IRB #: 16056-H42
(Assigned by IRB Office)

Approved
11/8/18
Cleveland VAMC
Institutional Review Board

CPA #: 8255
(Assigned by IRB Office)

***Form Directions**: Form is protected (user has limited access to the fill-in fields). Use the tab key or mouse to navigate the fill-in fields. Formatting is limited in the text fields (no bulleted lists, numbering, etc). In the event that the user is unable to navigate through the protected document or would like to format a document, the user can disable the "protected" feature (select "Review" then "Restrict Ending" then "Stop Protection"). Please do not delete or modify questions.*

Louis Stokes Cleveland Department of Veterans Affairs Medical Center Research Plan

Please contact the IRB office if you have any questions at (216) 791-3800 ext. 4658.

☐ **Request for Expedited IRB Review Form attached**

Human Subject Research: Human subject research means research involving interaction or intervention with living human beings or access to identifiable private information of living human beings.

Research Plan: The information requested in the Research Plan is designed to provide the IRB with the necessary information such that it can make the federally required determinations codified at 38 CFR Part 16, 21 CFR Parts 50, 54, & 56, and 45 CFR Part 46

The **Research Plan** is to be written so that the non-scientist/non-medical members of the IRB can understand the research proposed. Define all abbreviations and terms that are not part of common language.

Version Date: This should be updated subsequently with every modification to any part of the Research Plan. Any modification to this document, no matter how minor, must be reviewed and approved by the IRB prior to implementation. The Research Plan will be stamped with the date of IRB approval

Section 1 – General Information

1. **Version Date:** 10/29/2018
2. **Title of Project:** Cyclical muscle vibration in MS to improve walking.
3. **Principal Investigator (PI)** *(name & degrees)*: Stephen Selkirk, MD, PhD

   E-mail: Stephen.selkirk@va.gov

   Pager Number/Cell Phone Number: 440-552-0493
4. **Research Contact/Research Coordinator** *(name, degrees)*: Rudi Kobetic, MSBE

   E-mail: Rudolf.kobetic@va.gov

   Pager Number/Cell Phone Number: 216-791-3800 ext. 4696

Section 2 – Research Sites and Sponsor

5. Please list all Research Sites in addition to Louis Stokes Cleveland DVA Medical Center (LSCDVAMC);

International studies when the PI is the Lead Investigator list the countries:

a. When study procedures including analysis of identifiable samples or data involving LSCDVAMC enrolled subjects will be conducted at any site other than the LSCDVAMC please provide the following:

Name and contact information for the site:

Describe the plan for communicating protocol amendments, reports of serious adverse events, reports of unanticipated problems involving risks to subjects or others, interim reports, and DSMB reports to external sites.

*** When the LSCDVAMC is considered the coordinating center and the PI the lead investigator on cooperative research or a multi-center trial contact AO/Research Holly.Henry@va.gov.**

6. Sponsor or other Support *(list industry sponsor, government support, etc.)*:

VA SPiRE Grant from the Rehabilitation Research and Development Service of the Veterans Affairs.

Section 3 – Research Design and Procedures

7. Definitions- Provide a list of all abbreviations and specialized terms to be used in this document and their definitions:

Abbreviations / Specialized Terms *(Use the Enter key in this column to insert additional abbreviations and their definitions)*	**Definition**
BF	biceps femoris
BP	blood pressure
CNS	central nervous system
CV	cyclical vibration
EDSS	Kurtzke Expanded Disability Status Scale
EMG	electromyogram
HR	heart rate
LSCDVAMC	Louis Stokes Cleveland DVA Medical Center
MS	multiple sclerosis
RF	rectus femoris

Abbreviations / Specialized Terms *(Use the Enter key in this column to insert additional abbreviations and their definitions)*	Definition
TA	tibialis anterior
TFL	tensor fasciae latae
VGB	Volitional gait at baseline
VGP	Volitional gait post-training
VHA	Veterans Health Administration
VSCU	vibration stimulation control unit

8. **Provide a BRIEF SUMMARY of the background for this research.** DO NOT CUT and PASTE paragraphs that do NOT summarize the background.

   - *Include a critical evaluation of existing knowledge, and specifically identify the information gaps that your protocol is intended to fill.*
   - *Refer to appropriate citations in the scientific literature and include your references at the end of this section.*
   - *Include the rationale for conducting the research at the VA.*

   Multiple sclerosis (MS) is a chronic and progressive inflammatory demyelinating disease of the central nervous system (CNS) with an underlying neurodegenerative component that impairs walking ability in 50% to 75% of approximately 400,000 affected people in the U.S [1, 2, 3]]. Patients with MS generally develop weakness in their lower extremities of hip and knee flexors and ankle dorsiflexors requiring high effort to swing their leg forward for walking through hiking or circumduction. Dorsiflexion can be easily corrected with the simple ankle foot orthosis or surface electrical stimulation of the common peroneal nerve. However, there is currently no practical and clinically available solution to providing strong, repeatable and effectively coordinated hip and knee flexion for safer, more stable and natural gait required for overcoming uneven terrain, slopes, and stairs encountered in activities of daily living.

   This work is directly applicable to the health, wellbeing and functional independence of the disabled veteran from CNS disorders. More than 16,000 veterans with MS receive care in the VHS and over 6,000 of those have service connection for MS [5]. However, these numbers do not fully reflect the entire scope of the problem since they do not include the thousands of spouses, children or other family members who live with and care for veterans with MS and have had to alter their own lifestyles as a result of the motor dysfunction of their loved ones. Treatment of MS includes complex and expensive pharmacologic agents as well as multidisciplinary medical and rehabilitation services and assistive technology [5]. Gait impairment is associated with increased health complications, injury from falls, social isolation from immobility and decreased quality of life measures [4]. Therefore, preventing further disability by improving walking in veterans with MS is an important potential intervention.

