GAME PAD

Gamification-Augmented hoMe-based Exercise for Peripheral Artery Disease

Version 1.3

April 27, 2022

1. Background

1.1. Prevalence of Peripheral Artery Disease and Impact

Peripheral artery disease (PAD), defined as atherosclerotic narrowing or occlusion of at least one peripheral artery, affects > 200 million people worldwide and is associated with substantial morbidity and healthcare costs.[1–3] Though patients may develop atherosclerotic vascular disease in any peripheral vascular bed – cerebrovascular, mesenteric, upper extremity, lower extremity – symptomatic PAD most often involves the lower extremity, and most often presents as intermittent claudication. Intermittent claudication is characterized by leg soreness or heaviness with ambulation, and often causes substantial functional limitation.[4] Though a minority of patients with peripheral artery disease have classic intermittent claudication, a greater proportion have lower extremity symptoms, and even those who do not report claudication may have substantial unrecognized functional limitation.[4,5]

1.2. Supervised Exercise for Peripheral Artery Disease

Pivotal clinical trials in patients with intermittent claudication showed that supervised treadmill exercise improved walking performance and functional capacity. In a meta-analysis of these trials, which included 25 studies enrolling a total of 1054 patients, supervised treadmill exercise, as compared with observational control, increased maximum walking distance by 180 meters and pain-free walking distance by 125 meters.[6] Supervised treadmill exercise also improves six-minute walk distance and subjective measures of quality of life and functional capacity. Based on these trials, supervised treadmill exercise is a class IA recommendation in the American Heart Association/American College of Cardiology and Society for Vascular Surgery clinical practice guidelines.[7,8]

Supervised treadmill exercise programs are characterized by several features. Patients attend sessions in person 3 times per week, and walk on a treadmill while supervised by an exercise physiologist. Sessions initially last 15 minutes, with a goal of increasing to 45 or 50 minutes by the end of the program. Classically, exercise is high-intensity, and the treadmill's pace and angle is set so that patients develop near maximal or maximal leg pain while exercising. A typical supervised treadmill exercise program lasts 6 months. More recent data has challenged this paradigm: In a meta-regression of 25 supervised treadmill exercise trials, programs designed to produce only mild claudication pain, or even to allow patients to walk at their own pain-free pace, led to the similar improvements in maximum and pain-free walking distance compared with higher intensity programs, and programs lasting 12-26 weeks led to as much benefit as those with longer durations.[6]

Importantly, it is not only patients with classic claudication symptoms that benefit from supervised treadmill exercise. Two randomized controlled trials of supervised treadmill exercise included patients with and without classic claudication symptoms, and patients without classic claudication also increased treadmill walking time and 6 minute walk distance.[9,10]

1.3. Home-Based Exercise for Peripheral Artery Disease

Despite the benefits of supervised treadmill exercise, many patients do not participate. Supervised treadmill exercise requires patients to travel to a qualified exercise center three times per week, and though Medicare covers supervised treadmill exercise, patients with PAD tend to be older and have functional limitation,[11] and struggle with transportation and logistics. In a

systematic review of patients with PAD eligible for supervised exercise, 50% of patients refused participation and a further 19% reported that attending supervised exercise sessions would be too inconvenient.[12] A home-based walking intervention is likely to be more accessible to patients with PAD, and such interventions have been tested in 5 randomized controlled trials.

Gardner et al. randomized patients with PAD and intermittent claudication to either supervised treadmill exercise (3 times/week, 40 minutes per session, moderate to high intensity), home-based exercise, or control.[13] Participants randomized to home-based exercise were instructed to walk for 45 minutes, 3 times/week, at their own pace. They wore activity monitors to track exercise, and returned to the center every 2 weeks to meet with an exercise physiologist, review their progress, and set goals for the next 2 weeks. Both supervised treadmill exercise and home-based exercise increased maximal and pain-free walking distance at 12 weeks' follow-up compared with control.

In a similar study, Gardner et al. again randomized patients to traditional supervised treadmill exercise, home-based exercise, or an upper extremity exercise control.[14] Patients randomized to home-based exercise returned to the study center at 1, 4, 8, and 12 weeks for face-to-face meetings with an exercise physiologist to review their progress and set goals for the next 3-4 weeks. Both the supervised treadmill exercise group and the home-based exercise group increased treadmill walking time and 6 minute walk distance compared with control at 12 month follow-up, with the home-based walking group actually increasing 6 minute walk distance by more than the supervised treadmill exercise group.

