Continuous wearable monitor for the detection and release of freezing of gait.

Protocol Number: Version 4

National Clinical Trial (NCT) Identified Number: NCT06385392

Principal Investigator: Martha Nance, MD

Site/Sponsor: Struthers Parkinson's Center/National Institute on Aging

Institutional Review Board Number: A23-354

Funded by: National Institute on Aging

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CONFIDENTIALITY STATEMENT

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as consistent with the terms of the award.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

Investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator or Clinical Site Investigator:

Signed: _____ Date: _____

Name: Martha Nance, MD
Title: Medical Director, Struthers Parkinson's Center

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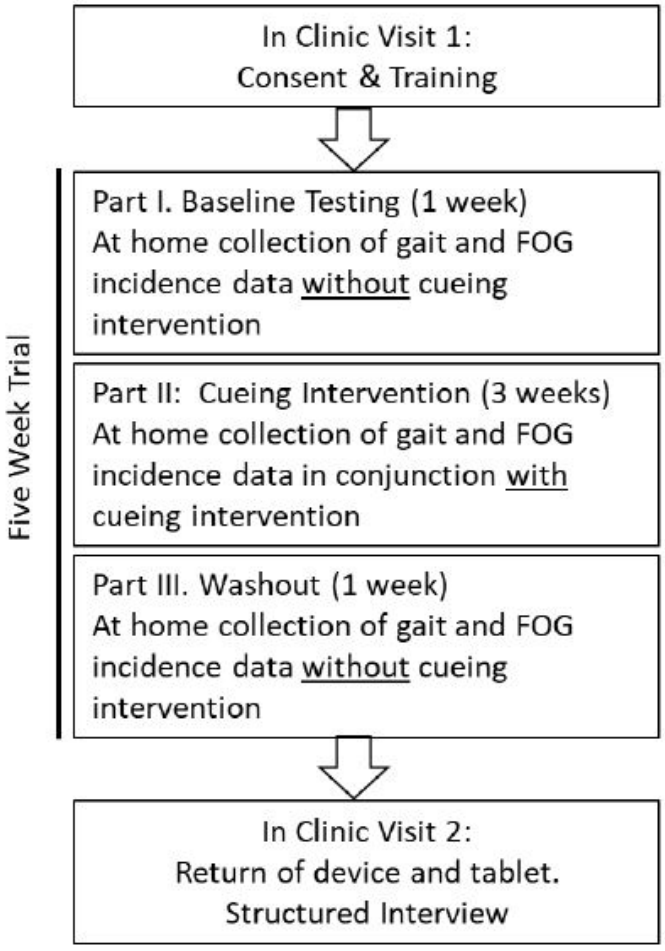
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Continuous wearable monitor for the detection and release of freezing of gait.
IRB Number:	A23-354
Study Description:	Proposed is a system (haptic module and insole device) for daily in-community use that detects the occurrence of freezing of gait (FOG) and triggers external cueing stimuli to unfreeze the individual. The purpose of the overall Phase II study is to: (1) Develop a production ready system, (2) Develop a companion mobile app for the proposed system and refine previously developed FOG detection algorithms, and (3) Validate the proper operation of the system and demonstrate its efficacy through lab and in-community testing. This study protocol will focus on validating the system and demonstrating efficacy through in-community testing.
Specific Aims:	Aim 1: Develop production ready insole and charging mat hardware. Aim 2: Refine and implement real-time FOG detection algorithm. Aim 3: Validate the system and evaluate its efficacy with clinical trials. **Note: This protocol will focus on the in-community testing of Aim 3.*
Endpoints:	Aim 3 - Primary Endpoint: Duration of FOG events.
Study Population:	36 individuals aged 45 or older with a diagnosis of Parkinson's disease will be recruited for this study to examine Aim 3.
Description of Sites/Facilities Enrolling Participants:	Participants will be enrolled at Struthers Parkinson's Center and HealthPartners Neuroscience Center for Aim 3.
Description of Study Intervention/Experimental Manipulation:	Participants will use the wearable haptic module and insole device for a duration of 5 weeks within their home and the community. Data will be recorded by the device.
Study Duration:	The total duration of this study is 1 year.
Participant Duration:	Participants should be able to complete all study-related tasks within approximately 7 weeks, depending on scheduling of the pre- and post-treatment visits.

