# Influence of Whole Body Vibration on Neuromodulation of Ankle Muscles in Persons with SCI

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**Document History**

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**Statement of Compliance**

This study will be carried out in accordance with Good Clinical Practice (GCP) as required by the United States Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312).

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Principal Investigator Signature Date

Edelle Field-Fote, PT, PhD, FAPTA \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

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**Table of Contents**

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1. Introduction
2. Study Aims
3. Study Design
4. Adverse Events
5. Data Management
6. Statistical Considerations
7. Ethical, Regulatory, and Administrative Considerations
8. Study Medication/Device/Intervention
9. References

### Introduction

Impairment of lower extremity volitional control following motor-incomplete spinal cord injury (SCI) has negative consequences for function, such as limited walking ability and poor balance.[1] Both deficits contribute to reduced quality of life.[2] In addition to the impairment of volitional motor output, SCI results in inadequate modulation of involuntary motor output, giving rise to spasticity.[3] Spasticity is associated with uncontrollable muscle contractions and stiffness,[4] and adds to the paresis-related impairment of volitional motor control. In fact, the spastic gait pattern that is common in persons with upper motor neuron disorders, is characterized by hyperreflexia of the plantar flexors at terminal stance.[5] This, combined with impaired volitional control of dorsiflexors during swing phase, results in poor toe clearance during walking and increases fall risk.

The mechanisms underlying spastic gait, disrupted dorsiflexor activation after corticospinal tract (CST) damage and hyperreflexive plantar flexors, provide targets for intervention. Afferent stimulation has been shown to impact spinal as well as corticospinal excitability. To decrease the negative consequences of spastic gait, afferent stimulation has been used in conjunction with rehabilitation.[6] A previous study in our lab demonstrated that afferent stimulation was associated with plasticity of corticomotor circuits controlling the upper extremity.[7] There is also evidence that afferent stimulation modulates spinal reflex activity.[8] A *gap* in knowledge, which is of great importance to address for the development of rehabilitation strategies, is whether diminished descending volitional drive or impairment of reflex modulation contributes more to spastic gait.

A small study from our lab assessed the impact of operant conditioning to either increase volitional dorsiflexor activation or to decrease plantar flexor reflex activity in persons with SCI.[9] Both groups improved, however, while the sample size was insufficient to identify between-groups differences, the group trained to increase volitional activation of the dorsiflexors exhibited larger effect sizes for walking outcomes. Notably, the effects on plantar flexor reflex modulation were also larger in the dorsiflexor activation group. This proposal is *innovative* because there has yet to be a study to examine how an intervention that targets the CST and spinal reflex circuits (SRC), simultaneously, impacts the different components of spastic gait after SCI.

To improve therapeutic outcomes in people with spastic gait, it is critical to understand the roles of the CST and SRC on functional outcomes related to ankle control and spasticity. In the current proposal we will build upon previous results using an intervention that is a potent activator of both spinal and supraspinal targets. Whole body vibration (WBV) is a robust form of afferent input that modulates the excitability of both the CST and SRC.[10] Therefore, the main question of the current proposal is whether changes in ankle control and spasticity after robust afferent stimulation are due more to corticospinal drive to the tibialis anterior (TA) or reflex modulation of the soleus (SOL). We predict that because corticospinal drive to the TA can also impact the SOL SRC, changes in the CST excitability to the TA will have a greater contribution to ankle functional measures than SOL SRC modulation alone. We also expect that there will be a significant increase in dorsiflexion during walking and reduced plantar flexor spasticity after WBV. This proposal will support future research to further improve spastic gait after upper motor neuron damage.

**2.0 Study Aims**

**Aim 1: Determine the contribution of TA CST and SOL SRC excitability to ankle volitional control after a single session of WBV in individuals with SCI.** Training activities for Aim 1 include: learning data acquisition, processing and analysis related to electrophysiological assessments of CST excitability using transcranial magnetic stimulation (TMS), spinal reflex excitability using Hoffmann [H]-reflex testing, and kinematic assessments using 3D inertial sensors.

