RxFunction™

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walk2Wellness: Long-term Use Effects of Walkasins® Wearable Sensory Prosthesis on Gait Function, Balance-Confidence, and Social Participation

NCT03538756

7576 Market Place Drive
Eden Prairie, MN 55344

July 30, 2019

RxFunction™
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- I have read this protocol, appendices, and amendment(s), if applicable, and agree to adhere to its requirements.
- I will provide copies of this protocol and all pertinent information to the study personnel under my supervision.
- I will discuss this material with study personnel and ensure they are fully informed regarding the device and the conduct of the study.
- I will conduct the study in accordance with the protocol and Good Clinical Practice guidelines, as well as local regulations, and I accept respective revisions to the protocol approved by authorized personnel of the Sponsor and by regulatory authorities.

Principal Investigator (print)

Principal Investigator (signature) Date

Institution Name/Location (print)

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Study Sites:	A list of study sites is maintained separately.
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Protocol Short Title:	walk2Wellness Study
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TABLE OF CONTENTS

1 Introduction and Background

1.1 Rationale for the Study

Approximately 4.8 to 6.4 million Americans, comprising 30-40% of the U.S. diabetic population, exhibit symptomatic diabetic peripheral neuropathy (PN) (Harris, Eastman et al. 1993; Martyn and Hughes 1997; Apfel 1999). The prevalence may be as high as 50% in diabetics over 60 years of age. Up to 20% of the elderly population may be affected by peripheral neuropathies (PN) (Harris, Eastman et al. 1993; Richardson and Ashton-Miller 1996); and epidemiological evidence has linked PN patients to an increased risk of falling (Richardson, Ching et al. 1992; Richardson and Hurvitz 1995) and decreased stability while standing (Geurts, Mulder et al. 1992) as well as when exposed to external postural perturbations (Inglis, Horak et al. 1994). Consequently, there is a need for developing cost-effective interventions for improving mobility and balance to manage fall risk in the elderly (Rubenstein, Robbins et al. 1990; Studenski, Duncan et al. 1991; Province, Hadley et al. 1995) and other clinical populations (Richardson, Ching et al. 1992; Richardson and Hurvitz 1995). Walkasins®, a lower limb sensory prosthesis that replaces lost foot pressure sensation with vibrotactile feedback around the lower calf, can address this need.

A growing body of research has investigated the use of vibrotactile feedback to enhance balance control following short-term use. Vibrotactile displays have been used successfully by the U.S. Navy to provide navigational cues that allow blindfolded pilots to control their aircraft (Rupert 2000; Rupert 2000). Sensory substitution devices to aid balance have provided auditory (Chiari, Dozza et al. 2005; Dozza, Chiari et al. 2005; Dozza, Chiari et al. 2005; Dozza, Horak et al. 2007), electrotactile (Tyler, Danilov et al. 2003), and vibrotactile feedback (Wall, Weinberg et al. 2001; Wall, Merfeld et al. 2002; Wall and Weinberg 2003; Wall, Oddsson et al. 2004).

More recent work has demonstrated the utility of vibrotactile feedback to improve postural control in patients (Horak, Dozza et al. 2009; Wall, Wrisley et al. 2009; Horak 2010; Wall 2010; Wall and Kentala 2010). None of these technologies, however, have been based on the measurement of foot pressure, nor have they been intended to be worn on a continuous basis as a balance prosthetic device (Statler, Wrisley et al. 2007, Wall 2012). In addition, current devices typically require a lab engineer on hand to ensure functionality.

1.2 Study Purpose

The purpose of this study is to investigate the long-term effects of Walkasins use on clinical and subject-reported outcomes of balance and gait function, quality of life, social activity/participation, pain, and medication use in persons with peripheral neuropathy who experience balance problems. The intent is to pool data from up to six sites for use in submission to CMS for Walkasins HCPCS code application.

In addition, because peripheral nerve deterioration diminishes the quantity and quality of afferent feedback to the spinal cord and brain, this chronic progressive disease process is associated with structural changes in the brain that include reduced cortical grey matter volume and decreased cortical thickness within the primary and secondary

somatosensory cortices (S1 and S2) and their connected neural networks (Selvarajah et al. 2014). Rocca et al. (2014) further demonstrated that individuals with mild-to-moderate PN, as compared to healthy controls, exhibit less resting-state functional connectivity within the somatosensory network as well as between the somatosensory network and other brain networks, including those responsible for attention and motor planning. Long-term use of Walkasins, which increase movement-related afferent feedback from the lower-extremity to the central nervous system, thus hold great promise to induce beneficial changes to brain structure and function. We will, therefore, conduct an exploratory study in which up to ten subjects who are interested and eligible for MRI brain scans will complete such scans at baseline and after 26 weeks of Walkasins use.

2 Study Summary and Hypothesis

2.1 Study Design Summary

This study involves an assessment of Walkasins through a randomized cross-over study, including pre- and post-assessments as well as periodic follow-ups. Up to six sites will participate with approximately 25 subjects per site.

2.2 Hypotheses

Subjects who receive tactile sensory balance information when wearing Walkasins every day will improve outcomes of gait, balance function, physical activity, and participation. The study should reflect expected realistic everyday use of Walkasins.

Over a 10-week period of continuous Walkasins use, subjects will show a sustained improvement of their Functional Gait Assessment (FGA) of at least 4 (the Minimally Clinically Important Difference or MCID, Beninato et al. 2014) compared to their initial assessment. We will specifically examine whether a linear multiple regression model and discriminant analysis based on initial baseline assessment data can help predict those patients who show a sustained long-term improvement of their FGA$\geq$4.

Over the extended long-term use reflected at 26 and 52 weeks, we expect to see clinical outcomes plateau across subjects at levels not different from those found after 10-weeks of use.

Furthermore, we expect that subjects who show a short-term improvement in their FGA ($\geq$4) with Walkasins on during the initial assessment session (“responders”) will have a statistically significant sustained long-term improvement in their FGA scores compared to subjects who don’t show a short-term benefit (“non-responders”). We hypothesize that “non-responders” will require longer exposure to the Walkasins sensory stimulus and that they will show an improvement of their FGA by at least 4 at the 10-week assessment compared to baseline testing.

2.3 Secondary Outcomes

Secondary outcomes include gait speed, 4-Stage Balance Test results, Timed Up and Go (TUG) results, and patient-reported outcomes that will be examined for trends over time. We expect to see trends of increasing gait speed, increased 4-Stage Balance Test times, and lower times in the Timed Up and Go assessment. We also expect to see trends of improvement in subject-reported outcomes that reflect comments from a recent case study of a patient using Walkasins on a long-term basis (>12 months), including increased participation in social and physical activities, higher self-confidence in balance-related activities, and less interference of pain in activities of daily living.

2.4 Rationale for the Selection of Functional Outcome Measures

- Functional Gait Assessment (FGA): The FGA is a reliable and valid measure of gait function related to postural stability and has been shown to be effective in classifying fall risk in older adults and predicting unexplained falls in community-dwelling older adults (Wrisley, Marchetti et al. 2004; Wrisley and Kumar 2010). It has also been validated in stroke survivors (Lin, Hsu et al. 2010) and patients with Parkinson's disease (Leddy, Crowner et al. 2011); and it has less floor and ceiling effect than the Dynamic Gait Index (Lin, Hsu et al. 2010). The FGA includes a 10-item scale where each item is scored from 0 to 3 (3 = normal, 2 = mild impairment, 1 = moderate impairment, 0 = severe impairment). The maximum score is 30. An increase $\geq$4 is considered the MCID for community-dwelling elderly individuals (Beninato et al. 2014).
- 10-Meter Walk Test (10MWT): The 10m-walk (Perera, Mody et al. 2006) is routinely done in rehabilitation and has excellent reliability in chronic stroke patients (Hiengkaew, Jitaree et al. 2012). In addition, gait speed has been found to be an important predictor of survival in older adults (Hardy, Perera et al. 2007), further emphasizing its importance as a clinical outcomes measure. Gait speed (10-meter walk using the middle 6 meters) will be assessed under two conditions: 1) instructed to walk at normal speed and 2) instructed to walk as fast as they can. A difference of 0.10m/sec is defined as the MCID (Perera, Mody et al. 2006).
- 4-Stage Balance Test: The 4-Stage Balance Test is part of the CDC-recommended test protocol for balance function (STEADI, http://www.cdc.gov/steadi/pdf/4-stage_balance_test-a.pdf). It includes four gradually more challenging postures the subject is exposed to:
  1) Stand with feet side by side.
  2) Stand with feet in semi-tandem stance.
  3) Stand with feet in tandem stance.
  4) Stand on one leg.

