Protocol Title: SCH: Context-aware Freezing of Gait mitigation in real-world setting

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Full Study Title: SCH: Context-aware Freezing of Gait mitigation in real-world setting

PROTOCOL DOCUMENT

4.2. Study Design:

4.2.a. Narrative Study Description

Design. This is a single site clinical trial involving 3 tasks with the purpose of development and testing feasibility of a device. In total, 32 participants with Parkinson's disease (PD) who experience freezing of gait (FoG) will complete this 3-year study. We will enroll up to 50 participants to account for screen fails and withdrawals.

Procedures. *All procedures are performed exclusively for research purposes*. After obtaining consent from the PD patient, a member of the research team will administer the Montreal Cognitive Assessment (MoCA) test to determine cognitive eligibility (must score at 21 or higher to be eligible). If the participant is eligible, they will be assigned a code number, then asked to complete a demographic form, a physical performance test (10-Meter Walk test) and the remaining scales in Table 1, to capture relevant physical and neuropsychological covariates.

Table 1. Physical and Neuropsychological Scales (total participant time for all the below measures is 30 minutes**).**

Factor	Validated Scale
Cognition	Montreal Cognitive Assessment [1]
Fatigue	Parkinson's Disease Fatigue Scale [2]
Balance Confidence	Activities-specific Balance Confidence (ABC) scale [3]
Fear of Falling	Falls Efficacy Scale-International [4]
Quality of Life	Parkinson's Disease Questionnaire-8 [5]
Freezing of Gait	New Freezing of Gait questionnaire [6]
Nonmotor Symptoms	MDS-UPDRS part 1 questionnaire [7]
Walking Speed and Step Length	10 Meter Walk Test [8]

All 32 participants will be screened with the same inclusion and exclusion criteria described in section 2.2 above. All will undergo the same consenting procedure described above. Each study participant will wear a safety belt and have trained spotters to deter falls. The specific procedures for each of the 3 tasks are as follows:

In Task 1, a convenience sample of five participants will be recruited for CNN model training. For each patient, we plan to collect data for 2.8 hours, among which at least 17 minutes will be FoG data. Each participant will be asked to wear one UG motion sensor (watch like device with a soft band) around each ankle to collect raw data that will be used to detect FoG and develop models. They will be video-taped (for the purpose of validating the FoG detection models) as they walk each of the five 5-meter FoG triggering courses illustrated in Figure 1. All assessments in Task 1 will be performed on PD participants who are OFF their PD medications (overnight washout) to maximize the amount of time spent in FoG, thereby minimizing the length of evaluation time [19]. It is common in both clinical practice and research studies to bring PD patients in for assessments off their PD medications; thus, this is not anticipated to be a barrier to recruitment. The 6 participants in Task 1 will not participate in Task 2 & 3.

Task #1: Each subject is expected to spend up to 4 hours in the clinical lab, one visit. This can be divided into two sessions if the subject prefers.

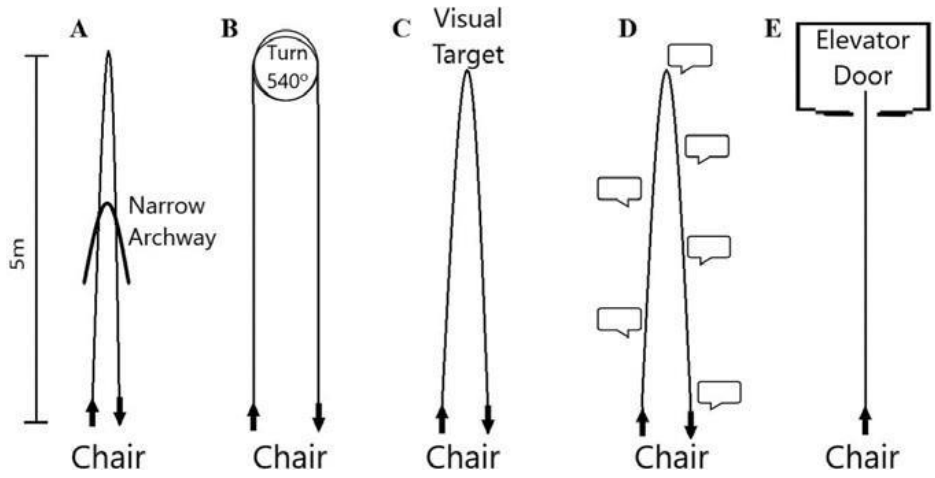

Figure 1: Five FoG Triggering Scenarios shall include a 5-meter walking path with one of 5 triggers inserted into the path: (A) walking through a narrow passage, (B) turning 540 degrees, (C) approaching a destination (e.g., chair), (D) walking while dual tasking (e.g., performing a verbal fluency challenge while walking), and (E) a time sensitive task such as walking through an elevator door before it closes.

