Study Title: Use of a Non-Invasive Brainstem Neuromodulation Device to Improve Neurovascular Status in Parkinson's Disease

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1. Protocol Summary

Synopsis

Title:
Use of a Non-Invasive Brainstem Neuromodulation Device to Improve Neurovascular Status in Parkinson's Disease

Study Description

This study is a single-site, double-blinded, randomized clinical trial (RCT), comparing responses to two different neurostimulation patterns. The study is designed to elucidate mechanism(s) of action for symptomatic benefits observed in Parkinson's disease (PD) patients treating twice daily with a solid-state, time-varying caloric vestibular stimulation (tvCVS) Device developed by Scion NeuroStim, LLC (SNS)[1]. Study participants will self-administer tvCVS treatments in the home setting over a period of 12 weeks. Changes in cerebral blood flow perfusion, cerebrovascular reactivity and functional connectivity between the pre-treatment baseline and the end of the treatment period will be monitored and will be compared to changes in validated standardized clinical measures of motor and non-motor symptoms in PD. The durability of effects will be evaluated at a post-treatment assessment conducted five weeks after treatment cessation.

Background, Rationale and Context

Caloric vestibular stimulation (CVS) is a technique developed more than a century ago and is commonly used to diagnose balance disorders or confirm absence or existence of brainstem function. Historically, water or air irrigators have been used to warm or cool the external auditory canal of patients. Both warming and cooling temperature changes lead to density changes in the endolymphatic fluid in the semicircular canals and create convection currents, which result in cupular deflection, change in the tonic firing rate of the vestibular nerves and elicit the vestibulo-ocular reflex or horizontal nystagmus [2]. Warming temperatures increase while cooling temperatures decrease the tonic firing rate of the vestibulocochlear nerves (see Figure 1).

The vestibular system (VS) is a unique target for therapeutic neuromodulation. Comparative studies estimate that the VS evolved ~500 million years ago to detect bodily movement and spatial orientation, and to provide an early sensory reference frame for developing sensorimotor

systems in the brainstem, cerebellum and cortex. As a result, vestibular signalling has become deeply integrated to balance, motion, body schema, mood, well-being and cognition, most notably memory [3]. This expansive reach of vestibular signalling (see Figure 1) makes the VS a promising therapeutic target to treat both the motor and non-motor symptoms associated with PD. Vestibular stimulation has been associated with release of a number of neurotransmitters including serotonin [4], histamine [5], acetylcholine [6, 7] and GABA [8]. It has also been shown to modulate various networks and nuclei in the brain including the basal ganglia [9] cerebellum, brainstem, hippocampus, insula [10], hypothalamus [11], thalamus [12], locus coeruleus [13] and prefrontal cortex [14], suggesting significant potential for CVS to modulate both motor and non-motor functions [2]. Furthermore, tracing studies [15-18], [19] have demonstrated monosynaptic or polysynaptic connectivity of the vestibular nuclei (VN) to several regions involved in the PD *motor* pathology including:

1. the dorsolateral striatum (caudate/putamen) via the thalamus and cortex, [20] where an imbalance in striatonigral and striatopallidal output due to loss of dopamine transmission is thought to underlie the bradykinesia symptoms in PD [21],
2. the pedunculopontine nucleus (PPN) located within mesencephalic locomotor region of the reticular formation [22], thought to be involved in gait and postural stability (as well as several non-motor functions) and which has recently become a target for DBS in PD [23-25], and
3. the cerebellum which has been implicated in the expression of levodopa-induced dyskinesia [26], is believed to play a modulatory roll in resting tremor, and is interconnected with several basal ganglia nuclei including the striatum via the thalamus as well as the globus pallidus external and subthalamic nucleus via the pontine nuclei [27].

The VN also provides direct and/or indirect inputs to many regions implicated in *non-motor* PD symptoms, including:

1. the corticolimbic network (anterior cingulate cortex, dorsolateral prefrontal cortex, amygdala and hippocampus), the dorsal raphe nucleus (DRN) and the parabrachial nucleus which have all been implicated in depression and anxiety [10, 15], [19]
2. the sensory association cortices, temporal-parietal regions, peri-sylvia, PPN and hippocampal structures implicated in memory and cognition [23, 28],
3. the pariaquaductal gray implicated in blood pressure/ orthostatic hypotension [29] and bladder control (the latter of which is also regulated by the hypothalamus, cerebellum, basal ganglia and frontal cortex [30]), and
4. the PPN and DRN implicated in sleep and arousal [23, 24, 31-33]. A role for the PPN and thalamus in visual hallucinations in PD has been established [34]. Furthermore, galvanic vestibular stimulation, a related approach, has been shown to increase deficient functional connectivity of the PPN in PD [35].

A number of pre-clinical and small proof-of-concept studies in PD have provided experimental evidence that vestibular stimulation may improve motor funtion and postural stability in PD[8, 36-39]. However, these studies utilize modes of vestibular stimulation that require 'in-clinic' administration and, thus, have limited potential for longitudinal therapy. By contrast, tvCVS can be safely self-administered in the home with the portable, solid-state TNM™ Device developed by Scion NeuroStim, LLC. The TNM™ Device discharges dose-controlled, time-varying

thermal waveforms via ear pieces housed in a headset (fashioned like music headphones)[2] (see Figure 2).

Previously, results from both a single case-study[40] and a single-site, double-blinded, randomized clinical trial (RCT) in which PD patients self-administered 19 minutes of tvCVS treatments twice daily for 8 weeks provided supporting evidence for the potential utility of the TNM™ tvCVS Device as an adjuvant to standard-of care therapies for mitigating both the motor and non-motor symptoms in PD [41, 42]. Participants in receipt of active treatment exhibited clinically relevant reductions in both motor and non-motor symptoms along with improved activities of daily living at the end of the treatment period that were significantly greater than those who had received placebo treatment. Furthermore, non-motor symptom improvements were observed across a broad spectrum of domains including sleep/fatigue, mood/cognition, attention/memory, gastrointestinal function, urinary function according to results from the Non-Motor Symptom

