PROTOCOL DOCUMENT

Complete Title: Momentum-enabled Treadling Methodology to Improve Gait and Enhance Mobility

Short Title: Treadling Intervention Study

FDA IND/IDE (if applicable): Not Applicable.

Sponsor: Treadwell Corporation via Subaward (National Institutes of Health)

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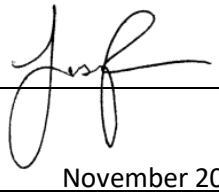
Version Date: November 26, 2018

I confirm that I have read this protocol and understand it.

Principal Investigator Name: Jason R. Franz

Principal Investigator Signature: 

Date: November 2018

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PROTOCOL SYNOPSIS

Study Title	Momentum-enabled Treadling Methodology to Improve Gait and Enhance Mobility
Funder	Treadwell Corporation via Subaward (National Institutes of Health)
Clinical Phase	Pilot
Study Rationale	Mobility impairment is a significant concern for the over 617 million people aged over 65 worldwide, with 17%, 28% and 47% of people aged 65-74, 75-84, and 85+ years respectively reporting that difficulty walking interferes with their daily activities. While there is a heterogeneous mixture of causes for mobility loss in older adults, peripheral arterial disease (PAD) is a significant concern. PAD is predominately a disease of the elderly, affecting 20 – 30%adults aged over 65 years old with prevalence increasing with age. Elderly individuals with PAD experience significant mobility impairment, including lower walking speed, reduced walking distance, and lower physical activity levels, often caused by pain associated with intermittent claudication (IC), which leads to reduced independence and decreased quality of life. Furthermore, older adults with PAD experience 73% more falls than healthy counterparts and a greater prevalence of stumbling and unsteadiness, likely due to luminal narrowing of the lower extremity arteries, which results in impaired perfusion of skeletal muscles and worsening motor skills. There is a significant need for treatments that improve mobility in elderly individuals with PAD. Current therapies attempt this in a variety of ways. Rigorous exercise is the gold standard to improve mobility, pain-free walking time, and independence and may delay disease progression in patients with PAD. However, pain significantly complicates this treatment. Pain occurs on exertion, only diminishes with rest, and returns upon re-exertion, which limits exercise in 35 – 50% of PAD patients. As a result, patients fail to comply with prescribed exercises, likely explaining why studies exploring at-home exercise have mixed results for demonstration of efficacy. Accelerating progress to and improving compliance with rigorous exercise treatment has the potential to substantially improve patient mobility and independence. In this proposal, Treadwell will explore the ability of a novel treadling methodology, facilitated by the company's innovative device (the TREDLR™) to improve exercise tolerance and mobility in patients with PAD. Treadling improves lower extremity hemodynamics by activating the calf pump muscle, targeting the plantarflexors, which are the most affected area in PAD. These muscles are also critical for walking performance as they provide more than 50% of the mechanical power needed for walking. The plantarflexor muscles also generate 70%–80% of the mechanical power needed for forward

	propulsion and swing initiation and are critical for modulating speed and step length in walking. For these reasons, we hypothesize treadling will improve plantarflexor-mediated mechanisms, leading to improved exercise tolerance and mobility in patients with PAD. In addition, the TREDLR™ is momentum-enabled; we hypothesize that this will result in less muscle engagement to activate the calf-pump mechanism, which may affect time to onset of pain. These collective hypotheses will be addressed in this research effort.
Study Objective(s)	The investigate the joint and muscle kinematic difference between treadling and conventional exercise, to explore improvements in mobility and exercise capacity in individuals who treadle compared to a control group, and to assess user affect and compliance with the device.
Test Article(s) *(If Applicable)*	The TREDLR™ involves an internal flywheel that generates momentum while the user initiates repetitive ankle flexion and extension movements.
Study Design	A randomized control design in which participants are randomly assigned to a 6-week treadling intervention or 6-weeks of usual physical activity.
Subject Population **key criteria for Inclusion and Exclusion:**	Inclusion Criteria 1. Age: 65+ years 2. Be able to walk without an assistive aid (i.e., walker, cane) 3. Have the capacity the provide written informed consent 4. Have previously diagnosed peripheral arterial disease (by self-sport) (for PAD subjects) Exclusion Criteria 1. Lower extremity injury or fracture within the last 6 months 2. Have a leg prosthesis 3. Prisoners 4. Individuals clearly lacking the capacity to provide informed consent 5. vestibular impairment
Number of Subjects	Up to 30
Study Duration	Subjects will participate in up to 20 total contacts, including 2 laboratory sessions (each lasting up to 3 hours) and, for those assigned to receive the treadling intervention, 3 sessions per week for 6 weeks). The entire study is expected to last three years, including time for study conduct and data analysis.
Study Phases **Screening** **Study Treatment** **Follow-Up**	(1) Screening and baseline laboratory visit: We will use an initial telephone screening (attached) to evaluate basic study eligibility. Subjects that meet inclusion/exclusion criteria following phone screening will be invited to participate in the study and complete Session 1 – a laboratory visit designed to establish baseline measures for all outcome measures.

