Protocol

1. Project Title:

A pilot study investigating the effects of vibrotactile stimulation (Not Impossible Vibrohealth) on motor control and symptoms in patients with movement disorders

2. Investigators:

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3. Abstract:

Non-invasive vibrotactile stimulation (VTS) of the skin has long been reported anecdotally to potentially improve motor control and reduce the motor symptoms of patients with movement disorders including Parkinson's disease. Though few rigorously controlled clinical trials have been performed on the effects of VTS, devices that provide VTS have received significant media attention as potential non-medical interventions for movement disorders. In this study, we will test the effect of VTS applied non-invasively to patients with movement disorders to determine if there are any beneficial effects of VTS on common tasks of motor control and/or abnormal motor symptoms in patients with PD, essential tremor (ET), and dystonia.

4. Background:

Movement disorders can be defined as neurologic syndromes in which there is either an excess or paucity of voluntary and/or automatic movements that is not due to weakness or spasticity. A prototypical example is Parkinson's disease (PD), a chronic progressive neurodegenerative disorder characterized by rigidity, bradykinesia, gait and/or postural instability, and resting tremor. [1] The classical PD tremor has a dominant frequency of 3–6Hz and is most often present at rest in the upper extremities of the affected subjects. Other movement disorders include essential tremor (ET, in which tremor is

predominantly present with action) and dystonia (in which tremor is associated with a syndrome of abnormal muscle contractions resulting in involuntary movements and postures). Although medical and surgical therapies are available for the symptomatic treatment of these movement disorders, current treatment options can produce significant side effects and often provide incomplete benefit for the motor symptoms of these diseases. Therefore, continued investigation of new potential treatment options is an important priority.

The application of external non-invasive vibrotactile stimulation (VTS) of the skin as a therapeutic intervention for movement disorders has been of interest since the 19th century, when Jean-Martin Charcot anecdotally observed a relief of symptoms following the use of a vibrating chair in patients with PD. [2] Since then, whole body vibrating massage has been investigated as a potential means to reduce the symptoms of PD, however results have been inconsistent. [3-7] Similarly, devices that provide VTS have been investigated in small studies for the amelioration of symptoms of essential tremor and dystonia, with only limited conclusions possible to date due to sample size and study design limitations. [8,9]

At the current time, it is estimated that at least 1 in 5 adults use at least one wearable health-related technology, and wearable devices intended to track the symptoms of PD [10] are already in clinical use. Wearable devices that provide VTS (such as the as the Vibrohealth system recently developed by Not Impossible Labs, https://www.youtube.com/watch?v=G7T53xN1IqI) have received significant attention in the lay press and within patient support groups. As more and more wearable devices (which may be marketed directly to patients) are developed, it will be critically important for academic clinical researchers to participate in testing the efficacy of these devices in rigorous clinical trials. This need for independent study has been recognized by the Parkinson's Foundation (PF), which has selected the University of Florida as a research site tasked with determining the optimal device settings and testing the Not Impossible Vibrohealth system as an adjunctive therapy for movement disorders. We will accomplish this through the following specific aims.

5. Specific Aims:

Specific Aim. Evaluate the feasibility, reliability, and clinical effects of VTS on basic tasks of motor control and on the motor symptoms of patients with movement disorders.

Hypothesis: VTS will produce beneficial effects on basic tasks of motor control and abnormal motor symptoms in patients with movement disorders. VTS Settings will include continuous stimulation between 60-120 Hz, intermittent stimulation at ½ baseline step frequency during walking, and sham stimulation (2 seconds of 30 Hz stimulation only at stimulation onset).

6. Research Plan:

6.1 Design Overview:

This cross-sectional pilot study aims to identify the optimal device settings and preliminarily test the efficacy of the Not Impossible VibroHealth device in improving basic measure of motor control and symptoms in patients with PD and other movement disorders in the off-medication state. After informed consent, screening, and recruitment, the effects of VTS will be evaluated on basic tests of motor control and common movement disorders symptoms.