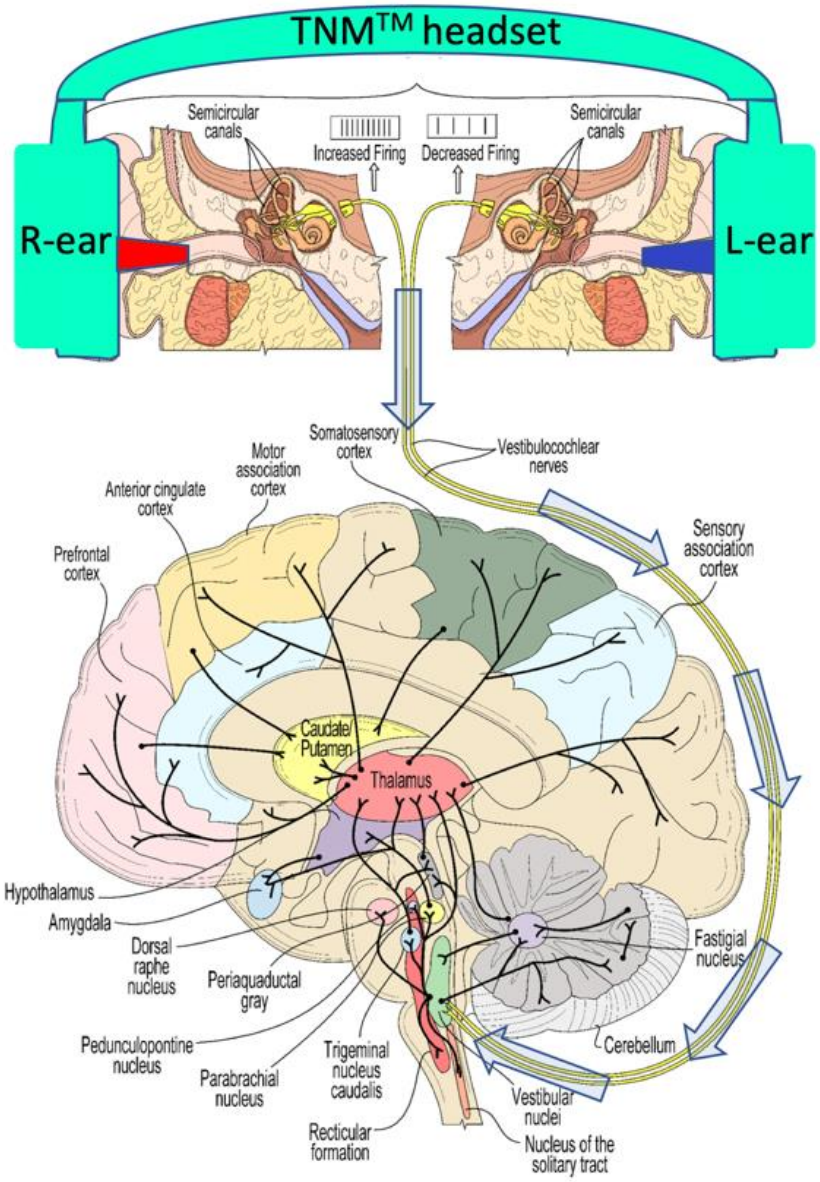

Figure 1. The effects of CVS on the vestibulocochlear nerves and the connectivity of the vestibular nuclei to brain regions implicated in Parkinson's disease[3-5]. The color of ear probes denotes temperature change with warming shown in red and cooling shown in blue.

Scale (NMSS) and the Montreal Cognitive Assessment (MoCA).

Active treatment was also associated with significant adjuvant improvement in motor function as indicated by the MDS-UPDRS motor exam, the Timed-Up-and-Go and the velocity of a self-selected 10-meter walk. These motor evaluations were consistently performed by a blinded assessor while subjects were in an 'on' state. The relative timing since their last DRT dose was maintained across all assessments. Likewise, participants in the active treatment arm also demonstrated therapeutic gains in activities of daily living according to the MDS-UPDRS parts I and II and the Modified Schwab & England scale. All therapeutic gains were achieved in patients whose oral medicine had been optimized prior to enrolment. Participant guesses about treatment allocation indicated that precautions taken to blind allocation were effective [42]. Subjects stated high satisfaction (85% reported a positive experience with the device), showed excellent treatment adherence (84 ± 5% for both groups), and reported no serious or unexpected adverse events. Notably, therapeutic gains were equivalent, and in many cases, even greater at a 1-month post-treatment follow-up indicating a degree of durable gains and suggesting engagement of a long-term mechanism of plasticity (see supporting materials). At 6 months follow-up, most of the gains had returned to near baseline levels although there was some evidence for residual effect. The similar trajectories across diverse domains over the treatment and post-treatment follow-up period suggest a single underlying mechanism for the effects.

The mechanism for symptomatic improvement in PD remains unknown. However, previous studies have demonstrated that tvCVS elicits strong oscillations in the pulsatility index, a measure of cerebrovascular flow dynamics, after approximately 4-5 minutes of stimulation [2]. Oscillations persist for several minutes post-treatment indicative of an entrainment effect. These effects are likely to lead to improvements in neurovascular status (i.e. improved cerebral perfusion and increased cardiovascular reactivity) that restore homeostasis to neurons and circuits affected by PD pathology.

Objectives

Primary Objectives: To test hypothesis that 12-weeks of BID tvCVS treatments increase cerebral blood flow perfusion as assessed by pseudo-continuous arterial spin labeling (pCASL). To test hypothesis that 12-weeks of BID tvCVS treatments increase cerebrovascular reactivity (CVR) in the brain as assessed by pCASL.

Secondary Objectives: To test hypothesis that 12-weeks of BID tvCVS treatments increase functional connectivity in the brain.

Exploratory Objectives: This study will seek to establish the relationships between changes in cerebral perfusion and CVR with improvements in clinical endpoints and to evaluate whether these changes are durable (at an assessment five weeks after the cessation of treatments). Furthermore, the feasibility of detecting change in cerebrovascular reactivity (CVR) as assessed via transcranial Doppler sonography (TCD) will also be explored as well as pulse wave velocity (PWV).

Study Design

A double-blinded, randomized trial comparing two different neurostimulation patterns will explore the effects of tvCVS treatments on changes in biomarkers of neurovascular status (i.e. cerebral blood flow perfusion and cerebrovascular reactivity) as well as their relationship to clinical endpoints. Eligible and enrolled participants will be randomly allocated in a 1:1 ratio using block randomization by the clinical site. Participants will be trained in the clinic to self-administer device treatment and then will continue to self-administer the ~19-minute treatments twice daily for 12 weeks in the home. Individual stimulation sessions will be spaced a minimum of 1 hour apart. Outcome measures will be administered at the baseline, the end of the 12-week treatment period and at 5 weeks post-treatment. Study participants will continue to take their approved PD medications throughout the study and will maintain patterns of usage throughout.

Previous evidence for efficacy demonstrated therapeutic gains as an adjuvant for standard of care treatment. Consistent with these observations, all outcome measures will be evaluated when study participants are in the on-medication state and at the same time relative to the last dose of anti-Parkinsonian medication across all assessments. Clinical measures will be captured at the baseline, at the end of treatment period, and again five weeks after cessation of treatment. Most of the planned clinical measures including the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) parts I, II, and IV, the Non-Motor Symptom Scale for PD (NMSS), the Montreal Cognitive Assessment (MoCA), the Parkinson's Anxiety Scale, the Geriatric Depression Scale, the Epworth Sleepiness Scale, and the Functional Assessment of Chronic Illness Therapy- Fatigue are suitable for virtual collection. The clinician reported outcomes and performance-based test will be administered via telemedicine visits using HIPAA-compliant platforms such as Webex. Case report forms (CRFs) for the patient reported outcomes will be provided to study participants via standard mail. At the end of each virtual visit, participants will be asked to complete these forms and bring them to the clinic the next day when they come for their in-clinic visit. In the case where an in-clinic visit may not be possible, participants will be asked to show completed forms to the coordinator via the telemedicine platform to confirm completeness, and forms will be collected at the next in person visit or can be mailed in by the participant.

The full MDS- UPDRS part III and the Timed Up and Go will be administered in the clinic. However, a modified MDS-UPDRS part III (excluding items related to rigidity or postural instability) will also be administered through the telemedicine platform. This measure will serve as backup for cases where participants may be unable to come into the clinic for regularly scheduled assessment (e.g. due to COVID-19 containment measures). MDS- UPDRS part III is the motor examination portion of the assessment and may be videotaped for review.

Recruitment:

In-clinic recruitment: For prospective study participants who agree to learn more about the study during a regularly scheduled visit in the movement disorder clinic, participants will be provided the opportunity to review the informed consent form (ICF) and ask questions of the PI. The PI or designee will verify participant comprehension of the ICF details. If they decide to sign the informed consent while in the clinic, participants will also be provided with Baseline visit CRFs, instructions for how to set up for the telemedicine visit and instruction to accommodate collection of the motor assessments during the telemedicine visit. The screening visit and baseline imaging/ Device training visits will be scheduled.

