Protocol for:

HM20015593 and NCT03883217

Optimizing Vibrational Therapy to Improve Gait and Balance in Parkinson's Disease

It was revised on 4/09/2021

STUDY DESCRIPTION

This is a single site study comprised of two phases that will be conducted in sequence. After consenting process is completed successfully the participant will be tested with the Montreal Cognitive Assessment (Dalrymple-Alford, 2010) for cognitive eligibility. Once this is established, the study will start.

Phase 1 (first year)

Using the PDVibe2 (described below), a phase Ib clinical trial will be conducted to identify the optimum dose (ff & va, and number of treatment sessions) required to treat gait disturbances in participants with mild disease (H&Y disease stage 2, Group A) and moderate disease (H&Y stage 3, Group B) PD; and safety and efficacy of treatment.

Each of the participants will complete 8 walking sessions in one week (no more than 2 in one day) wearing the PDVibe2 with vibration set to one of nine different settings.

Primary Objective 1a (year 1): To identify overall frequency (ff) and amplitude (va) settings that optimize improvement in gait characteristics for PD participants using a central composite design.

A purposive sample of 13 Group A and 13 Group B participants with PD gait disorders will be recruited. Participants within each group will be randomly assigned to one of nine different frequency (ff, in Hz) and amplitude (va, in % duty cycle) settings as prescribed by the central composite design (CCD, Myers, Montgomery, & Anderson-Cook, 2009). The CCD is an efficient experimental design used to estimate an optimal dose response to a treatment.

Primary Objective 1b (year 1): Using the PDVibe2, identify the minimum duration (number of treatment sessions) of vibration therapy required to optimize gait metrics in PD.

To assess optimal number of sessions of treatment, FAP scores after each walking session for both Group A and B will be monitored for a steady period of stability in scores. For instance, if walking initially improves and then stabilizes after 3 treatment sessions, the sessions in Phase 2 and future studies can be made shorter than the currently prescribed 8 sessions. If walking continues to improve by the 8th session, this would similarly inform the design of future studies.

Secondary Objective (year 1): To assess safety and tolerability of the device and protocol and efficacy of vibration therapy across a full range of vibration parameters.

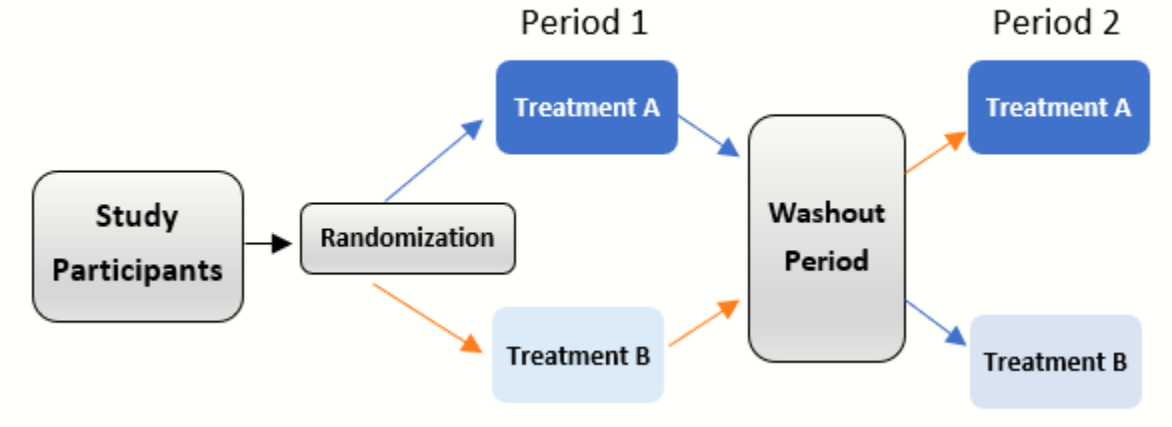
Outcomes measured will include the MDS-UPDRS part III, Primary Gait Screen, Timed Up and Go, Berg Balance Scale, PD Quality of life, Fall Efficacy and Freezing of Gait Questionnaire. Participants will be monitored by study staff for safety (falls, pain), fatigue, exertion, and tolerance of vibration stimulus. Pain will be assessed qualitatively and by using the Numeric Pain Rating Scale. Exertion will be measured using the BORG RPE scale. Falls will be tracked with a diary. A scripted interview will be used to capture all anticipated and unanticipated AEs.