1.2 SCHEMA


In Clinic Visit 1:
Consent & Training
Five Week Trial
Part I. Baseline Testing (1 week)
At home collection of gait and FOG incidence data without cueing intervention
Part II: Cueing Intervention (3 weeks)
At home collection of gait and FOG incidence data in conjunction with cueing intervention
Part III. Washout (1 week)
At home collection of gait and FOG incidence data without cueing intervention
In Clinic Visit 2:
Return of device and tablet.
Structured Interview

1.3 SCHEDULE OF ACTIVITIES

	Pre-screening Phone Call	**Pre-treatment Visit**	**Study Intervention**	**Post-treatment or Early Withdrawal Visit**
	Visit 1	*Visit 2*	*5 weeks*	*Visit 3*
Review Eligibility	X			
Informed Consent		X		
Demographics		X		
Medication tracking		X		X
Device Training		X		
Device Return				X
2-minute walk test		X		
New Freezing of Gait Questionnaire (NFOG-Q)		X		X
Characterizing Freezing of Gait Questionnaire (CFOG-Q)		X		
Falls Questionnaire		X		
Structured Interview				X
Weekly phone call			X	
Adverse Events (AE) Reporting			X	X
Treatment Adherence			X	
Daily FOG diary			X	

VISIT SCHEUDULE DESCRIPTION

All in-person visits will take place at: **Struthers Parkinson's Center 6701 Country Club Dr. Golden Valley, MN 55427 or HealthPartners Neuroscience Center, 295 Phalen Boulevard, St. Paul, MN, 55130.**

1. **Pre-screening Phone Call**
   - Duration: Approximately 30 minutes via phone
   - Research staff will:
     - Provide potential participants information about the study and ask whether they are interested in participating.
     - Determine whether they meet the inclusion/exclusion criteria for the study.
     - Ask for permission to communicate through e-mail for the study (e.g., for scheduling purposes).
     - Schedule the Pre-treatment Visit if the person is eligible for the study and e-mail them the Informed Consent and Health Insurance Portability and Accountability Act (HIPAA) forms.

2. **Pre-treatment Visit**
   - Duration: Approximately 120 minutes in person
   - Research staff will:
     - Review the Informed Consent and HIPAA documents with participants.
     - Answer any questions of participants and ensure they understand the expectations of the study.
     - Ask participants to sign the Informed Consent and HIPAA documents and provide them copies for their records.
     - Complete baseline assessments/questionnaires (2-minute walk test, NFOG-Q, CFOG-Q, Falls Questionnaire).
     - Train participants on how to use the haptic module and insole device and provide instructions for the daily FOG diary.

3. **Study Intervention**
   - Participants will wear the haptic module and insole device as often as possible for 5 weeks within their home and the community. They will also complete a daily FOG diary.
   - Research staff will:
     - Call participants weekly to check in regarding any issues with the device and complete the AE/SAE reporting form in REDCap (approximately 15-30 minutes).

4. **Post-treatment Visit**
   - Duration: Approximately 60 minutes in person
   - Research staff will:
     - Complete the AE/SAE reporting form in REDCap.
     - Complete NFOG-Q and structured interview with the participant.
     - Receive the device from participants and return it to the sponsor.

5. **Early Withdrawal Visit**
   - Duration: Approximately 60 minutes in person
   - Research Staff will:
     - Record the reason for study withdrawal.
     - Complete the AE/SAE reporting form in REDCap.
     - Complete NFOG-Q and structured interview with the participant.
     - Receive the device from participants and return it to the sponsor.

2 INTRODUCTION

2.1 BACKGROUND & STUDY RATIONALE

Parkinson's disease (PD) affects more than one million Americans, and its prevalence is expected to double by 2040.[1] Among the most treatment-resistant motor symptoms is freezing of gait (FOG). FOG is defined as "an episodic inability (lasting seconds) to generate effective stepping in the absence of any known cause other than Parkinsonism or high-level gait disorders".[2] This symptom affects more than 30% of all participants with PD and is characterized by episodic impairments in the ability to initiate gait and the spontaneous arrest of movement during stepping.[3,4] Incidence of FOG increases with severity and duration of PD with 80% of severely affected participants reporting freezing.[5] Episodes last from a few seconds to up to one minute and can be triggered by turning, approaching a narrow doorway or obstacles, or seemingly nothing in particular.[6] The incidence and severity of FOG episodes increases with disease progression. While levodopa and deep brain stimulation can often reduce the incidence and duration of FOG episodes, the efficacy of these treatments generally decreases over time.[6,7]