With the help of cyclical vibration (CV), many veterans with MS may experience improved walking since some of their motor, sensory and proprioceptive functions are preserved and can be amplified.

1. Grima DT, Torrance GW, Francis G, Rosner AJ, Lafortune L. Cost and health related quality of life consequences of multiple sclerosis. *Mult Scler* 6(2):91-98, 2000.
2. Matthews B. Symptoms and Signs of Multiple Sclerosis. In: Compston A EG, Lassman H, McDonaldWI, Matthews B, Wekerle H., editor. McAlpine's Multiple Sclerosis. 3 ed. London: Churchill Livingstone; pp. 145-190, 1998.
3. Jacobs LD, Wende KE, Brownscheidle CM et al. A profile of multiple sclerosis: the New York State Multiple Sclerosis Consortium. *Mult Scler* 5:369-376, 1999.
4. Minden SL et al. Quality of life in people with multiple sclerosis: data from the Sonya Slifka longitudinal multiple sclerosis study. *Journal of Health and Human Services Adminstration* 7:233- 267, 2007.
5. VHA Handbook 1011.

9. Provide a BRIEF SUMMARY of the purpose and scientific rationale for this research. DO NOT CUT and PASTE paragraphs that do NOT summarize the purpose and scientific rationale.

- *State clearly, in terms a non-scientist/non-medical person can comprehend, what you expect to learn from the study and the specific hypothesis (es) to be tested.*
- *The objectives should be stated in such a way that the reader can determine the appropriateness of the study design.*

The primary goal of this pilot study is to explore the feasibility of cyclic vibration of the lower extremity muscles to improve walking in veterans with gait deficits from MS. Vibration is perhaps the most potent mechanical stimulus for activating muscle spindle primary afferents (Ia) [1]. This facilitates excitability of corticospinal projections to the target muscles while the α-efferents to antagonists are inhibited. Since it has been shown that cyclical vibration promotes normal patterns of motor activity by modulating the excitability of motorneurons projecting to target muscles, *it is hypothesized that facilitatory effects of cyclical muscle vibration of hip, knee and ankle muscles improves 1) walking speed and foot-to-floor clearance through increased hip and knee pre-swing flexion and improved hip-knee coordination, 2) induces carryover effects that maintain improved walking after application and 3) produces no untoward sensations or adverse physiological responses.* In previous studies vibration to the dorsiflexor muscle tibialis anterior [2] alone and in combination with the hip abductor gluteus medius [3] resulted in improved walking speed in individuals with hemiplegia. Similarly, cyclical vibration increased muscle excitation with phase dependent changes in the timing of muscle activation during gait [4] and multi-channel complex vibration patterns exhibited gait-like leg movements that present a potential for rehabilitation [5].

Therefore, this pilot study is designed to explore the efficacy and safety of cyclical vibration at correcting the typical gait deficits that involve strength and coordination of multiple joints (hip, knee and ankle) in pre- and early swing and determine whether the new intervention warrants a full comprehensive study to quantify its facilitatory effects on gait improvement in veterans with MS.

1. Burke D, Hagbarth KE, Lofstedt l, Wallin BG. The response of human muscle endings to vibration of non-contracting muscles. *J Physiol,* 261(3):673-93, 1976.
2. Paoloni M, Mangone M, Scettri P, Procaccianti R, Cometa A, Santilli V. Segmental muscle vibration improves walking in chronic stroke patients with foot drop: A randomized controlled trial. *Neurorehabilitation and Neural Repair,* 24(3):254-262, 2010.
3. Kawahira K, Higashihara, Matsumot S, Shimodozono M, Eloh S, Tasnaka N, Sueyoshi Y. New functional vibratory stimulation device for extremities in patients with stroke. *Inter J Rehab Res,* 27(4):335:337, 2004.
4. Cotey D, Hornby TG, Gordon KE, Schmit BD. Increases in muscle activity produced by vibration of the thigh muscles during locomotion in chronic human spinal cord injury. *Exp Brain Res,* 196:361-374, 2009.
5. Duclos C, Kemlin C, Lazaret D, Gagnon D, Dyer JO, Forget R. Complex muscle vibration patterns to induce gait-like lower-limb movements: Proof of concept. *J Rehabil Res Dev*, 51(2):245-52, 2014. doi.org/10.1682/JRRD.2013.04.0079.

10. Describe the means of analyzing the data and evaluating the results.

- *State the anticipated methods to be used for analysis and interpretation of the data.*
- *The methods must compliment the design of the study and the nature of the data which is being collected.*

Primary outcome measures for testing hypotheses will be walking speed measured during 10m walk trials and foot-to-floor clearance as measured by vertical displacement of marker placed over the first metatarsal using our 16-camera VICON motion analysis system. Force sensing resistors (FSRs) will be used to detect any toe dragging as a result of insufficient foot clearance. Secondary measures will be peak hip, knee and ankle flexion during swing, hip-knee coordination changes, knee flexion during stance and in pre-swing, step length symmetry and 6min walking distance.

The within subject experimental design will be used because it requires fewer subjects with more statistical power while reducing the potential for systemic error or selection bias to test the effect of CV on walking. While practice and carryover effects are major disadvantages of this study design, proper precautions including rest periods between tests and randomization of testing order for treatment group will be instituted to minimize them[†]. In addition to comparison between treatment and control groups, subjects receiving CV can also serve as their own controls by first comparing volitional gait at baseline (VGB) with any gait correction with the CV approximating desired normal muscle activity (CVN). Next the volitional gait *post-* 12 sessions of training with vibration (VGP) will be compared to volitional gait at baseline (VGB). Thus, any improvements at baseline with CVN compared to volitional gait (VGB) can be attributed to short term effects of vibration. Improvements in volitional gait *post* training with vibration (VGP) compared to baseline gait (VGB) will be attributed to long term effects of vibration. The control group subjects will be evaluated at baseline (VGB) and after gait training (VGP) and compared to the intervention group to identify trends and further explore the potential effects of CV. While this study design has limited generalizability due to the inhomogeneity of the selected population, it can be quite useful for developing and refining CV intervention.

