes with risks, but we hope to minimize these risks in several different ways:
During the treadmill test, medical professionals will be monitoring your blood pressure, pulse, and oxygen saturation. You will be expected to wear sneakers and exercise clothing to limit mechanical falls while exercising. Those with chronic obstructive pulmonary disease, asthma, class III or IV heart failure, angina, an abnormal baseline stress test, or difficulty balancing while walking will not be eligible for the study. If you experience concerning symptoms during the treadmill test, the test will be stopped and appropriate interventions will occur to ensure the health and safety of the participant. You will be given the number of a provider to call if you experience symptoms while exercising at home.

• While exercising on the treadmill and at home, you will experience mild to severe claudication pain which will feel uncomfortable. However, experiencing this pain is a necessary component to our study and does not put you in danger.
• If you are an employee of YNHH or Yale University, your privacy will be respected. All parts of the study will be done out of sight of any other employees not directly involved in the study. If you choose not to participate, your employer will not be notified and in no way will this impact your performance evaluation.
• You will need to come to YNHH for 3 appointments ranging from 1-2 hours long; parking will be free for these appointments.

Benefits:

• This research may show the role of imaging in improving exercise adherence in adults with peripheral artery disease. Imaging may be a way to decrease the amount of medications and surgical interventions needed, decrease claudication pain associated fear, and improve health-related quality of life among adults with peripheral artery disease.
• We expect this study to benefit society at large by advancing scientific knowledge.

Economic Considerations

• You will be reimbursed for parking fees at YNHH for the three required appointments. Transportation costs to get you to YNHH will not be covered by the research study.
• You will be allowed to keep the FitBit provided to you during the study.
• The screening ABI/PVR and ultrasound, screening history and physical exam, monitored graded treadmill test, and monitored 6-minute walk test will be provided at no cost to you.

Treatment Alternatives/Alternatives

• Other treatment options to improve claudication symptoms and secondary outcomes are supervised exercise training, cilostazol, multi-drug regimens (anti-
platelet medications, lipid lowering medications, and blood pressure medications), and surgery. These treatments will not be used in this study.

Confidentiality

- Your data will be de-identified within 1 week of acquisition of all study data and it will remain unidentified indefinitely.
- All study data will be recorded on the computer and password protected.
- ABI/PVR results, ultrasound recordings, height, weight, BMI, hgb A1C, comorbid conditions, medications, age, race, and sex will be entered into your Electronic Medical Record (EMR) and will therefore be accessible to future providers who are in your EMR. Information within your EMR may also be shared with others who are appropriate to have access to your EMR (e.g. health insurance companies, disability provider).
- Only information that is necessary to complete the study will be collected.
- If you choose to have your FitBit connected to a phone application to record the data, only you will have access to this application. Research investigators will ask you to show this data at the follow-up appointment. They will only need the total number of steps for the three months, provided by the monthly summaries in the application.

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific permission for this activity is obtained.

Representatives from Yale University, the Yale Human Research Protection Program, and the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects) may inspect study records during internal auditing procedures. However, these individuals are required to keep all information confidential.

In Case of Injury

If you are injured while on the study, seek treatment and contact the study doctor as soon as you are able.

Yale School of Medicine and Yale-New Haven Hospital do not provide funds for the treatment of research-related injury. If you are injured as a result of your participation in the study, treatment will be provided. You or your insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.

You do not give up any of your legal rights by signing this form.
**Voluntary Participation and Withdrawal**

- You will have the ability to withdraw your data from the research, but only before it has been de-identified one week after data collection is complete.
- If you have required medical needs upon withdrawal, these should be stated. Any follow-up procedures or assessments accompanying the withdrawal should be clearly explained.

You are free to choose not to participate. If you do decide to become a subject, you are free to withdraw from this study at any time during its course. Refusing to participate or withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled (such as health care outside the study, payment for your healthcare, and your health care benefits). If you decide not to participate or you withdraw, it will not harm your relationship with your own doctors or with Yale-New Haven Hospital. We would still offer other treatment options.

The researchers may withdraw you from the research study if you develop serious side effects or are noncompliant.

**Questions**

We have used some technical terms in this form. Please feel free to ask about anything you don’t understand and to consider this research and consent form carefully – as long as you feel necessary – before you make a decision.