Clinicians have long recognized that one of the best methods to facilitate movement initiation in participants with PD is to provide them with a sensory cue (e.g., visual, acoustic, or somatosensory). Performance following a cue is often equivalent to, or greater than, that observed with levodopa replacement therapy.[8] Existing products that provide cueing such as the LaserCane[9] either use a continuous signal or periodic metronome-like signal, however, their effectiveness diminishes quickly over time.[10-12] It has recently been shown that the reliability and effectiveness of external cueing is critically dependent upon the timing and method of presentation of the stimulus. If the external stimulus is self-triggered (e.g., via button press, as is done in most commercially available cueing systems), the cue is ineffective in improving gait initiation.[13] If the cue is exogenously presented, the incidence of an inappropriate gait initiation sequences is reduced from 20% to less than 1% and the magnitude of force generation during stepping increases by an average of 45-71%.[14]

In this Phase II study, a system (haptic module and insole device) is being developed for daily in-community use that detects the occurrence of FOG and triggers external cueing stimuli to unfreeze the individual. IDL and its collaborators propose to: (1) Develop a production ready system, (2) Develop a companion mobile app for the proposed system and refine previously developed FOG detection algorithms, and (3) Validate the proper operation of the system and demonstrate its efficacy through in-lab and in-community testing. **This study protocol describes testing the usability and efficacy of the system in people with Parkinson's disease within their home and community (Aim 3; In-community testing).**

2.2 RISK/BENEFIT ASSESSMENT

2.2.1 KNOWN POTENTIAL RISKS

Potential risks associated with this proposed study are expected to be minimal. No experimental pharmacological intervention or invasive medical device intervention will be used in the study.

Haptic Module & Insole Device
The developed system consists of the sensing insole and the electronics enclosure. The insole slides into the subject's shoe, underneath their existing shoe insole (if removable) and connects to the electronics enclosure through a physical cable. The electronics enclosure clips onto the exterior side of the subject's shoe. The system will be designed to minimize volume (e.g., the insole is <1mm thick) and avoid any hard components in the shoe. Similar systems have been tested by Innovative Design Labs (e.g., RxFunction Walkasins and PhySens-IMM) and found to be a non-significant risk device. The Haptic Module wraps around the lower leg and can be worn on top of the clothing for comfort.

Potential risks of wearing the haptic module and insole device include:
- Foot/ankle pain or discomfort
- Skin irritation or wounds
- Falls

Assessments/Interview
Participants will be asked to complete the NFOG-Q, CFOG-Q, and the Falls Questionnaire. They will also be asked to complete a structured interview with questions about their experience with using the device within their home and community. Completing the questionnaire and answering the structured interview questions may be difficult or tiring for participants and/or may result in emotional side effects.

Loss of Confidentiality
There may be a slight possibility of breach of confidential information that was collected. However, the following procedures will be implemented to reduce this risk:
- Data collection and reporting tools will be developed and stored internally.
- Data collected and stored electronically will remain confidential and secure (e.g., secured server and password protected files [Research Electronic Data Capture; REDCap]).
- Study binders will be stored in a locked file cabinet within a locked office.
- After the study is closed, all subject identifiers will be destroyed.

2.2.2 KNOWN POTENTIAL BENEFITS

There are no known potential benefits to participants in this study. This study may help other people with PD in the future who have problems with walking and FOG.

2.2.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

We believe the potential risks to the participants in this study are minimal and that the benefit of testing the haptic module and insole device outweighs the potential risks.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
Aim 3: To validate the haptic module and insole device system and evaluate its efficacy with an in-community clinical trial.	Duration of FOG events.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Study Design:
This study is an unblinded, uncontrolled, unrandomized, 1-arm clinical trial.

Hypotheses:
We hypothesize that easy to use, accurate, exogenous cueing in response to FOG events will decrease duration these events.

Randomization:
N/A

Study Intervention:
Participants will be provided a haptic module and insole device to use within their home and community for 5 weeks. Additional details of the intervention are discussed in **Section 6.1**.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Justification for an unblinded study: This is a Phase II study. All participants will receive the intervention; therefore, participants and study staff will not be blinded.