**H1.1.** *WBV will improve volitional control of the ankle dorsiflexor muscles as evidenced by increased dorsiflexion during over ground stepping, increased dorsiflexor isometric force generation, and improved performance on an ankle control task.*

**H1.2*.*** *Changes in CST excitability to the TA will have a greater contribution to* *improvements in volitional ankle control than changes in SRC modulation in the SOL*.

**Aim 2: Determine the contribution of TA CST and SOL SRC excitability to ankle spasticity after a single session of WBV in individuals with SCI.** Training activities for Aim 2 will build on the data acquisition, processing and analysis from Aim 1, with additional training in the acquisition of biomechanical measures of ankle clonus using the clonus drop test protocol.

**H2.1.** *WBV will decrease plantar flexors spastic reflex activity as measured by biomechanical assessment of ankle angle at toe off during gait, and by the plantar flexor reflex threshold of the clonus drop test.*

**H2.2.** *Changes in CST excitability to the TA will have a greater contribution to* *decreases in ankle spasticity than changes in SRC modulation in the SOL*.

**3.0 Study Design**

**3.1 Definitions**

AMT: active motor threshold

CST: corticospinal tract

EMG: electromyography

LFD: low frequency depression

MEP: motor evoked potential

MSO: maximum stimulator output

MVC: maximum voluntary contraction

PF RTA: plantar flexor reflex threshold angle

SCATS: spinal cord assessment tool for spastic reflexes

SOL: soleus

SRC: spinal reflex circuit

TA: tibialis anterior

TMS: transcranial magnetic stimulation

WBV: whole body vibration

**3.2 General Selection Criteria**

**3.2.1. Inclusion Criteria:** Potential participants must meet all the following criteria to be eligible for the study:

* Be 18-85 years of age
* Be able to provide a letter of medical clearance for participation, if 70-85 years of age
* Have SCI level of T12 or above occurring more than 6 months ago
* Have motor-incomplete severity classification (AIS C or D)
* Have self-reported spasticity in at least one ankle
* Have a score of at least 2 on the SCATS clonus test in at least one ankle
* Ability to voluntarily move at least one ankle
* Ability to stand and take at least 4 steps with or without assistive devices
* Ability to follow multiple step commands
* Ability to communicate pain or discomfort
* Ability and willingness to consent to participate in the study and authorize use of protected health information.

**3.2.2 Exclusion Criteria:** Potential participants will be excluded from the study if they meet any of the following criteria.

* Implanted metallic device in the head and/ or pacemaker
* Use of ankle-foot orthoses
* History of seizures
* History of frequent and/ or severe headaches
* Prior tendon or nerve transfer surgery
* Current pregnancy
* Inability or unwillingness to consent and Authorization for use of PHI
* Progressive or potentially progressive spinal lesions, including degenerative, or progressive vascular disorders of the spine and/or spinal cord
* Neurologic level below spinal level T12
* History of cardiovascular irregularities
* Problems with following instructions
* Orthopedic problems that would limit your participation in the protocol (e.g. knee or hip flexion contractures of greater than 10 degrees).
* Active infection of any type, as infection may exacerbate spasticity resulting in inability to identify the influence of the treatment

**3.2.3 Special Considerations for Inclusion of Elderly Individuals**

Rationale: In compliance with the revised NIH Inclusion Across the Lifespan policy, the inclusion criteria has been expanded to include individuals from 18-85 years of age. As supported in Shenoy and Harugeri (2015), it is important to include advanced geriatric aged participants in the current study for the following reasons:

* To address the under-representation of this population in clinical trials on studies of neuromodulation.
* To avoid discrimination and ensure that the study is fair and equitable across a diverse background of participants.
* Though it will be likely rare for advanced geriatric aged persons to participate in this study, it is important to have evidence of how neuromodulation impacts this age group to ensure best practice.

