The Effectiveness of Daily Step-based Exercise Therapy Using Fitness Monitors for Peripheral Artery Disease: The EASY FIT Trial

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EASY FIT Clinical Trial:
Master Study Protocol

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1. Introduction

1.1 Study Background

1.1.1 Peripheral Artery Disease

Peripheral artery disease (PAD) is the third leading cause of cardiovascular morbidity, following coronary artery disease and stroke [1,2]. PAD occurs with the progression of atherosclerosis in lower extremity arteries. Patients with PAD classically present with claudication, but can also present with decreased exercise capacity and progressive functional impairment [3-6]. These symptoms are thought to result from the following potential mechanisms: lower extremity atherosclerosis and arterial obstruction leading to skeletal muscle ischemia and impaired cellular metabolism, mitochondrial dysfunction leading to the production of reactive oxygen species as well as free radicals, and subsequent endothelial dysfunction leading to impaired vasodilation and decreased hyperemia in the setting of increased metabolic demand [3-5].

The goals of therapy for PAD patients are to maximize their exercise capacity, improve their functional status, and improve their quality of life [5-9]. The standard therapies for symptomatic PAD are symptom-based exercise therapy and revascularization if indicated [5-9]. The exercise protocol for PAD patients that is recommended by clinical practice guidelines and has become standardized in clinical investigations is based on leg symptoms: walk at a constant speed (on a treadmill if possible) until there is mild to moderate claudication, rest until the pain has completely ceased, resume walking at the same speed, and increase the speed when one can walk 8 minutes without stopping for leg symptoms [5-9]. This exercise protocol is performed for 45 consecutive minutes, 3 to 5 days a week [5-9]. The benefits of exercise in PAD patients include increased vasodilation which leads to improved skeletal muscle perfusion as well as metabolism, enhanced mitochondrial function, and improved endothelial function [5-9].

PAD exercise programs can occur in a supervised setting or at home [6-9]. Supervised exercise programs utilize treadmill walking under the direct supervision of an exercise physiologist or a physical therapist who enforces the standard symptom-based exercise protocol [7]. There is substantial evidence demonstrating the effectiveness of supervised exercise programs for patients with symptomatic PAD [10-16]. However, Medicare and most private health insurance companies do not provide coverage for supervised exercise programs, limiting the feasibility of supervised exercise for most patients [5,17].

In contrast, home exercise programs offer an alternative treatment strategy that is more feasible for patients. Home exercise programs have also demonstrated significant efficacy of improving maximal walking ability for symptomatic PAD patients [17-24], and are based on the standard symptom-based exercise protocol without direct supervision [5-9,17-24]. Limitations to home exercise programs include the inability to objectively monitor exercise capacity at home in the absence of a treadmill, variable adherence rates to the standard protocol in the absence of direct supervision, and variable adherence rates to the performance of exercise for 45 minutes, 3 to 5 days a week, in the absence of a supervised program. In order to address these limitations, several investigators have studied the utilization of a fitness monitor during symptom-based home exercise sessions [17-21].

1.1.2 Daily Step-based Exercise Therapy

The recommended exercise goal for cardiovascular disease prevention is 10,000 steps a day [25]. On the other hand, a daily step count less than 5,000 has been associated with a negative impact on health [26]. Prior studies have explored the efficacy of step-based exercise therapy using fitness monitors on improving health in both patients with chronic disease and the adult population in general [27,28]. There are ongoing studies examining the effectiveness of step-based exercise therapy on improving cardiovascular health [29,30]. The effect of step-based exercise therapy using fitness monitors has not been studied in patients with symptomatic PAD.

In the current digital era, fitness monitors have sensors that can accurately and reliably measure the number of steps walked, distanced walked, time of physical activity, and sedentary time [31-33]. Given their affordability and their ability to measure these data points on a real-time basis, fitness monitors have

become a popular exercise accessory for the general population as well as patients with chronic disease [33-35]. Step-based exercise therapy using fitness monitors have the potential to improve human health through several different mechanisms. First, the quantification of exercise allows patients to set objective goals, self-monitor their progress, and modify their physical activity based on real-time data points [33]. In addition, fitness monitors are worn easily without limiting activities of daily living [33]. This allows patients to wear them 24 hours a day, and can facilitate potentially higher adherence rates to exercise. Finally, fitness monitors have the potential to promote behavior changes that are typically used in clinical behavioral interventions [36].