The Group Oriented Arterial Leg Study (GOALS) randomized patients with PAD to a group-mediated cognitive behavioral theory intervention or an attention control group.[10] Patients in the group-mediated cognitive behavioral theory arm met with other patients with PAD and a coach on a weekly basis, and spent 45 minutes discussing topics such as goal-setting, self-monitoring, and overcoming obstacles to home-based exercise, and then another 45 minutes walking around a track. Compared with control, the group-mediated cognitive behavior theory intervention arm increased treadmill walking distance, 6 minute walk, and other patient-reported measures of quality of life and functional capacity at 6 month follow-up.

Another trial, which enrolled patients with diabetes mellitus and PAD randomized patients to a group behavioral intervention similar to that studied in the GOALS trial versus attention control. Unlike the GOALS trial, this study did not show an improvement in treadmill walking distance.[15]

Though these trials tested home-based walking interventions, all required participants to come to in-person visits at least every 3 weeks, and most required at least weekly in-person visits. By contrast, the HONOR clinical trial tested a home-based walking program that included weekly visits during the first month of therapy, during which patients walked for exercise and were assisted with setting goals for exercise, followed by 8 months of a wearable monitor and telephone coaching.[16] The coach called participants weekly during the beginning of the study with gaps between calls gradually increasing to one month. Participants wore a FitBit monitor during the study, and the coach had access to FitBit data, which was used to help patients set goals for future exercise. At the end of 9 months, there was no difference between patients

randomized to the home-based walking intervention and the control arm on treadmill walking distance, 6 minute walk, or patient-reported measures of quality of life and functional capacity. The failure of the truly home-based walking intervention to change patients' behavior is consistent with multiple prior failures of workplace wellness programs and health and fitness apps to change participants' behavior: In all cases, the interventions have not appropriately leveraged principles from theories of health behavior.[17,18]

1.4 Behavioral Economic Approaches to Encouraging Physical Activity

In a recent clinical trial, a gamification intervention, leveraging insights from behavioral economics, successfully increased physical activity among overweight and obese adults compared with goal-setting alone.[19] In STEP UP, obese and overweight adults were provided with wearable fitness trackers and randomized to one of four interventions to increase physical activity: Goal-setting alone or goal-setting plus one of 3 different gamification strategies. In all arms, participants' baseline daily step count was determined using the wearable fitness tracker during the study's first two weeks, and then participants set a goal of increasing step count by 33, 40, or 50% over the next 6 months. In the gamification arm, participants participated in an intervention that employed behavioral economic principles to increase physical activity, in addition to goal setting.

Specifically, all three gamification interventions leveraged four key behavioral economic concepts, and participants were randomized to one of 3 additional strategies. First, participants signed a precommittment pledge to strive to achieve their goal, and participated in a ramp-up period, during which their daily step goal target increased gradually. Precommittment has been shown to motivate behavioral change, and the ramp-up period provides patients with achievable, incremental improvements.[20] Second, the gamification intervention leveraged prospect theory and loss framing, by providing patients with 70 points every Monday, and taking away 10 points each day if they failed to meet their daily step goal target.[21] Third, the gamification intervention leveraged the fresh start effect by giving participants a fresh set of 70 points each week.[22] Fourth, the gamification intervention leveraged achievable goal gradients, social status, and progression through the game by having patients move up or down through five levels at the end of each week based on the number of points they have accrued that week. All gamification intervention arm patients were further randomized into competition, cooperation, and support arms. In the competition arm, participants were put into a group with 2 other study participants, and could access a leaderboard that showed their relative progress versus the other 2 participants. In the cooperation arm, participants worked together in teams of 3, and a team member was randomly selected to represent the team for each day, making each team member accountable to the others. In the support arm, participants provided researchers with the email of a close friend or family member, who received weekly updates on the participants' progress. Each of the 3 behavioral economic-enhanced gamification interventions increased step count from baseline until 6 month follow-up more than goal-setting alone, demonstrating the power of such approaches to help participants increase physical activity.

1.5 Rationale for the GAME PAD Study

The STEP UP study showed the utility of gamification and behavioral economics to increase physical activity, succeeding in circumstances where interventions that did not leverage behavioral economic principles had previously failed. Prior studies of home-based exercise have either required frequent study center visits or have not been effective; however, these programs

that have not employed behavioral economic principles. This study seeks to test whether gamification and behavioral economic principles can be leveraged in a successful, fully home-based exercise program for patients with PAD.