Virtual recruitment: For participants who are recruited via alternative means (e.g. phone calls, telemedicine visits, etc.), an ICF, instructions for telemedicine visits and CRFs for the Screening visit will be mailed to the participant, and the screening visit will be scheduled. Participants must demonstrate comprehension of the ICF contents and sign the ICF during the telemedicine visit with the PI or designee bearing witness prior to completion of any additional study procedures.

Translational Data Warehouse recruitment: As an extension to virtual recruitment, the Translational Data Warehouse will also be used for cohort identification and to pull detailed data to recruit prospective study participants.

All virtual and in-clinic visits, assessments should be scheduled to begin approximately one hour after the participant's scheduled dose of oral DRT.

***Potential participant contact information including phone number, street address and email address will be collected and stored on a password-protected computer on a secure network. This information will be used to send materials and links for remote visits and to contact the participant throughout the study.

Screening visit (in clinic or remote):

Medical history and concomitant medications will be collected and the Montreal Cognitive Assessment (MoCA), the Movement Disorder Society- Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part I and the MDS-UPDRS part II will be administered. * Note, for the MDS-UPDRS part I, the rater will administer part IA and participants will be asked to verbally provide answers for part IB, a patient reported outcome. The following are required for study eligibility:

- MoCA score > 20
- MDS-UPDRS part I scores ≥ 9
- MDS-UPDRS part II scores ≥ 9

Upon the verification of eligibility, the remaining clinician-rated assessments will be completed (i.e. the modified MDS-UPDRS part III, the MDS-UPDRS part IV, the Non Motor Symptom Scale (NMSS), the MRI safety screen, COVID-19 related screening questions). A bilateral ear exam will be performed for eligible subjects. A bilateral ear exam may be performed for

subjects who are not eligible. If any ear abnormalities are noted during the ear exam (including pain, infection, damage/injury, or excessive earwax), it will be the participant's responsibility to resolve it before continuing in the study. If the subject chooses not to resolve any ear issues, including earwax removal, he/she will be excluded. The handout/guide listing the contact information to for study staff should participants have any questions or experience any AEs during the duration of the study will be reviewed. The clinical research coordinator will then confirm that the participant has received the patient reported outcomes (PROs) including the Geriatric Depression Scale (GDS), the Parkinson's Anxiety Scale (PAS), the Epworth Sleepiness Scale (ESS) and the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F). Participants will be asked to complete these assessments at the end of the virtual visit and reminded that they should complete the forms when in the "On" medication state and to bring them to their scheduled clinic visit.

*Note, visits for the baseline, end of treatment and post treatment follow-up should be set up for the same time of day so as to minimize variability that may result from the fluctuating kinetics of responses to dopamine replacement therapies. Care should also be given to minimize the duration of time between the remote clinical visits and the imaging visits making these next day if possible. If the same time of day is not possible, then it is ideal to schedule visit at a time that is the same relative to the scheduled dopamine replacement therapy.

Baseline imaging / Device training visit:

Participants will be screened for COVID-19 upon arrival to the clinic. A bilateral ear exam will then be performed. A pregnancy test will be performed for all female participants of childbearing age. The MDS-UPDRS part III and the Timed Up and Go (TUG) will then be administered. Participants will then undergo the Magnetic Resonance Imaging (MRI) protocol (see below) and the transcranial Doppler sonography recordings of a hypercapnia challenge. Pulse wave velocity may be measured at this time.

After the collection of baseline neuroimaging data, participants will return to the clinic where they and their caregivers will try on an unpowered Device, will be randomized and trained on the use and care of the tvCVS Device. The Device will be allocated to the participant and the coordinator should note the Device ID in the Device Inventory Control Log. The study coordinator will the assist the participant in adjustment of the headset settings. See Clinical Coordinator Quick Reference Guide for procedures. Once the participant confirms that the headset is comfortable enough to proceed, the participant will be randomized by selecting an envelope with printed bar code from the pack of four. Note that a given pack of 4 should be completed before a new pack is opened. The study coordinator will load the prescription on the Device and then place the unopened envelope in the study binder. * Envelopes should be only be opened under circumstances where treatment allocation must be known for management of an adverse event. Once the Participant has demonstrated proficiency in Device care and use procedures, they will take their designated Device home and will self-administer treatments twice daily during the treatment period. Participants will also be provided with a detailed handout (step-by-step guide with pictures), for self-administration of device treatments. Coordinators will also call the participant the next day to confirm that the participant was able to

administer treatments. If necessary, additional training sessions via telemedicine may be scheduled.

MRI protocol:

Participants will be scanned on a research-dedicated 3T Siemens Skyra system with a 32-channel head coil that is located on the Wake Forest medical school campus. The neuroimaging protocol will follow standard operational procedure of the Wake Forest University MRI Research Unit which have recently been modified to provide additional safeguards to limit risks of exposure to COVID-19. Imaging should occur in the on-state, and the time of treatment for the participant's last dopamine replacement therapy will be noted. The study will acquire multi-modal MRI lasting less than one hour and will include standard structural and functional imaging in the following sequential order:

- T1-weighted fMRI (structural scan): High-resolution T1-weighted images will be obtained using a fast gradient echo sequence: TR = 2300; TE = 2.98; 1 mm isotropic resolution.
- Resting state – functional magnetic resonance imaging (rs-fMRI) Blood-oxygen-level-dependent (BOLD) imaging to assess changes in functional connectivity: 10 minutes. Participants will have their eyes open, focusing on a crosshair.
- Resting state – pseudocontinuous arterial spin labelling (pCASL) to monitor whole brain cerebral blood flow (CBF): : tagging duration = 1.6 sec, TI = 3 sec TR = 4 sec, TE = 12 ms, reps = 81, FOV =17x21 cm, slice thickness = 4 mm, spatial resolution = 3x3mm, 24 axial slices with a single shot EPI acquisition, collecting 8 cycles where each cycles consists of 8 images acquired with unique phase offsets, acquisition time = 5 min. 36 sec.
- pCASL with hypercapnia challenge to monitor cerebrovascular reactivity: Resting End-tidal PCO2 (~40mmHg) for 3 min, increased end-tidal PCO2 by 8~10mmHg above resting for 3 min and returned back to resting end-tidal PCO2 for 1 min. End-tidal PO2 will be maintained at resting (~110 mmHg) during the paradigm. The duration of the hypercapnia run will be 7 minutes and CBF maps will be continuously acquired every 8 seconds.
- T2 FLAIR to detect white matter lesions: T2 FLAIR images will be obtained using a 3D inversion recovery gradient echo sequence: TI = 1.8 sec; TR = 5 sec; TE = 395 msec; 1 mm isotropic resolution

Transcranial Doppler (TCD) Sonography:

After the completion of the MRI scan, the coordinator will accompany the study participant to the clinic for TCD recordings. There, the participant will receive a second hypercapnia challenge (using the same conditions described above) while undergoing TCD recording. Pulse wave velocity (PWV) may be measured at this time.

Treatment period:

All participants will treat twice daily, at least one hour apart. Each treatment duration is 19 minutes 39 seconds. Participants will only wear the device when administering a treatment per protocol. The treatment period is anticipated to last for 12 weeks. However, treatment may be

extended for approximately 2 additional weeks in the case of scheduling conflicts (such as those imposed by standard operating procedures imposed by WFU to limit the spread of COVID-19). Patients should continue to treat twice daily up until the time of the end of treatment clinic visit.

Interim phone calls:

- Participants will be called the next day after their Device training visit to confirm that participants were able to successfully administer treatment in the home setting.
- Scheduled follow up phone calls will be made at week 3, week 6 and week 9. During these calls, the coordinator will ask about any adverse events, any changes to concomitant medications and to confirm no issues have arisen with use of the Device.
- Participants will also have received the contact information for the site coordinator so that they may report potential adverse events or issues with the Device in real time.