Justification for an uncontrolled/unrandomized study: This is a Phase II study. All participants will receive the intervention; therefore, there will be no control group and no randomization.

4.3 JUSTIFICATION FOR INTERVENTION

The Phase I effort successfully created a prototype insole, tested its robustness, and created an algorithm to detect FOG events (sensitivity 80%, specificity 92%). The proposed Phase II effort will transition the prototype insole into a production ready sate, augment it with a charging mat and external cuing device, and evaluate the efficacy of the system with in-lab and in-community clinical trials.

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed study/treatment visits and assessments. Study withdrawals are described in **Section 7**. The end of the study is defined as completion of the post-treatment visit shown in the Schedule of Activities, **Section 1.3.**

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Ability to provide and provision of signed and dated informed consent form.

- Age 45 or older
- Diagnosis of idiopathic PD, as determined by a movement disorders neurologist in accordance with the PD Society Brain Bank diagnostic criteria.
- Evidence of presence of freezing gait as a symptom. Determined from combination of clinical examination (observation of freezing) and NFOG-Q.
- Able to complete a 2-minute walk test at the pre-treatment visit.
- Currently on a stable prescription medication regimen for PD and willing to adhere to the regimen during the study.
- Ability to don and doff the insole and haptic module independently or have daily assistance during the study intervention.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

- Non-English speaking
- History of musculoskeletal disorders that significantly affect movement of lower limbs as determined at the time of enrollment.
- Other significant neurological disorders that may affect participation or performance in the study.
- Neuropathy at the ankle assessed at the pre-treatment visit using the haptic module.
- Hallucinations
- Non-ambulatory
- Legally Blind
- Symptomatic hypotension
- Any condition which would limit sensation in the legs or requires use of wraps, bandages or other items which may limit sensation in the legs (e.g., lymphedema) that would interfere with the performance of the haptic device, in the opinion of the Investigator

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

Pre-screening Phone Call:
All potential participants will undergo a pre-screening phone call to determine whether they meet the inclusion/exclusion criteria. Participants will be considered ineligible if they do not meet one or more of the inclusion criteria or meet one or more of the exclusion criteria during pre-screening. We will collect information on why participants are ineligible or decide not to move forward with the trial.

Pre-treatment Visit:
Screen failures are defined as participants who are considered eligible during the pre-screening phone call, but it was subsequently determined that they do not meet one or more of the inclusion criteria or meet one or more of the exclusion criteria at or after the Pre-treatment visit. We will collect information on why participants screen fail or decide not to move forward with the trial.

Rescreening:

Individuals who do not meet the criteria for participation in this trial (ineligible or screen failure) because of meeting an exclusion criteria that is likely to change over time (e.g., symptomatic hypotension) may be rescreened up to one time.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment: Individuals with PD will be recruited by clinician referrals from Struthers Parkinson's Center, HealthPartners Neuroscience Center, and other HealthPartners and Park Nicollet clinics. We will also advertise our research study by distributing flyers to physicians and throughout the clinics. Recruitment flyers will also be provided to community organizations, for example, Parkinson's Foundation and American Parkinson Disease Association. If we encounter difficulties with recruitment, we plan to submit an amendment to the IRB to contact HealthPartners patients and members and invite them to participate. To reach our target enrollment, we anticipate that we will need to screen 75 people, and of those 36 individuals will sign the informed consent.

Remuneration: Participants will be provided a gift card totaling $150 per participant at the post-treatment visit for completing the study (end of study). If participants choose to withdraw from the study early and complete the early withdrawal visit, they will receive a gift card payment of $75. For individuals traveling a long distance (≥ 50 miles each way), we can also reimburse for travel costs at a mileage rate of $0.67 per mile.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

The study intervention for all participants is the use of the haptic module and insole device within their home and community for 5 weeks. Participants will be asked to wear the devices as much as possible during the 5-week period. For example, whenever they don their shoes to walk around within their home or the community, they will also wear the devices. Participants will receive the system with cueing disabled. Cueing will be enabled at the end of week 1 and disabled at the end of week 4 automatically via the cellular base station provided to participants. If any issues occur with the remote enabling and disabling of the cueing devices, participants will be instructed to stop wearing the devices during weeks 1 & 5.