1.2 Study Rationale and Aim

The **E**ffectiveness of D**A**ily **S**tep-based Exercise Therap**Y** Using **FIT**ness Monitors for Peripheral Artery Disease (**EASY FIT**) Trial will be a single-center prospective non-inferiority randomized controlled trial comparing the efficacy of a novel 12-week daily step-based exercise program vs. the efficacy of a standard guideline-recommended symptom-based exercise program, on improving walking ability in patients with symptomatic lower extremity peripheral artery disease (PAD). We will enroll and randomize 40 patients to a novel 12-week step-based exercise program or a standard guideline-recommended 12-week symptom-based exercise program. To date, we believe that our study is the first to investigate the efficacy of a 12-week daily step-based exercise program on improving walking ability in patients with symptomatic lower extremity PAD. As such, our clinical investigation is a pilot study and will aim to assess the efficacy, safety, and feasibility of a novel daily step-based exercise program for this particular patient population. We believe that this pilot study will generate data for a larger trial in the future.

Compared to the standard guideline-recommended symptom-based exercise program, we hypothesize that a daily step-based exercise program using fitness monitors will be non-inferior in improving walking ability and quality of life for patients with symptomatic lower extremity PAD. We also hypothesize that a daily step-based exercise program will be safe and feasible.

1.3 Study Benefits and Risks

1.3.1 Study Benefits

The potential benefits of a daily step-based exercise program include increased walking ability and exercise capacity (as demonstrated by increased daily walking distance and increased daily time of physical activity), decreased sedentary time, improved quality of life, improved cardiovascular health, and improved general health.

1.3.2 Study Risks

The potential risks of a daily step-based exercise program and a symptom-based home exercise program are exercise-induced events: physical injury, myocardial infarction, and sudden cardiac arrest. The risk of a myocardial infarction during a cardiac rehabilitation exercise program is approximately 0.00013% or 1 event per 752,365 patient-exercise hours [37]. The risk of sudden cardiac arrest during a cardiac rehabilitation exercise program is approximately 0.00045% or 1 event per 219,970 patient-exercise hours [37]. Habitual exercise has been found to decrease the relative risk of sudden cardiac arrest [38].

1.3.3 Study Benefit-to-Risk Ratio Conclusion

Based on the large potential for benefit and the very small probability of adverse risk to the study population, we believe that this study has a favorable benefit-to-risk profile.

1.4 Study Funding

In August 2016, we were awarded an NC TraCS Pilot Grant (#2KR821606) for the execution of this study.

2. Study Objectives

2.1 Primary Endpoint

The primary endpoint will be the change in the mean daily walking distance over 7 consecutive days between baseline (prior to the exercise program) and after 12 weeks of the exercise program.

2.2 Secondary Endpoints

The secondary endpoint will be the change in quality of life between baseline (prior to the exercise program) and after 12 weeks of the exercise program. We will assess quality of life with 2 surveys that have been validated in PAD patients: the Peripheral Artery Questionnaire (PAQ) and the Vascular Quality of Life Questionnaire (VascuQol).

2.3 Safety Endpoints

The safety endpoint will be the occurrence of physical injury, myocardial infarction, or sudden cardiac death at 12 weeks.

3. Study Population

3.1 Inclusion Criteria

Patients are eligible for enrollment if they meet all of the following criteria.

1. Male or female with an age of 18 years or older

2. Diagnosis of lower extremity PAD, based on at least 1 of the following criteria:
   - Ankle-brachial index (ABI) of 0.9 or less in one or both legs
   - Invasive angiography demonstrating obstructive lower extremity artery disease
   - History of prior endovascular or surgical revascularization of lower extremity artery

3. Symptomatic lower extremity PAD characterized by:
   - Fontaine Stage IIa - intermittent claudication after walking > 200 meters
   - Fontaine Stage IIb - intermittent claudication after walking < 200 meters

4. Have a mobile phone with Wifi and Bluetooth capability

5. Have a safe and suitable walking environment (e.g. safe sidewalks next to home)

6. Have the ability to read and speak the English language

3.2 Exclusion Criteria

Patients are not eligible for enrollment if they meet any of the following criteria.