  Subjects pass each level if they can hold the stance for 10 seconds and then move on to the next stance. A fail of 1, 2, or 3 indicates at risk of falling. In addition, the researchers will record the time for each of the tests.

- Timed Up and Go (TUG): The TUG is also part of the CDC-recommended STEADI test protocol for balance function (https://www.cdc.gov/steadi/pdf/STEADI-Assessment-TUG-508.pdf). From a seated position in a standard armchair, the subject is asked to do the following:
  1) Stand up from the chair.
  2) Walk to a line on the floor 10 feet away normal pace.
  3) Turn.
  4) Walk back to the chair at normal pace.
  5) Sit down again.

  The tester will record the time taken from the command "Go" until the subject sits down again.

2.5 Justification for the Design of the Clinical Investigation

In a recent study at the Minneapolis VA Health Care System (MVAHCS) on **short-term** (a few hours) use effects of Walkasins in individuals with peripheral neuropathy (PN) and balance problems, the study team found an average increase in Functional Gait Assessment (FGA) score of 4.4±3.7 when subjects used Walkasins versus an increase of 1.5±1.2 when they did not.

The main objective of the current study is to show a **long-term** (10 weeks) sustained improvement in FGA score ≥4 following Walkasins use as compared to initial baseline assessment and to examine a potential relationship between initial baseline assessment data and long-term outcome. We believe our finding of a short-term FGA change >4 during Walkasins use justifies a pre-post study design to investigate the long-term effects of Walkasins use. We also intend to extend our observations of the short-term effects of Walkasins by replicating the randomized cross-over design of our previous short-term study during the initial assessment session. This study will help us further refine the prescription criteria for Walkasins and understand whether the presence of a short-term response is indicative of long-term improvements.

3 Investigational Device

3.1 Description

Walkasins consist of two parts for each leg: the leg unit and the foot pad (Figure 1). The leg unit wraps around the lower leg of the user and contains electronics for reading foot pad pressure signals, 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. These cues reflect real-time foot pressure information at a location above the ankle where skin sensation is still present. The leg unit has a power button, two status LEDs, and a reset button (not shown in Figure 1). Power is supplied by a rechargeable internal battery. The foot pad is a thin consumable sole insert that can be cut to size to fit into a regular shoe. The foot pad connects to the leg unit through a physical cable.

Figure 1.

3.2 Regulatory Classification

Walkasins meet the regulatory definition of a *non-significant risk* device because they do not meet the definition for a *significant risk* (SR) device.

Under 21 CFR 812.3(m), an SR device means an investigational device that:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. (https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf)

As a non-significant risk device, Walkasins . . .

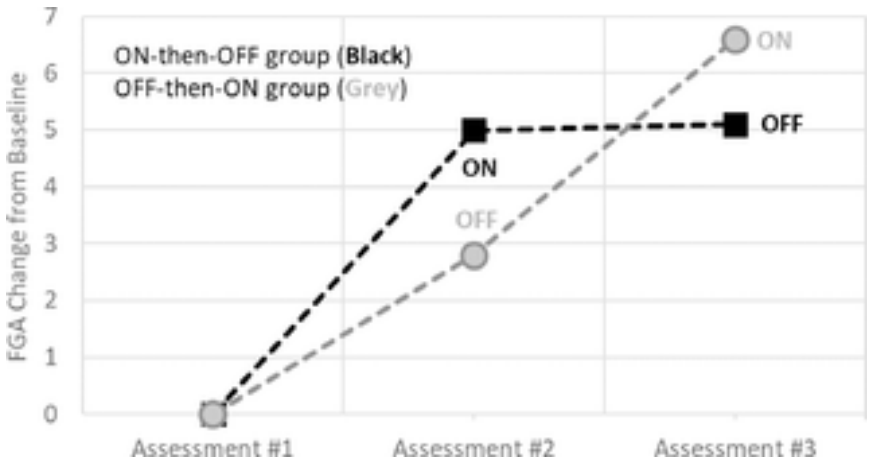
- Are worn on the foot and leg and are not intended as an implant, and they do not present a potential for serious risk to the health, safety, or welfare of a subject;
- Are not purported or represented to be for use in supporting or sustaining human life, nor do they present a potential for serious risk to the health, safety, or welfare of a subject;
- Are not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health, nor do they present a potential for serious risk to the health, safety, or welfare of a subject in this regard;

- Do not otherwise present a potential for serious risk to the health, safety, or welfare of a subject. (In the case study described below, the subject reported no adverse events during his long-term use of Walkasins.)

3.3 Clinical Data Published to Date

The following data from a study at the Minneapolis Veterans Affairs Health Care System (MVAHCS) were recently published by a peer-reviewed journal. Thirty-one subjects met inclusion criteria and were included for allocation. Twenty-seven of these subjects had a diagnosis of PN in their medical record, described as diabetic neuropathy (n = 14), idiopathic/unspecified neuropathy (n = 8), or neuropathies possibly related to alcohol dependence (n = 4) or b12 vitamin deficiency (n = 1). Exposure to agent orange was noted in the medical record of eight subjects.

No significant carryover effect based on sum of FGA scores across the three assessments was found (p = 0.92, [62]). Fig 2 shows consecutive changes in FGA scores across the three different assessments for each of the two groups, either using the device first ON-then-OFF or first OFF-then-ON. Larger changes in FGA score were seen when the device was turned ON, i.e., from Assessment #1 to Assessment #2 for the ON-then-OFF group and from Assessment #2 to Assessment #3 for the OFF-then-ON group. The ON-then-OFF group maintained their FGA score during their device OFF treatment at Assessment #3 (Fig 4). The OFF-then-ON group showed an improved FGA score during their device OFF session at Assessment #2.



At Assessment #2, 10 of 15 subjects (67%) in the group wearing the device turned ON improved their FGA score by at least four points compared to 5 of 16 (31%) in the group wearing the device turned OFF. The difference in proportion between the groups was statistically significant ($p<0.05$). At Assessment #3, 7 of 16 subjects (44%) in the group wearing the device turned ON improved their FGA score by at least four points from the prior treatment compared to 2 of 15 subjects (13%) in the group wearing the device turned OFF. The difference in proportion between the groups was not statistically significant (p = 0.063).

Overall, there were 24 observations of increases in FGA score of at least four points from the prior treatment across both ON and OFF treatments. These 24 observations represented 23 different subjects, i.e., one subject showed an FGA improvement of four points for both test treatments. Seventeen of the 24 observations occurred during device ON treatments and seven during device OFF treatments. Eight of the 31 subjects did not improve their FGA score by at least four points during either of the two test treatments. Consequently, 17 of the 31 subjects (55%) improved their FGA score by at least four points with the device turned ON as compared to 7 of 31 subjects (23%) when the device was OFF. The difference was statistically significant ($p<0.001$) and the effect size was near large (Hedges' g_{av} = 0.79, [67]).

All outcomes showed statistically significant improvements after ON treatments with large effect size for FGA scores, medium for 4-Stage Balance and small for gait speed [67]. The average change in FGA score after ON treatment was 4.4 points versus 1.5 points during the OFF treatment. The difference was statistically significant ($p<0.01$) and the effect size was large (Hedges' g_{av} = 0.82). After OFF treatment, only the FGA score showed a statistically significant increase although the effect size was small (Hedges' g_{av} = 0.24) compared to the ON treatment (Hedges' g_{av} = 0.82). No statistically significant changes were seen for gait speed or 4-Stage balance test after OFF treatment.