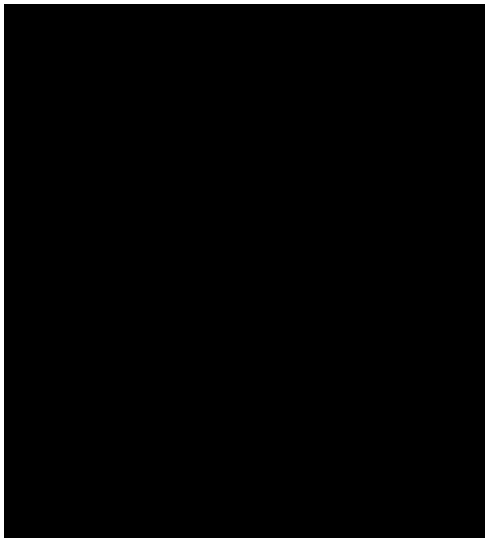
6.1.2 ADMINISTRATION AND/OR DOSING

The main purpose of this study is to establish the robustness and efficacy of the haptic module and insole device through long-term, continuous use while subjects proceed with their activities of daily living at home and in the community. Data will be collected in three parts. Part 1 will collect data for 7 days with the cueing intervention turned off to establish a baseline. Part 2 will collect data over 21 days with the cueing intervention turned on. Part 3 will examine the wash-out effects of cueing by collecting for an additional 7 days with the cueing intervention turned off. Throughout this trial, daily dairies of FOG episodes, user impressions, and adverse events will be collected. Data from the insole will automatically (no participant interaction for the duration of the study) be downloaded by the charging mat's nRF52840

BLE radio/processor and stored to a secure digital card. Participants will be contacted weekly by the research coordinator to discuss use of the device and compliance with protocol.

The sensing device consists of two parts for each leg: the Haptic Module and the Insole (Figure 1). The Haptic Module wraps around the lower leg (Figure 2) of the user and contains electronics for wireless communication, a microprocessor, and four vibrating motors that provide gentle tactile sensory cues to the front, back, medial, and lateral surfaces of the user's leg when a FOG event is detected. The Haptic Module has a power button, two status LEDs, and a reset button. Power is supplied by a rechargeable internal battery.

The Insole is a pressure-sensitive insert that fits in a regular shoe with a battery and electronics for sampling pressure measurements. The electronics are housed in a sealed plastic case that securely clips to the outside of the wearer's shoe (Figure 2). The insole has a single status light and no buttons. Users recharge the insole and haptics module via USB connectors.



Both the Haptics Module and Insole contain a PhySens™ Intelligent Motion Module (PhySens-IMM), Innovative Design Lab's (IDL) compact motion sensing and processing platform. The PhySens-IMM is designed to sense motion information using its onboard MEMS accelerometer, gyroscopes, magnetometers, and barometer and to process this information in real time using its onboard processors. Results are wirelessly transmitted via Bluetooth Low Energy (BLEv5) and stored on a local micro-SD card. Uses for the PhySens-IMM range from exercise recognition to camera orientation estimation to wheelchair performance monitoring. This device is part of the PhySens™ ecosystem that includes a variety of sensor types designed to monitor important aspects of daily life such as sleep, exercise, cognitive state, gait, etc. The data obtained from the PhySens-IMM is used to detect FOG events.

In previous studies, IRBs have determined that Walkasins meet the regulatory definition of a non-significant risk device because they do not meet the definition of a significant risk device. The device to be used in this study is based on the commercially available Walkisons device with the insole to haptics cable removed and integration of the PhySens-IMM.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

Training:
HealthPartners/Park Nicollet research staff will be trained by Innovation Design Labs, Inc. staff on how to use the haptic module and insole device.
Tracking:
All training sessions will be documented on a training log. This will include dates and times of the trainings and the names and signatures of those involved.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

N/A

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Participants will be asked to adhere to study visits and to complete study assessments. Participants will remain active unless withdrawn from the study (see **Section 7**). We will track participants' adherence to the intervention, as well as completion of the assessments. These will be documented in the relevant electronic case report forms (eCRF).