Table 2. Task 2 Neuropsychological Scales (total participant time for all the below measures is 88 to 118 minutes).

Anxiety	State Trait Anxiety Inventory (STAI- State & Trait) [9] Positive and Negative Affect Schedule (PANAS-State) [10] Semi-structured qualitative interview Salivary Alpha-Amylase [11-13]
Sleep	RegUlarity, Satisfaction, Alertness, Timing, Efficiency, and Duration (RU SATED) [14] Insomnia Severity Index (ISI) [15] Pittsburgh Sleep Quality index (PSQI) [16] Actigraph Consensus Sleep Diary [17]
Self-Efficacy	General Self-Efficacy Scale (GSE) [18]
Illness Self-Concept	Illness Self-Concept Scale (ISCS) [19-20]

The goals of **Task 2** are to (1) determine the optimal frequency and vibration settings to mitigate freezing of gait (FoG) and (2) explore the role of neuropsychological factors such as sleep and anxiety in FoG outcomes (see Table 1 & 2). Thus, response surface methodology is proposed. Specifically, a central composite design (CCD) [38] will be used to determine the best dose of vibration (frequency and amplitude) for each of five common triggers for FoG (Figure 1). Estimating the response surface requires only a small sample of human participants, e.g., one participant for each design point with five repeats at the center point. For the current project, a convenience sample of only 13 participants with PD who experience FoG in at least two of the scenarios, confirmed by a neurologist will be needed. The 13 participants will be asked to walk through each of five, 5-meter walking courses that will each include one of the triggering scenarios. Each of the 13 PD participants with FoG will be randomly assigned to one of 9 different *ff* and *va* settings as prescribed by the CCD. In the current case, the goal is to estimate the *ff* and *va* settings that will maximize the difference between the baseline (no vibration) and post-treatment time spent in a FoG state for each of the 5 triggering scenarios individually and in total. Measurements will be taken once at baseline and again in triplicate as they walk the paths wearing the FoG detection/vibration device.

Additional activities for Task 2 participants:

Visit #1: After the consenting process is completed, a sample of saliva will be collected (see procedure below) to measure salivary alpha amylase levels at baseline. The UG device and PDVibe3 will be placed on the participants who will then perform a 10-meter walk test on site and a baseline walk of the five triggering

scenarios. They will complete the questionnaires/scales listed in tables 1 and 2. Participants will then be instructed on how to wear the actigraph device on their dominant wrist (Actigraph GT9X Link) to collect objective sleep data for up to 14 days prior to their Visit #2. They will also be instructed on how to complete the sleep diary during the same time period during which the actigraph is collecting sleep data. Visit #1 will last approximately 90 minutes.

Participants will wear the ActiGraph GT9X Link for up to 14 consecutive, 24-hour days beginning at baseline, pre-intervention. Actigraphs are devices that are worn on the dominant wrist and contain a built-in accelerometer that records movements in order to estimate sleep parameters, including total sleep time, sleep-onset latency, wake after sleep onset, and sleep efficiency. Sleep data will be analyzed using the ActiLife 6.0 data analysis software platform and bedtime and waketime will be verified via sleep diary-reported data. Prior to receiving the actigraph, participants will receive verbal instructions regarding the purpose of the actigraph (i.e., that the actigraph records movement to estimate sleep parameters) as well as appropriate use (i.e. should be worn on the dominant wrist at all times for up to fourteen consecutive days unless bathing, swimming, etc.). Participants will be provided with moleskin as necessary to minimize risk of skin abrasion. Participants will be encouraged to reach out to study personnel with any questions or concerns related to wearing the actigraph device while at home.

Participant saliva will be collected with the aim to assess salivary alpha amylase, a biomarker shown to be a reliable indicator of anxiety and stress in individuals with PD. Saliva sample collection will occur three times over the course of Task 2- at baseline (Visit #1), pre walking tasks and post walking tasks (Visit #2). Saliva will be collected using a passive drool method, a method of saliva collection that requires participants to lean forward and allow saliva to naturally pool into the collection vessel rather than actively spitting. This method of saliva collection allows for whole saliva to be collected, avoiding localized salivary secretions and providing for a more consistent biospecimen. Saliva samples will be collected utilizing Salimetrics Saliva Collection Aid, a mechanism which fits securely into a collection vial designed to reduce sample foaming and facilitates direct sample collection and storage. Samples will be refrigerated within 30 minutes of initial collection and frozen at or below -20 degrees Celsius within 4 hours of collection. Samples can be stored for up to 6 months and will be stored until all participant samples are collected, at which point an alpha amylase assay will be run. Prior to participating in saliva collection, participants will receive verbal instructions on how to correctly provide a saliva sample. Participants will be advised to avoid eating a major meal for at least one hour and will be asked to rinse their mouths thoroughly with water 10 minutes prior to collection.