The table below shows the overall effects on outcomes following both the ON and OFF treatments combined for all subjects (i.e., between Assessment #1 and Assessment #3) following exposure to two balance training sessions, one with the device turned ON and one with the device turned OFF. After Assessment #3, 16 of the 31 subjects showed an increase of at least 0.13 m/s of their normal gait speed compared to Assessment #1. Fourteen of the 31 subjects performed the 4-Stage Balance Test for longer than 30 s after Assessment #3 compared to 5 subjects at Assessment #1. The change in proportion was statistically significant ($p<0.05$) and the effect size was large (Hedges' g_{av} = 0.80). The mean within-subject FGA score changed from 15.2 at Assessment #1 to 21.1 at Assessment #3. The change was statistically significant ($p<0.001$) and the effect size was large (Hedges' g_{av} = 1.14).

Effects of Both Treatments Assessment #1 to Assessment #3	**Assessment #1**	**Assessment #3**	**p-level**	**Hedges' g_{av}: (95% CI's)**
FGA score change ≥4 (n)	n/a	24 of 31	n/a	n/a
Gait speed Normal increase ≥ 0.13m/s (n)	n/a	16 of 31	n/a	n/a
4-Stage Balance Test >30s (n)	5 of 31	14 of 31	<0.05	0.80 (0.14, 1.46)
Subjects with FGA>22 (n)	0 of 31	16 of 31	n/a	n/a
	Mean (SD)	**Mean (SD)**	**p-level**	**Hedges' g_{av}: (95% CI's)**
FGA scores all (n = 31)	15.2(4.8)	21.1(5.2)	<0.001	1.14: (0.79, 1.56)
Subjects with FGA score >22 post sessions (n = 16)	18.3 (2.9)	25.1 (1.8)	<0.001	2.51: (1.69, 3.92)
Subjects with FGA score <23 post sessions (n = 15)	11.9 (4.3)	16.8 (4.0)	<0.001	1.11: (0.49, 1.84)
Gait speed Normal (m/s)	0.93 (0.22)	1.02 (0.21)	<0.005	0.41: (0.14, 0.69)
Gait speed Fast (m/s)	1.35 (0.29)	1.42 (0.32)	<0.05	0.22: (0.05, 0.40)
4-Stage Balance Test (s)	22.2 (7.5)	27.6 (7.5)	<0.001	0.70: (0.37, 1.06)

https://doi.org/10.1371/journal.pone.0216212.t003

Sixteen of the subjects ended the third test session with an FGA score higher than 22, i.e., in the normal fall risk range. Their mean FGA score at Assessment #1 was 18.3 compared to 25.1 at Assessment #3, respectively. The difference was statistically significant ($p<0.001$) and the effect size was large (Hedges' $g_{av} = 2.51$). The remaining 15 subjects who were still at high fall risk (FGA<23) after Assessment #3 did increase their FGA score from an average of 11.9 to 16.8. The change was statistically significant ($p<0.001$) and the effect size was also large (Hedges' $g_{av} = 1.11$) although less than half the magnitude of the normal fall risk group's effect size. Mean normal gait speed increased from 0.93 m/s at Assessment #1 to 1.02 m/s at Assessment #3 ($p<0.005$). The effect size was medium (Hedges' $g_{av} = 0.41$). Fast gait speed increased from 1.35 m/s to 1.42 m/s ($p<0.05$) representing a small effect size (Hedges' $g_{av} = 0.22$). The 4-Stage Balance test performance increased from 22.2 s at Assessment #1 to 27.6 s at Assessment #3 ($p<0.001$), a medium effect size (Hedges' $g_{av} = 0.70$).

A majority of patients in the current study improved their clinical outcomes of gait and balance function after a brief session with a physical therapist. These findings suggest new sensory balance cues provided to the lower limb can modulate the activity of relevant nerve afferents and become integrated into sensorimotor control of balance and gait within a single therapy session.

Figure 4 shows data that were recently presented at the American Physical Therapy Combined Sections Meeting in New Orleans by Dr. Diane Wrisley of a patient case study. It represents the first long-term Walkasins use data available where a patient is wearing the device as a sensory prosthesis on a continual/chronic basis. Most of the improvement noticed in the FGA score had occurred after 2-3 months of daily use. This patient continues to use the device and has nearly maxed out in several clinical outcomes including the FGA (maximum score is 30).

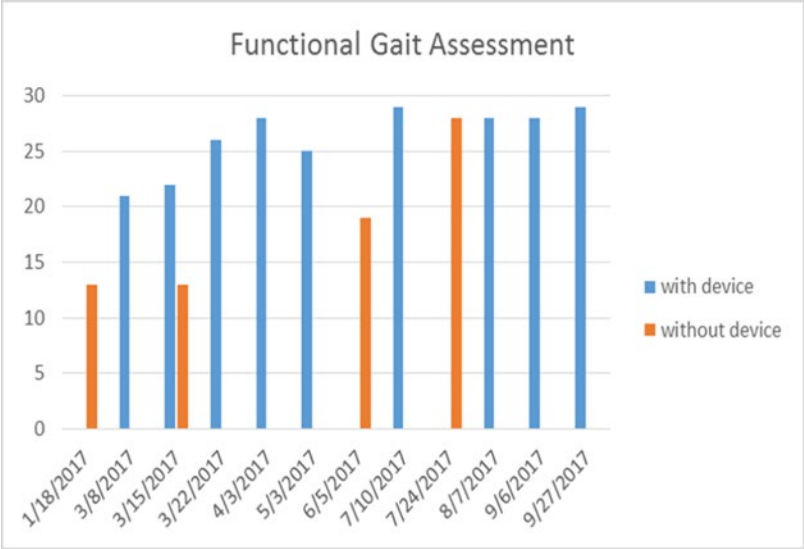


Figure 4. Long-term Change in FGA Score in One Subject.

3.4 Risks to Subjects

- Use of device/administration of physical stimuli: The device being tested may distract the subject while walking and increase the risk of falling. To prevent falling during the testing in the clinic/research site, a spotter will walk next to the subject to help him/her regain balance if a fall starts to occur.
- There is a very low chance that the subject will find the vibration uncomfortable. If this occurs, the subject can decide if he/she wishes to end participation in the trial.
- Use of medical records: The Sponsor and/or research site personnel may use the medical records to obtain information related to the cause of subjects' peripheral neuropathy or other medical history relevant to the study. There is a risk that study personnel may inadvertently see other information in subjects' medical records. The researchers will obtain HIPAA authorization for use of subjects' medical records.
- There may be other unknown side effects that could occur.

3.5 Approaches to Minimize Risks

All efforts will also be made to minimize potential risks by the following means:

- Investigators and study personnel will include individuals who are experienced in research and trained in the study assessments.
- Clearly defined inclusion/exclusion criteria ensure only appropriate subjects are enrolled.
- Maintaining subject safety through practices such as spotting the subject during study assessments will help to ensure subjects' physical safety.
- Regular monitoring and onsite visits to investigational sites will help to maximize consistency among the sites.

3.6 Device Labeling

Each Walkasins leg unit and foot pad carry a label comprised of the item serial number and company details as required by law. In addition, the plastic bags in which the devices are packaged bear the following label:

Caution: Investigational Device. Limited by Federal Law (USA) to Investigational Use.

3.7 Device Accountability, Storage, and Return

The Sponsor will ship the investigational device (Walkasins) only to the Principal Investigator (PI) or designee at each site. The Principal Investigator will maintain adequate records of the disposition of the investigational devices in the Device Accountability Log.

Device accountability records must be maintained at the study site and made available to RxFunction personnel or designees. The devices returned to the Sponsor and those devices dispensed at the study site will be recorded in the Device Accountability Log. The

Investigator must explain in writing the reasons for any discrepancy noted in device accountability.

When the study is complete, any unused investigational devices will be returned to the Sponsor, and a completed Inventory Accountability Report (or equivalent) will be generated for the site. The Inventory Accountability Report (or equivalent) will document the disposition of all investigational devices including those that have been returned to the Sponsor. Use of any investigational device outside of the protocol without prior IRB, Sponsor, and/or regulatory authority approval is strictly forbidden and may constitute grounds for removal of the Investigator/site from the study.

