Introduction:

Approximately 4.8 to 6.4 million Americans, comprising 30-40% of the U.S. diabetic population, exhibit symptomatic diabetic peripheral neuropathy (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). 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) and 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). Current devices typically require a lab-engineer "on hand" to ensure functionality.

Hypotheses and Objectives:

The purpose of this study is to investigate the effect of Walkasins (Figure 1), a new user-friendly and robust external lower limb sensory prosthesis developed by RxFunction Inc. under NIH funding through a Small Business Innovative Research grant, on the balance and gait of persons with peripheral neuropathy who also experience balance problems. Walkasins provide gentle vibrations to the skin around the lower leg that reflect changes in pressure under the foot sole indicating the state of balance. The user learns to use these vibrations to control balance.

Figure 1. The Walkasins incorporate a thin shoe insert that measures changes in foot pressure during body sway. Vibrations provided to the skin on the lower calf represent new sensory information that the patient learns to use to improve balance.

We hypothesize that patients who use the Walkasins turned on will receive balance information that will improve their outcomes on gait and balance function, whereas patients who wear Walkasins turned off will not improve their outcomes on gait and balance function.

Research Subject Recruitment and Inclusion/Exclusion Criteria:

In this study, we will recruit 30 Veterans who have been diagnosed with peripheral neuropathy and who have self-reported balance problems. The following inclusion and exclusion criteria will be used for the study:

Inclusion criteria

- Age: 18-90 years, male or female,
- Self-reported difficulty with balance,
- Diagnosed with sensory peripheral neuropathy (inability to perceive 10 g monofilament on the plantar surface of the foot at the big toe, 5th and 1st metatarsal),
- Functional Gait Assessment (FGA) <23 or fail on test 1, 2 or 3 on the 4-Stage Balance Test),
- Ability to understand informed consent,
- Living in the community,
- Shoe size between 8.5'' (women's 5) and 11.25'' (men's 12).

Exclusion criteria

- Inability to perceive vibration stimulation on the lower calf (e.g., inability to sense vibration from tuning fork on the calf),
- Use of ankle-foot orthosis for ambulation,
- Open wounds on the foot or calf,
- Musculoskeletal or other neurological conditions that impact gait and balance (for example total joint replacement, moderate to severe Parkinson's disease, stroke, etc.).

Fliers will be posted in the physical therapy gyms at the Minneapolis VA Health Care System to advertise the study. Subjects who see the flier will be asked directly about their interest in the study. Subjects will also be recruited by screening patient data within CPRS using the ICD-10 code for peripheral neuropathy. Subjects found in the screening process will first be contacted via a letter, and then called by the PI or a member of the study team to see if they are interested in participating in the study.

The study will involve one visit to the Minneapolis VA's Physical Therapy Department and should last between 2 to 3 hours. After arriving at the VA, the subject will go through the consent process with a member of the research staff. The consent process will happen within a private room in the Physical Therapy Department. Study staff will answer any questions related to the study and will ask the subject to answer questions that verify that they understand the study. After the consent process, the subjects will sign the appropriate forms indicating their consent to participate in the study and to allow the study team to use their data (explained in consent and HIPAA documents). After the consent process, the study staff will check the inclusion and exclusion criteria and will enroll the subject into the study if they meet all criteria.

Research Methodology:

After enrollment into the study, subjects will complete a health screening questionnaire and the Activities-specific Balance Confidence Scale:

- *Health Screening Questionnaire* – Subjects will fill out a screening questionnaire to assess common health issues related to neurological, musculoskeletal, cardiopulmonary disorders, and other systemic diseases as well as information on falls and currently used medications.

- *Activities-Specific Balance Confidence (ABC) Questionnaire* – Powell and Myers (1995) developed the Activities-Specific Balance Confidence (ABC) Scale in an effort to detect levels of balance confidence in elderly persons (see Appendix). The ABC scale is a one-page questionnaire that asks questions about balance confidence when performing 16 different tasks.

Subjects will then don the Walkasins device and complete baseline measures of the Functional Gait Assessment (FGA), 10 meter Gait Speed and 4-Stage Balance Test (see Figure 2 for protocol design). During baseline testing, the Walkasins will be turned off.