Phase 2 (anticipated to start year 2)

In this phase, participants will participate in a randomized, single blind, placebo controlled, crossover trial, phase IIa.

There are two periods with two treatments: A=walking while wearing the device with vibration turned on, and B=Walking while wearing the device, however, the vibration will be turned off (placebo). Each of the participants will be randomized to either treatment AB or treatment BA (see Revised Protocol for Phase 2 below). For Period 1, participants will complete 4 treatment sessions, occurring twice daily on 2 consecutive days. This will be followed by a 2-week washout period. Participants will be asked to return to complete 4 more treatment sessions, occurring twice daily on 2 consecutive days (Period 2). All participants will be exposed to optimum vibration dose determined by Phase 1. All participants will also act as their own control. See Dose Contingency Plan below. Individuals in Phase 1 will not be eligible to participate in Phase 2.

Revised Protocol for Phase 2:



Primary Objective (year 2): Test the efficacy of the PDVibe2 (set to the optimal global vibration frequency (ff) and amplitude (va) settings determined in Phase 1) for improving gait in a randomized placebo-controlled trial that will include up to 8 sessions of the Walking Protocol.

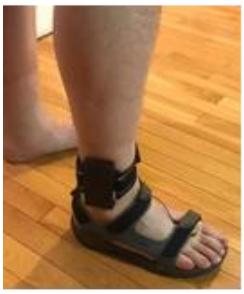
Secondary Objective(s): To assess safety and tolerability and efficacy of vibration therapy on function of participants.

Outcomes measured will include the MDS-UPDRS part III, Primary Gait Screen, Timed Up and Go, Berg Balance Scale, Fall Efficacy and Freezing of Gait Questionnaire. Participants will be monitored by study staff for safety (falls, pain), fatigue, exertion, and tolerance of vibration stimulus. Pain will be assessed qualitatively and by using the Numeric Pain Rating Scale. Exertion will be measured using the BORG RPE scale. Falls will be tracked with a diary. A scripted interview will be used to capture all anticipated and unanticipated AEs.

STUDY INTERVENTION

PDVibe2 Description - The PDVibe2 vibratory system is designed to be a light-weight and self-contained unit with on-board electronics for sensing, actuation, computation, and power. Each device contains two tactor actuators (EAI C2, https://www.eaiinfo.com/product/c2/), is driven by a light-weight battery, and contains custom electronics designed for the PDVibe2 unit. The device will have the ability to change the frequency of vibration of the motors that can be adjusted remotely by the investigator/user within the range of 1 to 300 Hz and amplitude 0 to .031 inches. The device will be placed over a soft sock on the

inner part of the ankle and on top of the foot with an elastic cuff that is adjusted to the comfort of the subject. The participant will then be fitted with a pair of water shoes that they will wear for the remainder of the trial with one tactor inserted on the medial ankle and the other on top of the foot near the toes. PDVibe2 is operated by a low-power battery. See pictures below.



Non-significant risk device - The PDVibe2 device is a non-significant risk device according to the guidelines of [21 CFR Part 812]. The PDVibe2 (1) is NOT intended as an implant; (2) is NOT used in supporting or sustaining human life; or (3) does NOT have substantial importance in diagnosing, curing, mitigating or treating disease; or (4) otherwise does NOT present a potential for serious risk to the health, safety, or welfare of a subject. The PDVibe 2 is on loan to VCU from Resonate Forward LLC who supplied this Investigational Device Exemption Document for the PDVibe2 device.