	(2) Training: Subjects that provide written informed consent and randomly assigned to receive the treadling intervention will complete 15-min treadling sessions 3x/week for 6 weeks. (3) Follow-up: All subjects will complete Session 2 – a laboratory visit designed to test for changes in all outcome measures.
Efficacy Evaluations	Primary Outcome Measure(s): 1. Change in Overground Walking Speed After Intervention [Time Frame: Baseline, 6 weeks] 2. Change in 6-min Walk Distance [Time Frame: Baseline, 6 weeks] Secondary Outcome Measure(s): 3. Change in Stride Length [Time Frame: Baseline, 6 weeks] 4. Change in Peak Ankle Power [Time Frame: Baseline, 6 weeks]
Statistical Analysis Plan	A mixed factorial will test for main effects of and interactions between group assignment (treadling, controls) and time (pre, post) on primary and secondary outcomes. Significance will be defined using an alpha level of 0.05.
Data And Safety Monitoring Plan	This study does not meet the criteria for an independent DSMP. The subaward PI (Dr. Franz) will oversee all conduct to ensure the safety of all participants and the integrity of the data. At least one research staff member will be monitoring the subjects' movement patterns during the data collection and throughout the intervention. If the subject experiences any discomfort, the data collection and/or the intervention itself will be stopped immediately. If any member of the research team encounters unanticipated problems (including by not limited to adverse events), we will make necessary adjustments to the protocol and, where appropriate, report these events to University administrative personnel.

1 BACKGROUND AND RATIONALE

1.1 Introduction

Mobility impairment is a significant concern for the over 617 million people aged over 65 worldwide, with 17%, 28% and 47% of people aged 65-74, 75-84, and 85+ years respectively reporting that difficulty walking interferes with their daily activities. While there is a heterogeneous mixture of causes for mobility loss in older adults, peripheral arterial disease (PAD) is a significant concern. PAD is predominately a disease of the elderly, affecting 20 – 30%adults aged over 65 years old with prevalence increasing with age.

Elderly individuals with PAD experience significant mobility impairment, including lower walking speed, reduced walking distance, and lower physical activity levels, often caused by pain associated with intermittent claudication (IC), which leads to reduced independence and decreased quality of life. Furthermore, older adults with PAD experience 73% more falls than healthy counterparts and a greater prevalence of stumbling and unsteadiness, likely due to luminal narrowing of the lower extremity arteries, which results in impaired perfusion of skeletal muscles and worsening motor skills.

There is a significant need for treatments that improve mobility in elderly individuals with PAD. Current therapies attempt this in a variety of ways. Rigorous exercise is the gold standard to improve mobility, pain-free walking time, and independence and may delay disease progression in patients with PAD. However, pain significantly complicates this treatment. Pain occurs on exertion, only diminishes with rest, and returns upon re-exertion, which limits exercise in 35 – 50% of PAD patients. As a result, patients fail to comply with prescribed exercises, likely explaining why studies exploring at-home exercise have mixed results for demonstration of efficacy.