Safety: The study will include contact guard precautions facilitated by a trained clinician during upright mobility activities to reduce fall risk. The current study selection criteria will require participants to be able to follow commands and communicate pain or discomfort. The abovementioned criteria will also prohibit persons with progressive or potentially progressive spinal lesions, cardiovascular irregularities, problems with following instructions, orthopedic problems that would eliminate ability to participate in protocol, and active infections from being able to participate in the study.

In order to ensure that advanced geriatric aged participants can safely participate in the study, a letter of medical clearance must be provided if participants are 70 years of age or older.

**3.3 Procedures**

**3.3.1 Study Design**

This is a cross over design study consisting of WBV and sham-electrical conditions. The study takes place over the course of **2** or **4** different days, depending on participant availability. On each of the study days there will be **1** or **2** sessions, with a total of 4 sessions. If participating in the study for 2 days, there will be 2 sessions per day (**Table 1**). If participating in the study for 4 days, there will be 1 session per day (**Table 2**). Each study session lasts approximately 3 hours bringing the total time of study participation to 12 hours. If participating in the 2-day study option, there is a 1-hour lunch break in between sessions. The days in which the sessions fall are flexible, but there should be no more than 1 week between study days, in order to decrease variability across sessions. Electrophysiological and functional measurements will be assessed pre-and post-intervention. All participants will receive the neurophysiological testing types in a randomized order (**Tables 1 & 2**). The WBV session will consist of 8 bouts of 45s vibration (50Hz) with a minute of rest in between each bout. We chose this parameter, because in the first phase of our current R01 study this dose resulted in the greatest decrease in spasticity.[11] The participants will stand on the vibration platform in a squat position with the knees flexed approximately 30 degrees while holding the hand rails during the vibration. During the 1-minute rest period, the participants will be seated. The sham intervention serves to account for any effects of standing and/or of repeated performance of the sit-to-stand behavior on neurophysiological outcomes. In the sham intervention participants will receive sham electrical stimulation (ES) while standing on the vibration platform for 8 bouts for 45s with a minute of rest in between without vibration.[11]

|  |  |  |
| --- | --- | --- |
| **2-Day Option** | | |
|  | AM Session | PM Session |
| **Group 1** | | |
| Day 1 | CST/ES/CST | CST/WBV/CST |
| Day 2 | SRC/ES/SRC | SRC/WBV/SRC |
| **Group 2** | | |
| Day 1 | SRC/ES/SRC | SRC/WBV/SRC |
| Day 2 | CST/ES/CST | CST/WBV/CST |

**Table 1: Testing Order for 2-Day Option.** Group 1 and Group 2 control for order effects of neurophysiological testing. The 4 sessions will occur over the course of 2 testing days.

|  |  |  |
| --- | --- | --- |
| **(2-day option)** | AM Session | PM Session |
| Group 1 | | |
| Day 1 | CST/ES/CST | CST/WBV/CST |
| Day 2 | SRC/ES/SRC | SRC/WBV/SRC |
| Group 2 | | |
| Day 1 | SRC/ES/SRC | SRC/WBV/SRC |
| Day 2 | CST/ES/CST | CST/WBV/CST |

**Table 1: Session Randomization.** Group 1 and Group 2 control for order effects of neurophysiological testing.

|  |  |  |
| --- | --- | --- |
| **4-Day Option** | | |
| **Group 1** | | |
| Days 1&2 | (Day 1) CST/ES/CST | (Day 2) CST/WBV/CST |
| Days 3&4 | (Day 3) SRC/ES/SRC | (Day 4) SRC/WBV/SRC |
| **Group 2** | | |
| Day 1&2 | (Day 1) SRC/ES/SRC | (Day 2) SRC/WBV/SRC |
| Day 3&4 | (Day 3) CST/ES/CST | (Day 4) CST/WBV/CST |