End of treatment visit (remote) – week 12:

During this remote visit, the study coordinator will administer the NMSS, the MDS-UPDRS parts II and IV as well as the modified MDS-UPDRS part III. They will also administer the MoCA, the MRI safety screening as well as a Device usability questionnaire. Participants will then be asked to completed the (PROs) including the Geriatric Depression Scale (GDS), the Parkinson's Anxiety Scale (PAS), the Epworth Sleepiness Scale (ESS), the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) and the Device Usability Questionnaire and to bring them to their scheduled imaging visit. Participants will also be told to bring their Devices with them to the next clinic but that they should continue with twice daily treatments until their imaging visit.

End of treatment visit (in clinic)- week 12, 1 day after remote visit:

Participants will be screened for COVID-19 upon arrival to the clinic. Effort should be made to schedule the imaging visit within 24 hours of the virtual visit. On arrival, **t**he MDS-UPDRS part III and the Timed Up and Go (TUG) will then be administered. The bilateral ear exam will be performed. Participants will then undergo the Magnetic Resonance Imaging (MRI) protocol and the transcranial Doppler sonography recordings of a hypercapnia challenge outlined above. Pulse wave velocity may be measured at the time of the transcranial Doppler sonography recordings. The PROs will be collected and checked for completeness. Participants will be asked to complete missing items or complete in full in the clinic if forms were left at home. Devices will be collected. The Inventory Control Log should be updated noting the return date of the Device. The Device should then be returned to Robling with a completed Device Return Form. **Should participants forget to bring their TNM™ Device to this visit, they will be provided with an addressed pre-paid FedEx box that can be used to ship the Device directly back to Robling. Coordinators should check tracking information and follow up with reminder phone calls to ensure return of the Device.

Follow up visit (remote) – week 17:

During this remote visit, the study coordinator will administer the NMSS, the MDS-UPDRS parts II and IV as well as the modified MDS-UPDRS part III. They will also administer the MoCA, the MRI safety screening. Participants will then be asked to complete the (PROs) including the Geriatric Depression Scale (GDS), the Parkinson's Anxiety Scale (PAS), the Epworth Sleepiness Scale (ESS) and the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) and to bring them to their scheduled imaging visit.

Follow up visit (in clinic)- week 17, 1 day after remote visit:

Participants will be screened for COVID-19 upon arrival to the clinic. Effort should be made to schedule the imaging visit within 24 hours of the virtual visit. On arrival, **t**he MDS-UPDRS part III and the Timed Up and Go (TUG) will then be administered. Participants will then undergo the Magnetic Resonance Imaging (MRI) protocol. A bilateral ear exam will only be performed if there were residual ear-related AEs at the last treatment visit.

SCHEDULE OF ACTIVITIES

Activity	Recruitment (if in person)	Screening visit (remote)	Baseline /device training visit week 0	Phone contact (1 day after training)	Phone contact week 3	Phone contact week 6	Phone contact week 9	Post-treatment remote visit	Post-treatment week 12 clinic visit	Follow up visit week 17 (remote)	Follow up week 17 clinic visit
Informed Consent	X	or here									
Try on unpowered device			X								
Review study inclusion/exclusion criteria	X										
Medical History and concomitant medications		X									
Watch informational video		X									
Non-Motor Symptom Scale		X						X		X	
MDS-UPDRS part I		X									
MDS-UPDRS part II		X						X		X	
MDS-UPDRS part III (on-state)		X	X					X	X	X	X
MDS-UPDRS part IV		X						X		X	
Timed Up and Go			X						X		X
Montreal Cognitive Assessment		X						X		X	
Geriatric Depression Scale		X						X		X	
Parkinson's Anxiety Scale		X						X		X	
Epworth Sleepiness Scale		X						X		X	
Functional Assessment of Chronic Illness Therapy - Fatigue		X						X		X	
MRI safety screening		X						X		X	
Temperature check/ COVID-19 screening questions			X						X		X
Device training			X								
Device usability questionnaire								X			
Check in to confirm first at-home treatment				X							
Ear physical exam			X						X		as needed
Pregnancy test (if appropriate)			X						X		
Review concomitant medications and adverse events			X	X	X	X	X	X	X	X	X
rs- pCASL			X						X		X
rs-fMRI BOLD			X						X		X
pCASL (hypercapnia challenge)			X						X		X
TCD (hypercapnia challenge)			X						X		
Device collection									X		
Pulse wave velocity			X						X		

Selection Criteria

Inclusion Criteria:

Each participant must have a pre-treatment history that, when initially screened by a principal investigator or designee, documents that she/he meets all elements of the following:

- Must be 21-85 years old.
- Diagnosed with Parkinson's Disease (meeting UK PD Society Brain Bank criteria)
- Responsive to oral DRT (dopamine replacement therapy) and treated with oral DRTs for a minimum of 3 years prior to screening visit
- Participants and investigators must expect that the participant will be able to remain on a stable regimen of concomitant therapies used for the management of PD motor and non-motor symptoms and not to introduce new medications used to treat motor or non-motor symptoms associated with PD during the clinical trial. See details in the **Concomitant Medication** Section.
- Must be able to voluntarily give written informed consent.
- Must be willing and able to comply with study requirements
- Must have ability to reliably use the investigational device
- Must be able to understand and complete all assessments (provided in English only) within a given on-state period
- Must be willing and able to undertake a 1-hour imaging session in an MRI magnet with a head coil in place during 3 separate clinic visits and a 1-hour imaging session using transcranial Doppler sonography during 2 separate clinic visits
- Must have a study partner and/or regular caregiver (defined as someone who sees the participant for more than one hour a day, 3x per week) that is willing to consent and participate in the trial
- Must have access and capability to complete assessments using telemedicine platforms
- Must demonstrate moderate burden of motor symptoms and non-motor symptoms in PD (MDS-UPDRS part II ≥ 9 and MDS-UPDRS part I scores ≥ 9)
- Must consent to being videotaped during motor examination visit
- Must be willing to answer questions related to sexual interest, arousal and performance in an interview with study staff

Exclusion Criteria:

- Participant anticipates being unable to attend all study visits and complete all study activities during the clinical trial
- Women of child-bearing potential who are pregnant or plan to become pregnant during the course of the study
    - Women of child-bearing potential (i.e., are not yet 3 years removed from their first menopausal symptom), who are not abstinent or exclusively in same sex relationships must:
        - test negative for pregnancy as indicated by a negative urine pregnancy test

    - agree to use an approved contraception method listed in the section **Concomitant Medications** for the entirety of the study
- Have experienced a myocardial infarction, angina or stroke within the past 12 months,
- Use of medications that regulate heart rate
- Have a history or prior diagnosis of dementia or adjusted score ≤ 20 on the Montreal Cognitive Assessment at the baseline visit. This exclusion criterion has been set specifically to improve the validity of scores assessed from the scaled questionnaires rather than reflecting a concern about safety for this population.
- Those receiving deep brain stimulation therapy
- Treated with a pump for continuous delivery of DRT (Dopamine replacement therapy)
- Use of Apomorphine rescue
- Works night shifts
- have any significant co-morbidity or illness which in the opinion of the investigator would prevent safe participation in the study, compliance with protocol requirements or which presents with symptoms that are also common in PD (e.g., stroke, brain tumor, epilepsy, Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, atypical Parkinsonism or aneurysm)
- Has history or evidence of unstable mood disorder or demonstrates evidence of suicidality. Participants that demonstrate risk of suicide should receive a referral for mental health counseling according to the mandates of the IRB or ethics review committee.
- Those with hearing aids that are implanted or cannot be easily removed and replaced
- Have cochlear implants
- Have chronic (> 3 months) tinnitus
- Those who have previously been diagnosed with traumatic brain injury with ongoing sequela
- Those with a recent history of substance abuse and/or dependence (alcohol or other drugs)
- Those who have a diagnosed vestibular dysfunction and/or balance dysfunction
- Those who have had eye surgery within the previous three months or ear surgery within the previous six months
- Those who have excessive earwax
- Those with active ear infections, perforated tympanic membrane or labyrinthitis, as identified by a general ear examination performed by medically qualified Investigators
- Those with a recent history of frequent ear infections (≥ 1 per year over the past two years)
- Those who have contraindications for MRI imaging, such as metal implants or a pacemaker that would preclude the MRI scan
- Those who are currently enrolled or have participated in another interventional clinical trial within the last 30 days
- Those who are taking antiemetics chronically (more than 2 times per week, consistently)
- Have sequelae from a COVID-19 infection that includes one or more of the exclusion criteria listed above
- Those who have a planned surgery scheduled to occur during the clinical trial that requires sedation and/or would typically be followed with a prescription for pain management