A one-way repeated measures ANOVA will be used to test for significant difference between means to test Hypotheses 1 and 2. The Tukey honestly significant difference multiple comparison test will be used between each pair of mean walking speeds, foot-to-floor clearance and maximum joint angles to determine 95% ($p < 0.05$) confidence intervals for

statistically significant differences between conditions (CVN-VGB, CVN-VGP, VGP-VGB) and between groups to identify trends across all subjects.

† Greenwald AG. With-in subject design: to use or not to use? *Psychological Bulletin*, 83(2):314-320, 1976.

11. Provide a BRIEF DESCRIPTION of how the estimated number of study subjects needed for this research was determined

- *If this is a quantitative study provide the method of determining sample size estimates.*
- *If multiple studies are planned provide a power analysis or justification for each one.*

A statistical power of 90% was used to determine the number of trials with VICON motion analysis system required for the testing and comparison of temporal and spatial gait parameters. The results indicated a requirement of 30 strides of data or roughly 6 trials (approximately 5 strides per trial) for each condition (volitional or CV). Because this is a two year feasibility study to determine the effect size a small sample of 6 subjects were chosen for intervention with six controls to obtain preliminary data for calculating statistical power for the number of subjects required in a larger study to determine the effect of vibration on improving gait in MS.

12. The research involves the following procedures conducted by and for what purpose:

PROCEDURE	PERFORMED BY:		PROCEDURE IS:	
	Research Staff	LSCDVAMC Clinical or Support Staff	Standard of Care*	For Research Purposes Only**
Audiotaping / Videotaping *Attach VA Form 10-3203* **REQUIRED ONLY FOR IN-PATIENT AND OUT-PATIENT SUBJECTS**	☒	☐	☐	☒
Biopsy	☐	☐	☐	☐
Blood collection	☐	☐	☐	☐
Chart review – prospective	☐	☐	☐	☐
Chart review – retrospective	☒	☐	☐	☒
Review of existing data (ex: registry, Database , etc.)	☐	☐	☐	☐
X-ray or Ionizing radiation exposure	☐	☐	☐	☐
Clinical Tests	☐	☐	☐	☐
Device implantation	☐	☐	☐	☐
Drug administration	☐	☐	☐	☐

PROCEDURE	PERFORMED BY:		PROCEDURE IS:	
	Research Staff	LSCDVAMC Clinical or Support Staff	Standard of Care*	For Research Purposes Only**
EEG, EKG , ECG...etc	☐	☐	☐	☐
Gene therapy, Genetic analysis	☐	☐	☐	☐
Pregnancy/Breastfeeding Screening	☐	☒	☐	☒
Interview, Questionnaire, Diary, Survey *(please attach)*	☐	☐	☐	☐
Stool collection, Urine collection, or any Non-surgical Specimen collection	☐	☐	☐	☐
Surgical procedure or Specimen removal during surgery	☐	☐	☐	☐
Tissue banking *(complete Section 12)*	☐	☐	☐	☐
Use of pre-existing tissues/specimens	☐	☐	☐	☐
Other *(list)*: **EMG and leg muscle vibration**	☒	☐	☐	☒

- **Standard of care procedures are procedures performed in the course of normal medical care.*
- ***Research Procedures are performed for the purposes of this research alone.*

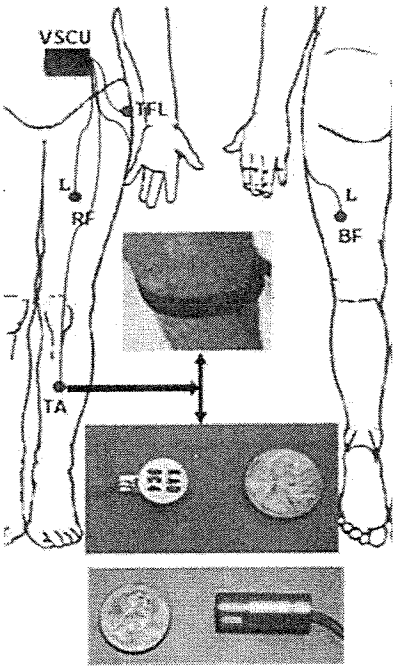
13. Please describe the research design and all study related procedures.

- *Describe **ALL PROCEDURES ASSOCIATED WITH THIS RESEARCH**. This includes standard of care and research procedures.*
- *For complex studies please include diagrams and tables. Be sure to describe when each procedure will be performed. Be sure to provide information for **each cohort, including normal controls**).*

Recruitment and baseline evaluation

Potential subjects will be identified via chart review or through referral and asked if they would be willing to participate in the study. If agreeing, they would undergo the consent process. Twelve subjects with gait disorders from MS will be recruited for participation in this study, with six subjects assigned to undergo CV gait training and six to control group for gait training without vibration. Subjects will be randomly assigned to either treatment or control group and matched by functional walking category based on speed for data analysis[†]. After signing the consent form agreeing to participate in the study and meeting inclusion/exclusion criteria, subjects will undergo baseline evaluation. This will include walking speed and distance and using VICON system for temporal and spatial parameters, kinematics and kinetics of gait and EMG activity during volitional gait at their preferred walking speed.

Retro-reflective markers will be placed on the bony landmarks and surface EMG electrodes over target muscles while the subject walks along the 10m walkway instrumented with force platforms. Standard analysis software provided with VICON system will be used to track markers in 3D and calculate all gait parameters so they can be correlated with muscle activity. The baseline evaluation will be done with and without vibration on treatment group and without vibration on control group. Data will be collected during 6 walking trials of at least 5 steps per trial (approximately 30 steps) within the visual field of the VICON motion analysis system under each condition. Sufficient resting time will be provided between trials to complete the assessment. Subjects will be encouraged to use their walking aid while a trained physical therapist provides standby guard during walking for their safety.