**Authorization and Consent**

I have read (or someone has read to me) this form and have decided to participate in the project described above. In general purposes, the particulars of my involvement and hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

By signing this form, I give permission to the researchers to use (and give out) information about myself for the purpose described in this form. By refusing to give permission, I understand that I will not be able to be in this research.

Name of Subject: ________________________________

Signature: _________________________________

Relationship: ________________________________

Date: ________________________________

__________________________________________
Signature of Principal Investigator/Person Obtaining Consent          Date
If you have further questions about this project of if you have a research-related problem, you may contact the Co-Principal Investigator, Sarah Fittro PA-SII at (xxx)-xxx-xxxx or the Principal Investigator, Catherine Yeckel, Ph.D. at (xxx)-xxx-xxxx.

If after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203-432-5919.

If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at 203-785-4688.
Appendix B. Sample HIC Preliminary Treadmill Test Consent Form
Created using 200 FR.1 HIC Consent For Participation in a Research Project Template

CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT
200 FR.1 (2016-2)

YALE UNIVERSITY SCHOOL OF MEDICINE-YALE-NEW HAVEN HOSPITAL

Study Title: Using Color Doppler Ultrasound to Promote Exercise in Adults with Peripheral Artery Disease
Principal Investigator: Catherine Yeckel, MS, Ph.D.,
Co-Principal Investigator: Sarah Fittro PA-SII
Funding Source: [Insert name of company or agency]

Invitation to Participate and Description of Project

You have already consented to participate in a research study designed to look at how color Doppler ultrasound can be used to promote exercise among adults with peripheral artery disease. The study will consist of 50 participants, but several early enrolled participants will be asked to trial the treadmill portion of the study which is the basis of this consent form.

In order to decide whether or not you wish to be a participant in this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, possible benefits, and possible alternative treatments. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

Graded Treadmill Test: Located at Yale New Haven Hospital Heart and Vascular Center
- You have already been deemed eligible for the study during the screening appointment; this treadmill test will occur at the end of the same appointment and will add approximately 30 minutes.
- Using ultrasound, the place where the blood vessel in your calf is not allow enough blood flow will be marked with a marker on your leg. Using Velcro straps and bioadhesive tape, the color Doppler ultrasound probe will be put over this spot to allow for continuous images and blood flow recordings as you complete the treadmill test.
- The treadmill test starts very slowly, at 2mph, 0% incline and will increase by 2% grade every two minutes. You will be asked to tell the technician when you are
experiencing mild, moderate, and severe calf pain. Blood pressure, heart rate, and oxygen saturation will be measured throughout the test for safety.

- It will not impact which group you are randomized to afterwards as the computer is responsible for this randomization.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

You will be told of any significant new findings that are developed during the course of your participation in this study that may affect your willingness to continue to participate.

**Risks and Inconveniences**

- Exercising on the treadmill comes with risks, but we hope to minimize these risks in several different ways:
  - During the treadmill test, medical professionals will be monitoring your blood pressure, pulse, and oxygen saturation.
  - You will be expected to wear sneakers and exercise clothing to limit mechanical falls while exercising.
  - Those with chronic obstructive pulmonary disease, asthma, class III or IV heart failure, angina, an abnormal baseline stress test, or difficulty balancing while walking will not be eligible for the study.
  - If you experience concerning symptoms during the treadmill test, the test will be stopped and appropriate interventions will occur to ensure the safety and health of the participant.

- While exercising on the treadmill, you will experience mild to severe claudication pain which will feel uncomfortable. However, experiencing this pain is a necessary component to our study and does not put you in any danger.

- If you are an employee of YNHH or Yale University, your privacy will be respected. The treadmill test will be done out of sight of any other employees not directly involved in the study. If you choose not to participate, your employer will not be notified and in no way will this impact your performance evaluation.

**Benefits:**

- Ensuring the graded treadmill component is properly designed is a critical part of this study. Allowing for this to happen will help the study be as effective as possible.

**Economic Considerations**

- You will be reimbursed for parking fees at YNHH for the appointment. You will not have to come to the hospital an additional time for this treadmill trial, it will
be part of the screening appointment. Transportation costs to get you to YNHH will not be covered by the research study.

- The monitored graded treadmill test will be provided at no cost to you.