TREATMENT PROTOCOL

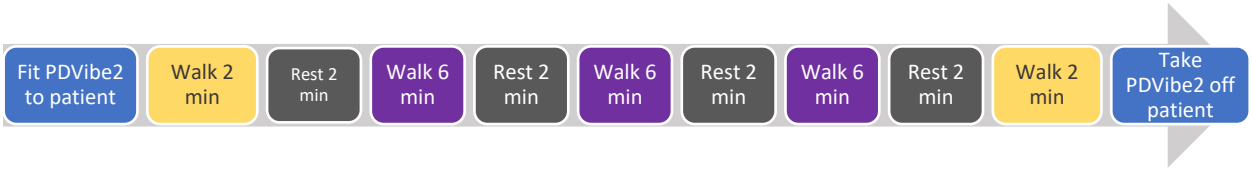
This treatment protocol has been established in preliminary studies using the PDVibe2 (Winfree, Pretzer-Aboff, Hilgart, et al., 2013).

Participants will be asked to refrain from starting new rigorous exercise routines but may continue established exercise programs. They will be asked to continue taking their PD medications as prescribed. Female participants will be asked if they are pregnant or may become pregnant during the course of this study. If the answer is yes, they will be advised not to participate since the safety of vibration therapy on an unborn child is unknown.

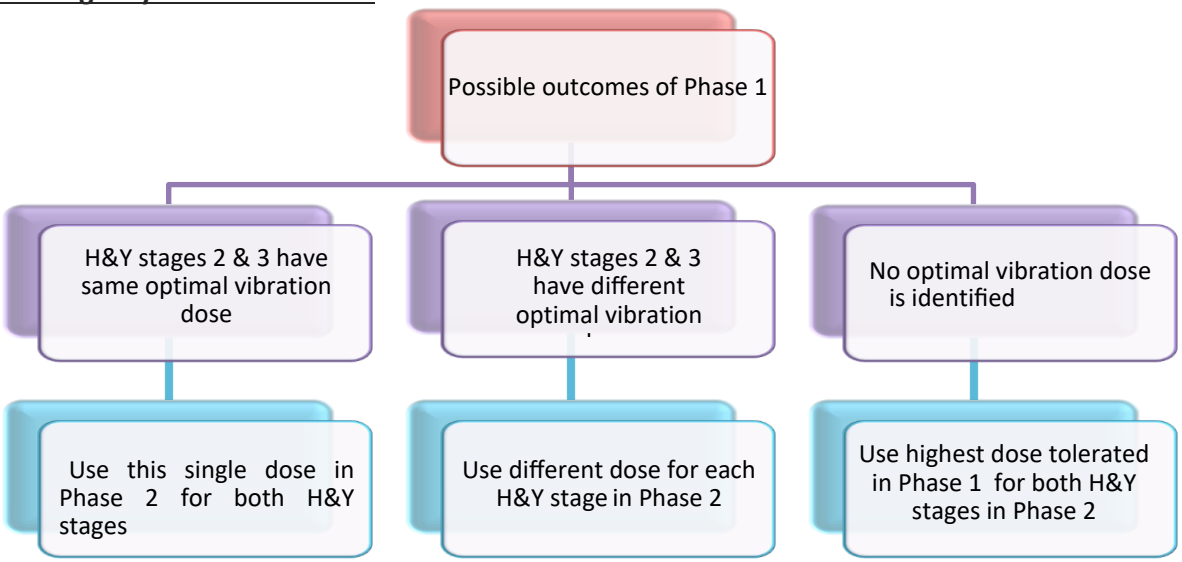
For all treatment and evaluation sessions, PD participants will be asked to take their PD medications as usual, and the treatment or evaluation session will start at least 30 minutes after dose intake or when participants confirm “on” periods (indicating that PD medication is effective). DBS, if present, will be left on. One walking session (treatment) consists of the participant walking back and forth on a straight path for a total of 22 minutes. The first and last two minutes comprise walking with the vibration turned off allowing for pre- and post-FAP measurements to be collected. The middle 18 minutes (vibration on) are broken into three 6-minute walking bouts. The participant can take as many breaks as needed and two- minute breaks (after each of three 6-minute walking bouts) will be encouraged to minimize a fatigue effect. Each participant will be asked to undergo two walking sessions (at least 3 hours apart) in one day, with a day off after two treatment days.

Walking Protocol (treatment) – Each 30-minute walking session is identical, except the vibration settings will vary according to randomization in Phase 1, and treatment assignment in Phase 2.