All unused investigational devices must be returned to the Sponsor when the study is complete. All investigational devices or any remaining components that are associated with a clinical device malfunction/failure must be returned to the Sponsor.

4 Study Population

4.1 Subject Selection

This study will recruit individuals who have been diagnosed with peripheral neuropathy and who have self-reported balance problems. Potential subjects must meet all the inclusion criteria and will be excluded if any of the exclusion criteria apply.

4.1.a Inclusion Criteria

- Age: 18-90 years, male or female
- Formal diagnosis of sensory peripheral neuropathy prior to participating in the study
- Self-reported balance problems
- Ability for transfers or ambulation on level surfaces at fixed cadence as assessed by trained study personnel during the FGA
- FGA <23, the cut-off score for high fall-risk and/or <8 on the Short Gait Assessment
- Ability to understand and provide informed consent
- Foot size that allows the Walkasins to function appropriately
- Must be able to complete all functional outcome measures without the use of an assistive device

4.1.b Exclusion Criteria

- Inability to perceive vibration from Walkasins leg unit
- Use of ankle-foot orthosis for ambulation that prevents donning of Walkasins

- Acute thrombophlebitis including deep vein thrombosis
- Untreated lymphedema
- Untreated lesion of any kind, swelling, infection, inflamed area of skin or eruptions on the lower leg near product use
- Untreated fractures in the foot and ankle
- Severe peripheral vascular disease
- Musculoskeletal or other neurological conditions that prohibit use of Walkasins as determined by clinician
- Weighs more than 300 pounds
- Plans to begin balance physical therapy (PT) during the first ten weeks of the trial (Ongoing or previous balance PT is not an exclusionary criterion.)

4.2. Subject Recruitment Plans

The study team will post fliers at various locations to advertise the study, and information about the study will be provided to clinicians who may provide patient referrals. Site personnel will provide an overview of the study to potential subjects and screen them over the phone to determine their eligibility for and interest in the study. Research sites may use other recruitment methods, subject to IRB review and approval.

4.3 Early Withdrawal of Subjects

Each enrolled subject will remain in the study until completion of the required follow-up period; however, a subject's participation in any clinical study is voluntary, and the subject has the right to withdraw at any time without penalty or loss of benefit. Reasons for withdrawing subjects include, but are not limited to, the following:

- Subject's death
- Subject's voluntary withdrawal
- Subject's withdrawal by study personnel as clinically indicated
- Subject lost-to follow-up

The reason for subject discontinuation will be documented on the CRF and source documents as appropriate. The Principal Investigator must also report all subject withdrawals to his/her IRB as defined by the IRB's procedure.

4.4 Data Collection and Follow-up for Withdrawn Subjects

If a subject decides to withdraw from the trial, a member of the research team will ask the subject to clarify whether he/she wishes to withdraw from all components of the trial or only from the primary interventional component of the trial (i.e., wearing the Walkasins device). If the latter, research activities for which the subject previously gave consent may continue (e.g., follow-up data collection activities for adverse events such as falls).

4.5 Subject Compliance Monitoring

The researchers will provide a calendar on which subjects can mark the days they wear their Walkasins to help determine the degree of subject compliance with study requirements. They will be asked at each visit to provide the calendar or an account/estimate of the number of days they wear/have worn their Walkasins to help ensure compliance with the study protocol. In addition, researchers will also ask subjects to mark falls on the same calendar to facilitate collection of this data point.

4.6 Prior and Concomitant Therapy

Individuals enrolled in this study may have received or be receiving physical therapy. This treatment will be noted as part of their medical history. Potential subjects who plan to initiate physical therapy for balance problems during the first 10 weeks of the trial will be excluded from participation.

5 Study Procedures

5.1 Telephone Screening

To help ensure that potential subjects will meet the eligibility requirements for the study, study staff will screen them over the phone prior to arranging their screening visit.

5.2 Informed Consent Process

The Principal Investigator, sub-investigator, or designee who has been trained on the protocol will explain the nature and scope of the study as well as risks and potential benefits of participation. The consent process will occur in a private room or space at the research sites. Study staff will answer any questions related to the study and will ask the subject to answer questions to verify that he/she understands the study.

After the consent discussion, all subjects will sign and personally date the Institutional Review Board (IRB) approved forms indicating their consent to participate in the study and to allow the study team to use their data (explained in the consent and HIPAA documents). The signed consent document will be stored in the subject's medical record, per local site requirements, and a copy of the signed consent form will be given to the subject.

When a consent form is not signed or properly dated before the procedure, the Investigator must inform the local IRB and the Sponsor of this deviation, per the IRB's requirements. The Sponsor has the responsibility to inform the regulatory authorities as required.

5.3 Screening Visit

Subjects will be considered enrolled in the trial at the time they sign the consent form and HIPAA authorization. After enrollment into the study, subjects will be tested to determine whether they can perceive vibration from the Walkasins leg unit. (Subjects who are unable to feel the vibration of the device will be excluded from continued participation in the study.)

Subjects who can feel vibration from the Walkasins leg unit will then complete a medical history form to assess common health issues related to neurological, musculoskeletal, and cardiopulmonary disorders as well as other systemic diseases and information on falls.

They will also undergo a brief assessment of their functional gait that includes the following tasks:

- Gait with Narrow Base of Support: Subjects will walk on the floor with arms folded across the chest, feet aligned heel to toe in tandem. The number of steps taken in a straight line are counted for a maximum of 10 steps.
- Gait with Eyes Closed: Subjects will walk at their normal speed for 20 feet with their eyes closed.
- Gait Level Surface: Subjects will walk 20 feet at their normal speed (time for 20').
- Gait with Horizontal Head Turns: Subjects will walk 20 feet while turning their heads.

Subjects who pass the screening criteria will be asked if they would be willing to participate in an optional MRI protocol. If so, they will be assessed for MRI eligibility at the end of this visit using a standard screening form. Subjects who are interested and eligible for the MRI will be scheduled for an MRI visit (Visit 1A) as well as a separate visit to assess the acute effects of Walkasins (Visit 1B). Subjects who are eligible for the study but uninterested and/or ineligible for an MRI will be scheduled only for the visit to assess the acute effects of Walkasins.

5.4 Baseline Visit: 1A

Structural and functional MRIs will be acquired using the following sequences:

Structural MRI Acquisition: We will acquire three-dimensional 1 mm isotropic T1 MPRAGE (TR=2530 ms, TE=3.04 ms, TI=800 ms, flip angle=10°, FOV=256x256x220 mm) that will be averaged during post-processing and 1 mm isotropic T2 (SPACE) images (TR=4000 ms, TE=406 ms, flip angle=90°, FOV=260x228x176 mm). T1 and T2 images will be used for co-registration of individual participant functional magnetic resonance imaging (fMRI) data into a standard stereotaxic space and for ascertaining changes in cortical thickness, cortical and sub-cortical brain volumes using Freesurfer (Patenaude et al. 2011).

Functional MRI Acquisition: Functional network organization will be evaluated with resting-state functional magnetic resonance imaging (rs-fMRI). Echo planar imaging data will be acquired with slices in an oblique 30-degree orientation relative to main magnetic field to optimize signal in ventral frontal regions (TR=2000 ms, TE=30 ms, flip angle=90°, FOV=220x220 mm, 3.4x3.4x3.5 mm2 voxels). We will collect one 13-minute scan to maximize test-retest reliability (Birn et al.). During resting-state scans, participants will be instructed to keep their eyes open, relax, and remain awake. Preprocessed time-series data will be extracted from spherical regions of interest (10 mm) and cross-correlated with every voxel in the brain to establish functional connectivity maps for relevant neural

networks. Within and between subject differences will be generated via ordinary least squares in FSL with thresholding set at Z=2.33 and cluster correction of p<0.05.

5.5 Baseline Visit: 1B

Subjects who meet all the eligibility requirements during the screening visit will return for the baseline visit.