6.2 Participants:

We will recruit 30 patients with PD who are between the ages of 18-80 years old and independently living in the community. Will additionally recruit up to 5 patients with ET and up to 5 patients with dystonia. To account for screening failures or patients who cannot tolerate the sensory stimulation, we anticipate screening and consenting ~50 individuals.

6.3 Recruitment:

Recruitment will occur exclusively through the UF movement disorders program at the Fixel Institute for Neurological Diseases at UF Health. We expect to recruit patients prior to and during routine scheduled clinic visits with e-consenting (electronic informed consent).

6.4 Inclusion/Exclusion Criteria:

6.4a. Inclusion criteria:

- Age 18-80 and able to provide informed consent.
- Have a diagnosis of Parkinson's disease, essential tremor, or cervical dystonia made by a movement disorders specialist.
- Medically optimized without planned medication changes for the duration of the study.
- For patients with ET, they will have a score of at least 2 on items 5 and 6 of the Fahn-Tolosa-Marin (FTM) Tremor Rating Scale.
- For patients with dystonia, they will have abnormal dystonic postures of the head and not isolated head tremor

6.4b. Exclusion criteria:

- The presence of additional neurologic diseases, that might confound testing or the coexistence of PD and ET together (action tremor that was present prior to the development of parkinsonism).
- Symptoms of peripheral neuropathy at the wrist (reduced vibratory, pinprick, or temperature sensation)
- Montreal cognitive assessment (MoCA) score < 20 or previously documented dementia
- Unable to walk without a walking aid (e.g. cane, stick, walker)

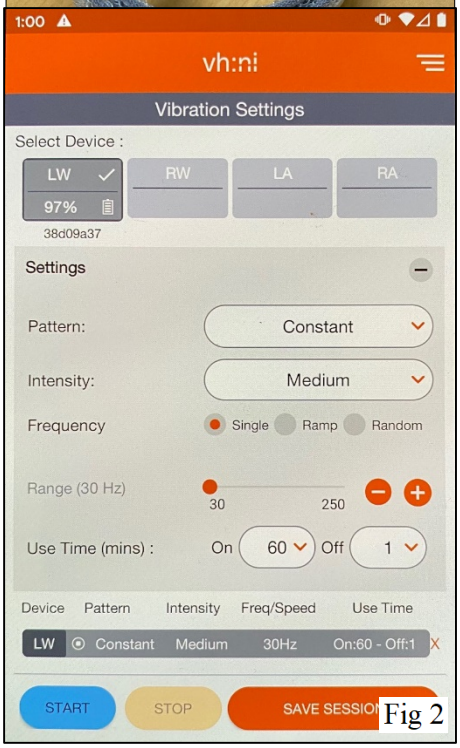

Fig 2

6.5 Device Description and Previous Studies

The Vibrohealth system consists of 4 vibrating devices on bands and a magnetic contact charger (**Figure 1**). The devices are paired with a cell phone application (to be used solely by research investigators) that adjusts the parameters of vibratory stimulation during research visits (**Figure 2**).

The device consists of an actuator/sensor that, when placed against the surface of the skin, produces a vibrotactile sensation (vibration) through rapid lateral (side to side) motion. The intensity of the vibration produced by the Vibrohealth device is far less than that produced by commercially available massagers that provide vibratory stimulation for relaxation using similar technology. The sensor in the device is a tri-axial accelerometer and gyroscope that measures position using the same technology as smartphones.

A previous version of the Vibrohealth device was evaluated in 2017-2018 on 52 patients with PD and resting tremor at the Mount Sinai Hospital in New York City in a study funded by the device developer (Not Impossible). The Vibrohealth device was deemed a nonsignificant risk device and was approved by full board IRB review (IRB #17-00555). There were no adverse events in any subjects receiving VTS. However, the stimulation setting intended to serve as a sham control setting (low amplitude continuous vibration) appeared to reduce resting tremor in approximately 60% of patients, suggesting that the vibration settings used in the protocol were inadequately investigated prior to study design. Though this study is being prepared for publication by the authors at Mount Sinai Hospital as a safety and feasibility study, the Parkinson

Foundation has decided to fund further pilot testing to ensure that any future clinical trials aimed at testing the efficacy of VTS are planned appropriately. We have tested the Vibrohealth device on 7 patients during our initial pilot testing since IRB approval without any adverse events.