**Confidentiality**

- Your data will be de-identified within 1 week of acquisition of all study data and it will remain unidentified indefinitely.
- All study data will be recorded on the computer and password protected.
- The ultrasound recordings will be entered into your Electronic Medical Record (EMR) and will therefore be accessible to future providers who are in your EMR. Information within your EMR may also be shared with others who are appropriate to have access to your EMR (e.g. health insurance companies, disability provider).
- Only information that is necessary to complete the study will be collected.

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

Representatives from Yale University, the Yale Human Research Protection Program, and the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects) may inspect study records during internal auditing procedures. However, these individuals are required to keep all information confidential.

**In Case of Injury**

Yale School of Medicine and Yale-New Haven Hospital do not provide funds for the treatment of research-related injury. If you are injured as a result of your participation in the study, treatment will be provided. You or your insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.

You do not give up any of your legal rights by signing this form.

**Voluntary Participation and Withdrawal**

- You will have the ability to withdraw your data from the research, but only before it has been de-identified one week after data collection is complete.
- If you have required medical needs upon withdrawal, these should be stated. Any follow-up procedures or assessments accompanying the withdrawal should be clearly explained.
You are free to choose not to participate. If you do decide to become a subject, you are free to withdraw from this study at any time during its course. Refusing to participate or withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled (such as health care outside the study, payment for your healthcare, and your health care benefits). If you decide not to participate or you withdraw, it will not harm your relationship with your own doctors or with Yale-New Haven Hospital. We would still offer other treatment options.

The researchers may withdraw you from the research study if you develop serious side effects or are noncompliant.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don’t understand and to consider this research and permission form carefully – as long as you feel necessary – before you make a decision.

Authorization and Consent

I have read (or someone has read to me) this form and have decided to participate in the project described above. In general purposes, the particulars of my involvement and hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

By signing this form, I give permission to the researchers to use (and give out) information about myself for the purpose described in this form. By refusing to give permission, I understand that I will not be able to be in this research.

Name of Subject: ________________________________

Signature: ________________________________

Relationship: ________________________________

Date: ________________________________

________________________________________
Signature of Principal Investigator/Person Obtaining Consent       Date

If you have further questions about this project or if you have a research-related problem, you may contact the Co-Principal Investigator, Sarah Fittro PA-SII at (xxx)-xxx-xxxx or the Principal Investigator, Catherine Yeckel, Ph.D. at (xxx)-xxx-xxxx.
If after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203-432-5919.

If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at 203-785-4688.
### Appendix C. San Diego Claudication Questionnaire

1. Do you get pain in either leg or either buttock on walking? If no, or uncertain, stop.
   - No……. 1 1
   - Yes……. 2 2
   - Uncertain…… 9 9

2. Does this pain ever begin when you are standing still or sitting?
   - No……. 1 1
   - Yes……. 2 2
   - Uncertain…… 9 9

3. In what part of the leg or buttock do you feel it?
   - a. Pain includes calf/calves
   - b. Pain includes thigh/thighs
   - c. Pain includes buttocks
   - No……. 1 1
   - Yes……. 2 2
   - No……. 1 1
   - Yes……. 2 2

4. Do you get it when you walk uphill or hurry?
   - No……. 1 1
   - Yes……. 2 2
   - Never walks uphill… 3 3

5. Do you get it when you walk at an ordinary pace on the level?
   - No……. 1 1
   - Yes……. 2 2
   - Uncertain….. 9 9

6. Does the pain ever disappear while you are walking?
   - No……. 1 1
   - Yes….. 2 2
   - Uncertain….. 9 9

7. What do you do if you get it when you walking?
   - Stop or slow down…. 1 1
   - Carry on…. 2 2

8. What happens to it if you stand still? If unchanged, stop.
   - Lessens or relieved… 1 1
   - Unchanged… 2 2

9. How soon?
   - 10 minutes or less… 1 1
   - More than 10 minutes.2 2
Appendix D. Recruitment Flyer

Volunteers Needed for Research on Peripheral Artery Disease

Do you have **pain in your calves when walking**? You may be eligible for a study that could improve your symptoms and overall health.