Vibratory stimulation system with inserts showing size and mounting of vibrators over TFL- tensor fasciae latae, RF- rectus femoris, BF- biceps femoris, and TA- tibialis anterior (VSCU-Vibratory Stimulation Control Unit).

Gait training

Each group will undergo twelve 2 hour sessions of standard gait training (up to 3x/week based on availability). Both groups will receive the same gait training while the treatment group will receive gait training with CV and control group without it.

Up to four vibrators per leg powered by the vibration stimulation control unit (VSCU) will be strapped or taped over ankle dorsiflexor tibialis anterior (TA), knee extensor and hip flexor rectus femoris (RF), knee flexor short head of biceps femoris (BF) and hip flexor and abductor the lateral portion of tensor fasciae latae muscles (TFL) as shown in figure. The cylindrical vibrators will be used to increase vibration intensity as needed. The CV paradigm resembling normal activity of muscles timed to gait events, as detected by accelerometers taped to the shoes and force sensing resistors placed in the insoles, will be imposed during walking. An average frequency of vibration will be set at 80Hz and as high as 150Hz. Physical therapist will conduct all gait training and encourage maximal voluntary effort during training while providing standby assist and spotting the subjects to ensure safety. During walking, heart rate (HR) will be monitored with the chest strap monitor and receiver watch and recorded before and after each walk. Blood pressure (BP) will be measured before and after each session of CV training and evaluation. In addition, subjects will be asked during each session if they experience any untoward sensation. BP and HR during gait training with vibration will be monitored and compared to baseline values. An increase in BP and HR of >20% and experiencing untoward sensation will be considered significant to reject Hypothesis that CV produces no physiological changes.

Gait evaluation after gait training

After twelve 2 hour sessions of gait practice with cyclical vibration emulating normal muscle activity of lower extremities, baseline speed and distance trials and VICON gait assessment with and without vibration will be repeated to test hypotheses. The primary outcome measures for testing hypotheses will be walking speed and foot-to-floor clearance as measured by vertical

displacement of marker placed over the first metatarsal. Force sensing resistors (FSRs) will be used to detect any toe dragging as a result of insufficient foot clearance. Secondary measures will be peak hip, knee and ankle flexion during swing, hip-knee coordination changes, knee flexion during stance and in pre-swing and step length symmetry.

† Perry J, Garrett M, Gronley JK, Mulroy SJ. Classification of walking handicap in the stroke population. *Stroke 26:982-989, 1995.*

‡ Kossev A, Siggelkow S, Schubert M, Wohlfarth K, Dengler R. Muscle vibration: Different effects on transcranial magnetic stimulation and electrical stimulation. *Muscle and Nerve*, 22(7):946-948, 1999.

14. Will the research involve the following?

☐ **N/A Chart/Data Review**

Placebo Group	☒ **No**	☐ **Yes** *(describe)*:
Other Control Group	☐ **No**	☒ **Yes** *(describe)*: Will be individuals with gait deficits from MS who will undergo the same gait training as treatment group but without cyclical vibration as described under #13 "research design and all study related procedures".
Randomization	☐ **No**	☒ **Yes** *(describe)*: Subjects will be randomly assigned to either treatment or control group using a coin toss.
Deception	☒ **No**	☐ **Yes** *(describe)*:

15. Does the research involve the use and/or disclosure of Individually Identifiable Health Information in any form or medium?

☐ **No** ☒ **Yes** **If yes, complete the required HIPAA Waiver/Authorization forms.**

16. Does the study include the administration of a study agent that does not require FDA approval and does not require an IND (e.g. vitamins, food supplements, isotope tracers, alternative medicines, etc.)?

☒ **No** ☐ **Yes** *-provide a detailed description of the procedures used to assure patient safety:*

17. Will radioactive material be administered or will subjects be exposed to ionizing radiation?

- *Ex. Radiographic equipment, fluoroscopic equipment, and CT scanners, etc.*

☒ **No** ☐ **Yes**

18. In your judgment, could the objectives of the research be met in a way that presents less risk to subjects?

☒ **No** ☐ **Yes** *please explain*:

Section 4 – Subject Selection, Recruitment, and Vulnerable Populations

19. Anticipated duration of entire study reported in years: 2

20. Estimated number of subjects to be studied at the LSCDVAMC or charts/records to be reviewed.

- *Provide answers for **each cohort** including normal controls; (patients, family members, treating physicians,)*:
  - Up to 350 chart/record reviews.
  - Up to 48 subjects with gait deficits from MS will be screened to get 12 subjects to complete the study.

21. Estimated number of subjects to be studied or charts/records to be reviewed at all sites

- *Provide answers for **each cohort** including normal controls; (patients, family members, treating physicians,)*

N/A SINGLE SITE ☒

22. Duration of individual subject participation

*Provide answers for **each cohort** including normal controls; (patients, family members, treating physicians,).* Up to 1 year

Chart/record review ☐ **N/A**

23. Age range of subjects

- *provide answers for **each cohort**, including normal controls*:

☒ **Adults 18 years or greater**

☐ **Specific age range** (list age range):

☐ **Children –waiver from VACO:** ☐ **attached** ☐ **pending-** ***provide submission date:***

***Contact AO/Research holly.henry@va.gov for guidance..*

24. Which of the following will be recruited or reviewed for this study *(check all that apply)*?

☐ **Veteran Inpatients**

☒ **Veteran Outpatients**

☐ **Veteran Families**

☐ ***Normal volunteers**

☒ ***Non-Veterans;** **Provide justification:** Non-veterans will be recruited only if not enough veterans are willing to participate. Patients with MS will be recruited by referral from treating physicians who will be informed verbally of the study.