Any health condition that may limit full participation in an exercise program	1. Wheelchair bound 2. Use of a walking aid (e.g. cane, crutch, walker) 3. Below or above the knee amputation 4. Leg pain at rest 5. Acute or critical limb ischemia 6. Ischemic ulceration or gangrene 7. Diabetes mellitus complicated by neuropathy 8. Walking impairment due to another cause than PAD
Any health condition that may be unsafe to participate in an exercise program	9. Ongoing evaluation for coronary artery disease (e.g. awaiting a stress test or cardiac catheterization) 10. Angina with CCS class 3-4 symptoms 11. Active coronary artery disease or ischemic heart disease requiring the initiation or uptitration of an anti-anginal medication 12. Myocardial infarction in the last 3 months 13. Congestive heart failure with NYHA class 3-4 symptoms 14. Active congestive heart failure requiring the initiation or uptitration of diuretic therapy 15. Active arrhythmia requiring the initiation or uptitration of an anti-arrhythmic medication 16. Severe valve disease, or valve intervention in the last 12 months
Any health condition that may influence study outcomes independently	17. Active cancer or malignancy (not in remission) 18. End-stage renal disease requiring dialysis 19. Advanced liver disease (defined as cirrhosis) 20. Thyroid disease with abnormal TSH in the past 3 months 21. Severe cognitive dysfunction (defined as dementia)

3.3 Study Drop-Out Criteria

Every 4 weeks of the 12-week exercise program and every 4 weeks of the 9-month extension phase: the study investigators will conduct phone calls and chart review for all enrolled patients to assess for any drop-out criteria and adverse events.

Patients will be prematurely discontinued from the study if they develop any of the following drop-out criteria (identical to the exclusion criteria):

1. Wheelchair bound
2. Use of a walking aid (e.g. cane, crutch, walker)
3. Below or above the knee amputation
4. Leg pain at rest
5. Acute or critical limb ischemia
6. Ischemic ulceration or gangrene
7. Diabetes mellitus complicated by neuropathy
8. Walking impairment due to another cause than PAD
9. Ongoing evaluation for coronary artery disease (e.g. awaiting a stress test or cardiac catheterization)
10. Angina with CCS class 3-4 symptoms
11. Active coronary artery disease or ischemic heart disease requiring the initiation or uptitration of an anti-anginal medication
12. Myocardial infarction in the last 3 months
13. Congestive heart failure with NYHA class 3-4 symptoms
14. Active congestive heart failure requiring the initiation or uptitration of diuretic therapy
15. Active arrhythmia requiring the initiation or uptitration of an anti-arrhythmic medication
16. Severe valve disease, or valve intervention in the last 12 months
17. Active cancer or malignancy (not in remission)
18. End-stage renal disease requiring dialysis
19. Advanced liver disease (defined as cirrhosis)
20. Thyroid disease with abnormal TSH in the past 3 months
21. Severe cognitive dysfunction (defined as dementia)

Patients will be prematurely discontinued from the study if they develop any of the following adverse events:

1. Physical injury
2. Myocardial infarction
3. Sudden cardiac arrest

4. Study Design

4.1 Screening, Enrollment, and Randomization

The study investigators will identify patients with an ABI of ≤ 0.9, screen these patients for eligibility, and notify the physician(s) of any eligible patient(s). The physician(s) will inform the eligible patient(s) about the study and ask the patient(s) for permission to have the study investigators meet the patient(s) at their next clinic visit. The study investigators will meet with these patients; discuss the study objective, process, benefits, risks, and alternatives; and obtain written informed consent and HIPAA authorization. Once the patients have provided written informed consent and HIPAA authorization, they will be enrolled into the study and randomized.

4.2 Treatment

4.2.1 Standard Medical Therapy

Both the control group and the intervention group will receive standard medical therapy: lipid-lowering therapy; antiplatelet therapy with aspirin 81mg daily or clopidogrel 75mg daily; anti-hypertensive therapy for patients with hypertension; and smoking cessation therapy [7,8]. Given that all these medical therapies are the standard of care for PAD patients, these medications will be initiated and/or managed by the usual care provider. The study team will only provide advice about the standard of care.

4.2.2 Fitness Monitor

Both the control group and the intervention group will receive a Fitbit Flex which has been validated for step count measurement. During enrollment, the study investigators will set up the Fitbit Flex for all patients. This set-up process will be the only stage where patients will need to have online access. In order to set up the Fitbit Flex, all patients will need to have a mobile phone with WiFi and Bluetooth capability. The study investigators will download the free Fitbit application onto the mobile phone for each patient, create a free online Fitbit account for each patient, and pair the Fitbit Flex to the mobile application. Once the Fitbit Flex and the mobile application are paired, the Fitbit Flex can sync data to the online Fitbit account wirelessly through Bluetooth. Patients will be instructed to sync their Fitbit data to their online Fitbit account every 4 weeks.