You May Qualify If You:
- Have calf pain when walking
- Do not have asthma, COPD, heart failure, or coronary artery disease
- Have not recently started medications to help with the calf pain

Participation Involves:
- Three appointments at Yale New Haven Hospital that involve questionnaires, treadmill tests, and diagnostics
- 12 weeks of home exercise

Compensation
- You will use a FitBit during the study and keep it as compensation
- Free Parking at Yale-New Haven Hospital

FOR MORE INFORMATION:
Please contact Sarah Fittro at (xxx)-xxx-xxxx or Email: sarah.fittro@yale.edu
Appendix E. Healthy Versus Atherosclerotic Color Doppler Ultrasound

This is a healthy artery. The vessel is fully filled with blood moving in the same direction represented by the red color filling the vessel walls. This is not seen in the affected vessels of peripheral artery disease patients.

This is an unhealthy artery. Only a little bit of blood is passing through the vessel presented by the small portion of red color. The rest of the vessel is filled with plaque which is preventing adequate blood flow. This is seen in patients with peripheral artery disease.
Appendix F. Health-Related Quality of Life Short Form-36 Questionnaire

SF-36 QUESTIONNAIRE

Name: ____________________________ Ref. Dr: ____________________________ Date: _______

ID#: ____________________________ Age: _________ Gender: M / F

Please answer the 36 questions of the Health Survey completely, honestly, and without interruptions.

GENERAL HEALTH:
In general, would you say your health is:
☐ Excellent ☐ Very Good ☐ Good ☐ Fair ☐ Poor

Compared to one year ago, how would you rate your health in general now?
☐ Much better now than one year ago
☐ Somewhat better now than one year ago
☐ About the same
☐ Somewhat worse now than one year ago
☐ Much worse than one year ago

LIMITATIONS OF ACTIVITIES:
The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.
☐ Yes, Limited a lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Lifting or carrying groceries
☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Climbing several flights of stairs
☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Climbing one flight of stairs
☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Bending, kneeling, or stooping
☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all
Walking more than a mile
☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Walking several blocks
☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Walking one block
☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Bathing or dressing yourself
☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

PHYSICAL HEALTH PROBLEMS:
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Cut down the amount of time you spent on work or other activities
☐ Yes ☐ No

Accomplished less than you would like
☐ Yes ☐ No

Were limited in the kind of work or other activities
☐ Yes ☐ No

Had difficulty performing the work or other activities (for example, it took extra effort)
☐ Yes ☐ No

EMOTIONAL HEALTH PROBLEMS:
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Cut down the amount of time you spent on work or other activities
☐ Yes ☐ No

Accomplished less than you would like
☐ Yes ☐ No

Didn't do work or other activities as carefully as usual
☐ Yes ☐ No

SOCIAL ACTIVITIES:
Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?
☐ Not at all ☐ Slightly ☐ Moderately ☐ Severe ☐ Very Severe

PAIN:
How much bodily pain have you had during the past 4 weeks?
☐ None ☐ Very Mild ☐ Mild ☐ Moderate ☐ Severe ☐ Very Severe
During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?
- Not at all
- A little bit
- Moderately
- Quite a bit
- Extremely

ENERGY AND EMOTIONS:
These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

Did you feel full of pep?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a very nervous person?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt so down in the dumps that nothing could cheer you up?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt calm and peaceful?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you have a lot of energy?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time
Have you felt downhearted and blue?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel worn out?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a happy person?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel tired?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

SOCIAL ACTIVITIES:
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?
- All of the time
- Most of the time
- Some of the time
- A little bit of the time
- None of the Time

GENERAL HEALTH:
How true or false is each of the following statements for you?

I seem to get sick a little easier than other people
- Definitely true
- Mostly true
- Don't know
- Mostly false
- Definitely false
I am as healthy as anybody I know

- Definitely true
- Mostly true
- Don't know
- Mostly false

I expect my health to get worse

- Definitely true
- Mostly true
- Don't know
- Mostly false

My health is excellent

- Definitely true
- Mostly true
- Don't know
- Mostly false
Appendix G. Walking Impairment Questionnaire

Walking Impairment Questionnaire

A. WALKING IMPAIRMENT: These questions ask about the reasons why you had difficulty walking. We would like to know how much difficulty you had walking because of each of these problems during the last week. (By difficulty, we mean how much physical effort it took to walk because of each of these problems.)