Concomitant Medications

The investigator should review other medications taken by the participant with properties that mimic anti-nausea, anti-dizziness or anti-histamine drugs as these may reduce responsiveness of the vestibular system to caloric stimulation. Such medications should be avoided within 4 hours prior to study device treatment.

The use of the following medications used to treat motor and non-motor symptoms associated with PD will be permitted during the study as long as the type or dose does not change during the course of the study or the 4 weeks immediately preceding the study: oral DRTs (e.g., levodopa/carbidopa or dopamine agonist based therapies), anti-cholinergics, MOA-B inhibitors, COMT inhibitors, amantadine, therapies to promote sleep including melatonin or benzodiazepines such as Klonopin, drugs to treat urinary frequency such as oxybutynin, tolterodine, trospium, solifenacin succinate, darifenacin, mirabegron, and fesoterodine fumarate.

The use of selective serotonin reuptake inhibitors (SSRIs) or other anti-depression/anti-anxiety medications will also be permitted during the study so long as the type and or dose does not change during the trial or the 12 weeks preceding the trial.

Changes to medications for motor symptoms and NMS of PD are not permitted during the study unless it is the opinion of the investigator that they are medically necessary for the health and safety of the patient. Reasons for changes in medications used to treat motor symptoms or NMS of PD will be recorded and participants who make changes in PD medications or add new medications likely to modulate symptoms associated with PD during the study will be excluded from the PP and mITT analysis.

Medications prescribed for other concomitant illnesses are allowed as long as they are not listed in the **Excluded Concomitant Medications and Drugs** list.

When medications are prescribed for indications other than symptoms associated with PD, physicians will be encouraged to utilize the one that is least likely to impact motor and non-motor symptoms associated with PD.

Females of childbearing potential who engage in heterosexual intercourse during the clinical trial must utilize one of these approved methods of contraception:

- Oral Hormonal Contraception
- Patch Contraception
- Hormonal Ring
- Intrauterine Device (IUD)
- Contraceptive Implantation
- Contraceptive Shot
- Barrier Method, including:
    - Male Condom
    - Female Condom
    - Diaphragm
    - Cervical Cap with spermicide

- Contraceptive Sponge
- Spermicide

Excluded Concomitant Medications and Drugs

- Antipsychotic Medications (i.e., either neuroleptics or atypical antipsychotics)
- Anti-emetics (e.g., 5-HT3 receptor antagonists, D2 receptor antagonists, H1 Receptor antagonists, muscarinic antagonists, synthetic cannabinoids, corticosteroids or SP/NK1 receptors antagonists) prescribed chronically (taken more than 2 times per week, consistently)
- Cannabinoids (e.g., marijuana, tetrahydrocannbinol nabilone or cannabidiol) within 4 weeks of screening.
- Any drug that has not been legalized on a United States Federal level
- Controlled substances that have not been prescribed under the care of a licensed professional.

Sample size:

Up to 20 study participants will be enrolled in the study at one clinical site, Wake Forest School of Medicine, in the United States. Wake Forest School of Medicine (WFSM) has the expertise in the conduct of clinical trials for Parkinson's disease therapeutics. A maximum of 4 participants may be enrolled in any given month.

Interventions and Interactions

Description of Study Intervention

The generation 3.2 TNM™ Device has been approved by the FDA for the prevention of episodic migraine in adolescent and adult patients 12 and older. The Device has been designated as non-significant risk (NSR) by the FDA for studies in PD, and thus, is suitable for home use.

Figure 2. TNM™ device and treatment. (A) Schematic showing device design of the Generation 4.0 TNM device. **(B)** Patient undergoing treatment while wearing the TNM headset and lying on an incline wedge pillow. **(C)** Example of target and actual thermal profiles of the saw-tooth, time-varying thermal waveform used for active treatment.

The next generation device (4.0) which has been adapted to improve usability for patients with PD will be utilized in this study. See Scion TNM™ 4.0 Clinical Quick Reference Guide (QRG) for more details. The device delivers software-driven, time-varying thermal waveforms to modulate neural areas, including the brainstem, by means of CVS. The device is fashioned like a set of music earphones, with two independently controlled thermoelectric devices attached to aluminum earpieces that fit inside the ear canals and abut, but do not enter, the bony canals (see Figure 2A). Specific details regarding the device design have been previously published [2].

For treatment, all participants will recline on a 22° wedge pillow (provided by Scion) to position the horizontal semicircular canal in the optimal orientation for maximal caloric effect. Participants will start and stop the device with a single push button to activate a run. Starting and stopping the device requires an extended push (2 seconds) to avoid false activations due to short button pushes. The OLED display provides a "countdown" icon to provide the subject with feedback on how the treatment session is proceeding. The display also tells the subject how many treatments are left within the prescription period. The device provides an audio alert that denotes the start and completion of a treatment run. The same visual and auditory information will be presented for both neurostimulation patterns.

Device treatment does not require active engagement of the subject. Therefore, participants will be told that they should feel free to read, watch television or rest so long as they remain in the supine position for the duration of treatment.

For the stimulation 1 treatment, time-varying saw-tooth waveforms (shown in Figure 2C) are delivered. The waveform schedule for active treatment participants will consist of a warm sawtooth delivered to one ear and a cold sawtooth delivered to the other ear (see Figure 1C for an example). The warm sawtooth will go from body temperature to 42 °C, and the cold sawtooth will go from body temperature to 17 °C. The two waveforms will be delivered simultaneously but will have different oscillation frequencies. After each 2-day period, the warm and cold waveforms will be switched so that the opposite ears will receive the different caloric stimulation. Thus, every 2 days, the ear receiving the cold stimulus will be switched to the warm stimulus and vice versa. This protocol will be followed for 84 days. Additional window days will be available to accommodate for potential scheduling conflicts.

For the stimulation 2 treatment, no power will be delivered to the heating and cooling elements within the headset. However, the aluminum earpieces, which will be room temperature at the start of the treatment, will provide an initial cooling stimulus when placed within the ear canals, and thus provide a minimal amount of vestibular stimulation. During the treatment, the earpieces will eventually warm to body temperature. Of note, this condition provides the minimum level of stimulation that is possible while keeping the Device the same. All other sensory experiences associated with device treatment will be the same including auditory sensations from the start and stop tones of the device and the faint whirring noise provided by the activity of cooling fans within the headset, the pressure sensations from the headset, the visual displays on the LED screen, and the choreography of staring, conducting and stopping a treatment.

Intended Use:

The TNM™ Device is intended to stimulate the brainstem through the vestibular system via external ear canals using software-controlled thermal waveforms.