Walking Protocol (placebo) - In Phase 2, the control arm will wear the PDVibe2, but the vibration will not be turned on, as illustrated here:



Dose Contingency Plan for Phase 2:



Dose Determination: The dose of vibration (ff, va) in Phase 2 will be contingent on results from Phase 1. Possible scenarios are depicted above.

Duration Determination: Phase 1 results will determine number of treatment sessions for Phase 2. If the minimum number of treatment sessions required to stabilize FAP in Phase 1 is different for H&Y stages 2 and 3, we will use the higher of the two numbers in Phase 2.

Study Intervention Compliance - For both Phase 1 and 2, compliance to the intervention will require participation in up to 8 sessions of walking. If a participant misses one or more walking sessions, the research team will attempt to reschedule them within one week of last treatment. Participants will be considered compliant if they participate in at least 80% of treatment sessions. Subjects who drop out before completing the protocol will be replaced (up to 8 replacements) but all participants with post-therapy data will be included in the analysis (intention-to-treat analysis). Fall diaries are expected to be filled out by participants and if needed with the assistance of a family member. The use of the fall dairy will be explained to the participants/caregivers on the first visit by the study coordinator, who will also review the diary with the participant on subsequent visits.

Participant Discontinuation/Withdrawal from the Study - Participants may withdraw voluntarily from

the study, documentation will include a reason for withdrawal if offered by the participant. The medically responsible investigator may decide to withdraw a participant from the study if they have a serious adverse event or are unable to comply with the study protocol.

Lost to Follow-Up - A participant will be considered lost to follow-up if he or she fails to return for 2 or more scheduled visits and is unable to be contacted by the study site staff. Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (i.e., 3 telephone calls). These contact attempts will be documented in the participant's study file. 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".

STUDY OUTCOMES

After the informed consent is signed, a qualified member of the research team will administer the Montreal Cognitive Assessment (part of the eligibility criteria). If the participant scores < 21 the study will STOP. If the participant qualifies to continue in the study, a qualified member of the research team, blinded to the treatment assessment will obtain the following assessments for all participants in Phases 1 and 2. If the assessment is paper and pencil, a member of the research team will assist the participant in filling out the form as necessary.

All outcome measures for both studies will be assessed before the start of vibration therapy, immediately after the final treatment session, and again up to 14 days (for Phase 1), and from 6 – 10 days (for phase 2)after completion of the treatment sessions. A staff member who is blinded to vibration (ff/va) assignment will conduct treatment and evaluation sessions. Safety and tolerability will be assessed across the full range of vibration parameters. See the schedule of activities (Section 1.2) for a detailed list of all assessments done at each study visit. All instruments are psychometrically sound, with good reliability and validity and have been used in other PD investigations.

Schedule of research activities - This is a schedule of research activities for Phase 1, and a proposed schedule of research activities for Phase 2. The number of treatment sessions in Phase 2 may be less than 8 depending upon the results of Phase 1. The Dose Contingency Plan for Phase 2 is illustrated above.

Phase 1:

	Day -13 to -1	Day 0-7		Day 8 to 21
Face to face visits	Visit 1 (screen)	Visits 2-8	Visit 9	Visit 10 (exit)
Obtain Descriptive Data*	✎			
Eligibility Screening	✎			
Informed Consent	✎			
MoCA	✎			
Randomization	✎			
MDS-UPDRS Parts II – IV	✎		✎	✎
MDS-UPDRS Part III only		✎		
Timed Up & Go	✎		✎	✎
Berg Balance Scale	✎		✎	✎
FoG Questionnaire	✎		✎	✎
Parkinson's Disease Questionnaire - 39	✎		✎	✎

Fall Efficacy Scale - International	✎		✎	✎
Numeric Pain rating scale	✎	✎	✎	✎
Borg RPE Scale	✎	✎	✎	✎
Primary Gait Screen	✎		✎	✎
2-minute walk for FAP score on Zeno walkway pre-vibration	✎	✎	✎	✎
6-minute walks for FAP score on Zeno walkway (x3) ON vibration		✎	✎	
2-minute walk for FAP score on Zeno walkway post vibration		✎	✎	
Qualitative Questionnaire		✎	✎	✎
AE Inquiry (including fall diary inspection)	✎	✎	✎	✎
*Race, education, age at start of PD symptoms, year and age when PD diagnosis made, medical history, height, weight, leg length, medications list; MoCA – Montreal Cognitive Assessment; MDS-UPDRS – Movement Disorders Society United Parkinson's Disease Rating Scale; AE – Adverse Event				