Visit #2: In addition to what is described in Task #1 above, saliva samples will be collected from participants before and after their participation in the walking tasks. They will also complete 2 surveys, the STAI-State and PANAS-State after they finish walking. The sleep diary that was filled out at home will be collected from participant and actigraphy will be retrieved. Following completion of walking tasks, participants will be invited to schedule a time to engage in a semi-structured qualitative interview virtually or by phone. Visit #2 will last approximately 120 to 180 minutes).

Visit #3: Participants will engage in a semi-structured interview via telephone or virtually according to participant preference. The interview will ask participants to reflect on and engage in discussion related to experiences of FoG; perceptions of the association between sleep, anxiety, and FoG; illness self-concept; mobility self-efficacy; general feedback about the interview and participation in the study overall (see submitted interview protocol document). Visit #3 will last approximately 30 to 60 minutes.

Participants will be ON their PD medications during this phase of testing. The study staff, except for the PC, will be blinded to the treatment allocation. The PC will be setting the VibeForward vibration parameters (*ff* and *va*) for each participant according to a randomized list generated by the co-I and biostatistician, Dr. R.K. Elswick Jr. All participants will wear safety belts and have trained spotters to deter falls. Participants will be asked to also participate in Task 3.

Task #2: Each subject is expected to spend up to 5 hours in the clinical setting, across three visits.

In Task 3 we will test the device at the optimal vibration setting in a "real world" setting. Due to the innovative nature of studying this device in a real-world environment, no pilot data exists from which to run a traditional power analysis. However, Van Belle proposed that a minimum of 12 observations should be used to calculate confidence intervals based on the t-statistic with n – 1 degrees of freedom. This rule is based on the fact that the half-width confidence interval for the mean decreases rapidly up to n = 12, at which point the decrease is less dramatic and the half-width curve begins to asymptotically decrease. Thus, in order to ensure the good estimates of the means and variances (pre- and post-) [39] a convenience sample of thirteen volunteers who have been diagnosed with PD by a neurologist and who exhibit FoG will be asked to participate in the testing of the device.

Participants will walk the pathway once without vibration (pre-treatment), and then three times with vibration (post treatment). They will be ON their medications. We will compare the differences in the duration and number of FoG episodes, time walking through the path, average stride length, and speed of walking. It is anticipated that "pre" versus "post" trials for each of these five variables will be compared using a paired t-test.

All participants in Task 3 will be described in terms of demographics, disease, and psychological characteristics as in Task 2. Detailed field notes will be made of observations from study staff and comments from subjects to record the extent and type of unpredictable challenges faced by each participant. Qualitative questions will be asked after each participant finishes the walking portion of the study. If a participant from Task 2 does not participate in Task 3, they will be replaced. The replacement will then complete the baseline walking portion and scales (Table 1) from Task 2 at a separate visit prior to completing Task 3. Patients from Task 2 will be reconsented for Task 3.

When the PC contacts participants who have already completed Task 2 to participate in Task 3, the PC will ask if they want to participate in a follow-up phone call with the interviewer they spoke with earlier. If yes, the interviewer will contact the participants and will share the main overall themes that surfaced from qualitative analysis of completed interviews. Participants will be asked (via phone, zoom, or in-person) to provide their feedback on these overall themes. Their feedback will then be incorporated into final analysis and interpretation of qualitative interviews. It is anticipated that this will take from 15 – 30 minutes. Participants can decline this portion of the study.

Participants in Task 3 will walk the 5 triggering scenarios (Figure 1) in a community setting (at the Short Pump Town Center) while wearing the UG device and the PDVibe3. Prior to walking in the community setting, participants will be consented and complete the questionnaires in Table 3 in a private VCU space (at the Short Pump Pavilion clinic).

Table 3. Physical and Neuropsychological Scales (total participant time for all the below measures is 30 minutes**).**

Factor	**Validated Scale**
Cognition	Montreal Cognitive Assessment [1]
Freezing of Gait	New Freezing of Gait questionnaire [6]
Motor Symptoms	MDS-UPDRS part 3 [7]
Walking Speed and Step Length	10 Meter Walk Test [8]
Fatigue	Rating of Fatigue Scale [21]

Task #3: Each subject that completed Task 2 is expected to spend up to 5 hours in the community setting (outside setting), and clinical setting, across two visits. Each subject that did not complete Task 2 is expected to spend up to 8 hours in the VCU clinical setting and an outside community setting, across two visits.