Preparation/Handling/Storage/Accountability:

Study devices must be stored in a secure area with limited access. Storage rooms used for this purpose must have locked access. Only delegated research staff should be allowed to enter. Doors shall remain locked at all times.

Upon receipt, the shipment of study devices should be inventoried. Discrepancies or damaged shipments should promptly be brought to the attention of the Device sponsor. Copies of the packing slips should be retained, and the inventory should be documented on the Investigator Inventory Control Form located in the regulatory binder for the study.

Study coordinators should complete the Investigator Inventory Control Form whenever one of the following event occurs: 1) devices are received from the Device Sponsor, 2) devices are dispensed to participants, 3) devices are returned from participants and 4) devices are shipped

back to the Device Sponsor. In the case of a damaged or failed device, coordinators should contact the Device sponsor clinical research associate (CRA) for instructions, as soon as possible.

After the study participant returns the device to the clinic. The study coordinator will then complete a Device Return Document and ship the Device back to Robling using the shipping information provided on that form.

Randomization, Blinding and Unblinding:

The Generation 4.0 TNM™ device uses a bar code reader to import a coded waveform. The use of the bar code aids blinding during randomization since the QR code is not readable by staff members. Bar codes will be printed on sealed envelopes that contain the treatment allocation information inside. A note will be printed across the seal of all envelopes and the study staff will be instructed that envelopes should only to be opened at the site in the case of a SADE or UADE that requires the designated Unblinding Investigator to become unblinded to treatment allocation.

For randomization, the training coordinator will simply scan the bar code on the envelope and then leave the unopened envelope in the study participant's binder. Should treatment allocation information be required for handling of an AE, a CRF providing the details of the incident will be documented. The Device Sponsor's CRA will check to ensure envelopes have remained sealed at monitoring visits and at study close out.

Packets containing 4 sealed envelopes with the printed bar codes for randomization assignments will be provided by the Device sponsor. Each batch will contain two stimulation 1 and two stimulation 2 assignments. The envelopes will be randomly shuffled by an agent not involved with the study. A given packet will be completed before the next packet is opened. The device-training coordinator will load the treatment onto the device, will record the device number allocated to the participant and will train the participant according to the training script provided (see Study Coordinator Quick Reference Guide). If the participant makes a comment about feeling warming or cooling sensations that may potentially unblind the study staff to treatment allocation, this information is not to be shared with other study staff including other coordinators, the principal investigator, Device sponsor CRA, data analysts or the study statistician. All assessments will be performed by a study coordinator that does not take part in the interim phone calls. Participants will be told that pain should not be associated with treatment, and if they do experience pain, that they should stop treatment and contact the coordinator immediately and/or seek medical attention if necessary. However, they will also be told that in the absence of pain, for the integrity of the trial, they should not discuss their treatment experience with anyone associated with the study (e.g. other research staff, their caregiver or other people they may know are participating in the trial). The exception being when they are specifically asked about their treatment experience in the Device Usability Questionnaire at the end of the treatment period.

Unblinding at the study site will only occur in the case of a SADE (serious adverse event at least possibly related to the device) or UADE (serious and unanticipated/unexpected adverse events at least possibly related to the device) that also requires cessation of device treatment. If this situation seems likely, the Unblinding Investigator, noted in the Delegation of Authority Log, should contact SNS to request approval to unblind. Upon receipt of written permission from the

Sponsor, the Unblinding investigator may open the randomization envelope to obtain the treatment allocation. The safety event will be reported as required by this protocol. Should treatment allocation information be required for handling of an AE, a CRF providing the details of the incident will be completed.

Analysis of all study endpoints will be completed by individuals blinded to treatment allocation. The participants will be told, within the informed consent document that they may not directly benefit from taking part in the study. Participants will be told that the device stimulates the brainstem but will NOT be told that the device provides caloric vestibular stimulation (CVS) or that the device works by modulating temperature of the ear probes.

The study team will work to develop a culture of collaboration and mutual respect with the study participants. Participants will be told that their participation in the trial and adherence to the study protocol will help to develop a potential new treatment for PD patients. Participants will also be reminded that the success of the study is dependent on their willingness to participate in a blinded fashion, and should they be tempted to try to investigate more about the device during the clinical trial, engagement in these activities are likely to corrupt the integrity of the study results. Participants will be offered the opportunity to learn about their stimulation condition after the completion of the study.

Site personnel should encourage study participant adherence to Device usage throughout duration of the trial but maintain a neutral position regarding efficacy to promote scientific integrity of the study.

Study Intervention Adherence:

The actual, measured temperature profile for each run will be saved to Device memory, as will the time and date of each treatment run. A team at Robling will download the Device adherence and temperature recording data via a USB port that is covered by a hatch on the device body. They will provide treatment adherence data to the study coordinator and the raw files which can be evaluated to confirm treatment allocation will be saved in a central repository and shared with Scion NeuroStim after study database lock.

Discontinuation of Study Intervention:

AEs will be summarized by the Device sponsor CRA. Device sponsor management and the site PI will regularly convene to monitor and review AE reports. All AEs will be evaluated on an individual basis to determine whether the occurrence may be related to device use. Should a serious adverse event (SAE) occur that is deemed to be likely related to device use, the potential for the universality will be assessed within 48 hours. If evidence suggests that treatments with the device could create a safety concern for participants, the study Device sponsor will be pause or stop the study early, as appropriate.

It should be noted that the above scenario is considered to be highly unlikely. The device has been designated as NSR by the FDA, and there were no reports of significant or unexpected AEs

that were potentially related to device in either the PD single-site RCT or the episodic migraine RCT.

Participant Discontinuation/Withdrawal from the Study:

Withdrawal Criteria

Study participants must be withdrawn from the clinical trial if any of the following events occur:

- the participant is significantly and willfully non-adherent to the requirements of the protocol (principal investigator & Device Sponsor decision),
- the participant develops an illness (adverse event) that would interfere with his/her continued participation,
- the participant withdraws his/her consent,
- the principal investigator feels that it is the participant's best interest to be withdrawn,
- SNS discontinues the study or has achieved the targeted enrollment

If the study participant is discontinued from the participation in the study for any reason, the principal investigator must make every effort to perform all evaluations for the final visit, collect the device from the participant (if it is still within their possession) and document the reasons for discontinuation. If the participant withdraws from the study due to an adverse event that is potentially related to use of the device, the coordinator should continue to follow up with the participant at regular intervals, and at least every two weeks until the AE resolves or until the participant withdraws consent for the follow-up procedure. Reasons for study withdrawal should be documented on the subject disposition form.

Lost to Follow-up

As part of the study intake during Screening Visit, the contact information for both the study participant and the caregiver will be collected and kept confidential and private by the clinical site. During each study visit or interim phone contact, participants will be asked to confirm the date/time of their next scheduled study visit. If a participant misses a scheduled visit or phone call, the coordinator should call the participant the same day to reschedule the visit. The rescheduled visit/call should occur as soon as possible after the missed appointment and within 5 business days. The reason for rescheduling a study visit should be documented. If the participant does not respond within 24 hours, the coordinator will also contact the caregiver. If there is no response from the participant, the coordinator will attempt to contact the caregiver and will continue to contact both the participant and caregiver daily for 1 week or until contact is made. If the prior step is unsuccessful, the coordinator is required to reach out to the participant's caregiver, or other contact(s) provided. If the prior step is unsuccessful, the coordinator is required to reach out to the participant once a week over the next 6 weeks. All contact attempts must be documented. If all telephone attempts are unsuccessful, the coordinator will follow up by sending a letter to the participant.
Study participants will be considered "lost to follow-up" if they are enrolled and participating in the clinical trial, missed a clinical study visit and become unreachable (via phone or mail) during the study.