☒ **Men**

☒ **Women**

*According to VHA Handbook 1605.04 Notice of Privacy Practices VHA must provide a copy of its VHA Notice of Privacy Practices to all non-Veteran patients (e.g., active duty personnel or those seeking care in humanitarian circumstances) receiving care or treatment at a VHA health care facility

or non-Veteran research subjects enrolled in an approved VHA research study with clinical trials. VA Form 10-0483 Acknowledgement of the Notice of Privacy Practices should be signed by the non-Veteran research subject at the time of consent and given a copy of the Notice of Privacy Practices. Once the Acknowledgement Form is signed please send a copy to the Privacy Officer. If additional information is needed please contact your Facility Privacy Officers Joseph Picklo or Tomica Jefferson joseph.picklo@va.gov / phone 8214102 tomica.jefferson@va.gov / phone 8214101.

25. Which vulnerable population(s) will be TARGETED for recruitment in this study:

- *Indicate only those populations that are specifically targeted for the research described in this document.*
- ***It is not necessary to check any box if, for example, your study will include a full range of subjects, some of whom may be elderly or subjects who might incidentally be employees.***

☐ **N/A Chart Review** (*proceed to Item 30*)

☒ **NONE** (*proceed to Item 26)*

☐ **Medical students, house staff, or Employees of the VAMC or Case**

☐ **Pregnant Women OR Women who are Breastfeeding, Human Fetuses, or Neonates**

☐ **Children – Complete Section 14 "Children as Research Subjects"**

☐ **Prisoners (The LSCDVAMC does not conduct research involving prisoners)**

☐ **Targeting Persons over Age 65**

☐ **Persons with Acute/Severe Mental/Physical Disabilities** *(describe)*:

☐ **Persons with Cognitive, Social, Economic, or Educational Disadvantages** *(describe)*:

☐ **Others** *(describe)*:

a. Provide the Scientific and Ethical reasons for Targeting these vulnerable populations in the research:

b. What additional safeguards or provisions will be used to protect the rights and welfare of the identified targeted vulnerable subjects?

☐ **Surrogate consent**

☐ **Subject assent**

☐ **Use of a consent or Medical monitor**

☐ **Use of a waiting period**

☐ **A patient advocate will participate in the informed consent process**

☐ **Key elements of informed consent will be presented orally**

☐ **No supervisor or rater will be involved in obtaining consent**

☐ **Other - Describe Additional safeguards you plan to use:**

c. **Describe the procedures used to ensure that the subject's legally authorized representative is well informed regarding his/her role and obligation to protect persons with impaired decision making capacity:**

26. Procedures for Recruiting Subjects -check all that apply and attach all recruitment materials:

☐ **Not Applicable**

☒ **Materials; Recruitment Letter, Posting on Bulletin Board, Brochure, Flyer, Post card, etc.**

☐ **Media; Internet Ads, Press Releases, Newspaper, Radio**

☒ **Investigator's Patient Population**

☒ **Physician Referral**

☐ **Letters to Physicians/Clinicians**

☐ **Other** *(describe)*:

27. Will VA computer systems be used to identify potential subjects?

- *e.g. VISTA, CPRS, Pharmacy Databases, other clinical databases, etc,*

☐ **No** ☒ **Yes- Describe how the computer will be used to identify patients. List all systems used and all information to be collected:** The PI will use VISTA, CPRS and the Cleveland SCI/D catchment registry. These systems will be used to generate a list of patients with MS within the SCI Center catchment area. The list will include patient name, etiology of MS, social security number and primary VA care site.

28. Will subjects be identified and/or recruited in clinics and/or inpatient wards at the LSDCVAMC?

☐ No ☒ Yes- **explicitly describe your process for identifying and/or recruiting these patients:** *(address all cohorts):* PI is attending physician in neurology and SCI wards treating patients with MS. He will describe this research study to potential volunteers and provide them with contact information for further evaluation for participation in the study.

29. In addition to the consent form will any other materials be given to the subject?

☐ **N/A Chart/data review**

☒ **No** ☐ **Yes- check all that apply and submit for IRB review:**

☐ **Letter**

☐ **Information Sheets**

☐ **Questionnaire, Survey, Diary**

☐ **Other** *(flyer, brochure, describe):*

30. Please list by bullet point inclusion/exclusion criteria for the study.

- *Entry criteria should be as detailed as necessary to define the subject population(s) under study and reduce confounding design. Include precise criteria for age, gender, and other relevant factors.*

- *List specific exclusion criteria which could interfere with the study design or place a subject at risk during the study.*

- *Provide answers for **each cohort**, including normal controls.*

Suitable candidates will be identified via chart reviews before undergoing the consent process and evaluation.

Inclusion criteria:

- MS diagnosis reviewed and confirmed by neurologist
- Kurtzke Expanded Disability Status Scale (EDSS) >3
- Age >18
- Fixed gait deficiency defined as being present for at least 3 months without improvement
- Hip, knee and ankle muscle weakness or increased extensor tone with difficulty to initiate a step
- Ability to ambulate at least 10ft with contact guard.
- Muscle vibration without untoward sensation.
- Sufficient upper extremity function to use walking aids as needed (walkers, crutches, canes).
- Hip, knee and ankle joint range within normal limits.
- Absence of untreated psychological and cognitive problems or chemical dependency.
- No acute orthopedic or medical complications that would interfere with participation in study activities.

Exclusion criteria:

- Presence of demand pacemakers.
- Uncontrolled, functionally limiting edema of the affected limb/s.
- Uncontrolled seizures/epilepsy.
- Severe untreated depression affecting ability to participate in research.
- Botulin toxin treatment injected into the lower extremities within 12 months.
- Peripheral neuropathy in lower extremities.
- Respiratory disease severely limiting ability to walk.
- Uncontrolled chronic pain that limits short distance walking.
- Cardiac arrhythmias with associated hemodynamic instability contraindicating walking.
- Lower extremity injuries that limit range of motion or function required for stepping.
- Women during pregnancy.
- Patients with a relapse in the 3 months prior to presentation for study evaluation.