Accelerating progress to and improving compliance with rigorous exercise treatment has the potential to substantially improve patient mobility and independence. In this proposal, Treadwell will explore the ability of a novel treadling methodology, facilitated by the company's innovative device (the TREDLR™) to improve exercise tolerance and mobility in patients with PAD. Treadling improves lower extremity hemodynamics by activating the calf pump muscle, targeting the plantarflexors, which are the most affected area in PAD. These muscles are also critical for walking performance as they provide more than 50% of the mechanical power needed for walking. The plantarflexor muscles also generate 70%–80% of the mechanical power needed for forward propulsion and swing initiation and are critical for modulating speed and step length in walking. For these reasons, we hypothesize treadling will improve plantarflexor-mediated mechanisms, leading to improved exercise tolerance and mobility in patients with PAD. In addition, the TREDLR™ is momentum-enabled; we hypothesize that this will result in less muscle engagement to activate the calf-pump mechanism, which may affect time to onset of pain. These collective hypotheses will be addressed in this research effort.

1.2 Name and Description of Investigational Product or Intervention

Treadwell Corporation's technology is a patented treadling methodology facilitated by a prototype treadling device (US Patent 7,883,451). The device, the TREDLR™ (Fig. 1), is fabricated with an internal flywheel mechanism that facilitates the natural flexion and extension movements of the ankles by lifting the forefoot to assist the anterior compartment muscles, allowing minimal exertion from the user. As a result, treadling is user-initiated, non-jarring, non-fatiguing, and improves blood flow in the lower extremities.

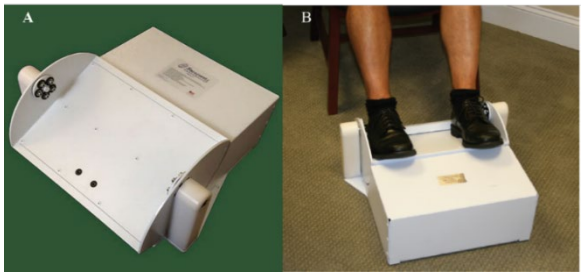

Fig. 1: The TREDLR™
The TREDLR™ device (A) and demonstration of use (B).

1.3 Relevant Literature and Data

An early version of the TREDLR™ demonstrated safety and ability to increase blood flow in the lower limbs in two independent studies. Hope *et al*[1] (2011) measured arterial and venous flow velocities with ultrasound and demonstrated significant increases in both arterial and venous flow velocities during treadling in comparison to resting and cool down periods ($p < 0.001$) while heart rate, blood pressure, respiratory rate, and body temperature remained constant. Maximum velocity in the femoral vein (FV) increased on average from 0.1 to 0.285 m/s (~3 fold), and minimum velocity in the FV increased on average from 0.01 to 0.07 m/s within 2 minutes of the start of treadling[1]. Hemodynamic changes also occurred in the superficial femoral artery (SFA). Mean end-diastolic velocity (EDV) in the SFA rose from a resting velocity of 0.01 m/s to a mean average treadling velocity of 0.165 m/s (1580%), and mean peak systolic velocity (PSV) values in the SFA increased from a resting value of 0.75 to 1 m/s (33%).

Hope *et al.* (2011) replicated earlier studies conducted by Currie *et al* (2010)[2], who also showed that blood flow velocity changes induced by treadling are comparable to exercise without being fatiguing or increasing vitals with dynamic peripheral vascular sonography to assess hemodynamic changes during lower limb movement. All studies were conducted with subjects that displayed a variety of negative health symptoms (e.g. coronary artery disease, hypertension, PAD, and diabetics) with no reports of adverse events, indicating that the TREDLR™ is safe to use with a broad range of cardiovascular and metabolic diseases.

2 STUDY OBJECTIVE

This is a pilot study of a new exercise device (TREDLR) designed to facilitate repetitive ankle flexion/extension movements (i.e., "treadling") through a momentum-driven internal flywheel while seated. The specific goals of this project are to understand the joint and muscle kinematic difference between treadling and conventional exercise, to explore improvements in mobility and exercise capacity in individuals who treadle compared to a control group.

3 INVESTIGATIONAL PLAN (brief overview)

3.1 Study Design

Subjects will be randomized into a treadling group (n=15) or a control group (n=15). Treadling subjects will do so 3x per week (15 min sessions) for 6 weeks. The control group will be instructed to continue their normal daily activities. Pre-Post measurements will include walking performance, leg joint biomechanics (i.e., angles, moments, powers), and calf muscle contractile behavior via ultrasound.