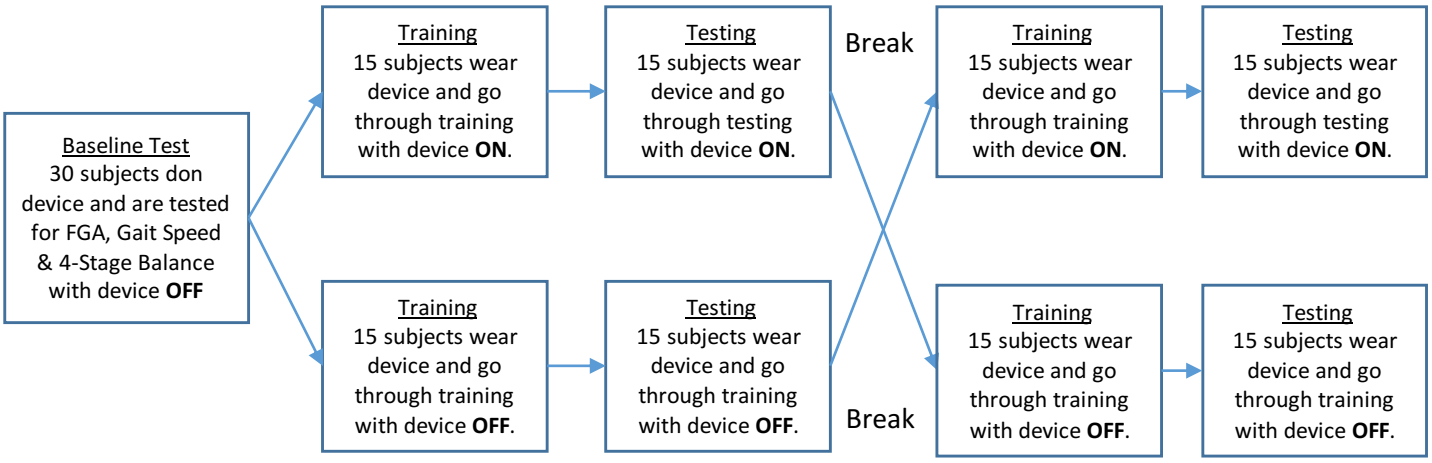

Figure 2: Cross-over study design.

- *Functional Gait Assessment* – 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 flooring 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. A difference of 8 points between measurement times is defined as the MCID in persons with vestibular disorders (Marchetti and Whitney 2010).

- *10 meter Gait Speed* – The 10m-walk (Perera, Mody et al. 2006) is routinely done in rehabilitation, has excellent reliability in chronic stroke patients (Hiengkaew, Jitaree et al. 2012) and physical therapists are well- trained in reliably performing this measure. 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, 2) instructed to walk as fast as they can. A difference of 0.10m/sec is defined as the minimal clinically important difference (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 if they can hold the stance for 10 s and then move on to the next stance. A fail of 1, 2 or 3 indicates at risk of falling. In addition we will record time for each of the tests.

Subjects will then be randomized into two groups according to their gait function (as measured by the FGA) and use of an assistive device (normal use is permitted, but not during the research study). Group A will initially be trained and tested with the Walkasins turned on, then following a 60 minute break, will be trained and tested with the Walkasins turned off. Group B will initially be trained and tested with the Walkasins turned off, then following a 60 minute break, will be trained and tested with the Walkasins turned on. During testing, subjects will complete trials of Functional Gait Assessment, 10 meter Gait Speed and the 4-Stage Balance Test. All training and testing will be done by a physical therapist.

Data Analysis:

The primary outcome measures of this study include the Functional Gait Assessment, 10 meter Gait Speed test, and the 4-Stage Balance Test. Using a between-group parametric statistical model, we will compare baseline measures from both groups to post-training outcomes following the first training session. We expect that Group A (i.e., the group that first trained with the Walkasins on) will have a statistically significant improvement in functional gait and balance measures compared to Group B (i.e., the group that first trained with the Walkasins off). We will also compare baseline measures to the post-training outcomes for Group A following the second training session (i.e., with the Walkasins off) to confirm that the 60 minute break between training sessions allowed for a washout effect of the first training. If we are able to confirm a washout effect, we will pool our data (n=30) to compare the outcome measures from baseline and post-training with the Walkasins turned on.

Risk to the Subjects and Approaches Taken to Minimize Risk:

- 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, a spotter will walk next to the subject to help regain balance if a fall starts to occur.

- Video recordings and photographs - We will take videos and photos of the person using the Walkasins for use in publications and presentations. There is a risk that their identity will be disclosed by being recognized in these publications and presentations. We will collect their separate consent for use of pictures and video.

- Use of medical records - We may use the medical records to obtain information related to the cause of their peripheral neuropathy, for example, to be used in describing subjects in the study. There is a risk that study personnel may inadvertently see other information in their medical record unrelated to their neuropathy that may be private in nature. We will obtain HIPAA authorization for use of the medical records.

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Appendix: Activities-specific Balance Confidence Scale

The Activities-specific Balance Confidence (ABC) Scale*

Instructions to Participants:
For each of the following, please indicate your level of confidence in doing the activity without losing your balance or becoming unsteady from choosing one of the percentage points on the scale form 0% to 100%. If you do not currently do the activity in question, try and imagine how confident you would be if you had to do the activity. If you normally use a walking aid to do the activity or hold onto someone, rate your confidence as it you were using these supports. If you have any questions about answering any of these items, please ask the administrator.

The Activities-specific Balance Confidence (ABC) Scale*

For each of the following activities, please indicate your level of self-confidence by choosing a corresponding number from the following rating scale:

0% 10 20 30 40 50 60 70 80 90 100%
no confidence completely confident

"How confident are you that you will not lose your balance or become unsteady when you…

1. …walk around the house? ____%
2. …walk up or down stairs? ____%
3. …bend over and pick up a slipper from the front of a closet floor ____%
4. …reach for a small can off a shelf at eye level? ____%
5. …stand on your tiptoes and reach for something above your head? ____%
6. …stand on a chair and reach for something? ____%
7. …sweep the floor? ____%
8. …walk outside the house to a car parked in the driveway? ____%
9. …get into or out of a car? ____%
10. …walk across a parking lot to the mall? ____%
11. …walk up or down a ramp? ____%
12. …walk in a crowded mall where people rapidly walk past you? ____%
13. …are bumped into by people as you walk through the mall?____%
14. … step onto or off an escalator while you are holding onto a railing? ____%
15. … step onto or off an escalator while holding onto parcels such that you cannot hold onto the railing? ____%
16. …walk outside on icy sidewalks? ____%

*Powell, LE & Myers AM. The Activities-specific Balance Confidence (ABC) Scale. *J Gerontol Med Sci* 1995; 50(1): M28-34