**Table 2: Testing Order for 4-Day Option.** Group 1 and Group 2 control for order effects of neurophysiological testing. The 4 sessions will occur over the course of 4 testing days.

|  |  |  |
| --- | --- | --- |
| **(4-day option)** |  |  |
| Group 1 | | |
| Days 1&2 | (Day 1) CST/ES/CST | (Day 2) CST/WBV/CST |
| Days 3&4 | (Day 3) SRC/ES/SRC | (Day 4) SRC/WBV/SRC |
| Group 2 | | |
| Day 1&2 | (Day 1) SRC/ES/SRC | (Day 2) SRC/WBV/SRC |
| Day 3&4 | (Day 3) CST/ES/CST | (Day 4) CST/WBV/CST |

**Table 2: Session Randomization.** Group 1 and Group 2 control for order effects of neurophysiological testing.

**3.3.2 Schedule of Events**

**Screening, consent and enrollment.** Study staff will meet with prospective participants to explain study details and screen participants to determine whether they meet eligibility criteria. Once eligibility and desire to participate in the study has been confirmed, informed consent will be obtained from the participants by a member of the investigative team authorized to consent for this study. The conversation is expected to include a thorough discussion of what is expected to happen during the study, risks and benefits of study participation, and any possible alternatives. Subjects will be given sufficient time to review the documents and ask questions. All participants will be informed that their involvement in the study is voluntary and that they may withdraw at any time while their medical care will not be affected by their decision on whether or not to participate. If they decide to participate, they will then sign the informed consent document and a copy will be given to them. After the participant has given consent, a trained clinician on our study staff will perform the SCATS clonus test on each ankle to determine if they are eligible to continue with the study. To be enrolled the participant must have a score of at least 2 on the SCATS clonus test in at least one of their ankles. Upon enrollment in the study, demographic characteristics and medical history of the participant will also be obtained.

All the participants will complete 4 testing sessions for the purpose of this study.

**Testing Procedures**

Neurophysiological and functional testing will be conducted before and after each intervention (**Figure 1**). All neurophysiological tests will be conducted with the participants in a seated or supine position.



**Figure 1: Study procedure.** We will determine the effects of WBV on neurophysiological and functionally-relevant measures by testing LFD, MEP, ankle volitional control and spasticity before (pre-) and after (post-) the WBV and sham interventions. The WBV intervention will consist of 8 bouts of 45s vibration (50Hz, 4mm) with a minute of rest in between. The sham intervention will consist of sham electrical stimulation and the same standing and sitting procedure as WBV, without vibration.

***Questions.*** Before any study procedures, participants will answer a brief series of questions to determine if they should not participate in corticospinal excitability testing (Cortical Stimulation Safety Screen). On one testing day, they will also answer a series of questions about how their spasticity affects their daily life from the Spinal Cord Injury Spasticity Evaluation Tool (SCI-SET).

***Corticospinal excitability*** will be measured before and after each single-session intervention. To measure corticospinal excitability, we will elicit MEP in the TA using TMS over the primary motor cortex (M1). The MEPs will be induced using a Magstim 200 stimulator (The Magstim Company Ltd., Whitland, UK). A double cone TMS coil will be placed over Cz, the anatomical area of M1 that corresponds with lower extremity corticomotor representation. A magnetic pulse will be triggered to elicit an electrical response in the targeted motor areas. Recording electrodes will be placed, in a standardized location over the TA and SOL muscles to record MEPs.