<table>
<thead>
<tr>
<th>Reason for Difficulty</th>
<th>Leg</th>
<th>Degree of Difficulty</th>
</tr>
</thead>
<tbody>
<tr>
<td>01. Pain, aching, or cramps in calves (or buttocks)?</td>
<td>□ Both □ Right □ Left</td>
<td>□ 4 □ 3 □ 2 □ 1 □ 0</td>
</tr>
<tr>
<td>02. Pain or aching in thighs?</td>
<td>□ Both □ Right □ Left</td>
<td>□ 4 □ 3 □ 2 □ 1 □ 0</td>
</tr>
<tr>
<td>03. Pain, stiffness, or aching in joints (ankles, knees, or hips)?</td>
<td></td>
<td>□ 4 □ 3 □ 2 □ 1 □ 0</td>
</tr>
<tr>
<td>04. Weakness in one or both legs?</td>
<td></td>
<td>□ 4 □ 3 □ 2 □ 1 □ 0</td>
</tr>
<tr>
<td>05. Pain or discomfort in your chest?</td>
<td></td>
<td>□ 4 □ 3 □ 2 □ 1 □ 0</td>
</tr>
<tr>
<td>06. Shortness of breath?</td>
<td></td>
<td>□ 4 □ 3 □ 2 □ 1 □ 0</td>
</tr>
<tr>
<td>07. Heart palpitations?</td>
<td></td>
<td>□ 4 □ 3 □ 2 □ 1 □ 0</td>
</tr>
<tr>
<td>08. Other problems? (please list)</td>
<td></td>
<td>□ 4 □ 3 □ 2 □ 1 □ 0</td>
</tr>
</tbody>
</table>
B. WALKING DISTANCE: Please report the degree of physical difficulty that best describes how hard it was for you to walk on level ground without stopping to rest for each of the following distances during the last week.

<table>
<thead>
<tr>
<th>Distance</th>
<th>None</th>
<th>Slight</th>
<th>Some</th>
<th>Much</th>
<th>Unable</th>
</tr>
</thead>
<tbody>
<tr>
<td>09. Walking indoors (i.e., around the home)?</td>
<td>☐ 4</td>
<td>☐ 3</td>
<td>☐ 2</td>
<td>☐ 1</td>
<td>☐ 0</td>
</tr>
<tr>
<td>10. Walking 50 feet?</td>
<td>☐ 4</td>
<td>☐ 3</td>
<td>☐ 2</td>
<td>☐ 1</td>
<td>☐ 0</td>
</tr>
<tr>
<td>11. Walking 150 feet (1/2 block)?</td>
<td>☐ 4</td>
<td>☐ 3</td>
<td>☐ 2</td>
<td>☐ 1</td>
<td>☐ 0</td>
</tr>
<tr>
<td>12. Walking 300 feet (1 block)?</td>
<td>☐ 4</td>
<td>☐ 3</td>
<td>☐ 2</td>
<td>☐ 1</td>
<td>☐ 0</td>
</tr>
<tr>
<td>13. Walking 600 feet (2 blocks)?</td>
<td>☐ 4</td>
<td>☐ 3</td>
<td>☐ 2</td>
<td>☐ 1</td>
<td>☐ 0</td>
</tr>
<tr>
<td>14. Walking 900 feet (3 blocks)?</td>
<td>☐ 4</td>
<td>☐ 3</td>
<td>☐ 2</td>
<td>☐ 1</td>
<td>☐ 0</td>
</tr>
<tr>
<td>15. Walking 1500 feet (5 blocks)?</td>
<td>☐ 4</td>
<td>☐ 3</td>
<td>☐ 2</td>
<td>☐ 1</td>
<td>☐ 0</td>
</tr>
</tbody>
</table>

C. WALKING SPEED: Please report the degree of physical difficulty that best describes how hard it was for you to walk one city block on level ground at each of these speeds without stopping to rest during the last week.