6.5 CONCOMITANT THERAPY

N/A

6.5.1 RESCUE THERAPY

N/A

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

When a participant who signed the consent form chooses to discontinue participation in the study or study intervention, or if the principal investigator (PI) and co-investigators determine that a participant should discontinue participation, they will be withdrawn from the study. A withdrawal will either be defined as 'Participant Withdrawal' or 'PI Withdrawal'. The participant will be asked to complete an early withdrawal phone call within 14 days from the date the intervention was discontinued. The purpose of the phone call will be to record any adverse events (AEs) or serious adverse events (SAEs) that may have occurred after the discontinuation of treatment. Research staff will attempt to call the participant up to 3 times.

The data that will be collected at the time of study withdrawal will include the following:
- The reason(s) for discontinuation of the study intervention.

The data that will be collected during the early withdrawal phone call will include the following:
- AEs or SAEs that occurred since the time of withdrawal.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue a participant from the study for the following reasons:

1. Significant study visit or intervention non-compliance.
2. Lost-to-follow up; unable to contact subject (see **Section 7.3, Lost to Follow-Up**)
3. Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study.
4. The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

The reason for participant discontinuation or withdrawal from the study will be recorded on the relevant eCRF.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to attend any scheduled study visit and study staff are unable to contact the participant after at least 3 attempts.

The following actions must be taken if a participant fails to attend any required study visit:

- Study staff will attempt to contact the participant, reschedule the missed visit, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, telephone calls or e-mail – if no answer leave a voicemail on the first and last attempt). These contact attempts will be documented.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Demographics: Demographic information will be collected, including gender, age, race, ethnicity, height, weight, marital status, and employment status.

Protected health information collected: Name, medical record number, birth date, phone number, address, email address, and medical history, including date of PD diagnosis.

New Freezing of Gait Questionnaire (NFOG-Q): The NFOG-Q[15] is a self-report questionnaire with 9 items that measure FOG.

Characterizing Freezing of Gait Questionnaire (C-FOGQ): The C-FOGQ[16] is a self-report questionnaire that provides insights into the triggers of freezing.

Falls Questionnaire: The falls questionnaire is a 4-item self-report survey including questions about any recent falls. The questionnaire was developed by the Dr. Colum MacKinnon at the University of Minnesota.

FOG Diary: Participants will be provided paper diaries to keep track of their FOG events and will be asked to report the information during the weekly phone call for the 5-week intervention.

Adherence: The participant's adherence to using the haptic module and insole device will be measured. Daily use of the device will be recorded during the weekly phone call for the 5-week intervention.

Structured Interview: Participants will be asked to complete a structured questionnaire at the post-treatment visit. The interview will include questions about their experience with using the device within their home and community.

8.2 SAFETY ASSESSMENTS

Assessment of Adverse and Serious Adverse Events:
AEs and SAEs will be monitored by research staff throughout the study. Research staff will immediately notify the PI and utilize the eCRF to record and categorize any AEs or SAEs. The PI will review all AEs or SAEs and report them accordingly, as discussed below.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

This protocol uses the definition of AE from 21 CFR 312.32 (a): any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention related.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

This protocol uses the definition of SAE from 21 CFR 312.32 (a): An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or study clinician, it results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

1. **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
2. **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
3. **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All AEs will have their relationship to study procedures, including the intervention, assessed by an appropriately trained clinician based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study procedures administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study procedures should be clinically plausible. The event must be pharmacologically or phenomenologically definitive.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study procedures, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study procedures). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study procedures administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study procedures) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study procedures administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

The study PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant.

All AEs, not otherwise precluded per the protocol, will be captured on the appropriate eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

Study staff will record events with start dates occurring any time after study enrollment until study completion. At each in-person visit or phone call, study staff will inquire about the occurrence of AE/SAEs since the last inquiry. All reported events will be monitored until resolution or study completion. Any reported event that is definitely or probably related to the intervention will be followed until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

In consultation with the PI, a trained member of the study team will be responsible for reviewing the AEs with the data safety officer (DSO). Together they will conduct an evaluation of AEs and shall report the results of such evaluation to the reviewing IRB either at the time of continuing review or within 10 working days of becoming aware of the event if the event is considered to be serious or meets the definition of an unanticipated problem involving risks to study subjects or others.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

In consultation with the PI, a trained member of the study team will be responsible for reviewing the SAEs with the DSO. The research team member will conduct an evaluation of SAEs and shall report the results of such evaluation to the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Following review of any AEs/SAEs, the PI will follow the DSO's and IRB's recommended actions. This may include, but is not limited to, modifying the informed consent document or process, re-consenting current participants, providing information to past or current participants (e.g., whenever the information may relate to the participant's willingness to continue), and modifications to the protocol/research plan.