2. Study Objectives

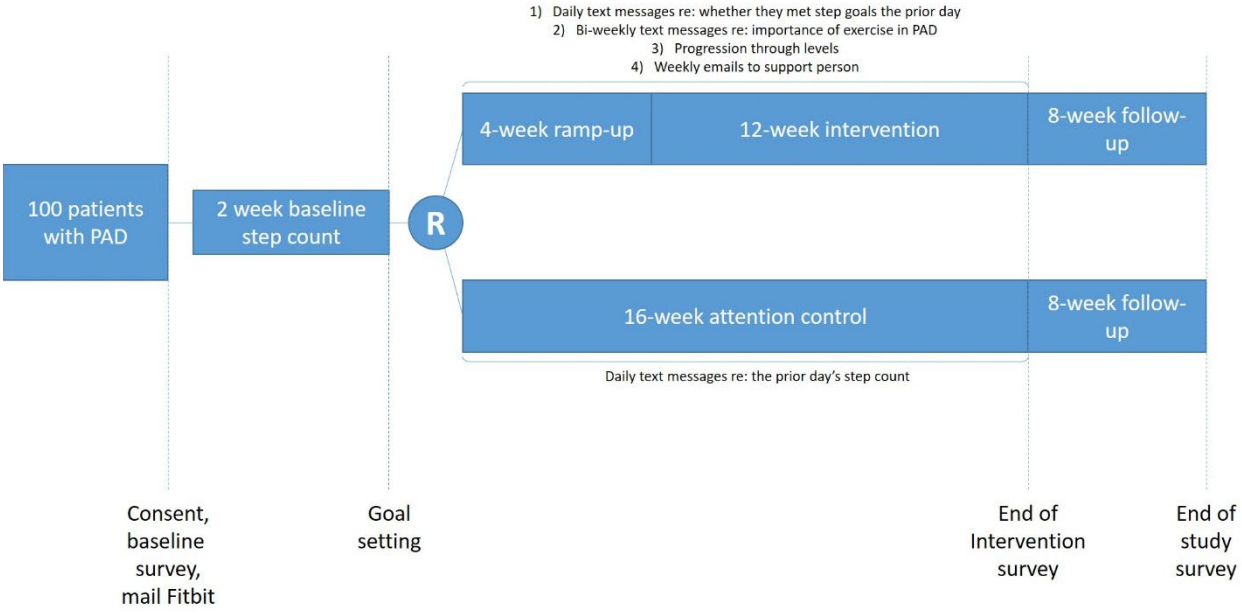
The objectives of this study are the following:

1. To test the effectiveness of a gamification-enhanced home-based walking program, as compared with a home-based walking program using goal-setting and automated coaching alone, to improve walking endurance in patients with peripheral artery disease
2. To identify psychometric features associated with response to gamification in patients with peripheral artery disease

3. Study Design

3.1. General Overview

The GAME PAD study is a two-arm randomized controlled trial aimed at evaluating whether a home-based walking program with automated coaching augmented with gamification and behavioral economic principles improves functional capacity in patients with PAD. The study will randomize 100 patients with PAD to a 16-week home-based walking program using goal-setting alone (attention control) or to the same home-based walking program with automated coaching augmented with gamification and behavioral economic principles. There will be a 2-week run-in period to obtain baseline measures of physical activity, followed by a 16-week intervention period, and an 8-week follow-up period (see study protocol figure below).



The study will be conducted using Way to Health, a research information technology platform at the University of Pennsylvania used previously for physical activity behavioral interventions.

After institutional review board (IRB) approval of the study, patients who meet the eligibility criteria will be contacted by email, phone call or letter to invite them to participate. Those who

qualify and express interest will provide online informed consent to the study procedures. All patients will receive a wearable activity tracker (Fitbit Inspire) that will enrolled in the Way to Health platform. The Fitbit and Way to Health platform will continuously track patients' steps and survey patients regarding pain with walking monthly. Within the Way to Health platform, patients will be randomized to one home-based exercise program or the other. All other management decisions are completely at the discretion of the care providers. Data capture will include:

- **Baseline case report form** (for each patient) collecting clinical information abstracted from the medical record
- **Patient-reported quality of life and functional limitation related to PAD** collected via telephone survey and/or the Way to Health platform at the time of enrollment and at 16- and 24-week follow-up
- **Psychometric features** collected via in-person survey at the time of enrollment
- **Daily step count** and calculated **exercise minutes** collected via FitBit charge
- **Patient-reported pain with ambulation** collected via the Way to Health platform at monthly intervals