☐ **N/A Chart/data review**

31. By role, (PI, Coordinator, etc.) who will assess for eligibility and how will this be accomplished?

PI and study staff will assess clinical eligibility and physical therapist will assess functional eligibility. The clinical eligibility will be assessed through review of medical history. Functional eligibility will be determined through manual muscle testing of strength and tone and standard clinical 10 m and 6 minute walking tests.

32. Are any subjects excluded on the basis of race, ethnic group, understanding of English, socioeconomic status, education, gender, or pregnancy?

- *Note: It is appropriate to indicate that you do not anticipate encountering potential subjects who do not speak English* ***based on the population to be studied***

☐ **No** ☒ **Yes** - *(provide justification)*: Understanding English because the subjects must be able to follow instructions during 12 sessions of therapy. Pregnant women will be excluded because the effects of cyclical vibration on fetus are not known.

☐ **N/A Chart/data review**

33. Will subjects be reimbursed or paid an incentive for participating?

☐ **No (skip to item #35)** ☒ **Yes**

☐ **N/A Chart/data review (skip to item #38)**

34. How and when will they be paid?

☒ **Cash** ☒ **Check** ☒ **Other** -please explain: Subject preference, agent cashier.

☒ **Prorated** -provide schedule: Subjects will receive prorated compensation for travel expenses on the day of initial consent and evaluation for round trips to the LSCDVAMC from their place of residency at the federally approved rate per mile. If the total reimbursement for travel and subject fees exceed $600/year, the subjects will be informed that the VA will report proceeds to the IRS. Subjects will be informed that he/she may have a tax liability on the amount of compensation accrued.

☒ **Fixed** -provide schedule: In addition, a fixed reimbursement of $50 per visit for gait evaluations. The same IRS reporting expectations will apply.

35. Will subjects be responsible for any of the costs related to the research?

☒ **No** ☐ **Yes**- please explain:

36. Will treating physicians, clinicians, or researchers be compensated or paid an incentive for referring or enrolling subjects?

☒ **No** ☐ **Yes** -please explain:

37. Please describe steps you will take to ensure that subject selection is fair and equitable:

Subject selection will be based on inclusion criteria. As many subjects as possible will be recruited from different races, nationalities, gender and age to increase the diversity of participants.

Section 5 – Risks and Benefits

38. Please list by bullet and describe the reasonably foreseeable physical, psychological, social, economic, and privacy risks, side effects, or discomforts associated with the research and their expected frequency and severity.

- *If this study is a retrospective chart review, or involves only the analysis of data, risk may still be present in the form of data security concerns.*

Burns and electrical hazards: There is a possibility of electrical shock, including electrical burn, whenever electricity is used to power vibrators or sensors. Measurement instruments are designed to prevent any current flow at levels that could produce tissue damage, and the risk of an electrical burn has been minimized. All instrumentation is tested regularly for electrical safety. The vibrators are battery powered.

Skin irritation: The conductive gels of surface EMG electrodes and tapes or adhesives used to secure vibrators and sensors to their body can irritate their skin. Subjects may experience a temporary redness under the tape in contact with their skin. This possibility will be minimized by carefully monitoring the skin under recording electrodes and around any tapes or adhesive bandages during each experimental session.

Sprains and falls: There is a small risk of losing balance while walking with vibration that could lead to a stumble or fall. Sprains or other injuries to user's joints or lower extremities are also possible. There have been no injuries resulting from falls in the studies leading to this investigation and these risks will be minimized by walking with a stand-by assist and using walking aids.

Videotaping and pictures: Study subjects may be videotaped or pictures may be taken of them while walking with cyclical vibration or without it which could potentially compromise their privacy. They will be asked to sign VA Form (10-3203) to give permission to be photographed and videotaped.

Confidentiality of patient information: A random numbering system will be used for subject identification (e.g. MSV-###). All data and subject information will be entered in records using this code system. The proposed study poses minimal risks to the privacy of the subjects because the code system will be protected from improper use or disclosure by storing all records in a locked office in a locked cabinet in the Motion Study Laboratory at the LSCDVAMC. All computers with stored data including photographs and video recordings and patient information will be password protected behind VA firewall accessible only to study staff.

The code system will not be reused or disclosed to any other person or entity outside the VHA other than those identified in the protocol, except as required by law, for authorized oversight of this research study.

Potential security breach (risks associated PHI/PI data collection): There is a risk that PHI/PI collected from the study participant may be disclosed to staff or persons not associated with this study or authorized to receive such information. All efforts will be made to maintain confidentiality of subjects' PHI/PI pertaining to this study.

***Certificate of Confidentiality:**

- Certificates of Confidentiality are issued by the National Institutes of Health (NIH) to protect identifiable research information from forced disclosure.
- They allow the investigator and others who have access to research records to refuse to disclose identifying information on research subjects in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level.
- Certificates of Confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation.
- By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by assuring confidentiality and privacy to subjects.
- **For more information, see http://grants1.nih.gov/grants/policy/coc/index.htm.**

39. Is this project principally concerned with the collection of sensitive information such as sexual attitudes, use of drugs or addictive products, and illegal conduct that would need to be protected against subpoena or forced disclosure in order to protect subjects?

☒ No

☐ Yes- will an application for a *Certificate of Confidentiality be submitted to the National Institute of Health upon IRB approval (or approval contingent on the issuance of such a certificate)?