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

Women who are currently pregnant or planning to become pregnant are not excluded from this study. If any participant becomes pregnant, the participant may remain in the study until study completion.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
2. Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

The PI will report unanticipated problems (UPs) to the reviewing IRB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number.
- A detailed description of the event, incident, experience, or outcome.
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP.
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs will be reported to the IRB as soon as possible, but no later than 10 working days after the investigator first learns of the event.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Following IRB review of any unanticipated problems, the PI will follow the DSO's and IRB's recommended actions. This may include, but is not limited to, modifying the informed consent document or process, re-consenting current participants, providing information to past or current participants (e.g., whenever the information may relate to the participant's willingness to continue participants), and modifications to the protocol/research plan.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- **Primary Endpoint: Duration of FOG events.**
  We hypothesize that easy to use, accurate, exogenous cueing in response to FOG events will decrease duration of these events.

9.2 SAMPLE SIZE DETERMINATION

The primary outcome measures of the in-community trial of the device will be the duration of freezing events. This will be assessed both with the NFOG-Q and the quantitative data obtained from the device. In a recent trial (CuePed) examining the effects of phasic (intermittent) visual cueing on gait and freezing, Marsh et al. (2019) showed an average 37% decrease in the duration of freezing events with cueing during a 2-minute walk test and a 47% decrease when navigating a freezing provoking environment. The sample size in that study was 20 individuals. Similarly, Ledger et al. (2008) estimated that a clinical trial of auditory cueing for freezing, and gait would require approximately 24 participants per group in order to detect a 20% reduction in freezing at a power level of 80% and a significance threshold of $p < 0.05$. Based on these studies we have estimated an effect size of 0.29. To test the primary hypothesis using a repeated-measures ANOVA (two conditions: sham vs. intervention) a sample size of 29 individuals will be required based on $p < 0.05$, power = 0.85 and an effect size = 0.29). Assuming a 20% attrition, we plan to recruit 36 individuals for this trial.

9.3 POPULATIONS FOR ANALYSES

N/A

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Statistical analyses will be performed using the data collected from the insole device. Data from baseline assessments will be summarized and used to describe the population. Discrete variables will be

summarized using frequencies and percentages, while continuous variables will be summarized by means and standard deviations.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

The primary outcome measures from this experiment will be the duration of FOG episodes detected by the insole device. A linear mixed effects model (LME, implemented in R) with within-subject factors of intervention (cueing vs. non-cueing) and time (pre vs. post intervention) will be used to test the primary hypothesis. Interaction effects will be tested using Tukey's Honestly Significant (HSD) test. The threshold for significance will be set at the $p < 0.05$ level. Secondary variables such as the incidence of FOG episodes will be assessed using a Chi-squared analysis.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

N/A

9.4.4 SAFETY ANALYSES

AE/SAEs will be reported as described in section 8.3 of this document. They will be classified by severity, relationship to study procedures, and expectedness. No other formal safety analyses will be conducted.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Demographic data will be summarized using descriptive statistics (e.g., mean and standard deviation, or frequency and proportion).

9.4.6 PLANNED INTERIM ANALYSES

N/A

9.4.7 SUB-GROUP ANALYSES

N/A

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

N/A

9.4.9 EXPLORATORY ANALYSES

N/A

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and written documentation of informed consent will be completed prior to starting the study intervention. The following recruitment and consent materials are submitted with this protocol:

- Informed Consent Form & HIPAA
- Recruitment Flyer

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

At the end of the pre-screening phone call, all eligible participants will be provided a copy of the consent and HIPAA forms via e-mail. At the pre-treatment visit, research staff will review the consent and HIPAA forms with the participant. The participant will be allowed time to review all documents and ask any questions prior to signing. Research staff will answer any questions and confirm that the participant understands the information in the forms. To obtain signature, the e-consent framework in REDCap will be utilized. Following the consent conversation, the participant will electronically sign the consent and HIPAA forms in REDCap. The research staff member will also sign the consent. A fully executed PDF copy of the consent and HIPAA will be provided to the participant for their records as well as saved via the auto-archiver function in REDCap.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigators, the funding agency, the IRB and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB, and the funding agency and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to the study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

1. Determination of unexpected, significant, or unacceptable risk to participants.
2. Insufficient compliance of study staff to the protocol (e.g., significant protocol violations).
3. Data that are not sufficiently complete and/or evaluable.