3.2. Site

GAME PAD will enroll patients from the University of Pennsylvania Health System, which consists of five large hospitals including the Hospital of the University of Pennsylvania, Penn Presbyterian Medical Center, Pennsylvania Hospital, and Chester County Hospital, and from Cardiovascular Solutions of Central Mississippi, a private cardiovascular practice primarily serving a socioeconomically depressed region. Regardless of site, all patients will be consented and trial participation will be managed virtually through the Way to Health platform by study staff from the University of Pennsylvania, and no clinical personnel from any site will participate in research procedures or have access to any participant data.

3.3. Patient Selection Criteria

3.3.1. Inclusion Criteria

Patients are eligible to be included in the study if they are ≥ 18 years of age and meet all of the following criteria:

1. Peripheral artery disease, defined as ankle-brachial index < 0.90, lower extremity CT scan or ultrasound consistent with PAD, angiography with ≥ 70% stenosis in any lower extremity artery, or a history of medical or surgical revascularization
2. Owns a smartphone or tablet operating the iOS or Android operating system

3.3.2. Exclusion Criteria

Patients are excluded if they meet any of the following criteria:

1. Unable or unwilling to provide informed consent, including but not limited to cognitive or language barriers (reading or comprehension)
2. Critical limb ischemia, defined as rest pain, ulceration, or tissue loss involving the lower extremity
3. Planned lower extremity revascularization
4. Prior above or below the knee amputation
5. Require a wheelchair or the use of a walking aid other than a cane
6. Currently participating in a supervised exercise program for patients with PAD

7. Anticipated life expectancy less than 6 months
8. Any other reason why it is not feasible to complete the entire 6-month study
9. Step count > 7500/day during the baseline data collection period

4. Study Procedures

4.1. Screening and Informed Consent

Patients with peripheral vascular disease will be identified within the electronic health record and Penn Data Store, the health system's clinical data warehouse, by ICD-10 codes consistent with peripheral artery disease (I70.2x, I70.3x-I70.7x, I73.9) or peripheral artery disease on their problem list. They will be invited to participate by email, and will be randomized to opt-in or opt-out approaches. Patients randomized to the opt-in approach will be instructed to call a study coordinator or visit the Way to Health platform to enroll in the study; patients randomized to the opt-out study will be notified that they will be called by a study coordinator unless they decline to participate. This sub-study will be detailed in a separate protocol. Potentially eligible patients may also be identified by their cardiologist or vascular surgeon when seen in clinic, and directed to contact the study team or to visit the study website to learn more an enroll. These patients will not be included in the opt-in versus opt-out substudy.

Interested patients will visit the study website on the Way to Health platform to learn more about the study, create an account, provide informed consent, and complete initial baseline eligibility surveys. Study coordinators will be available to assist patients with this process, as necessary.

We will follow an IRB-approved approach taken by many studies using the Way to Health platform to obtaining informed consent. Upon reaching the portal, potential participants will be asked to create an account and will then be informed of the details of the study, including its objectives, duration, requirements, and financial payments. The Way to Health portal will then take interested participants through an online informed consent. The consent document will be divided into sections and potential participants will have to click a button to advance through each section. This is to help ensure that participants read the consent form thoroughly by breaking down the form into manageable blocks of text. Each section will have a button allowing the user to contact a researcher via email or by telephone if they have questions about the consent form. Successive screens will explain the voluntary nature of the study, the risks and benefits of participation, alternatives to participation, and that participants can withdraw from the study at any time. On the final consent screen, potential participants who click a clearly delineated button stating that they agree to participate in the study will be considered to have consented to enroll. Participants will be provided with details regarding how to contact the research team via email or phone at any time if they subsequently wish to withdraw from the study. This contact information will remain easily accessible via the participants' individual Way to Health web portal dashboards throughout the study.

Support partners will provide verbal informed consent via telephone for their name, email address, and phone number to be stored in the study database.

4.2. Baseline Questionnaire

After providing informed consent, participants will complete an online questionnaire to confirm eligibility and complete the study surveys.