3.2 Study Duration, Enrollment and Number of Subjects

This study will last up to 36 months. Subject recruitment and data collection will take up to 24 months. The remaining 12 months will focus on data analysis, data interpretation, and manuscript preparation. We will recruit up to 30 older adults to participate

3.3 Study Population

Inclusion Criteria:

1. Age: 65+ years
2. Be able to walk without an assistive aid (i.e., walker, cane)
3. Have the capacity the provide written informed consent
4. Have previously diagnosed peripheral arterial disease (by self-sport) (for PAD subjects)

Exclusion Criteria:

1. Lower extremity injury or fracture within the last 6 months
2. Have a leg prosthesis
3. Prisoners
4. Individuals clearly lacking the capacity to provide informed consent
5. vestibular impairment

4 STUDY PROCEDURES (what will be done)

Screening: We will use an initial telephone screening (attached) to evaluate basic study eligibility. We will not retain phone screening data for subjects that do not qualify for the study or for subjects that do not provide written informed consent. In these cases, we will destroy telephone screening data. Subjects that meet inclusion/exclusion criteria following phone screening will be invited to participate in the remainder of the study. Prospective subjects who provide written informed consent during their initial visit will then complete a more detailed health questionnaire (attached).

Study Activities Schedule: All subjects will complete an initial session lasting up to 3 hours to collect baseline biomechanics data. Subjects will then be randomly assigned to a treadling group (n=15) or a control group (n=15). Those subjects assigned to the treadling group will treadle 3x per week (15 min sessions) for a total of 6 weeks. Control subjects will be instructed to continue their usual daily activities. Finally, all subjects will complete a final session lasting up to 3 hours, identical in nature to the baseline session.

Location: Applied Biomechanics Laboratory, University of North Carolina, Chapel Hill, NC.

Subjects will be invited to complete written informed consent, a health questionnaire, and the experimental procedures outlined below.

TREDLR Device: This study makes use of a device called the TREDLR, made by Treadwell Corporation. The device is completely unpowered, and is essentially a simple footstool that allows the feet to rotate back and forth (like tapping your toes). This rotation is subtle (i.e., well within the ankle's range of motion) and is facilitated by a small flywheel that helps the user to "drive" these rotations more easily.

Baseline and Follow-Up Study Measurements: We will record the following subject characteristics: inclusion/exclusion criteria, birth date, height, weight, and typical weekly exercise. The following measures will be collected during walking, cycling, and treadling trials described below: forces between subjects' feet and ground (measured using force-plates), the motion of subjects' torso, pelvis, and legs (measure using 3D motion capture), leg muscle activity patterns (measured using electromyography).

Baseline and Follow Up Study Procedures: Subjects will first visit the Applied Biomechanics Laboratory to participate in the consenting process and, for those who are eligible and agree to participate, a baseline session that will take up to 3 hours. Subjects will first walk 30 ft three times at their self-selected preferred walking speed. Subjects will walk at their preferred speed on a force-sensing treadmill for 5 min. During treadmill walking, subjects will be comfortably fit with a safety harness and instructed on all safety procedures.

To conclude these sessions, subjects will perform a 6 min walk test, attempting to walk as far as they safely can in 6 min. Finally, subjects will be randomly assigned to the treadling group or the control group. The treadling group will be instructed on the use of the TREDLR for subsequent training.

Within-Training Study Measurements: The following measures will be collected during each session of the training period from the TREDLR devices: session begin and end times and number of cycles per session.

Within-Training Study Procedures: We will make devices accessible to study participants to facilitate their regular use during supervised training sessions, which involves use of the TREDLR 3x per week for 15 min each.

Subject Completion/ Withdrawal procedures

If subjects are unable to complete the protocol or suffer a musculoskeletal injury before or during the time period when they are involved in the study, they will be withdrawn from the study.

5 STUDY EVALUATIONS AND MEASUREMENTS (how measurements will be made)

3D motion capture and an instrumented treadmill will record the position and orientation of body segments and joints and ground reaction forces. Using custom software, we will compute the mean and standard deviation of overground walking speed, 6-min walk distance, stride length, and peak ankle power. Efficacy measurements will be made using the change in each outcome measure following the 6-week treadling intervention or control period.

6 STATISTICAL CONSIDERATION

Using a conservative 80% power and an alpha level of 0.05, n = 10 subjects are required to resolve a minimal detectable change of 58.21 meters in 6-min walk distance (m) [3, 4]. For walking speed (m/s), the minimal detectable change is 0.108 m/s (80% power, alpha = 0.5, with n = 13 subjects), which would be considered clinically meaningful[5]. The ability to resolve these changes justifies the size selected for our intervention and control cohorts.