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, IRB, or other relevant regulatory or oversight bodies.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific

study participant will be held in strict confidence within the research team. No personally identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

All research activities will be conducted in as private a setting as possible.

All study regulatory binders will be stored in a locked file cabinet within a secure office. The internal study monitor, representatives of the IRB, or regulatory agencies, may inspect all documents and records required to be maintained by the investigator, for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be password-protected and stored on REDCap, a secure web-based system. Only research study staff will have access to the data. Individual participants and their research data will be assigned a unique study identification number. While the study is active, subject identifiers (e.g., name, MRN) will be stored in REDCap, however, after the study is closed all subject identifiers will be removed.

The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

N/A

10.1.5 KEY ROLES AND STUDY GOVERNANCE

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10.1.6 SAFETY OVERSIGHT

Although this study is considered minimal risk, safety will be monitored by a DSO. The DSO will be an independent individual who is not participating in the trial and has no direct affiliation with the research team. The Data safety monitoring plan will be established prior to initiation of the study. The DSO responsibilities include but are not limited to the following:

- Monitoring the study for compliance to the protocol.
- Stopping the study if the rate of SAE's raises safety concerns. The details will be specified in the data safety monitoring plan.

Throughout the trial, the DSO will review accumulating safety data to monitor for incidence of trends that would warrant termination of the trial. The frequency of the DSO meetings, responsibilities, membership, and procedures will be documented in the data safety monitoring plan.

10.1.7 CLINICAL MONITORING

N/A, refer to next section.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Study staff will perform internal quality management of study conduct, data collection, documentation, and completion.

Quality control procedures will be implemented as follows:

Informed consent --- The PI and study staff will review both the documentation of the consenting process and 10% of the completed consent documents. Feedback will be provided to study staff to ensure proper consenting procedures are followed.

Source documents and the electronic data --- Data will be directly entered into eCRFs in REDCap. REDCap utilizes date, time, and user stamping for quality tracking.

Intervention Fidelity — Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in **Section 6.2.1, Interventionist Training and Tracking**.

Protocol Deviations – The PI and study team will review documented protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Most of the data collected for this study will be collected directly by the insole device. Other data collection (e.g., demographics, assessments, interview) will be the responsibility of the research study staff under the supervision of the PI. The PI will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Data collected by research staff will be entered directly into

eCRFs in REDCap. The data system includes password protection and internal quality checks by study staff to identify data that appear inconsistent, incomplete, or inaccurate.

10.1.9.2 STUDY RECORDS RETENTION

Investigator records will be retained in accordance with regulatory, organizational and sponsor or grantor requirements, but no less than 6 years following the completion of the research. All records will be maintained securely with limited access. Disposal of investigator records will be done in such a manner that no identifying information can be linked to research data.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

It will be the responsibility of the PI to use continuous vigilance to identify, document, and report deviations as soon as possible, but no later than 10 working days after identification of the protocol deviation. Minor deviations, which do not impact participant safety, compromise the integrity of study data and/or affect the participant's willingness to participate in the research are to be reported at the time of continuing review. Protocol deviations will be addressed in study source documents and sent to the reviewing IRB per their policies. The PI will be responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with HealthPartners Institute has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event

CFOG-Q	Characterizing Freezing of Gait Questionnaire
CFR	Code of Federal Regulations
DSO	Data Safety Officer
eCRF	Electronic Case Report Forms
FOG	Freezing of gait
GCP	Good Clinical Practice
ICH	International Council on Harmonisation
IRB	Institutional Review Board
NFOG-Q	New Freezing of Gait Questionnaire
OHRP	Office for Human Research Protections
PD	Parkinson's disease
PI	Principal Investigator
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
UP	Unanticipated Problem

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
2.0	04/15/24	Response to IRB Review	Response to IRB Review
3.0	06/04/24	Add CT.gov #	Add CT.gov #
4.0	11/19/2024	Updated I/E criteria	Age has been a limitation to recruitment, There are no safety/efficacy concerns using the device in an older population as long as they meet all other I/E criteria

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