The study investigators will have access to all online Fitbit accounts for the study duration (3 months for the primary and secondary endpoints, and 1 year for the exploratory endpoints). There will be no patient-identifying information in any online Fitbit account. Instead, each patient will be assigned a random alpha-numeric code, which will be used as the patient name on the online Fitbit account.

At the end of the study, all patients will be allowed to keep their Fitbits at no cost, indefinitely.

4.2.3 Control Group

The control group will receive the following 12-week symptom-based exercise prescription, which is adapted from clinical practice guidelines [5-8].

- Walk on a flat surface at a constant speed until there is mild to moderate pain
- Rest until the pain has completely ceased
- Resume walking at the same speed
- Increase the speed when you can walk 8 minutes without stopping for leg symptoms
- Continue this exercise routine for 45 consecutive minutes, 3 to 5 days a week.

4.2.4 Intervention Group

The intervention group will receive the following 12-week step-based exercise prescription. The exercise goal of 5,000 daily steps is based on prior evidence demonstrating that a daily step count of less than 5,000 is associated with a negative impact on health [26].

- Week 1: walk at least 3,000 steps every day.
- Week 2: walk at least 3,500 steps every day.
- Week 3: walk at least 4,000 steps every day.
- Week 4: walk at least 4,500 steps every day.
- Weeks 5-12: walk at least 5,000 steps every day.

4.3 Follow-up

The study follow-up period will be 14 weeks. Week 1 will be a baseline assessment period during which we obtain baseline data. Weeks 2 through 13 will be the period of the study intervention. Week 14 will be the endpoint assessment period during which we obtain endpoint data.

Week 1
Discussed in Section 5.1 (Study Assessments, Baseline Assessment Period)

Weeks 2 to 13
Every 4 weeks of the 12-week exercise program: the study investigators will conduct both chart review and phone calls for all enrolled patients to assess for any drop-out criteria and adverse events. In addition, the study investigators will instruct patients regarding any concerning symptoms that should be reported to the study team or should require emergent medical attention (by calling 911). In order to assess compliance to the study protocol, all patients will transmit data from their fitness monitors to their online Fitbit accounts every 4 weeks.

Week 14
Discussed in Section 5.2 (Study Assessments, Endpoint Assessment Period)

5. Study Assessments

5.1 Baseline Assessment Period

Week 1 will be the baseline assessment period, during which both the intervention group and the control group will wear their fitness monitors for 7 consecutive days. In addition to their usual daily activities, all patients will be instructed to walk continuously for at least one extended period of time on a daily basis. Given that this is a pilot study of a novel exercise program in PAD patients, the duration and frequency of these extended periods of time will be at the patients' discretion.

At the end of Week 1: the study investigators will conduct both chart review and phone calls for all enrolled patients to assess for any drop-out criteria and adverse events. In addition, the study investigators will instruct patients regarding any concerning symptoms that should be reported to the study team or should require emergent medical attention (by calling 911). Both groups will transmit the data from their fitness monitors to their online Fitbit accounts. Finally, both groups will also complete quality of life surveys (PAQ and VascuQol).

Prior to starting the Week 1 baseline assessment period, patients who undergo peripheral angiography will need to be cleared for full activity by the treating interventional cardiologist. The study investigators will ask the patients' treating interventional cardiologist 1 week after the procedure to verify the patients' clearance for full activity, and then call the patients with instructions to start the Week 1 run-in period.

5.2 Endpoint Assessment Period

Week 14 will be the endpoint assessment period and will be structured identically to Week 1, during which both the intervention group and the control group will wear their fitness monitors for 7 consecutive days. In addition to their usual daily activities, all patients will be instructed to walk continuously for at least one extended period of time on a daily basis. Given that this is a pilot study of a novel exercise program in PAD patients, the duration and frequency of these extended periods of time will be at the patients' discretion.

At the end of Week 14: the study investigators will conduct both chart review and phone calls for all enrolled patients to assess for any drop-out criteria and adverse events. In addition, the study investigators will instruct patients regarding any concerning symptoms that should be reported to the study team or should require emergent medical attention (by calling 911). Both groups will transmit the data from their fitness monitors to their online Fitbit accounts. Finally, both groups will also complete quality of life surveys (PAQ and VascuQol).