Analysis Plan

Group-wise comparisons will be made using an analysis of covariance adjusting for baseline severity and white-matter lesion burden. The results by group will be presented as group means/medians and treatment differences with corresponding 95% confidence intervals. Tests for assumptions will be conducted prior to analysis. In the case of non-normality, equivalent non-parametric approaches will be utilized. In order to evaluate whether the physiological changes explored in this study serve as the underlying mechanism for the reduced PD symptoms from TNM™ Device therapy, we will run correlational analyses between the imaging measures and the clinical measures using the change scores from the end of treatment and the post-treatment follow-up relative to the baseline measure.

Analysis effort will first focus on evaluating changes in cerebral perfusion and cardiovascular reactivity after 12 weeks of tvCVS therapy and how these changes related to those observed in the clinical endpoints. Once these study result have been summarized and provided to the Michael J Fox Foundation, changes in functional connectivity will be explored.

Human Subjects Protection

Risk Benefit Assessment

There is a long-standing history to support the safety of caloric vestibular stimulation (CVS) as a technique as the approach has been used diagnostically for more than a century in patients from infancy through late adulthood. The low incidence of AEs and lack of serious AEs, unexpected AEs or negative sequela on measures of mood, cognition or balance in the previous episodic migraine study [43] supports the safety of the time-varying TNM™ therapy. The low incidence of AEs that could potentially be related to device-use in the PD single-site RCT study [1] as well as a cross-over study and two case-studies further exemplify the safety of TNM™ therapy in PD populations. The United States Food and Drug Administration has designated the device to be of non-significant risk for studies of Parkinson's disease (and migraine), and thus suitable for home-use.

Prospective participants will be told that the main purpose of the research will be to generate scientific data and to contribute to medical knowledge, regardless of any benefits to individual participants, and that alternative treatments are available. Prospective participants will be made aware of the existence of two different neurostimulation patterns and that they should not necessarily expect that their symptoms will improve as a result of participating in the trial. They will also be told that participants are expected to provide honest and accurate answers and should not worry about disappointing the staff if they do not feel better during the treatment period, rather the most important thing is to accurately report their symptoms. Potential participants should be made aware that for this research partnership, interactions with study personnel are likely to differ from the interaction they typically experience in the therapeutic partnership they experience in the clinic. More specifically, participants should expect that interactions may be

more neutral and focused on data collection than they may be used to on clinical therapeutic visits.

Recruitment Methods

The study will take place at Wake Forest School of Medicine (WFSM) which is a high-volume PD referral center with an active movement disorder practice. The majority of study participants are expected to be drawn from their patient population. Adults who have been diagnosed with PD and meet inclusion/exclusion criteria will be recruited. In addition to direct recruitment from the Movement Disorder Clinic at WFSM, the trial will also be registered under Fox Trial Finder and clinicaltrials.gov prior to the execution phase. Following IRB approval, flyers will be posted on bulletin boards in the Movement Disorder Clinic at WFSM, as well as throughout the institution. The Translational Data Warehouse will also be used to identify and recruit prospective study participants. Potential candidates from the clinic population may also be sent mailers informing them of the study opportunity and providing contact information (see Recruitment Mailer). It must be emphasized that the main purpose of the research will be to generate scientific data and to contribute to medical knowledge, regardless of any benefits to individual participants, and that alternative treatments are available. Interested patients will then meet a study coordinator and the PI or IRB approved designated site personnel during their visit to review the study details, purpose, procedure, risk, benefits, alternatives to participation, exclusion and inclusion criteria, and an IRB approved-ICF should be provided to the patient. Alternatively, participants may review this material during a virtual visit using Webex or similar approved telemedicine platform.

Informed Consent

A voluntarily signed and dated informed consent, approved by the IRB, will be obtained from each study participant prior to involvement in any study-related activity. If the potential participant is recruited in the clinic, the participant will be given the opportunity to review the informed consent form (ICF) and ask questions relating to its content in a private room. Study staff will verify that potential participants understand the content of the ICF and will witness the signature. Potential study participants should also be afforded the opportunity to take the consent form home, prior to signing, and discuss with family members, as needed. In this case, potential participants will be told to call the phone number listed on the ICF to schedule a remote visit if they decide they are interested in participating and will also be told to hold off on signing the ICF until the remote screening visit. Review, signature and dating the ICF will be the first task completed during the remote screening visit. The PI or designee witnessing the signature should request that the participants hold up the ICF on the video (using a HIPAA compliant platform such as WebEx), and a screen shot will be taken and saved within the study records. Participants will be asked to mail their ICF to the site using a pre-addressed stamped envelope provided by WFU. Potential participants who demonstrate eligibility and are enrolled in the study will be given a copy of the signed consent form at their baseline clinic visit. For screen failures, a copy of the signed consent form will be returned via mail.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify participants, and maintaining all study information in a secure manner. To help ensure participant privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection, participant identifying information will be destroyed 3 years after completion of the study, consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

A data safety monitoring board (DSMB) is not required for this clinical trial. The study will utilize an investigational device designated as non-significant risk (NSR) by the FDA. Scion NeuroStim, will be responsible for conducting clinical trial monitoring. Scion NeuroStim, will appoint a qualified CRA to oversee the progress of the clinical trial, and to ensure that it is conducted, recorded, and reported in accordance with the protocol, SOPs, Good Clinical Practice (GCP), and the applicable regulatory requirement(s). The CRA will be appropriately trained on the study protocol and will be familiar with all study procedures. The designated CRA shall remain blinded to study treatment allocations.

Clinical monitoring will focus on the following key processes of the study to ensure protection of rights and well-being of study participants and the integrity of the data:

- Maintenance of the Investigator Site File (ISF) and required essential documents
- Verification that informed consent was obtained appropriately
- Adherence to protocol eligibility criteria
- Source document verification
- Adherence to treatment plan with procedures for documenting appropriate accountability and administration of the investigational product while ensuring integrity of the randomization process, maintaining the blind, and treatment allocation concealment at the site level
- Protocol compliance and timely documentation of procedures and assessments specifically:
    - Data points/Study end points
    - Protocol-required safety assessments
    - Documenting, evaluating, and reporting Serious Adverse Events (SAEs) and Unanticipated Adverse Device Effects (UADEs) with follow up

To ensure study activities are being performed per the protocol, on-site monitoring visits will be utilized to monitor the clinical site for missing data, data irregularities, protocol deviations/violations, non-compliance, and any other deficiencies identified. Any issues identified, will be documented, evaluated, and escalated to the appropriate level in a timely manner. As soon as the CRA becomes aware of the issue, appropriate corrective and preventative action will be taken and communicated, to the appropriate parties, which may include:

- Device Sponsor management
- Investigational site
- IRB
- FDA, when appropriate

Data Collection and Processing

All data requested on the case report forms (CRFs) are considered required. Data points left blank on the CRF will be queried. If queries are not resolved or data points are not collected, they will be considered protocol deviations unless otherwise specified. The PI must ensure the accuracy and completeness of the reported data and must provide his/her signature and date on the appropriate CRFs. Any changes or corrections to data previously submitted will require a new signature by the PI to acknowledge/approve the changes. The clinical site will be appropriately trained on data collection prior to study start up. On-site data review will be performed to identify potential data discrepancies. Queries will be created and issued to the site for appropriate response. The site staff will be responsible for resolving all queries in the database in a timely manner. The study managers and CRA will be responsible for data verification, validation and quality assurance. The study team shall have exclusive access to the data for the period required to conduct the study, analyze the results and disseminate all findings. Twelve months after study closure, the main study outcomes will be made publicly available on clinicaltrials.gov. An IRB-approved summary of the study results and outcomes will be sent to the study subjects.