Phase 2:

Option 1:	**Day 1**	**Day 2-3**	**Day 4-18**	**Day 19-20**	**Day 26-30**
Option 2: If participant opts for visit 1 & 2 to occur the first day	**Day 1-2 (Visit 1/2)**		**Day 3 - 17**	**Day 18 – 19 (Visit 3/4)**	**Day 25 – 29 (Visit 5)**
Face to face visits	**Visit 1** (screening + baseline data collection)	**Visit 2/3**	**Two-week washout** (no visits)	**Visit 4/5**	**Visit 6** (follow up data collection – 6 to 10 days after treatment 5 completed)
Obtain Descriptive Data*	✎				
Eligibility Screening	✎				
Informed Consent	✎				
MoCA	✎				
Randomization	✎				
MDS-UPDRS Parts II, III, and IV	✎	✎post v. 3 only		✎pre v. 4 only ✎post v. 5 only	✎
MDS-UPDRS Part III only (pre-treatments)		✎		✎	
Timed Up & Go	✎	✎post v. 3 only		✎pre v. 4 only ✎post v. 5 only	✎
Berg Balance Scale	✎	✎post v. 3 only		✎pre v. 4 only ✎post v. 5 only	✎
FoG Questionnaire	✎	✎post v.3 only		✎pre v. 4 only ✎post v. 5 only	✎

Parkinson's Disease Questionnaire - 39	✎				✎
Numeric Pain rating scale	✎	✎		✎	✎
Borg RPE Scale	✎	✎		✎	✎
Primary Gait Screen	✎	✎post v.3 only		✎pre v. 4 only ✎post v. 5 only	✎
2-minute walk for FAP score on Zeno walkway pre-vibration	✎	✎		✎	✎
6-minute walks for FAP score on Zeno walkway (x3) ON vibration	✎	✎		✎	
2-minute walk for FAP score on Zeno walkway post vibration	✎	✎		✎	
Qualitative Questionnaire	✎	✎		✎	✎
AE Inquiry (including fall diary inspection)	✎	✎		✎	✎

Demographic and Descriptive data – Descriptive data including age, DOB, sex, weight, height, leg length, history of falls, co-morbidities, year and age when PD was diagnosed, year and age when PD symptoms first noticed, and a list of medications will be collected from all subjects.

Primary Outcomes (Phases 1 and 2):

Functional Ambulation Profile (FAP) Score – The FAP score, considered to be the gold standard for spatiotemporal gait parameter analysis, has been selected as the primary outcome measure (Nelson, 1974; Nelson, Zwick, Brody, et al., 2002; Gouelle, 2014). For each walking session (at a self-selected speed), the FAP score will be calculated prior to, during, and after vibration. The FAP score in healthy adults ranges from 95 to 100 points and is calculated from data collected by the Zeno walkway and the participant's physical measurements (e.g. leg length). Step length, step time, degree of symmetry, dynamic base of support and the use of ambulatory aids are factored into the score (Nelson, 1974). The Zeno instrumented walkway (PKMAS) is a 20-foot computerized instrumented walkway containing sensor pads. While the subject walks, the system continuously scans the sensors to detect pressures, and transfers the information to the computer for calculating, recording and storing gait characteristics. This device has been used extensively to evaluate PD gait. Walking across the Zeno walkway is part of the walking protocol. As such it allows an FAP score to be calculated at the beginning and end of every treatment session.

Secondary Outcomes (Phases 1 and 2):

Movement Disorder Society Unified Parkinson Disease Rating Scale (MDS UPDRS) - parts II-IV (Goetz, et al., 2008). The total summed score for MDS UPDRS Parts II – IV will be used to assess the total burden of motor PD symptoms as well as their impact on activities of daily living. All items are rated using a scale of 0 = normal to 5 = severe.