During the pre-intervention period an active recruitment curve will be obtained by increasing the intensity of the TMS stimulation by intervals of 10% maximal stimulator output (MSO); starting at 40% MSO and increasing to 100% MSO while the participant is seated with their ankle dorsiflexed (TA) at 10-15% of their maximal volitional contraction (MVC) which will be monitored by background electromyography (EMG).[12] Five recordings at each MSO intensity will be obtained with 5 seconds of rest in between. From these recordings an active motor threshold (AMT) will be determined as the percent MSO at which 50% of stimuli are above 50µV peak to peak amplitude after baseline EMG subtraction. After we determine the AMT we will elicit 20 stimulations at 120% of the AMT and average the peak-to-peak amplitudes of the TA MEP. During the post-intervention test we will administer only 20 stimulations at 120% of the AMT and compare the average peak-to-peak amplitudes with the pre-intervention values. Because it can be difficult to evoke MEPS in persons with SCI, we expect that for some individuals, stimulation at 120% AMT will be above the maximum output of our TMS device. In such instances, we will acquire 20 stimuli at 100% MSO. An increase in the average peak-to-peak amplitude would indicate increased corticospinal excitability to the TA muscle. We do not expect to observe a change in SOL CST excitability.

The hyperexcitability of the ***spinal stretch reflex circuit*** will be tested by measuring modulation of the H-reflex, which is the electrical analog to the monosynaptic stretch reflex.[13]The H-reflex is induced by electrically stimulating Ia sensory nerve afferents, which activates motoneurons in the spinal cord to induce a muscle twitch. Although the H-reflex cannot readily distinguish between the contributions of other afferent pathways (i.e. group II) that are known to contribute to exaggerated stretch reflex, it has been frequently used to measure hyperreflexia in persons with spasticity. Since the purpose of this study is to distinguish the contributions of exaggerated stretch reflex and CST descending drive on spastic gait, the H-reflex is a good fit for the current proposal.

The component of SRC excitability being assessed in the current proposal is presynaptic inhibition of the Ia circuit. We selected this approach because impaired inhibition of the Ia circuit is strongly implicated in spasticity. We can assess changes in Ia presynaptic inhibition by testing homosynaptic/ low frequency depression (LFD).[13–15] LFD is a good test for the assessment of presynaptic inhibition because there is evidence that change in LFD is due to changes in supraspinal presynaptic inhibition.[15] Pre-intervention, we will record a recruitment curve of H-wave and M-wave values by placing stimulating electrodes over the posterior tibial nerve and recording electrodes over the muscle belly of the SOL. Based on these values we will determine a stimulus intensity that will elicit an H-wave at 15-20% of Mmax. We will use paired-pulse stimulation (1s interstimulus intervals (ISI); 10 trials with 10s rest between trials) at this intensity to assess LFD before and after the intervention.[9, 15] As a control, we will also administer the paired-pulse stimulation at 10s ISI. An increase in LFD could be indicative of increased presynaptic inhibition.

A ***toe tapping task*** will be administered in which subjects will be seated with their foot positioned on a pressure sensitive switch embedded in a platform.[9] The subject will be asked to perform the toe tapping task, wherein they will voluntarily contract and relax the dorsiflexors as quickly as possible for 10s for 4 trials with a 60s rest in between. The mean number of taps in the best 3 trials will be calculated. A higher number of taps would be indicative of increased ankle motor control.

***Dorsiflexion during swing phase*** will be measured during 3, 10-meter walking tests. Using the inertial based motion tracking system (XSENS), we will be able to record bilateral ankle joint angles during swing phase. The average angle will be compared before and after each intervention.[12] An increased dorsiflexion angle during swing phase would be indicative of less toe drag/foot drop and increased ankle motor control.

***Maximal Volitional Contraction (MVC)*** of the TA will be averaged across 3, 3s trials, pre- and post-intervention. Participants will be asked to maximally dorsiflex their ankles against a dynamometer on a fixed frame. Increased MVC are associated with increased ankle strength.

**Plantar flexor Spasticity.** To measure the effects of WBV on SOL spasticity we will administer the ankle clonus/drop test.[16] During the test participants will be in a seated position with their knees at a 90 + 10-degree angle. The ball of the foot being tested will be placed on the edge of a 10cm high platform and the horizontal arm of an adjustable T-bar will be positioned 10cm above the knee. The leg will be grasped below the knee joint and lifted until the knee contacts the T-bar. The leg will then be released allowing the foot to strike the platform to induce a rapid plantar flexor stretch. Ankle angle will be recorded using an inertial based motion tracking system (XSENS). The angle at which clonus is elicited, plantar flexor reflex threshold angle (PF RTA), will be recorded. A decrease in plantar flexor spasticity will be indicated by a decrease in PF RTA. We will administer the ankle clonus test 3 times per ankle before and after both interventions.