The baseline survey will consist of the San Diego Claudication Questionnaire and the Walking Impairment Questionnaire to characterize limb symptoms and functional limitations,[23,24] the Patient-Reported Outcomes Measurement Information System (PROMIS) measures of mobility, pain interference, and satisfaction with social roles and activities,[25] and the SF-36 physical functioning scale.[26] Patients will also complete several questionnaires to obtain a psychometric profile: the Big Five Inventory survey to evaluate personality characteristics, the Grit Scale to assess perseverance, the Self Efficacy for Exercise Behaviors survey, the PHQ-9 questionnaire to assess mental health state, and the MOS Social Support survey.

4.3. Determination of Baseline Step Count and Goal-Setting

Eligible participants will be mailed a wearable activity tracking device to wear for about two weeks to collect a baseline step count. They will also receive an email with baseline information about home-based exercise in PAD, including information about the benefit of walking in relieving PAD symptoms and improving functional capacity, and instructions for exercise in PAD.

The patients will be told to wear the device for two weeks to get accustomed to it. During this period, we will use a protocol from prior work to estimate a baseline step count using the second week of data. The first week of data will be ignored to diminish the tendency for use of devices in week 1 of receiving a new device to be significantly higher than what might be observed at steady state. To prevent risk of mismeasurement, we will ignore any daily values less than 1000 steps because evidence indicates these values are unlikely to represent capture of actual activity.[27,28] At least four days of data must be available during that second week to estimate baseline measures; otherwise the period will be extended, and patients will be called to inquire if there are any issues with using the device. In prior work, we typically have 6 to 7 days of data from more than 90% of participants.[29] Participants who do not complete this run-in phase will not be randomized into the trial, nor will patients with step counts > 7500 steps/day during the run-in phase.

Once baseline measures have been established, eligible participants will be contacted to choose their goals using an approach we have found to work well in previous studies. They will be given their baseline step count and asked to select a step goal increase of 33%, 40%, 50% or choose a custom goal as long as it is at least 1500 steps greater than baseline. We have used this approach in the past because it gives participants the options of setting their own goal but also steers people to choose one of the options provided, any of which would be terrific from the standpoint of increasing physical activity. Leaving it completely open-ended risks having participants either pick goals that are ‘too easy’ or not likely to be attainable. In prior work, we find that on average participants chose ambitious goals and more than half selected a 50% step increase.

To achieve their goal, patients will be recommended to begin walking for 15 minutes daily at their own pain-free pace or with minimal pain, gradually increasing the duration to 30-60 minutes daily, and to stop and rest if the pain becomes more significant, and then resume walking.

4.4. Randomization

Participants that have established baseline measures and finished goal selection will be randomly assigned to attention control or the automated coaching + gamification intervention using a 1:1 allocation and stratifying on baseline step count (< 2500 steps, 2500 – 5000 steps, > 5000 steps)

with block randomization and block sizes of 2 using an electronic number generator through the Way to Health research technology platform.

4.5. Study Arms

4.5.1 Attention control

Via the Way to Health platform, all patients will receive daily text messages that inform them their previous day's step count.

4.5.2. Automated Coaching Plus Gamification Intervention

Similar to patients randomized to the attention control arm, patients in the intervention arm will receive daily text messages that inform them whether they did or did not meet their step goal. In addition, they will receive biweekly text messages including encouragement to walk for exercise, reminders about their goal step increase, reminders about optimal practices for home-based walking in patients with PAD, and information about the benefit of exercise in improving PAD symptoms and functional capacity.

Patients randomized to the intervention arm will have a 4-week ramp-up towards their step goal. The net difference between baseline and their goal will be divided by 4 and the participant will be asked to achieve the 25% increase each week for the 4-week ramp-up and then maintain the step goal for the remaining study period. For example, a participant with a baseline of 5000 steps and goal of 7400 steps will be asked to achieve goals of 5600 steps in week 1, 6200 in week 2, and so on through the 4-week period. We have found that the rate of goal attainment is high using this gradual approach rather than encouraging the participant to go from 5,000 to 7,400 steps immediately. Following the ramp-up period, the participant will be asked to maintain their goal during the remainder of the study.

Other components of the gamification intervention are as follows:

1) Pre-commitment: First, each participant signs a pre-commitment contract agreeing to try their best to achieve their daily step goal. Pre-commitment has been demonstrated to help motivate behavior change.

2) Points: At the start of each week, the participant will receive 70 points (10 for each day that week). Points are endowed rather than given after goal achievement to leverage loss aversion – a concept from prospect theory that reveals that individuals are more motivated by losses than gains. Each day the participant is informed of their step count. If the step goal was achieved, he or she retains their points. However, each day the goal is not met, they are informed that they lost 10 points. Points are replenished at the start of the week to leverage the "fresh start effect" – the concept that individuals are more motivated for aspirational behavior around temporal landmarks such as the start of the week.