6. Statistical Analysis

The primary endpoint of the mean daily walking distance (in steps) over 7 consecutive days will be assessed at baseline and at 3 months. Mean improvement in steps walked from baseline to 3 months will be calculated separately for the intervention and the control group. Noninferiority of the intervention group will be assessed by comparing mean improvement in steps walked, using a 1-sided t-test with a margin of noninferiority of 500 steps. Pedometry data from 22 patients with coronary artery disease undergoing 4 month behavioral intervention suggests the mean improvement in steps walked will have a standard deviation of 161 (VanWormer J, Boucher J, Pronk N, Thoennes J. Lifestyle behavior change and coronary artery disease: effectiveness of a telephone-based counseling program. J Nutr Educ Behav. 2004 Nov-Dec; 36(6):333-4.). With a sample size of 20 patients per group, we expect 90% power to demonstrate noninferiority of the intervention group (difference in mean improvement of -350 steps, which is within the margin of noninferiority).

The mean difference in the mean daily walking distance between the study groups will be analyzed by multiple linear regression, controlling for baseline mean daily walking distances. All outcomes will be analyzed by intention-to-treat.

7. Data Management

In order to protect patient confidentiality, we will abide by the following policies for data management.

All paper data will be stored in a study binder that will be stored and locked in a locker. Only the study personnel listed on this IRB protocol will have access to the study binder, and the key to the locker for the study binder.

All electronic data will be stored in an online project database which is a secured web-based application. Only the study personnel listed on this IRB protocol will be authorized users for the project database, and will have access to the project database.

We will use online randomization software to generate a random numeric code for each patient. Patient identifying data (specifically name, date of birth, medical record number, telephone number, and Fitbit serial number) will be stored only as electronic data on a single form in the online project database. The random numeric code for each patient will be documented on this single form with the patient identifying data. This single form will be the key to the random numeric codes, and will be stored separately from the research data. Only the study personnel listed on this IRB protocol will have access to this key. The rest of the online forms will use the random numeric codes to identify patients. All paper forms will use the random numeric codes to identify patients. All online Fitbit accounts will use the random numeric codes to identify patients.

Only the individuals listed on the IRB protocol will have access to any study data (the study binder in the locker, the online Fitbit accounts, and the study database).

At the completion of the data analysis, all online data will be destroyed and all paper data will be disposed in the HIPAA-protected waste bins.

8. Study Conduct

8.1 Public Availability

Per the NC TraCS Regulatory Core, the study information for this clinical trial will be posted on the publicly available clinical trial database www.ClinicalTrials.gov.

8.2 Ethical Considerations

The study will be conducted in accordance with ICH Good Clinical Practice guidelines and ethical principles outlined in the Declaration of Helsinki 2008 including:

Institutional Review Board (IRB) review and approval
Prior to initiating the study, the investigators will obtain approval from the IRB.

Written informed consent
Each screened patient will be informed about the study aim, procedures, benefits, risks, and consequences. Each enrolled patient will provide his or her written informed consent which will be stored in the study binder.

Written HIPAA authorization
Each screened patient will be informed about the study procedures of reviewing his or her medical record throughout the study. Each enrolled patient will provide his or her written HIPAA authorization which will be stored in the study binder.

8.3 Data and Safety Monitoring

An Independent Data Monitoring Committee will not be necessary for this study because of the small size of the study population, the very small probability of adverse risk to the study population, and the very favorable benefit-to-risk profile of the study.