**Biomechanical assessment of ankle angle at toe off during gait** will be captured during the 3, 10 meter walk tests before and after the intervention. The angle of both ankles at toe off will be measured using XSENS. The average angle will be compared before and after the interventions. Increased plantar flexor angle at toe off will be indicative of increased gait function.

**Heart rate and %SpO2.** To control for any cardiovascular changes, we will be capturing heart rate and %SpO2 using a finger pulse oximeter, before and after each intervention.

**3.3.3 Laboratories**

The Hulse Spinal Cord Injury Research Laboratory will be used for all study sessions.

4.0 Adverse Events

**4.1 Definitions**

Adverse Event (AE) - any untoward physical or psychological occurrence or undesirable and unintended effect for a subject that may present itself during interventions and interactions used in the research or the collection of identifiable private information under the research, regardless of whether there may or may not be a relationship with the research intervention.

Unanticipated Adverse Event – any adverse event, the specificity, frequency or severity of which is not consistent with either:

* The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in the protocol related-documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and other relevant sources of information, such as product labeling and package inserts; or
* The expected natural progression of any underlying disease or condition of the subject(s) experiencing the adverse event

Anticipated Adverse Event: - an adverse event that is not an unanticipated adverse event. The following adverse events are considered as anticipated:

Unanticipated Adverse Device Effect – any 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.

Related or possibly related to the research: - an event is related to the research if, in the opinion of the Principal Investigator, it could not have been produced by the subject’s clinical condition or environment, follows a known pattern of response to intervention, disappears or decreases with reduction in dose or cessation of intervention and/or recurs with re-exposure and/or it was more likely than not to be the result of the collection/disclosure of identifiable private information in the research and/or the interventions used in the research.

Unrelated to the research: - an adverse event is unrelated to the research if, in the opinion of the Principal Investigator, the adverse event is clearly due to extraneous causes (e.g., underlying disease or environment), does not follow a known pattern of response to intervention, and/or does not reappear or worsen with re-introduction of the intervention.

Serious Adverse Event: an event is considered serious if it results in death, is life-threatening, requires hospitalization or prolongation of hospitalization, causes persistent or significant disability or incapacity, is a birth defect or congenital malformation, represents, in the Principal Investigator’s judgment, other significant hazards or potentially serious harm to research subjects or others, or any other event as described in the research process.

**4.2 Reporting**

Each subject will be observed and queried in a nonspecific fashion at each contact during the study for any new or continuing symptoms since the last contact. All adverse events will be reported on the appropriate electronic Case Report Form (eCRF). Details will include the type of event, date of onset, duration, intensity, causality relationship to the study drug(s) (if applicable), and outcome. Wherever possible, a diagnosis rather than symptom(s) will be reported.

If an adverse event should occur, every attempt will be made to obtain as much information as possible about event evaluation and outcome. Documents of this follow-up will be maintained with the patient’s study records.

If a serious adverse event occurs, the treatment will be interrupted or discontinued at the physician investigator's discretion.

All protocol deviations will be reported to the investigator and the Institutional Review Board (IRB).

All adverse events will be reported to the IRB. All serious adverse events will be reported immediately to the IRB and the FDA (if applicable).

Endpoints will be adjudicated by the Principal Investigator. A written report detailing the endpoint adjudication will be provided by the Principal Investigator.

* 1. **Potential Side Effects**

TMS will be uncomfortable for some individuals, and does have the potential to cause headaches. In rare cases, repetitive TMS (a form of high frequency TMS that will not be used in this study) has been associated with seizure and hearing loss. However, these side effects have not been reported with the use of single pulse TMS for diagnostic purposes.