3) Levels: At the end of the week, if the participant has 40 points or more, he or she will advance one level. The levels include: blue (lowest), bronze, silver, gold, platinum (highest). If he or she has less than 40 points, he or she will drop down one level at the end of the week. This creates a sense of achievable goals (goal gradients) and uses loss aversion to help motivate ongoing efforts to not lose status. Each participant begins the intervention in the silver level. By starting them in the middle, the higher levels seem within reach and they will feel a sense of loss from dropping

down a level in the first week if they don't achieve 40 points; this may motivate them to initiate greater activity. After 8 weeks, we will reach out to individuals that are stuck in lower levels of blue or bronze and restart them back at silver. This allows for another "fresh start" and creates a new endowment effect as someone who is already at the bottom would otherwise not be able to drop down further and experience loss aversion. At the same time, we will also inquire if he or she would like to adjust their step goal as long as they are within the range of a 33% to 50% increase. In previous studies, we've found that some individuals set overly ambitious goals at the start of the intervention and that for participants who have trouble achieving their initial goals, we can re-engage them if goals are reset to a more reasonable level.

4) Supportive sponsor: Each participant will select a family member or friend of their choice who will serve as a supportive sponsor. This person will receive a weekly email with the participant's progress including accumulated points, level in the game, and average step count. This supportive sponsor will help to enhance social incentives to motivate the individual towards his or her goal. We will encourage participants to select someone with whom he or she comes into frequent contact and is close to such as a partner, family member, or friend that they see often. Prior to starting in the study, we will conduct a three-way phone call with the participant and their supportive sponsor. We will provide an overview of study procedures for their arm assignment, and then prompt the participant and supportive sponsor to discuss ways in which they can help the participant meet their step goals. At least 3 goals will be decided upon during the conversation, and if needed, we will provide suggestions for supporting the participant. The goals that are decided upon will be entered into a survey by study staff, and will be included in weekly emails to the supportive sponsor. After 8 weeks, we will reach out to the participant and supportive sponsor if the participant is stuck in lower levels of blue or bronze to determine if changes should be made to the original support goals. Participants without a supportive sponsor will not be excluded from study participation, and will complete a slightly modified version of the baseline and 8-week phone call, if necessary, in two-way conversations with study staff.

The intervention will end after 16 weeks, but participants will continue to receive a daily text message stating whether they achieved their step goal on the prior day during the 8 week follow-up period.

4.6. End-of-Study Questionnaire Completion

At the end of the 16-week intervention, patients will be alerted by the Way to Health platform to return to the website to complete an end-of-study questionnaire consisting of the San Diego Claudication Questionnaire, the Walking Impairment Questionnaire, the Patient-Reported Outcomes Measurement Information System (PROMIS) measures of mobility, pain interference, and satisfaction with social roles and activities, and the SF-36 physical functioning scale. Patients will complete the same questionnaire again 8 weeks later.

4.7. Subject compensation

Patients will be paid $25 for enrolling in the study and completing baseline surveys, $25 for completing the 16-week intervention with step count data available for ≥ 60% of days and completing the 16-week survey, and $25 for completing the study with step count data available for ≥ 60% of days and completing the 24-week survey.

5. Statistical Methods

5.1 Primary and secondary outcome measures

The study's primary outcome measure will be change in daily step count from baseline to the intervention period for patients in the intervention arm versus patients in the attention control arm.

Secondary outcome measures will include:

1) Change in daily step count from baseline to the follow-up period
2) Change in daily number of minutes engaged in light, moderate, or vigorous physical activity from baseline to the intervention period, and from baseline to the follow-up period
3) Change in daily number of minutes engaged in moderate, or vigorous physical activity from baseline to the intervention period, and from baseline to the follow-up period
4) Change in Walking Impairment Questionnaire score from baseline to the end of the intervention period, and from baseline to the end of the follow-up period
5) Change in PROMIS mobility, pain interference, and satisfaction with social roles and activities scores from baseline to the end of the intervention period, and from baseline to the end of the follow-up period
6) Change in SF-36 physical functioning scale from baseline to the end of the intervention period, and from baseline to the end of the follow-up period