☐ Yes ☐ **No provide a justification as to why a Certificate of Confidentiality will not be obtained:**

40. Describe all procedures that minimize risks, please include study and standard of care procedures:

Although the results of this study may appear in scientific publications, patient records will remain confidential at all times and subjects will not be identified by name or in any other manner that might violate the privacy, confidentiality or security of participant information. All records of research participation will be stored in locked files in a secure location within the Motion Study Laboratory at the LSCDVAMC. Secured files will only be accessible to investigators and designated study staff by key. Vibrators used in this study that come in direct contact with the subject are battery powered, thus the risk of electrical shock has been minimized. In addition, instruments used for gait assessment will be tested by the APT Center's electrical safety officer before use to minimize the risk of electrical shock. Physical therapist will walk with subjects during gait training to provide standby assistance as needed to ensure subject safety and minimize the risk of falls. Subjects' skin will be monitored to make sure there are no allergic reactions to the tape used to attach vibrators to the skin.

41. **Describe alternative procedures or course of treatment, if any, which might be advantageous to the subject. State if no alternatives exist or if this is not a treatment study.**

There are alternative procedures for obtaining coordination of hip, knee and ankle with surface electrical stimulation and hip assist orthoses.

Minimal Risk: Minimal risk means that the risks of harm anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

42. **Please give your overall risk classification for the research:**

☒ **Minimal Risk**

☐ **Greater than Minimal Risk**

43. **Will subjects receive any direct benefit from this research?**

☒ **No** ☐ **Yes** -describe the direct benefits:

44. **Please explain briefly why you consider the risks associated with the study to be reasonable in relation to its benefits?**

The vibration applied to the lower extremity muscles is similar to that normally used in massage therapy. In this study, the cyclical vibration provides mechanical stimulus for activating muscle spindle primary afferents (Ia) to promote normal patterns of motor activity by modulating the excitability of corticospinal projections to the target muscles while the α-efferents to antagonists are inhibited to improve walking.

Section 6 – Informed Consent

45. **Type and number of Consent-**

- *When more than one consent form is being used a descriptor MUST be in the header section describing the population and/or phase of the study*:

☒ **Written Informed Consent –number used in this study:** 1

☐ ***Oral Script/Letter/Information Sheet- number used in this study** ***Submit Request for Consent Waiver Form-waiver of documentation of informed consent**

☐ **No informed consent at all in this study- Submit a Request for Consent Waiver Form-waiver of informed consent and proceed to item 53**

46. **Will all adult subjects have the capacity to give informed consent?**

☒ **Yes** ☐ **No- Describe range of impairment.**

- *Research involving more than minimal risk, capacity should be determined by a psychiatrist, clinical psychologist, or other qualified professional not otherwise involved in the research.*
- *Individuals who lack the capacity to consent may participate in research only if a legally authorized representative gives consent on their behalf.*

47. Will anyone other than the subject be authorized to provide consent or permission for the subject's involvement in the research?

- *e.g., parents, court ordered guardian, spouse, etc.*

☒ **No** ☐ **Yes** -please explain:

48. Describe <u>how</u> and <u>where</u> informed consent will be obtained:

The informed consent processes for study participants takes place continuously from the initial inquiry and recruitment. At the time of first contact with an interested individual, the details of participation and potential risks are described and only follow-up and demographic information included on the Initial Contact Worksheet form will be collected. This information will then be presented at the Clinical Board meeting to decide whether the inquiry should be followed by the consent process for participation in the study. Potential subjects and their families interact one-on-one with members of the research team as all procedures and potential risks and benefits are explained. Samples of the vibratory system components are used to demonstrate the operation of the device and completely explain the procedures involved. Candidates are asked to describe the study process and the risks and benefits of the study, to assure that they understand all aspects of the study. Questions are actively solicited and addressed by the research staff and the Principal Investigator.

The Informed Consent document will be given to the subject to read through privately. If requested, the consent could be mailed to the subject for private review with family/significant other/s prior to the consenting with the study staff. Subjects can write any questions directly on the consent for in-depth review during the consenting process which will take place in the Motion Study laboratory. Dialogue between subject and research staff is encouraged to promote adequate understanding of the research study. After consent form is signed, the originals will be maintained on file while participants will be provided signed copies.

49. Will there be an opportunity for potential subject to take the consent form home to discuss participation and options with family members?

☒ **Yes** ☐ **No** - please explain:

50. List by role who will be obtaining informed consent from subjects or their legally authorized representatives:

- *ex. study coordinator, co-investigator, research nurse, research assistant, PI*

Study staff will obtain informed consent.

51. Please describe how informed consent will be obtained from subjects who do not read or understand English;

- *identify any languages likely to be encountered, and attach a copy of a translated and authenticated informed consent document*
- *It is appropriate to indicate that you do not anticipate encountering potential subjects who do not speak English based on the population to be studied*

Subjects who do not read or understand English will be excluded because they must be able to comprehend information about the device and provide information to the study staff about how the device is enhancing or not-enhancing their ability to walk.

52. Describe who *(by Role ex. PI, Coordinator, etc.)* **and how it will be determined that subjects and/or legally authorized representative understand the research and their rights.**

- *ex. question and answer, repeat back parts of the research, describe a procedure...etc*

The study staff obtaining informed consent will determine the subjects' understanding of the study by asking them questions. Any misunderstanding will be corrected by reviewing the topic in question.

Section 7 – Privacy and Confidentiality

Privacy - refers to a person's desire to control the access of others to themselves. For example, persons may not want to be seen entering a place that might stigmatize them, such as a pregnancy counseling center that is clearly identified as such by signs on the front of the building. Privacy concerns people, whereas confidentiality concerns data. The research proposal should outline strategies to protect privacy including how the investigator will access information about potential subjects.