Site Communication

The CRA will be the main contact for the clinical site and will correspond with the site study coordinator at least once per month via telephone to discuss milestone progression and convey relevant information from the Device sponsor. The CRA will also prepare an update on participant recruitment, highlight relevant and perhaps unforeseen developments that have occurred and report information to the Device sponsor. The clinical site will be provided with a telephone number on which they can contact the CRA who will respond within 24 hours to urgent inquiries. Device sponsor management will convene a meeting of the entire study team at study start to reconfirm study objectives, protocol and procedure. The clinical site will be visited by the CRA on a regular basis as outlined below.

Monitoring Visits

The CRA will work with the site Principal Investigator (PI) and site study coordinator to schedule on-site monitoring visits. Prior to the visit, the PI will receive a visit confirmation letter, agenda and a list of study items to be monitored. The PI and research staff will be expected to secure a workspace for the CRA and to be available during the visits to facilitate monitoring activities. The CRA will discuss findings and answer questions from the study staff at the end of each monitoring visit day. This is also a good time to discuss any corrective actions that need to be taken.

Types of monitoring visits for this study are listed below.

- Site Initiation Visit (SIV) - conducted prior to site activation to confirm preparedness for protocol execution, satisfactory site facilities, clarify the applicable regulations and requirements of the protocol, carefully review the process of implementing the protocol at the site and conduct any necessary training prior to activating the site for enrollment.
- Interim Monitoring Visits (IMVs) - conducted to confirm participants' rights are being protected; the study is being conducted according to the protocol and applicable regulations, including GCP; confirm accurate reporting of participant safety data and study endpoints.
- For-cause visits (FCVs) - conducted to address any unanticipated issues that arise which require training, remediation or other situations in which the site requires assistance. For-cause visits can be mandated by the Device sponsor or can be requested by the site.
- A Close-Out Visit (COV) - conducted to ensure that all study data and other study documentation is complete and accurate and that all study records have been reconciled.

The CRA will document the monitoring activities and findings for each visit in sufficient detail, and the report will be provided to Device sponsor management for review and follow-up. In addition, the CRA will send the site PI a follow-up letter recapping the visit activities and action items the site must do, or correct, before the next visit. The follow-up letter will become part of the Investigator Site File and the Device Sponsor Trial Master File, and it will be used as a reference in any subsequent monitoring visits.

Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be documented and promptly reported by the principal investigator or designated member of the research team to the IRB and Device sponsor or appropriate government agency if appropriate.

AEs, ADEs, SAEs, SADEs and UADEs will be defined per ISO14155:2011 and/or 21 CFR Part 812, as described below.

Adverse Event (AE):

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device and the procedures involved. For users and other persons, this definition is restricted to events related to the investigational device. AEs will be collected starting from the time the subject signs informed consent until the follow-up period is completed.

Serious Adverse Event (SAE):

A Serious AE (SAE) is an AE that has

a) Led to death,
b) Led to serious deterioration in the health of the subject, that either resulted in

1) A life-threatening illness or injury, or
2) A permanent impairment of a body structure or a body function, or
3) In-patient or prolonged hospitalization, or

4) Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) Led to fetal distress, fetal death or a congenital abnormality or birth defect

Adverse Device Effect (ADE):

An Adverse Device Effect (ADE) is an AE related to the use of an investigational medical device.

This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Traditional, diagnostic CVS has been used for roughly a century, and there are no reports in literature of significant adverse events.

Therapeutic CVS has been studied for use in prevention of episodic migraine and in treatment of symptoms of Parkinson's Disease. Results of these studies (including one multisite RCT and one single-site RCT, respectively), resulted in neither serious nor unanticipated/unexpected adverse events related to the study device. Additionally, there was no reduction in balance and no negative change in either mood or cognition.

The following AEs are known, possible side effects of using the investigational device:

More likely:
- Drowsiness
- Dizziness (whirling or spinning sensation; may also be called "giddiness" or vertigo)
- Treatment site discomfort (skin itching, skin irritation felt within the ear canal or around the ear canal or pressure felt within ear canal)

Less likely:
- Nausea
- Vomiting
- Tinnitus
- Headache

All of the potential AEs noted above are expected to resolve soon after use of the investigational device is stopped.

Serious Adverse Device Effect (SADE):

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Adverse Device Effect (UADE):

An Unanticipated Adverse Device Effect is a *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.

Procedures for AEs

- **Documentation and assessment**
    - Following the informed consent process, clinical study participants will be routinely monitored for AEs at study visits and during telephone contacts from the clinical research staff. All AEs, regardless of treatment group, severity or suspected causal relationship to the investigational device, will be recorded on the participants' source documentation.
    - For all AEs, sufficient information will be obtained as to 1) determine the severity of the event (i.e., whether the event should be classified as "*serious"*); 2) assess the casual relationship between the adverse event and the investigational device; and 3) determine the outcome of the event.
    - AEs will be followed until the event (or its sequelae) resolves or stabilizes at a level acceptable to the investigator and Device sponsor.

- **Causality and Severity assessment**
    - The investigator will promptly review documented AEs to determine 1) if there is a reasonable possibility that the adverse event was caused by the investigational device or other study treatments and 2) if the adverse event meets the criteria for "*serious."*
    - If the investigator's final determination of causality is "of possible or probable relationship to the investigational device or other study treatments," the adverse event will be classified as "*associated with the use of the investigational device or other study treatments"* for reporting purposes and escalated to the Device sponsor for further evaluation. If the investigator's final determination of causality is "*not related* to the investigational device or other study treatments," this determination and the rationale for the determination will be documented.

- **Investigator Reporting AEs to the Sponsor and responsible IRB**
  Reporting to the Sponsor:
    - Adverse events will be submitted to the Sponsor.
    - All serious and/or unanticipated adverse events will be submitted to the sponsor as soon as possible, but in no event later than 10 days after the investigator first learns of the event.
    - All serious and/or unanticipated/unexpected adverse events that involves a death must be reported within **24 hours** of discovery.

  Reporting to the IRB:
    - Investigators are additionally required to submit to their IRB a report of Unanticipated Adverse Device Effect (UADE) as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (21 CFR 812.150(a)(1)). However, if the UADE involves a death, it must be reported within 24 hours of discovery.

      UADEs will require unblinding but written permission must first be obtained by the study sponsor.

- **Sponsor Reporting AEs to the FDA or Competent Authority:**
  Upon receiving a report of a serious or unanticipated adverse device effect (or unexpected serious adverse device event), the Sponsor will immediately conduct an evaluation of the event/effect and report the results as follows:

    - The Sponsor will report the results of an UADE to FDA, reviewing IRB, and participating investigators within 10 working days after the sponsor first receives notice of the effect (21 CFR 812.46[b], 21 CFR 812.150[b][1]). Thereafter, the sponsor shall submit such additional reports concerning the effect, as needed.

    - If the Sponsor determines that an UADE presents an unreasonable risk to participants, the Sponsor shall terminate all investigations or parts of investigations presenting that risk as soon as possible, no later than 5

working days after the sponsor first received notice of the effect.

Device Deficiencies

A device deficiency is an inadequacy of a medical device related to its identity, quality, durability, reliability, safety, or performance, such as malfunction, misuse or use error and inadequate labeling.

All device deficiencies will be documented, and the device should be returned to the device manufacturer for analysis, if possible. Instructions for returning the investigational device will be provided. Device deficiencies should also be documented in the study participant's source documents in the study binder. Device deficiencies are NOT to be reported as AEs. However, if there is an AE that results from a device deficiency, that specific event would be recorded on the appropriate CRF.

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