6.6 Screening/Baseline Interview and Measures:

Recruitment will be conducted at the UF Health Fixel Institute for Neurological Diseases via pre-review of outpatient appointments, review of the IRB approved movement disorders database, and during standard of care (SOC) visits. Clinic providers involved with the research study who provide clinical care/intervention for treatment may also discuss the protocol/research with their patient. If participants are identified through pre-review of outpatient records/lists/appointments, providers associated with clinical care for the subject will be notified of the subject's potential availability. No other information will be collected during the pre-screening process. The provider will then mention the study to the patient, if appropriate. When interested, subjects will either contact us about the study or the clinic providers will notify study coordinators of participant interest.

Study personnel will tell the potential participants about the study. The study personnel will consist of the investigators (UF faculty), staff study coordinators, and clinical movement disorders fellows. All study coordinators will be appropriately trained to meet HIPPA and IRB requirements. The pre-screening of records will only be carried out by study coordinators who already have approved EPIC medical record access.
Patients will also be identified using the Fixel Institute for Neurological Diseases patient database (Quantifying Deficits in Patients with Movement Disorders). Patients who have provided informed consent to have their medical information stored in the database and have indicated that they would like to be contacted about future research studies may be contacted (IRB201501166). Potential participants will be identified using database queries including diagnosis, age, location, most recent UPDRS, and most recent clinical visit. These identified potential participants will then be contacted by study coordinators to inform and invite them to participate in this research study.

Once a potential participant's interest in participating in the study is established, the study personnel will read from an approved telephone script to provide details about the study and the inclusion and exclusion criteria. If potential participants are still interested and are eligible to participate in the study, they will then be scheduled for an e-consenting appointment.

6.7 Duration of Study and Overview of Procedures and Protocol:

Testing will occur over the course of a single day at the Fixel Institute for Neurological Diseases. Similar to new patient clinical evaluations, subjects will be instructed to withhold any PD, ET, or dystonia medications for 12 hours prior to testing. The study visit will last up to 4 hours and will include a variety of motor tasks and clinical tests (described in detail below) both on and off VTS. For Parkinson's disease and essential tremor patients, the devices will be worn on the wrist and/or ankles. For patients with dystonia, the devices will be adhered to the skin of the neck using medical grade double sided tape and a latex medical wrap. Patients with PD will undergo a more comprehensive testing evaluation, while patients with ET or dystonia will undergo a brief, more focused evaluation. Subject responses will not be compared across diseases given the preliminary nature of the research and analysis. Outcomes to be measures are described below in the order that they will be tested for each individual subject group (PD, ET, dystonia).

Baseline testing:

MDS-UPDRS: Select measures from the motor section of the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRs). [11] The MDS-UPDRS is a revision of the Unified Parkinson's Disease Rating Scale (UPDRS) originally developed in the 1980s. The scale is used in the clinic as well as in research to measure PD symptom severity. Individual measures are rated as 0 (normal) to 4 (severe).

Montreal Cognitive Assessment (MoCA): The MoCA is a cognitive screening test designed to assist Health Professionals in the detection of mild cognitive impairment and dementia. It will be used to exclude patients with cognitive impairment significant enough to confound the research variables of interest.

6.7a: Outcomes to be measured in subjects with PD:

Quantitative Tremor Assessment: An external accelerometer (Delsys Trigno; https://delsys.com/trigno/) will be adhered to the skin of the dorsum of the hand and will be used to quantify displacement of the hand due to tremor in the settings listed below. Delsys Trigno sensors have been used in multiple prior UF IRB approved studies and is FDA and CE registered with FCC ID, and is certified IEC601-1 (General Requirements for Medical Devices) and IEC601-1-2 (electromagnetic compatibility requirements for Medical Devices) with a UL recognized Internal Battery.