They will begin by completing the following measures:

- Concomitant Medications Log: Study staff will review the subject's current medication list and record the medication names, indications, dosages, etc. in REDCap Cloud.
- Activities-Specific Balance Confidence (ABC) Questionnaire: Powell and Myers (1995) developed the Activities-specific Balance Confidence (ABC) Scale to detect levels of balance confidence in elderly persons. The ABC scale is a one-page questionnaire that asks questions about balance confidence when performing 16 different tasks.
- Vestibular Activities of Daily Living Scale (VADL): The VADL was developed to assess self-perceived disability in individuals with vestibular impairment. It evaluates the effects of vertigo and balance disorders on independence in everyday activities of daily living. (https://www.sralab.org/rehabilitation-measures/vestibular-disorders-activities-daily-living-scale)
- Falls Efficacy Scale-International (FES-I): The Falls Efficacy Scale International (FES-I), a 16-item questionnaire, measures an individual's "fear of falling" or "concerns about falling." It is suitable for use in research and clinical practice. (https://sites.manchester.ac.uk/fes-i/)

Next, subjects will be assessed using the monofilament test and vibration (tuning fork) test. Then subjects will don the Walkasins device, and their baseline scores on the FGA, 10MWT, TUG, and 4-Stage Balance Test will be assessed. (If subjects score >22 on the FGA, the accepted cut-off score for high risk fallers, they will be excluded from continued participation.)

Then subjects will complete the following self-reported outcome measures:

- Patient Health Questionnaire (PHQ-9): The PHQ-9 is a concise, self-administered tool for assessing depression. It incorporates DSM-IV depression criteria with other leading major depressive symptoms into a self-report instrument that is commonly used for screening and diagnosis. (http://www.apa.org/pi/about/publications/caregivers/practice-settings/assessment/tools/patient-health.aspx)
- Pain Interference Short Form 6b: The PROMIS Pain Interference instruments (adult and child) measure the self-reported consequences of pain on relevant aspects of a person's life and may include the extent to which pain hinders engagement with social, cognitive, emotional, physical, and recreational activities. The Pain Interference short form is universal rather than disease-specific. (https://cde.drugabuse.gov/instrument/0a47fbff-5f72-2281-e050-bb89ad4358ae)

- Pain Intensity Form 1a: The PROMIS Pain Intensity instrument assesses how much a person hurts. The Pain Intensity short form is universal rather than disease specific. (https://www.assessmentcenter.net/documents/PROMIS%20Pain%20Intensity%20Scoring%20Manual.pdf)
- Ability to Participate Short Form 8a: The PROMIS Ability to Participate in Social Roles and Activities assesses the perceived ability to perform one's usual social roles and activities. Items are worded negatively in terms of perceived limitations, but responses are reverse-coded so that higher scores represent fewer limitations (better abilities). The measure does not use a time frame (e.g. over the past seven days) when assessing ability to participate in social roles and activities. (https://www.assessmentcenter.net/documents/PROMIS%20Ability%20to%20Participate%20in%20Social%20Roles%20and%20Activities%20Scoring%20Manual.pdf)
- Satisfaction with Participation in Social Roles Short Form 8a: The PROMIS Satisfaction with Social Roles and Activities items assess satisfaction with performing one's usual social roles and activities (e.g., "I am satisfied with my ability to participate in family activities"). (https://www.assessmentcenter.net/documents/PROMIS%20Satisfaction%20with%20Participation%20in%20Social%20Roles%20Scoring%20Manual.pdf

Subjects will then be randomized by minimization (Han et al. 2009) to one of two study groups to balance the two groups during the baseline assessment with respect to the FGA score, age, and use of an assistive device. (Normal use of an assistive device is permitted, but not during any clinical assessment.)

Subjects randomized to Group A will initially be trained on the *Walkasins Learning Protocol* (a set of standardized standing and walking balance exercises) and tested with Walkasins turned on; then following a 60-minute break, Group A subjects will be trained on the *Walkasins Learning Protocol* and tested with Walkasins turned off. The second group (Group B) will initially be trained on the *Walkasins Learning Protocol* and tested with the Walkasins turned off; then following a 60-minute break, Group B subjects will be trained and tested with the Walkasins turned on. (See Figure 5 below for protocol design.)

During testing, subjects will complete trials of the FGA, 10MWT, TUG, and the 4-Stage Balance Test. (A trained member of the study team will conduct these assessments at the research sites.)

When subjects have completed the clinical assessments and subject-reported outcome measures, the researchers will train the subjects on how to use the device at home (e.g., how to charge the device and what to do if they encounter any problems). The subjects will then leave the site with the device for use at home and a calendar on which to mark their daily use of Walkasins as well as any fall events.

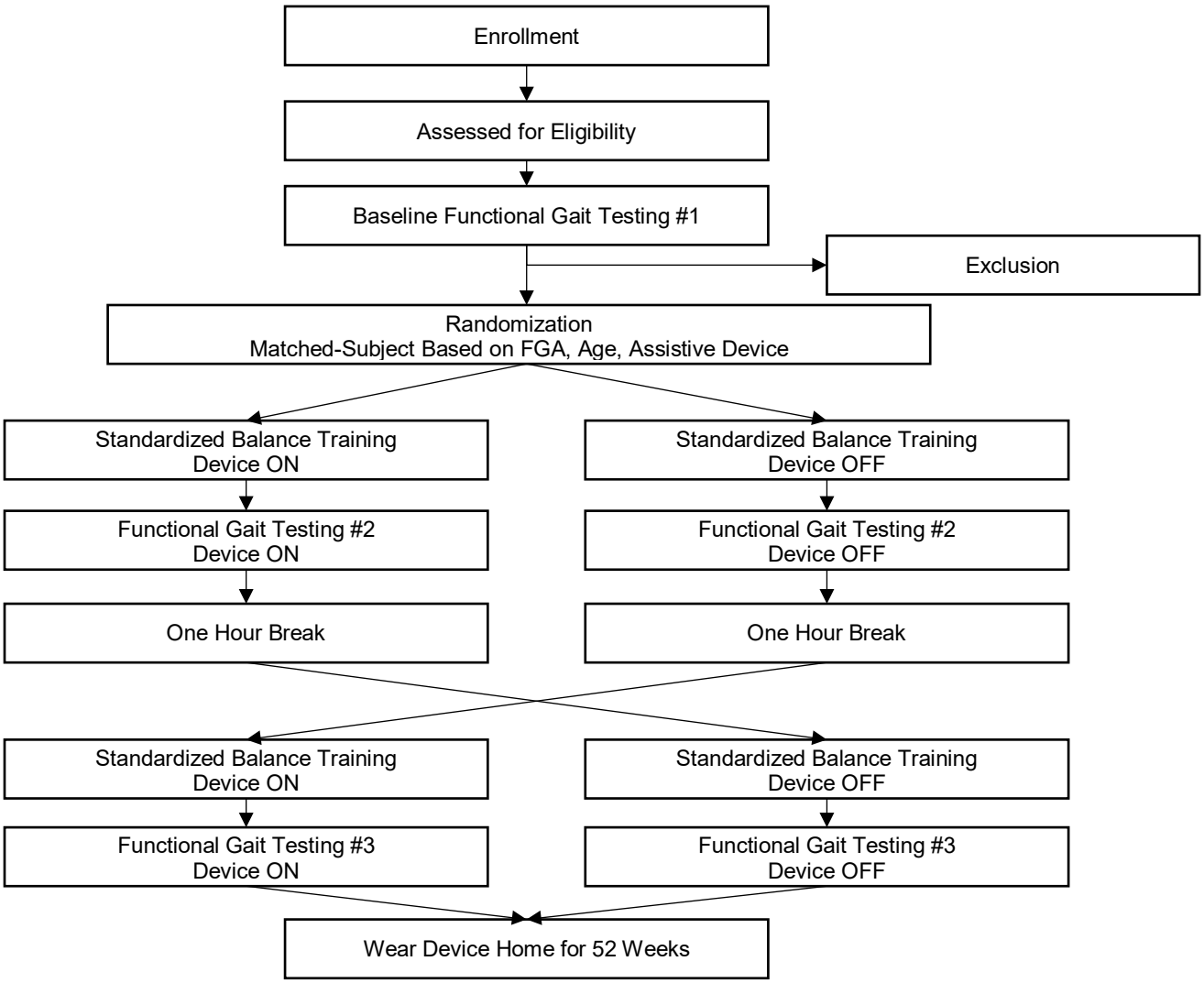


Figure 5.