6.1 Statistical Methods

A mixed factorial will test for main effects of and interactions between group assignment (treadling, controls) and time (pre, post) on primary and secondary outcomes. Significance will be defined using an alpha level of 0.05.

6.2 Interim Analysis

Given the non-invasive nature of the experiment and the relative risk involved, there are no criteria that will be used to stop the entire study prematurely.

7 STUDY INTERVENTION (drug, device or other intervention details)

Treadwell Corporation's technology is a patented treadling methodology facilitated by a prototype treadling device (US Patent 7,883,451). The device, the TREDLR™ (Fig. 1), is fabricated with an internal flywheel mechanism that facilitates the natural flexion and extension movements of the ankles by lifting the forefoot to assist the anterior compartment muscles, allowing minimal exertion from the user. Subjects randomly assigned to the treadling group will use the device 3x per week for 15 min each for a total of 6 weeks.

8 SAFETY MANAGEMENT

If a subject needs immediate medical assistance, we will call "911" for emergency services. Should a subject need non-urgent medical or psychological follow-up, research members will contact UNC Health Care to provide referrals.

At least one research staff member will be monitoring the subjects' movement patterns during the data collection and training sessoins. If the subject experiences any discomfort, the data collection will be stopped immediately.

If any member of the research team encounters unanticipated problems (including by not limited to adverse events), we will make necessary adjustments to the protocol and, where appropriate, report these events to IRB personnel. Our goal with protocol adjustments will be to further lessen the likelihood of unanticipated problems.

If subjects are unable to complete the protocol or suffer a musculoskeletal injury before or during the time period when they are involved in the study, they will be withdrawn from the study.

9 DATA COLLECTION AND MANAGMENT

We will minimize the breach of confidentiality as follows. All research will be conducted with only members of the research team present. The collection of information about subjects will be limited to the amount necessary to achieve the aims of the research. We are not utilizing computer-generated questionnaires. All data will be coded with unique subject identification numbers except consent forms (which are directly identifiable). Only members of the core research team will have access to the list that pairs subject names with numbers. This list will be kept separately from electronic data on password protected hard drives connected to a secure network and managed by Dr. Jason Franz. Subject data folders will be maintained in a secure filing cabinet where only the core research team has access. This filing cabinet is located in the Applied Biomechanics Laboratory. Electronic data will be stored on computers managed via a secure School of Medicine network with password access.

10 RECRUITMENT STRATEGY

Only persons with a prior knowledge of the research will be approached and identified in person. This may include, for example, an informational gathering at retirement community. This interaction will be limited to information contained in the email template and recruitment flyer, or to information needed to address any questions asked about the research by persons in attendance. Subjects recruited using the flyer or email template will contact a member of the research team by phone or email if interested in being recruited to participate. Once preliminary communication has been established, subjects will be invited to complete the telephone screening to assess basic eligibility criteria. If the subjects email or leave a phone message with their contact information, the study team will return the message to implement the telephone script. Chapel Hill is a popular community for people following retirement and has a high density of retirement communities and senior centers. Thus, there is a very high likelihood of having access to the projected number of subjects.

11 CONSENT PROCESS

All study procedures will be described to the subjects prior to their visit to the lab and prior to obtaining consent. This includes a phone screening in which subjects will be described the details of the study purpose and procedures. All subjects will have ample opportunities to ask questions regarding the protocol prior to signing the consent. In addition, no member of the research team will recruit or consent any student from a class over which they preside. We will not exclude potential subjects based on race, sex, gender, or ethnicity and thus we will ensure equal access to participation including women and minorities.

12 PLANS FOR PUBLICATION

The publication policy will be based on the relative scientific contributions of each investigator and other key personnel.

13 REFERENCES

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4. McDermott, M.M. and T.S. Polonsky, *Home-Based Exercise: A Therapeutic Option for Peripheral Artery Disease.* Circulation, 2016. **134**(16): p. 1127-1129.
5. Goldberg, A. and S. Schepens, *Measurement error and minimum detectable change in 4-meter gait speed in older adults.* Aging Clin Exp Res, 2011. **23**(5-6): p. 406-12.