* 1. **Safety**

This study will be conducted in accordance with the principles of Good Clinical Practice as outlined in the Declaration of Helsinki and the International Conference on Harmonization.

All efforts will take place to ensure patient safety. Each subject will be monitored for safety throughout the trial utilizing clinical evaluations and laboratory markers.

Laboratory markers and/or clinical evaluations that are out of normal range will be recorded as adverse events and reviewed with the investigator.

SAE’s noted to be intervention related will be reported as appropriate, and interventions will be discontinued per the decision of the investigator.

All subjects will be triaged to the appropriate medical care based on investigators decision upon review of abnormal events.

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**5.0 Data Management**

Following completion of the consenting process (including informed consent and Authorization for Use/Disclosure of PHI) and determination that the subject meets all of the inclusion and none of the exclusion criteria, enrollment will occur, and data collection will commence.

**5.1 Case Report Forms**

Hospital, office, and research records for any admission or visit (including admission notes, discharge notes, operative reports, test results, and lab reports) are considered source documentation and will be collected and reviewed to confirm clinical events and may be utilized for data analysis. Data will be collected on all subjects via an eCRF. The CRF will contain no subject names. The subject code field will be a patient study number, numbered sequentially as entered into the electronic database. A separate master code list will be constructed by the investigator/study coordinator that will list the patient name with the designated subject code. This list will be maintained in a password protected file to which access is restricted.

Upon completion of data collection, an eCRF will be printed for the subject, signed by a Principal Investigator, and filed in the subject’s research chart.

**5.2 Database**

The research database will be maintained in electronic form by Jasmine Hope. Statistical analyses will be the responsibility of Jasmine Hope. The electronic database will be backed up per institutional guidelines.

**5.3 External Documentation:**

During administration of the patient questionnaire, if it is identified that a subject sought treatment from a source outside of the Hulse Spinal Cord Injury Research Laboratory after enrollment into the protocol, additional data will be obtained from external physician offices or hospitals to document and verify events. All data will be entered onto the follow-up eCRF.

**5.4 Quality Control**

Jasmine Hope will fulfill the responsibilities of the data manager including collecting and tracking data forms and instituting quality control measures for data entry verification and study compliance. She will request further documentation such as physician and/or procedure notes when complications are observed and reported. Jasmine Hope will also be responsible for auditing the database and confirming the overall integrity of the data. She will ensure that all information pertaining to significant new developments and unanticipated adverse events are provided to the appropriate regulatory authorities, the investigators, and to the IRB.

Monitoring of the study will be conducted at regular intervals in order to ensure proper study operations and maintain Good Clinical Research Practice. These inspections are conducted in order to verify adherence to the protocol and the completeness and accuracy of the data being entered into the eCRF.

**6.0 Statistical Considerations**

**6.1 Statistical Analyses**

All data will be analyzed using SPSS (SPSS Inc., Chicago. IL, USA) with the level of significance set at p< 0.05. To compare the effect of a single session of WBV and the sham condition we will use paired t-tests to identify differences in each of the outcome measures related to the 2 aims. While this approach involves the use of multiple comparisons, this is appropriate for an exploratory study and these direct comparisons will allow us to identify the measures that are most sensitive to change.[17] Following the comparison of the sham vs real WBV, we will perform a multiple linear regression (MLR) analysis to determine whether CST or SRC makes the largest relative contribution to ankle control (Aim 1) and spasticity (Aim 2) under each of the two conditions (sham vs real WBV).

**6.2 Sample Size**

Published recommendations in rehabilitation research suggest that a well-designed pilot study is important to produce preliminary data and provide an estimate of the variance that can be used in a formal sample size calculation when planning for a subsequent larger study [18–20].The literature suggests that a sample size of 12 individuals per group is appropriate since it allows for precise estimation of mean values and variability. Further increase in N does not make any profound difference in sample estimations while any precision gains are outweighed by practicalities regarding recruitment and funding limitations [18]. Therefore, in the proposed pilot study we plan to enroll a total of 12 individuals. Finally, to account for 15% attrition we will recruit 14 subjects over 2 years to meet the target sample size.