5.6 Schedule of Assessments

Clinical Measures	Baseline	Week 2	Week 6	Week 10	Week 26	Week 52
FGA	X	X	X	X	X	X
10MWT	X	X	X	X	X	X
TUG	X	X	X	X	X	X
4-Stage Balance	X	X	X	X	X	X
Monofilament	X			X	X	X
Vibration Assessment (128Hz and Walkasins leg unit)	X			X	X	X

Subject-Reported Outcomes	Baseline	Weeks 2 & 10	Weeks 6, 26, 52
Subject Medical History Form	X		
Activities-Specific Balance Confidence Score	X	X	X
Vestibular Activities of Daily Living Scale	X	X	X
Falls Efficacy Scale-International	X	X	X
PHQ-9	X	X	X
PROMIS Pain Interference Short Form 6b	X	X	X
PROMIS Pain Intensity Form 1a	X	X	X
PROMIS Ability to Participate Short Form 8a	X	X	X
PROMIS Satisfaction with Participation in Social Roles Short Form 8a	X	X	X
Concomitant Medication Use Form	X	X	X
User Experience Survey		X	

5.7 Follow-up Visits

Subjects will be assessed at the research site at Weeks 2, 6, 10, 26, and 52, following the assessment schedule above. (Subjects will wear their Walkasins devices [turned on] for all functional assessments during the follow-up visits.) All the assessments are the same as those completed during the baseline visit, except that at Weeks 2 and 10, subjects will also take the User Experience Survey. This RxFunction survey collects information concerning the subjects' experience with their Walkasins.

Between in-person visits, study sites will contact subjects via telephone periodically between Weeks 10 and 26 (e.g., Weeks 14, 18, 22) and between Weeks 26 and 52 (e.g., Weeks 30, 35, 40, and 45) to remind them of study requirements and to collect follow-up information regarding health changes, adverse events, pain scores, device usage, and device functioning. If subjects report adverse events and/or falls during these contacts, site personnel will record the details on the appropriate CRFs in REDCap Cloud.

Subjects' levels of physical activity or inactivity while wearing the device will also be measured through an internal step counter in Walkasins. At each scheduled follow-up visit, the step data will be directly downloaded from the Walkasins. (This is a hardwired connection with the processor in the device and downloading counters in the memory for "load-cycles" [steps] and how many times the vibrator motors have been active. It will be downloaded to a company laptop and later entered in REDCap Cloud. There will be no subject identifiers on the laptop other than the subjects' ID numbers and the corresponding counts.)

If subjects encounter any issues with their Walkasins during the at-home trial, they may call the customer service number at RxFunction, Inc. (Subjects will receive a contact card with RxFunction's customer service number on it.) They will be instructed to call the number and tell the RxFunction representative that they are participating in a research

study. (They will not be required to give their name or any personally identifiable information.) RxFunction, Inc., will assist subjects in troubleshooting their devices and may ask for the subject's ID number or a serial number for the device. If the problem cannot be resolved during the phone call, RxFunction, Inc. will inform the study designee at the site and provide the serial number; the designee will ship or provide new Walkasins devices to the subject. If acceptable to the participating institution, RxFunction may also ship the device directly to the subject with his or her permission.

Subjects who complete an MRI at baseline will be scheduled for an additional MRI visit at Week 26. Unscheduled visits may occur for device replacement or other reasons as needed.

6 Statistical Plan

6.1 Sample Size Determination and Power

The primary endpoint of the study will be changes in the FGA score from initial baseline assessment to 10 weeks of Walkasins use. The baseline average FGA score in a recent study was 15.2 with a standard deviation of 4.8. The data was normally distributed according to Shapiro-Wilk Test. To detect a mean difference in pre- and post-FGA score >4, we need to study at least 20 subjects using a significance level of 0.01 and a power of 0.8.

Significance level is set to 0.01 and the power at 0.8.

6.2 Expected Drop-out Rate

The expected ~20% drop-out rate is based on the Study Quality Assessment Tools available on the website of the National Heart, Lung, and Blood Institute (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). Therefore, we plan to recruit up to 25 subjects (at each site) who must pass the eligibility criteria to enter the study (20/0.8=25).

6.3 Control of Systematic Error/Bias

Potential subjects may be recruited from the Investigators' usual patient load or from individuals who initiate contact with the researchers after seeing a recruitment flier or being referred by a clinician. All individuals having signed the Informed Consent Form and meeting the inclusion/exclusion criteria will be eligible for randomization in the study. The reasons for exclusion (i.e., for subjects who sign an informed consent form but are not randomized) will be indicated on the appropriate CRF in REDCap Cloud. Thus, consecutively eligible subjects will be randomly allocated into the study, minimizing selection bias.

To control for inter-observer variability, the Sponsor will provide training to the research teams.

6.4 Interim Analysis

No formal interim analyses are planned for stopping this trial early for efficacy.

6.5 Analysis Plan

The outcome measures of this study include changes in subjects' FGA scores and 10MWT, TUG, and 4-Stage Balance Test times. Using a within-subject parametric statistical model, we will compare baseline measures from the first study visit to post-training outcomes.

We expect that subjects who show a short-term improvement in their FGA (>4) with Walkasins on during the initial assessment session will also have a statistically significant sustained long-term improvement in their FGA scores compared to subjects who do not show a short-term benefit. We will use regression analysis to investigate trends in changes over time in the different outcomes.

6.6 Specification of Subgroups for Analysis

A separate post-hoc analysis will be conducted at 10 weeks on clinical outcomes between short-term "responders" vs. "non-responders." The recent short-term study found that 17 of 31 subjects immediately improved their FGA score by at least 4 (responders) when using Walkasins. We hypothesize that "non-responders" who do not show immediate short-term improvement of their FGA score require longer exposure to the Walkasins sensory stimulus and that they will show an improvement of their FGA by at least 4 at the 10-week assessment compared to baseline testing.

6.7 Exploratory Analysis of MRI Data

Statistical analysis related to MRI data will be performed using IBC SPSS Statistic 19 for Windows with alpha set at $p<0.05$. Repeated-measures analysis of variance with time (baseline, 24-week follow-up) will be used to examine potential changes in brain structure and function associated with long-term Walkasins usage. Separate models will be used for each dependent variable, which will include cortical volume and cortical thickness of the somatosensory network, as well as the strength of resting-state functional connectivity within this network. Effects of covariates, including age, sex, and average daily Walkasins use, will also be explored. Using linear regression analysis, we will also investigate whether observed changes in structural and functional brain outcomes are predictive of functional improvements associated with Walkasins usage over the same time period.

6.8 Missing Outcome Data

No imputation methods will be used to infer missing values of any outcome measures.

7 Data Management

7.1 Confidentiality and Security

The Investigator and the associated institution will permit direct access to source data/documents for study-related monitoring, audits, IRB review, and regulatory inspections.

Subjects providing informed consent agree to allow the Sponsor or designee access and copying rights to pertinent information in their medical records (e.g., diagnosis and adverse events) concerning their participation in this study. The Investigator will obtain, as part of the informed consent process, permission for study monitors or regulatory authorities to review, in confidence, any records identifying the subjects in this study. This information may be shared with regulatory agencies; however, the Sponsor undertakes to make every effort to protect the subject's privacy by eliminating any information permitting identification of the subject.

The Sponsor and all research team members will observe standard data confidentiality and security measures including, but not limited to, the following:

- Research staff will collect only the minimum identity information needed. (See CRFs for information to be collected.)
- Identifiers should be removed from data files whenever possible and must be encrypted if stored electronically. Identifiers will be stored in a physically separate and secure location from the data files and the key to the code.
- If it is necessary to use portable devices for initial collection of identifiers, the data files will be encrypted, and the identifiers will be moved to a secure system as soon as possible. Any portable devices will be stored in secure locations when they are not in use.
- Physical and electronic access to identifiers will be limited to authorized research personnel only.
- Identifiers and contact information will not be distributed without the specific consent of research participants.