- Part II concerns ''motor experiences of daily living,'' and is designed to be completed by the participant without the investigators input. There are 13 questions with an overall score range of 0 – 65. Research coordinator will be available to assist with filling out the questionnaire if participant requires assistance. Estimated time is < 10 minutes for participant to complete.
- Part III is a "motor evaluation" that will be conducted and scored by a qualified research team member. There are 33 scored items, several with right, left or other body distribution scores. The

Part III score range is 0 – 132. This evaluation will be videotaped and scored by a study investigator blinded to participant group assignment. Estimated time to complete is approximately 5 minutes.
• Part IV concerns ‘‘motor complications’’ questions that the investigator will ask the participant. The Part IV score range is 0 – 24. Estimated time to complete is < 5 minutes.

MDS UPDRS Parts II – IV total scores will be used as a participant descriptor. At baseline, parts II – IV of the MDS UPDRS will take approximately 20 minutes to complete. Part III only will be repeated during vibration and post intervention data collection times and will take approximately 5 minutes to complete each time.

Primary Gait Screen - The Primary Gait Screening test will be conducted using the Zeno walkway and PKMAS software (Havertown, PA). This test will allow us to assess characters of gait as the subject initiates walking, walks straight, and during turns. The procedure is as follows: The subject starts on the Zeno, facing the active area, they stand still for 10 seconds. The start of the walking will be a volitional start. The subject ambulates, at their self-selected speed, approximately 18', turning at a line or a small cone (on the 2' wide Zeno). They continue to the start position where they stop and stand still for 10 seconds.

Berg Balance Scale - (Berg, Wood-Dauphinee, Williams, & Maki, 1992). The BBS assesses balance via performing 14 functional activities. Each item is scored along a 5-point scale, ranging from 0 to 4. Zero indicates the lowest level of function and 4 the highest level of function. The total score is a summation of all items and ranges from 0 to 56. Higher scores indicate less risk of falls. A cutoff score of 45 has been traditionally identified as a useful cutoff to predict falls in those who scored below 45.

Timed Up & Go (3 trials) - (Podsiadlo & Richardson, 1991). The TUG consists of one item. The protocol starts with the participant sitting in a chair, standing up, walking 3 meters, turning around, walking back to chair, and sitting down again. Participants are timed in seconds. TUG is used to identify/screen elderly individuals who are prone to falls. Lower numbers are better.

Freezing of Gait Questionnaire - (Giladi, Shabtai, Simon, et al., 2000). The FOGQ is a six-item questionnaire that uses a 5-point scale that ranges from 0 = absence of symptoms to 4 = most severe stage. The total score ranges from 0 to 24; higher scores correspond to more severe FOG.

Parkinson’s Disease Questionnaire 39 – (Peto, et al., 1995). This is a 39 item self-report questionnaire assesses how often patients experience difficulties across the 8 quality of life dimensions of functioning and well-being. A five-point ordinal scoring system ranges from 0 Never to 5 = Always or cannot do at all. Scores are calculated for each dimension (sum of items divided by number of items /100; total score is summative.

Fall Efficacy Scale – International – (Dewan & MacDermid, 2014). This survey includes 16 items assessing fear of falling in different scenarios, in a community dwelling older population. Individuals are instructed to rate each activity on a four-point Likert scale, depending on how they concerned that they may fall when performing certain activities. Items are scored from 1 = Not at all concerned to 4 = very concerned. The total score ranges from 16 – 64. The higher the score the greater the fear of falling.

Falls diary: Participants will be given a Falls Diary and instructed on its use. Family member will be included in the instruction discussion in the event the participant needs assistance. Each day the subject will indicate if there was a fall, if yes, they will further classify the fall as no injury, bruise or cut, muscle or

ligament injury, or broken bone. Dairy's will be reviewed at next study visit.