- 1. Sitting at rest
- 2. Sitting with both arms outstretched
- 3. Sitting at rest while performing a distracting cognitive task (reciting the months of the year backwards)
- 4. Transition from rest to posture (arms held directly in front of patient) for 10 seconds

Kinesia One accelerometer: The following select measures of MDS-UPDRS Part III: Motor Examination will be repeated before and during VTS:

3.4 Finger tapping
3.5 Hand movements
3.6 Rapid alternating movements (pronation-supination of the hands)

These measures will be quantified using the Kinesia one accelerometer system (http://glneurotech.com/kinesia/products/kinesia-one/), which uses a propriety algorithm

to calculate a severity score on a 0-4 scale that has been shown to highly correlate with clinician ratings. The Kinesia one system has been used in multiple prior UF IRB approved studies and is FDA cleared to market and CE marked. The device is placed on the index finger during testing and senses movement.

Reaction time task: Subjects will look at a central fixation symbol on computer screen and press a computer keyboard/mouse button when the GO signal appears. The time between the onset of the fixation cross and the green GO signal will vary so that the onset of the GO signal will not be predictable. The time between appearance of the GO signal and recorded keyboard response will be recorded as reaction time. [13]

Functional Dexterity Task (FDT): The FDT is a pegboard assessment of manual dexterity. It is a square pegboard with 16 holes and 16 pegs. Using a stopwatch, the examiner measures the time that it takes for the subject to turn over all the pegs on the board, as quickly as possible, using one hand at a time. A 5-s penalty is added every time the subject supinates or touches the board for assistance, while a 10-s penalty is added if the subject drops a peg. Two scores are obtained: the net time (in seconds) quantifies the speed of the hand dexterity; the total score (time plus penalties) quantifies the quality of the performance. The test ends when both hands have completed the task and the total score for each hand determines the functional level.

Timed-up-and-go (TUG) gait task: Subjects are asked to stand up from a chair, walk 3 meters to a horizontal line marked with red tape on the floor, turn around, walk back and sit down, at a comfortable pace. [12] Two outcome assessments will be used during the TUG task. After obtaining video consent during the informed consent process, we will videotape the TUG test which will be scored by a blinded rater for number of freezing episodes and TUG completion time in seconds. The TUG task will be performed on the instrumented GAITRite mat (https://www.gaitrite.com/) which is located in the clinic and is routinely used for clinical care. The GAITRite mat measures and records spatiotemporal components of gait including stride length, regularity, cadence, left-sided step length,

right-sided step length, velocity, and an overall functional ambulation score. The GAITRite mat is FDA registered, CE Certified and ISO standard compliant.

Clinical Global Impression (CGI-I) Scale: The Clinical Global Impression-Improvement (CGI) scale was developed for use in NIMH-sponsored clinical trials. [14] It is a 7-point scale that requires the clinician to assess how much a specific symptom has improved or worsened relative to a baseline state prior to an intervention.

6.7b: Outcomes to be measured in subjects with ET:

FTM-TRS: Select measures from the Fahn-Tolosa-Marin Tremor Rating Scale (FTM-TRS). [15] The FTM-TRS is the most commonly used rating scale in clinical trials of essential tremor. It rates tremor on a scale of 0 (no tremor) to 4 (severe). Select measures of FTM-TRS to be tested are as follows:

5. right upper extremity tremor (rest, posture, action):
6. left upper extremity tremor (rest, posture, action):
10. Handwriting
22. Spiral drawing

Clinical Global Impression (CGI-I) Scale: as described above in PD section.

6.7c: Outcomes to be measured in subjects with dystonia:

TWSTRS: Select measures from the motor section of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). [16] The TWSTRS is the most commonly used rating scale to rate dystonia severity in patients with cervical dystonia. Ratings vary depending on the individual questions. Select measures of the TWSTRS section A to be tested are as follows:

1. Rotation
2. Laterocolis

3. Anterocollis/retrocollis
4. Lateral shift
5. Sagittal shift

Clinical Global Impression (CGI-I) Scale: as described above in PD section.