7.2 Case Report Forms and Source Documents

Subject data will be collected in REDCap Cloud, a secure Electronic Data Capture (EDC) system. The Investigator's electronic signature for specific Case Report Forms/Events will be documented in compliance with FDA Regulation 21 CRF: Part 11 – *Electronic Records: Electronic Signatures*. Each study user will have a unique login to access the REDCap Cloud system and perform data entry.

For the duration of the study, the Investigator will maintain complete and accurate documentation including but not limited to medical records, study progress records, case report forms, signed consent forms, device accountability records, correspondence with

the IRB and Sponsor, adverse event reports, and information regarding subject discontinuation or completion of the study.

Source documents are defined as original documents, data, and records. Regulations require that the Investigator maintain source documents in the subject's medical records, which confirm the data entered on the electronic case report forms.

7.3 Records Retention

The Investigator/Site will maintain all records pertaining to this study for a minimum of two (2) years following study completion or as otherwise instructed by the Sponsor or per local requirements, if longer. ICH guidelines require that essential documents be retained until at least two (2) years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two (2) years have elapsed since the formal discontinuation of clinical development of the investigational product.

To comply with these requirements, the Investigator will not dispose of any records relevant to this study without either 1) written permission from the Sponsor or 2) providing an opportunity for the Sponsor to archive the records with an external vendor. The Investigator shall take responsibility for maintaining adequate and accurate source documents of all observations and data generated as required during this study. Such documentation is subject to inspection by the Sponsor or its agents, the IRB, or other regulatory agencies.

The Sponsor will notify the Investigator of the date of marketing approval or discontinuation of the study. The Investigator will obtain permission from the Sponsor in writing before destroying or transferring control of any study records.

8 Safety and Adverse Events

8.1 Definitions

Adverse Event (AE): Any untoward medical occurrence in a subject administered a study product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product whether it is related to the study product. Elective procedures for a pre-existing condition are not considered AEs.

Serious Adverse Event (SAE): An important medical event that may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate clinical judgment, may jeopardize the subject and/or may require intervention to prevent one of the outcomes listed in this definition.

If the adverse event meets any of the criteria below, it is regarded as a serious adverse event.

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability/incapacity
- Results in medical or surgical intervention to prevent permanent impairment to body structure or a body function
- An important medical event that may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, it may jeopardize the subject and/or may require intervention to prevent one of the outcomes listed in this definition.

Adverse Device Effect (ADE): An adverse device effect is defined as any adverse effect that is related or whose relation to the study device is unknown.

Serious Adverse Device Effect (SADE): Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

Unanticipated Adverse Device Effect (UADE): Unanticipated adverse device effect includes any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

8.2 Classification of the Event's Relationship to the Device

Determination of whether there is a reasonable possibility that an investigational product or device caused or contributed to an AE is primarily determined by the Investigator and recorded on the CRFs per the categories in the table below. Determination should be based on assessment of temporal relationships, biologic plausibility, association (or lack of association) with underlying disease, and presence (or absence) of a more likely cause.

Definitions for determination of the relationship include the following:

Relationship of Adverse Event and Study Device

CATEGORY	DEFINITION
Highly Probable	The AE is related to the study device. There is objective evidence establishing a cause and effect relationship between the AE and the study device.
Probable	The AE is likely related to or caused by the study device. There is no other likely explanation for the event.
Possible	The AE could be related to or caused by the study device; however, there is no evidence establishing a link/relationship. The subject's condition or concomitant therapy could have caused the AE.
Unlikely	It is improbable that the AE is related to the study device. There is no evidence that the study device caused the reported event (e.g., the AE can reasonably be explained by the subject's condition or other cause/concomitant therapy or the temporal sequence between the study intervention and the AE is such that the relationship is improbable).
Unrelated	There is no relationship between the study device and the AE.

8.3 Safety and Compliance Monitoring

The Investigator will monitor the occurrence of adverse events for each subject during the study. All adverse events (AEs) reported by the subject, observed by the Investigator, and/or documented in medical records will be recorded on the adverse event CRF, whether believed by the Investigator to be related or unrelated to the investigational device. Beginning with study enrollment, any new event/experience that was not present at baseline or worsening of an event present at baseline is considered an adverse event.

All adverse events will be followed until they are adequately resolved or stabilized. Serious adverse events and unanticipated adverse device effects will be collected and monitored throughout the entire course of the study.

Unchanged, chronic conditions are not adverse events and should not be recorded on the adverse event CRF.

8.4 Reporting Procedures

Investigators will report each adverse event or complication that meets the definition of a serious adverse event or serious adverse device effect to the Sponsor within two (2) business days upon discovery. The investigators will complete the Adverse Event Form (and any related form) and will report the event to the Sponsor within two business days of the Investigators' knowledge of the event. The Investigators will further report the event to the IRB according to the overseeing IRB's reporting requirements. The subject's course must be monitored until the event has subsided or, in a case of permanent impairment, until the event stabilizes, and the overall clinical outcome has been ascertained.

If the Investigator believes that an adverse event meets the definition of an unanticipated adverse device effect, the Investigator must report the event to the Sponsor within two business days of the Investigator's knowledge of the effect. The Sponsor will make the final determination whether an adverse event meets the definition of an unanticipated adverse device effect. The Principal Investigator must report any UADE to the reviewing IRB according to the institution's IRB reporting requirements. If the relationship of the unanticipated effect to the device is unknown, the Investigator is also required to follow these reporting obligations.

The Sponsor will ensure that all UADE reporting requirements are followed.

8.5 Reporting to Regulatory Authorities by Sponsor

The Sponsor or designee will be responsible for reporting adverse events to the appropriate regulatory authorities per local regulations.

9 Quality Control and Quality Assurance

9.1 Study Monitoring Plan

The Sponsor's designee will monitor the study over its duration according to the pre-specified monitoring plan. RxFunction will employ centralized monitoring as often as feasible to verify site compliance with the study protocol as well as Good Clinical Practice (GCP) standards. Although centralized monitoring will be the company's primary method of site monitoring, RxFunction will conduct onsite monitoring visits as necessary and will notify sites at least one week in advance of an onsite visit.

The study monitor may inspect all study documents and records that are maintained by the Investigator/site, including medical records (office, clinic, or hospital), for the subjects in this study. The Investigator/site will permit access to such records. Source documentation must be available to substantiate proper informed consent procedures, adherence to protocol procedures, adequate reporting and follow-up of adverse events, accuracy of data collected on case report forms, and device information.

The Investigator and/or research coordinator will be available for monitoring visits. It is expected that the Investigator will provide the study monitor with a suitable working environment for review of study-related documents.

9.2 Auditing and Inspecting

The study site may also be subject to a quality assurance audit by RxFunction, Inc. or its designees as well as inspection by appropriate regulatory authorities.

The Investigator and research coordinator must be available to respond to reasonable requests and queries made during the quality assurance assessment process or regulatory inspections.

9.3 Protocol Deviations

It is the Investigator's responsibility to ensure that there are no deviations from the protocol in full compliance with all established requirements of the IRB. The Investigator will not deviate from the protocol for any reason except in cases of medical emergencies when the deviation is necessary to protect the life or physical well-being of the subject.

All deviations must be reported to the Sponsor within five business/working days of their discovery. In subject-specific deviations from the protocol, the Protocol Deviation CRF will be completed. The occurrence of protocol deviations will be monitored by the Sponsor or designee. Investigators will inform their IRB of all protocol deviations in accordance with their IRB's reporting policies and procedures.

If an Investigator does not comply with the Investigator Agreement or protocol, the Sponsor will notify the Investigator of the site's non-compliance. Continued non-compliance may result in further escalation in accordance with the Sponsor's or its designee's standard operating procedure (SOP).

9.4 Criteria for Suspending/Terminating a Study Center

RxFunction reserves the right to stop the enrollment of subjects at a study site at any time after study initiation if enrollment is significantly slower than expected or if the center has multiple or severe protocol violations without justification or fails to follow remedial actions.