**6.3 Estimated Duration of the Study**

This study will be completed during a 2-year period. For both aims, subject recruitment, data collection and reduction will occur continuously during Years 1 & 2. Data analysis and manuscript preparation/submission will take place in Year 2. To monitor data quality, quality assurance checks will be performed throughout the duration of the study.

**7.0 Ethical, Regulatory, and Administrative Considerations**

**7.1 Informed Consent**

The principles of informed consent are described in the Code of Federal Regulations 21 CFR, part 50 and 45 CFR, part 46. Once the Investigator has determined the patient’s eligibility for the study, the background of the proposed study and the benefits and risks of the procedures and study must be explained to the subject. The subject must be able to comprehend the informed consent form and must sign it prior to performing any study specific procedures or prior to receiving medication. The subject will receive a copy of the informed consent. The original signed informed consent and Authorization for Use/Disclosure of PHI will be maintained in the subject’s research chart. Only those subjects who sign the IRB approved informed consent prior to participation are eligible to be in the study. Failure to provide written informed consent renders the patient ineligible for the study.

**7.2 Confidentiality**

All information and data collected and/or sent to study personnel concerning subjects or their participation in this study will be considered confidential. Only authorized personnel will have access to these confidential files. Authorized FDA personnel have the right to inspect and copy all records pertinent to this trial. All data used in the analysis and reporting of this evaluation will be without identifiable reference to any patient.

**7.3 Institutional Review**

The Principal Investigator will obtain approval for the study from IRB. All changes to the protocol must be reviewed and approved prior to implementation. The Principal Investigator will be responsible for obtaining annual IRB renewal through the duration of the study, or more frequently if required by the IRB. As Study Coordinator, Jasmine Hope will maintain all regulatory documents.

**7.4 Protocol Interpretation and Compliance**

The procedures defined in the protocol will be carefully reviewed by the Investigator and research staff prior to the time of study initiation to ensure appropriate interpretation and implementation. Any changes to the protocol in the form of an amendment must be submitted to the IRB.

**7.5 Completion of Case Report Forms**

The Principal Investigator or his designee will be responsible for completing, in a timely manner, an eCRF for each patient who is registered to participate in this study. The Principal Investigator will sign and date the indicated places on the eCRF. This signature will indicate that a thorough inspection of the data therein has been made and will thereby certify the contents of the form.

**7.6 Maintenance of Study Documentation**

It is the responsibility of the Principal Investigator to maintain a comprehensive and centralized filing system of all study-related documentation, which is suitable for inspection at any time by the FDA. Elements should include:

* Subject files – containing the completed CRFs, supporting source documentation, and the Informed Consent.
* Regulatory Files – containing the protocol with all amendments and accountability records.
  1. **Final Study Report**

Upon completion of the study, the Principal Investigator is required to submit a final study summary report for the patients enrolled in the study

* 1. **Record Retention**

All records, which are part of this study, will be retained for a period of two years following discontinuation/termination of the study.

**8.0 Study Medication/Device/Intervention/Other Procedure Details**

**Blinding:** Assessors of the clinical measures will remain blinded to the randomized intervention order throughout the duration of the study.

**Assignment of Intervention:** Participants will be randomized to Group 1 or Group 2 (see **Table 1**) to determine the testing type to be received first (CST or SRC).

**Dosing and Treatment:** Only a single session of the sham and WBV will be received within each session. The total number of sessions for each participant will be four, with the total number of sham treatments received to two and the total number of WBV treatments received to two.

**Identity of Medication/Device/Treatment:** WBV will be delivered using the Power Plate Pro Vibration Platform.

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