5.2. Sample Size

Patients with PAD walk approximately 3900 steps/day (SD 2689 steps).[16] With a home-based exercise program, the mean change in steps/day over 4.5 months for patients with PAD was a decrease by 200 steps (SD ~2000 steps).[16] By contrast, a gamification intervention similar to the one proposed increased step count by > 900 steps/day (SD ~2400 steps).[19] With 100 patients (50 in each arm), the study will have 80% power to detect an 1100 step difference in change in daily step count between the two arms with alpha set at 0.05

5.3. Data Analyses

Data for all consented patients, whether or not they completed all protocol requirements, will be included for analysis. Patient demographics, risk profiles, clinical characteristics, and baseline questionnaire results will be reported. In addition to change in number of steps from baseline, secondary outcomes will include change in daily exercise minutes, and change the Walking Impairment Questionnaire, the Patient-Reported Outcomes Measurement Information System (PROMIS) measures of mobility, pain interference, and satisfaction with social roles and activities, and the SF-36 physical functioning scale. In exploratory analyses, we will identify baseline psychometric properties associated with greater change from baseline in daily steps, and greater response to the gamification intervention.

All analyses will be performed using intention-to-treat. Data can be missing for any day if the participant did not use the activity tracking device or did not upload data. For the main analysis, we will use multiple imputation for step values that are either missing or for values less than 1000 steps because evidence suggests these are not accurate measures of actual activity. We will perform five sets of imputations and results will be combined using Rubin's standard rules. We will perform sensitivity analyses to assess the robustness of the findings using only collected data with and without step values less than 1000 steps. The primary analysis will fit mixed effects

regression models to evaluate changes in physical activity outcomes measures adjusting for each participant's baseline step, time at the observation level using calendar month fixed effects, participant random effects, and adjusting for repeated observations of participant step counts. We will compare changes in daily step count and physical activity from baseline to the intervention period, excluding weeks 1-4 (the ramp-up period). We will repeat these analyses, comparing changes in daily step count and physical activity from baseline to the follow-up period. Secondary analyses will fit mixed effects regression models adjusted for other variables of interest such as participant characteristics. Exploratory analyses will fit mixed effects regression models to evaluate associations of participant characteristics or behaviors with strong or poor performance in the outcome measures. In a subgroup analysis, we will separately analyze subgroups reporting and not reporting exertional lower extremity symptoms.

For changes in survey measure scores from baseline to the end of the intervention, and from baseline to the end of follow-up, we will compare the intervention and control arms using paired t-tests, without adjustment for baseline characteristics.

6. Human Research Protection

6.1 Data confidentiality

Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study. Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords. Wherever feasible, identifiers will be removed from study-related information. Precautions are in place to ensure the data are secure by using passwords and encryption, because the research involves web-based surveys.

6.2 Subject confidentiality

Research material will be obtained from participant surveys and wearable devices. All participants will provide informed consent for access to these materials. The data to be collected include data on participant characteristics and behaviors and step counts. Research material that is obtained will be used for research purposes only. The same procedure used for the analysis of automated data sources to ensure protection of patient information will be used for the survey data, in that patient identifiers will be used only for linkage purposes or to contact patients. The study identification number, and not other identifying information, will be used on all data collection instruments. All study staff will be reminded to appreciate the confidential nature of the data collected and contained in these databases. The Penn Medicine Academic Computing Services (PMACS) will be the hub for the hardware and database infrastructure that will support the project and is where the Way to Health web portal is based. The PMACS is a joint effort of the University of Pennsylvania's Abramson Cancer Center, the Cardiovascular Institute, the Department of Pathology, and the Leonard Davis Institute. The PMACS provides a secure computing environment for a large volume of highly sensitive data, including clinical, genetic, socioeconomic, and financial information. Among the IT projects currently managed by PMACS are: (1) the capture and organization of complex, longitudinal clinical data via web and clinical applications portals from cancer patients enrolled in clinical trials; (2) the integration of genetic array databases and clinical data obtained from patients with cardiovascular disease; (3) computational biology and cytometry database management and analyses; (4) economic and health policy research using Medicare claims from over 40 million Medicare beneficiaries. PMACS requires all users of data or applications on PMACS servers to complete a PMACS-