<table>
<thead>
<tr>
<th>Speed</th>
<th>None</th>
<th>Slight</th>
<th>Some</th>
<th>Much</th>
<th>Unable</th>
</tr>
</thead>
<tbody>
<tr>
<td>16. Walking 1 block slowly?</td>
<td>☐ 4</td>
<td>☐ 3</td>
<td>☐ 2</td>
<td>☐ 1</td>
<td>☐ 0</td>
</tr>
<tr>
<td>17. Walking 1 block at an average speed?</td>
<td>☐ 4</td>
<td>☐ 3</td>
<td>☐ 2</td>
<td>☐ 1</td>
<td>☐ 0</td>
</tr>
<tr>
<td>18. Walking 1 block quickly?</td>
<td>☐ 4</td>
<td>☐ 3</td>
<td>☐ 2</td>
<td>☐ 1</td>
<td>☐ 0</td>
</tr>
<tr>
<td>19. Running or jogging 1 block?</td>
<td>☐ 4</td>
<td>☐ 3</td>
<td>☐ 2</td>
<td>☐ 1</td>
<td>☐ 0</td>
</tr>
</tbody>
</table>

D. STAIR CLIMBING: For each of these questions, please report the degree of physical difficulty that best describes how hard it was for you to climb stairs without stopping to rest during the last week.

<table>
<thead>
<tr>
<th>Stairs</th>
<th>None</th>
<th>Slight</th>
<th>Some</th>
<th>Much</th>
<th>Unable</th>
</tr>
</thead>
<tbody>
<tr>
<td>20. Climbing 1 flight of stairs?</td>
<td>☐ 4</td>
<td>☐ 3</td>
<td>☐ 2</td>
<td>☐ 1</td>
<td>☐ 0</td>
</tr>
<tr>
<td>21. Climbing 2 flights of stairs?</td>
<td>☐ 4</td>
<td>☐ 3</td>
<td>☐ 2</td>
<td>☐ 1</td>
<td>☐ 0</td>
</tr>
<tr>
<td>22. Climbing 3 flights of stairs?</td>
<td>☐ 4</td>
<td>☐ 3</td>
<td>☐ 2</td>
<td>☐ 1</td>
<td>☐ 0</td>
</tr>
</tbody>
</table>
Appendix H. Fear-Avoidance Beliefs Questionnaire (FABQ)\textsuperscript{7}

**Fear-Avoidance Beliefs Questionnaire (FABQ)**
Here are some of the things which other patients have told us about their pain. For each statement please circle any number from 0 to 6 to say how much physical activities such as bending, lifting, walking or driving affect or would affect your back pain.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Completely Disagree</th>
<th>Unsure</th>
<th>Completely Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. My pain was caused by physical activity</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Physical activity makes my pain worse</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Physical activity might harm my back</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. I should not do physical activities which (might) make my pain worse</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. I cannot do physical activities which (might) make my pain worse</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The following statements are about how your normal work affects or would affect your back pain.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Completely Disagree</th>
<th>Unsure</th>
<th>Completely Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. My pain was caused by my work or by an accident at work….</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. My work aggravated my pain</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. I have a claim for compensation for my pain</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. My work is too heavy for me</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. My work makes or would make my pain worse</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. My work might harm my back</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. I should not do my normal work with my present pain</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. I cannot do my normal work with my present pain</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. I cannot do my normal work till my pain is treated</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. I do not think that I will be back to my normal work within 3 months</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16. I do not think that I will ever be able to go back to that work…</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix I. Sample Size Calculation

Data from the Duscha Study\textsuperscript{8} (n=20):

Standard of Care/Control Group:

- Pre-intervention mean claudication onset time: 252±256s
- Post-intervention mean claudication onset time: 231±196s
- Mean difference: -21s

Mobile Health/Experimental Group:

- Pre-intervention mean claudication onset time: 320±226s
- Post-intervention mean claudication onset time: 525±252s
- Mean difference: 205s

Sample size calculation based on a t-test for 2 independent samples with common variance:

Alpha (level of confidence, $\alpha$): .05 (two-tailed hypothesis)
B (Type II error, $\beta$): .18, therefore, 82\% power
Effect size based on mean differences among the two populations: -21s and 205s

\[ \text{N}=44 \text{ (22 per group)} \]

Factoring in a 10\% drop-out and ensuring an even number of subjects to make groups even results in a **required sample size of n = 50**.

Power and Precision, Version 4.0. Biostat.Inc. Englewood, New Jersey was used for calculation.
References


Bibliography


Dumville JC, Lee AJ, Smith FB, Fowkes FG. The health-related quality of life of people with peripheral arterial disease in the community: the Edinburgh Artery Study. *The*