Possible reasons for suspending/terminating a study center include:

- Failure to obtain IRB approval
- Failure to obtain written Informed Consent
- Failure to report SAEs/UADEs to RxFunction within two business days of knowledge
- Failure to complete case report forms in a timely manner
- Loss of (or unaccounted for) investigational product inventory

10 Ethical Considerations

10.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki and with the regulations and guidelines of FDA (all state/local regulations), whichever affords the greater protection to the subject.

10.2 Institutional Review Board Approval

A copy of the protocol, proposed consent form, other written subject information, and any proposed advertising material must be submitted to the IRB for written approval. The Sponsor must receive a copy of the written IRB approval of the protocol and consent form

before the Sponsor will ship investigational devices to the site and before the site may recruit subjects into the study.

When the Investigator is under the oversight of a local IRB, the Investigator must submit and, when necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the consent form. The Investigator should notify the IRB of deviations from the protocol or SAEs/UADEs occurring at the site and other SAE/UADE reports received from RxFunction in accordance with local IRB procedures.

The Investigator will be responsible for obtaining IRB approval and annual renewal throughout the duration of the study when he/she is under the oversight of a local IRB. Copies of the Investigator's reports and the IRB's written approval of continuance must be submitted to RxFunction, Inc.

10.3 Informed Consent Form

A sample consent form may be provided for the Investigator to prepare for use at his/her site. The written Informed Consent documents should be prepared in the language(s) of the potential subject population and will be administered according to local requirements.

The reviewing IRB and the Sponsor must first approve the consent forms that are used. The consent forms used in this study will be in accordance with the current guidelines as outlined by the GCP guidelines, Declaration of Helsinki, and the International Conference on Harmonization (ICH) as well as local requirements and FDA regulations.

Prior to participation in the clinical trial, each subject must give written informed consent after the context of the study has been fully explained to him/her. The subjects must also be given the opportunity to ask questions and to have those questions answered to their satisfaction.

Written informed consent must be recorded appropriately by means of the subject's dated signature. The subject will receive a copy of the consent form.

10.4 Protocol Amendments

This protocol will be followed exactly and altered only by written amendments. Administrative changes that do not affect the risk/benefit ratio to the subject (e.g., editorial changes for clarity) may be made without any further approvals. Any change that would require alteration of the consent form must receive approval from the sites' IRBs prior to implementation. Following approval, the protocol amendment(s) will be distributed to all sites with instructions to append them to the protocol.

10.5 Emergency Actions

RxFunction, Inc., accepts the right of the Investigator to deviate from the protocol in an emergency when necessary to safeguard the physical well-being of a study subject. The Investigator must give notice of any emergency deviations and justification for the

deviation to RxFunction and the IRB as quickly as possible after the episode, in any event no later than 24 hours after the emergency.

10.6 Conflicts of Interest

"A conflict of interest exists when two or more contradictory interests relate to an activity by an individual or an institution. The conflict lies in the situation, not in any behavior or lack of behavior of the individual" (https://ori.hhs.gov/education/products/ucla/chapter4/default.htm).

The Investigator is responsible for submitting information regarding potential conflicts of interest to the IRB and/or the appropriate oversight committee at his/her institution. In addition, the Investigator must provide assurance to the Sponsor that he/she or any member of his/her research team is not a member of the IRB or that he/she did not participate in the review of this study.

11 Study Administration

11.1 Participating Sites

The Sponsor will select Investigators who are qualified by training and experience and are legally entitled to perform clinical research and to participate in the investigation of the study device. Sites will be selected based on the qualifications of the Principal Investigator. All Investigators must be trained to the protocol and study procedures prior to enrolling subjects.

11.2 Investigator Responsibilities

The Principal Investigator at each site will do the following:

- Agree to, sign, and adhere to the Investigator Agreement (or a contract/clinical trial agreement).
- Agree to participate in Investigator meetings as scheduled by RxFunction, Inc.
- Be willing to perform and capable of performing treatment procedures as outlined in this protocol.
- Comply with all required elements of this protocol (e.g., perform testing and follow-up as specified, especially during personnel transitions).
- Agree to obtain written informed consent before any study-specific procedures are performed in accordance with GCP.
- Complete all case report forms (CRFs) in a timely manner.
- Agree to comply with all applicable national and local laws, regulations, and guidelines, including Good Clinical Practices.

11.3 Training

In addition to providing documentation of their human subjects protection training (e.g., CITI), all Investigators and study personnel are required to attend Sponsor training sessions, which may be conducted at a site initiation visit or other appropriate training sessions. Phone or web-based training will take place as required. Training of Investigators and study personnel will include, but is not limited to, the investigational plan, investigational device usage, protocol requirements, randomization instructions, case report form completion, and study personnel responsibilities. All Investigators and study personnel must sign a training log upon completion of the training. The Investigators and study personnel must not perform any study-related procedures prior to being trained.

11.4 Pre-Study Documentation Requirements

Prior to shipment of investigational product, the site must provide the following documents to RxFunction:

- Signed and dated Investigator Agreement
- A copy of the written IRB approval of the protocol
- A copy of the written IRB approval of the consent form
- A copy of the curriculum vitae of the Principal Investigator and sub-investigator(s), if applicable

11.5 Subject Stipends or Payments

Subjects will receive compensation for their participation in the study based on the schedule below.

Visits	Compensation Amount
Screening	$25
Baseline	$50 for Randomized Subjects
Follow-up Visit 1: Week 2	$25
Follow-up Visit 2: Week 6	$25
Follow-up Visit 3: Week 10	$25
Follow-up Visit 4: Week 26	$25
Follow-up Visit 5: Week 52	$50
Baseline MRI Visit	$50
Week 26 MRI Visit	$50

RxFunction will also provide reimbursement for parking fees, if applicable, and/or bus or cab fare for subjects who are unable to secure other means of transportation to and from the research sites.

11.6 Study Timetable

The screening visit will last about 1.5 hours; the baseline visit will take approximately four (4) hours, and subsequent visits will last about 1.5 hours for a total of 13 hours over the

course of the study. The seven scheduled follow-up visits by telephone will last 10-15 minutes each—about 2 hours.

The study will be considered complete (regarding the primary endpoint) after all subjects have completed the 52-week follow-up period or ended their participation in the study.

Study Procedures	Baseline	Week 2	Week 6	Week 10	Week 26	Week 52
Informed Consent & HIPAA	X					
Subject Medical History Form	X					
FGA	X	X	X	X	X	X
10MWT	X	X	X	X	X	X
TUG	X	X	X	X	X	X
4-Stage Balance Test	X	X	X	X	X	X
Filament & Vibration Assessment	X			X	X	X
ABC Score	X	X	X	X	X	X
Vestibular Activities of DLS	X	X	X	X	X	X
Falls Efficacy Scale--International	X	X	X	X	X	X
PHQ-9	X	X	X	X	X	X
Pain Interference Form 6B	X	X	X	X	X	X
Pain Intensity Form 1a	X	X	X	X	X	X
Ability to Participate Form 8a	X	X	X	X	X	X
SPSR Form 8a	X	X	X	X	X	X
Concomitant Medication Use	X	X	X	X	X	X
Fall Events Form (if needed)	X	X	X	X	X	X
User Experience Survey		X		X		

11.7 Criteria for Termination of the Study

RxFunction, Inc., reserves the right to terminate the study but will exercise this right only for valid scientific or administrative reasons and/or reasons related to protection of subjects. Investigators and their associated IRBs will be notified in writing in the event of termination.

Possible reasons for study termination include the following:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study.
- A decision on the part of RxFunction to suspend the study or discontinue development of the device.

12 Publication Plan

Recognizing the importance of this investigation, Rx Function, Inc., as the sponsor of this study, is committed to the dissemination of the results. At the study's conclusion, a multicenter abstract to be presented at a scientific meeting and/or a manuscript to be submitted to a peer-reviewed journal will be prepared by the Scientific Advisor together with the leads of each site. The publication of the principal results from any single center experience within the study can occur following the preparation and publication of the multicenter results.

Submission of all abstracts and publications regarding the primary and secondary endpoints from the study requires approval by the Sponsor.

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