7. Outcome and Statistical Approaches:

For essential tremor and dystonia, the aims of this unblinded pilot study are to identify the optimal settings of VTS that are most promising to be tested in future clinical trials, statistical analysis will be limited to basic measures of central tendency. We will compare scores and values on the individual outcome measures listed above both on and off VTS, and within disease group means for each measure will be used to help guide the choice of settings to be tested in future studies. This pilot study will not be powered for between disease groups analysis or to test the efficacy of VTS for ET, or dystonia.

For Parkinson's disease, we expect to have data sufficient to justify exploratory statistical analysis. We have estimated that the number of patients included will allow for statistical analysis of patient's task performance before and during VTS. This was based on a medium effect size (cohen's d = 0.50) for the comparison of tremor power during VTS versus baseline. With an alpha of 0.05 and power of 0.80, the required sample size is 27 (based on a one-sided paired sample t-test). Thus, by recruiting 30 participants with PD, our sample size will give us sufficient statistical power to detect an effect with medium effect size. Statistical analysis will consist of a repeated measures ANOVA on the change in tasks performance scores relative to baseline. All post-hoc analyses will be corrected for multiple comparisons using Bonferroni correction.

8. Methodological Limitations and Potential Challenges:

Potential challenges that may occur during the study include subject discontinuation prior to completion of data collection due to boredom or irritation of the skin from vibration. Partial collected data will still be useful in helping to guide the choice of simulation

parameters in future clinical trials to test the potential of VTS as an adjunctive therapy to improve motor control or reduce the symptoms of PD, ET, or dystonia.

9. Data Management Plan:

All data (including videos) collected from subjects will be stored in encrypted computer files with secure passwords. All data entered into such electronic storage files will be assigned subject ID numbers that are de-identified to ensure that all information is protected. Data will be kept in a password protected encrypted database which can only be accessed by the investigator and their staff. All data and assessments will be under the direction of the Co-PI's who will supervise research coordinators and assistants. Subject numbers will be assigned consecutively as follows:

Subjects with PD: PD1, PD2, etc. to PD30
Subjects with ET: ET1, ET2, etc. to ET5
Subjects with dystonia: DYT1, DTY2, DYT3, etc. to DYT5

De-identified data may be compared with data collected by other testing sites funded by the Parkinson's Foundation. No data that includes any HIPAA identifiers will be available to Not Impossible or to other research groups or anyone outside of the study researchers and coordinators noted in this protocol.

10. Possible Discomforts and Risks:

In general, the risks are minimal for individuals who participate in this study. As the intensity of the vibration produced by the Vibrohealth device is far less than that which is produced by commercially available massagers that provide vibratory stimulation to the body, the incidence and severity of any adverse effects is expected to be limited, and no adverse events occurred in a previous trial using the Vibrohealth device in over 50 patients with PD and in our pilot testing at UF of 8 subjects. With regard to discomforts and risks, first the VTS stimulation could be annoying or unpleasant, and there is the possibility of minor skin irritation at the site where the wearable devices are placed.

Second, subjects will be asked to come to testing sessions OFF medications (as is done during standard-of-care initial clinic visits) in order to reduce confounding effects of medications, which could be temporarily uncomfortable. Third, patients may also find the tasks and scales tedious or boring. To minimize fatigue associated with completion of screening and tasks, subjects will be allowed to take frequent breaks to rest as needed. Patients will have the option of discontinuing testing at any time, and data that is partially collected may still be useful given the preliminary nature of the study. Though unlikely, it is possible skin irritation might persist outside of the testing period. Should this occur, the patient would be instructed to seek routine medical care. It is also possible that there are unknown risks for participating in this study.

11. Possible Benefits:

It is possible that VTS might temporarily improve tasks of motor control or reduce movement disorders symptoms. Subjects will also have the satisfaction of knowing that they are helping to test wearable devices that may have potential as adjunctive therapies for movement disorders in a controlled unbiased setting.

12. Conflict of Interest:

The study investigators have no conflicts of interest.

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