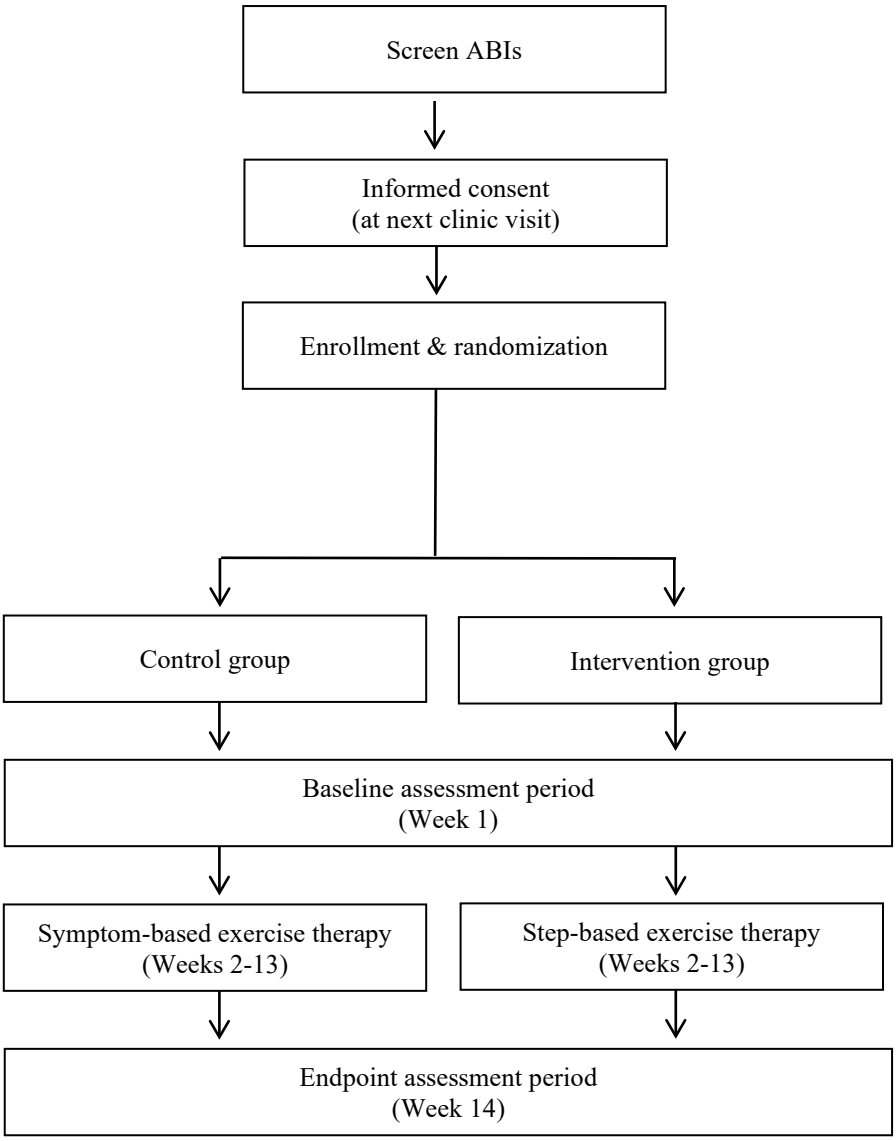
Subjects walking outdoors will be exposed to conditions like steep inclines, hot weather, rainy weather, snowy weather, and ice. These conditions may increase the risk of injury or adverse events. We will advise and strongly recommend patients to avoid walking in any of these these conditions (steep inclines, hot weather, rainy weather, snowy weather, and ice). We will ask patients to seek emergent medical attention by calling 911 if they are exposed to these conditions and have injury or an adverse event.

8.4 Study Stopping Rules

The study will be prematurely stopped if the study intervention (a daily step-based exercise program) is associated with an increased risk of adverse events and/or harm to patients.

9. **Appendices**

9.1 **Study Flow Diagram**



9.2 **Control Group: Symptom-based Exercise Protocol** [6-8]

Week	Exact Dates *	Frequency	Exercise Prescription
1	(Run-in period)	Daily	Walk as much as possible
2		3-5 days a week	1. Walk on a flat surface at a constant speed for 45 consecutive minutes 2. Rest when you have leg pain (3 or 4 on a pain scale between 1 and 5, where 1 is no pain and 5 is severe pain) 3. Start walking when your leg pain has stopped 4. Repeat these walking/rest cycles 5. If you are able to walk for 8 minutes without stopping, increase your walking speed.
3		3-5 days a week	
4		3-5 days a week	
5		3-5 days a week	
6		3-5 days a week	
7		3-5 days a week	
8		3-5 days a week	
9		3-5 days a week	
10		3-5 days a week	
11		3-5 days a week	
12		3-5 days a week	
13		3-5 days a week	
14	(Endpoint period)	Daily	Walk as much as possible

* The exact dates will be written on the exercise prescription for each patient.

9.3 **Intervention Group: Step-based Exercise Protocol**

Week	Exact Dates *	Frequency	Exercise Prescription
1	(Run-in period)	Daily	Walk as much as possible
2		Daily	Walk at least 3,000 steps
3		Daily	Walk at least 3,500 steps
4		Daily	Walk at least 4,000 steps
5		Daily	Walk at least 4,500 steps
6		Daily	Walk at least 5,000 steps
7		Daily	Walk at least 5,000 steps
8		Daily	Walk at least 5,000 steps
9		Daily	Walk at least 5,000 steps
10		Daily	Walk at least 5,000 steps
11		Daily	Walk at least 5,000 steps
12		Daily	Walk at least 5,000 steps
13		Daily	Walk at least 5,000 steps
14	(Endpoint period)	Daily	Walk as much as possible

* The exact dates will be written on the exercise prescription for each patient.

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