Borg Scale of Perceived Exertion (RPE) – (Borg, 1998). The Borg Scale considers the person's fitness level. It matches how hard they feel they are working during exercise with numbers from 6 to 20; thus, it is a "relative" scale. The person can rate their effort using this scale: *Very light: 9 to 10; Very, very hard: 19 to 20; Somewhat hard: 13 to 14; or Very hard: 17 to 18*. During the intervention participants will be asked to walk at their usual pace. We will rate their exertion, if the participant reports scores higher than 14, we will encourage slowing down or rest. A score of 13 or 14 on this scale indicates "somewhat hard" exercise, though it still feels okay to continue.

Adverse events and Qualitative Questions as determined by scripted questions – The following questions will be asked of each participant to assess adverse reactions to the device, vibration, and walking protocol. Assessments will occur with each study visit:

- Numeric Pain Rating Scale plus qualitative pain questions – (McCaffery, et al., 1989). Participants will be asked if they are experiencing pain. If yes, they will be asked to describe the onset of pain, location of pain, consistency, severity of pain (0 = no pain to 10 = worst pain ever), what makes it better and what makes the pain worse, is it tolerable, and if they used any treatment to ease the pain.

- Additional Questions for Phase 1: In this study all participants will receive vibration at different settings. They will be asked: How are you feeling? Is the device comfortable? Can you feel the vibration? What does it feel like? Is it tolerable? Are you having any unexpected sensations in your feet or elsewhere? If yes, where? Is there anything else you would like to comment on?

- Additional Questions for Phase 2: In this study when the participants are in the control (treatment B) we will not specifically ask about vibration so that we do not unblind the research team in the room who are collecting data. Therefore, questions will include: How are you feeling? Is the device comfortable? Are there any unexpected sensations that you are feeling in your feet, ankles, toes or anywhere else? Is there anything else you would like to comment on?

STATISTICAL ANALYSIS

Descriptive statistics will be used to characterize participants and groups: frequencies for categorical variables, mean/standard deviation for normally distributed continuous variables, and median/ interquartile range for continuous variables with skewed distributions. Because of the exploratory nature of this pilot intervention study, no adjustment for multiplicity is planned with alpha set at 0.05 for determining significance.

Phase 1, Primary Objective 1a: The goal is to estimate the ff and va settings that will maximize the Functional Ambulation Profile (FAP) score. Using response surface based on the FAP score obtained from the Zeno walkway (instrumented walkway) there will be an estimate yielding an optimal frequency and amplitude setting. This analysis will be repeated for Group A and B cohorts of 13 H&Y stage 2 and H&Y stage 3 PD participants with gait disorders to discern possible differences in dose per severity of disease. In addition, differences between H&Y stages 2 and 3 will be tested. If there are differences between the stages, the ff and va that yields the optimal FAP score, will be estimated separately by H&Y stage.

Phase 1, Primary Objective 1b: To assess optimal length of treatment, FAP scores after each walking session for both groups will be monitored for a steady period of stability in scores. For instance, if walking initially improves and then stabilizes after 3 treatments, the sessions for Phase 2 and future studies will be made shorter than the prescribed 8 sessions. If walking continues to improve by the 8th session, this would similarly inform the design of future studies. Participants will be closely monitored for safety (falls, pain, fatigue, exertion) and comfort. This information will be useful in all future device and parameter testing.

Phase 2, Primary Objective: An analysis of covariance (ANCOVA) will be used to compare the FAP scores between the two treatment arms (placebo vs active). The ANCOVA model will contain effects for treatment (placebo or active)). The baseline FAP score (measured prior to any vibration therapy) will serve as a covariate.

Phases 1 and 2, Secondary Objectives: Secondary outcomes include safety data, questionnaires, and tests of function. Specifically, these include the MDS-UPDRS part II – IV, TUG, BBS, PDQ-39 , Self-efficacy for falls, and the FOG-Q. Function tests will be assessed per schedule outlined in Phase 2 table above, by the blinded research team.

Participants will be monitored by treatment- blinded study staff for safety (any falls, pain), fatigue, exertion, and tolerance of treatment sessions. Pain will be assessed qualitatively and by using the Numeric Pain Rating Scale. Exertion will be measured using the BORG Rating of Perceived Exertion (RPE) scale. Falls at home and in study visits will be tracked throughout the protocol using a falls diary.