hosted cybersecurity awareness course annually, which stresses federal data security policies under data use agreements with the university. The curriculum includes Health Insurance Portability and Accountability Act (HIPAA) training and covers secure data transfer, passwords, computer security habits and knowledge of what constitutes misuse or inappropriate use of the server. We will implement multiple, redundant protective measures to guarantee the privacy and security of the participant data. All investigators and research staff with direct access to the identifiable data will be required to undergo annual responsible conduct of research, cybersecurity, and HIPAA certification in accordance with University of Pennsylvania 334 regulations. Data will be stored, managed, and analyzed on a secure, encrypted server behind the University of Pennsylvania Health System (UPHS) firewall. This server was created for projects conducted by the Penn Medicine Nudge Unit related to physician and patient behavior at UPHS. All study personnel that will use this data are listed on the IRB application and have completed training in HIPAA standards and the CITI human subjects research. Data access will be password protected. Whenever possible, data will be deidentified for analysis.

6.3 Subject privacy

Interested participants will be directed to the Way to Health portal where they will be asked to enter data related to eligibility and their demographic characteristics. Enrollment will include a description of the voluntary nature of participation, the study procedures, risks and potential benefits in detail. The enrollment procedure will provide the opportunity for potential participants to ask questions and review the consent form information prior to making a decision to participate. Participants will be told that they do not have to answer any questions if they do not wish and can drop out of the study at any time, without affecting their medical care or the cost of their care. They will be told that they may or may not benefit directly from the study and that all information will be kept strictly confidential, except as required by law. Subjects will have access to a copy of the consent document. All efforts will be made by study staff to ensure subject privacy.

6.4 Data disclosure

The following entities, besides the members of the research team, may receive protected health information (PHI) for this research study: Wells Fargo, the company which processes study related payments. Patient addresses and account balances will be stored on their secure computers. Fitbit, the company that designs and manufactures the wearable devices used in the study to track participant physical activity. Twilio, Inc., the company which processes some 359 study-related messages. Twilio will store patients' phone numbers on their secure computers. Qualtrics, Inc., the company which processes most study-related surveys. Qualtrics will house de-identified answers to these surveys on their secure servers. The Office of Human Research Protections at the University of Pennsylvania -Federal and state agencies (for example, the Department of Health and Human Services, the National Institutes of Health, and/or the Office 364 for Human Research Protections), or other domestic or foreign government bodies if required by 365 law and/or necessary for oversight purposes.

6.5 Data safety and monitoring

The Principal Investigator will be responsible for monitoring the study. All participants will be given anticipatory guidance on when to seek medical attention. In addition, participants will be asked to report to the study team any injuries or medical care that they feel resulted from

participation in the study. They can either call the study team or send an email. The research coordinator will call the participant to collect information regarding the issue and then the PI will review and determine whether it is ok to proceed, further investigation is needed, or the participant should stop the study. For this study there will be no stopping rules or endpoints and thus no planned interim analyses.

6.6 Risk/benefit

6.6.1 Potential study risks

The program will use a gradual increase in physical activity during the first month that should pose little health risk to participants. Participants are given guidance on when to seek medical attention and a reporting protocol is in place to capture any changes in symptoms with physical activity. Another potential risk of this study is a breach of participant confidentiality. We will minimize this risk by using secure data methods as described previously. Due to the financial incentives in this study, we will be collecting social security numbers so that we can complete W-9 forms for participants. Social security numbers only will be used to generate W-9 forms and will be deleted once they are no longer needed. We will also collect home addresses to mail incentive payments. This will be done through a University of Pennsylvania approved partnership with Wells Fargo. Accidental disclosure of social security numbers could lead to identity theft. We will use commercial-grade encryption to protect social security information in transit. Names and addresses will be stored in encrypted databases. These data will be viewable only by the respective participants, the study coordinator(s) and the project manager(s). All other members of the research team will be able to view only participant ID numbers. Even the study arms will be identified by code letters until both the statistician and PI agree that analysis is complete.

6.6.2 Potential study benefits

Through participation in this study, each participant will have the potential to increase physical activity which could improve their health and reduce their risk for future disease. If this approach is effective, it could have tremendous benefits for society if adopted on a wide scale to help individuals. It is expected that other people will gain knowledge from this study and that participation could help understand how to effectively motivate individuals to change behavior. Participants may also receive no benefit from their participation in the study.

6.6.3 Risk/benefit assessment

Anticipated risks of this study should be minimal and the risk/benefit ratio is very favorable. To minimize the chance for serious and unexpected adverse events, study participants will be screened through exclusion criteria for any health conditions that may be exacerbated by participating in this study. We have previously outlined the procedures that will be used to prevent a breach of participant data.

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