In developing strategies for the protection of subjects' privacy, consideration should be given to:

- Methods used to identify and contact potential subjects
- Settings in which an individual will be interacting with an investigator
- Appropriateness of all personnel present for research activities
- Methods used to obtain information about subjects and the nature of the requested information
- Information that is obtained about individuals other than the "target subjects," and whether such individuals meet the regulatory definition of "human subject" (e.g., a subject provides information about a family member for a survey)
- How to access the minimum amount of information necessary to complete the study

Confidentiality - methods used to ensure that information obtained by researchers about their subjects is not improperly divulged. Confidentiality refers to the researcher's agreement with the subject about how the subject's identifiable private information will be handled, managed, and disseminated. The research proposal should outline strategies to maintain confidentiality of identifiable data, including controls on storage, handling, and sharing of data. When appropriate, certificates of confidentiality could be used to maintain the confidentiality of identifiable data

When the IRB evaluates research proposals for strategies for maintaining confidentiality, where appropriate, consideration will be given as to whether:

- Methods to shield subjects' identity adequately protect subject privacy
- There is a long-range plan for protecting the confidentiality of research data, including a schedule for destruction of identifiers associated with the data
- The consent form and other information presented to potential research subjects adequately and clearly describe confidentiality risks.
- The informed consent process and the informed consent document, and if applicable the Authorization Form, clearly delineates who will have access to the subject's information and under what circumstances data may be shared (i.e., government agencies, sponsors).

53. **Describe when and where subjects will provide their information. Include the nature of the information and who will receive and use the information. Document the provisions used to protect privacy interests of those subjects when gathering their information and data.**

To protect the privacy of participants, the Informed Consent form is discussed with participants in the Motion Study Laboratory or in a quiet area at a scheduled time convenient to both the participant and research staff. The participant is free to include members of his/her family or significant other/s in this process. The nature of the information they give is their own medical history, their disability and how it affects their daily life. This information is used to assess appropriateness of the individual to enter the study. Once enrolled in the study, subjects are requested to report any incident that is considered an "adverse event". Adverse events are gathered and reported per IRB and or regulatory requirements. The purpose of collecting the medical history is to review needed information about inclusion/exclusion criteria, evaluate their disability and how they could improve by using the CV, and evaluate their overall health and its effect on their disability. Only study staff will receive and use the information. All information provided by subjects is kept in a locked cabinet in a locked office.

54. **Will researchers have access to identifiable private information about potential subjects <u>outside</u> of this research project?** *Ex. PI is provider who has access to medical records for clinical care*

☐ **No** ☒ **Yes- please explain:** If the subject is under primary care of the PI then he has access to medical records for clinical care.

55. **Will Researchers collect identifiable private information on anyone other than the subject?**

- *Ex. family members, friends, colleagues, classmates...etc.*

☒ **No** ☐ **Yes -please explain:**

56. **At the time data are transcribed or recorded for this study they are?**

☐ **Fully identifiable- list identifiers to be collected:**

☒ **Coded with a unique identifier- describe the code:** MSV followed by a randomly generated number (e.g. MSV-###).

a. Who will have access to the key? PI, physical therapist, study coordinator/staff

b. Where is the key maintained? Two locking barriers must be in place between the coded data and the key. Motion Study Laboratory, B-B322, locked file cabinet, in a locked room.

☐ **De-identified-by Privacy Officer or Statistician.**

☐ **Other** *(describe)*:

57. **How will electronic research data be secured while the study is active?**

☐ **No electronic data will be stored**

☐ **VA encrypted laptop**

☐ **Encrypted VA device/media- describe:**

☒ **VA network drive;**

☐ **M: drive; whose?**

☒ **S: drive**

☒ **Folder access password protected**

☐ **Other drive location** *(for example P: drive)*:

☐ **Folder access password protected**

58. How will hardcopy research data be secured while the study is active? Two locking barriers must be in place.

☐ **No hardcopy data will be stored**

☒ **Locked office and locked file cabinet**

☒ **Data coded by PI or study staff with a master list secured and kept separately**

☐ **Data de-identified by Privacy Officer or Statistician-** *(***VA does not consider coded data to be de-identified)**

☐ **Other -specify:**

59. Provide the physical location including room number (and address if outside of this VA) where all electronic and hardcopy data will be stored: B-B322

60. Is identifiable information physically or electronically sent TO the LSCDVAMC from other institutions or locations?

☐ **No** ☒ **Yes** - contact Privacy Officer Joseph Picklo or Tomica Jefferson joseph.picklo@va.gov / phone 8214102 tomica.jefferson@va.gov / 8214101 or Information Security Officer Bruce Frankford bruce.frankford@va.gov / phone 821 1604 – prior to submitting to the Research Service.

****If yes complete the following:**

a. LSCDVAMC investigator will receive:

☒ **Hardcopy information or specimens**

☒ **Electronic information**

b. What are the procedures for transporting and/or transmitting identifiable information securely?

If PHI is needed, authorization is obtained for medical records to either be sent or faxed to us. When PHI is requested from another institution, records are sent directly to study staff from other Medical Institutions. Faxed information is study personnel specific, with a cover sheet. The staff in the Motion Study Laboratory is very aware that any information related to subjects should be placed in a secure area once it is received. All identifiers that link participants to the study will be maintained in accordance with the record control schedule.

c. What will be the final disposition of the identifiable data transferred to the LSCDVAMC?

- **Record Control Schedule 10-1 indicates that all research records must be retained indefinitely**

Final disposition of the identifiable data transferred to the LSCDVAMC will be maintained in accordance with the VA policy.

61. Is identifiable information physically or electronically sent FROM the LSCDVAMC to other institutions or locations?

☒ **No** ☐ **Yes** contact Privacy Officer Joseph Picklo or Tomica Jefferson joseph.picklo@va.gov / phone 8214102 tomica.jefferson@va.gov / 8214101 or Information Security Officer Bruce Frankford bruce.frankford@va.gov / phone 821 1604 – prior to submitting to the Research Service

****If yes complete the following:**

a. The LSCDVAMC investigator will send:

☐ **Hardcopy information or specimens**

☐ **Electronic information**

b. What are the procedures for transporting and/or transmitting identifiable information securely?

c. What will be the final disposition of the identifiable data transferred offsite?

- **Record Control Schedule 10-1 indicates that all research records must be retained indefinitely**

All identifiable data transferred to the LSCDVAMC will be maintained in accordance with the local record control schedule in a secure location in the motion study lab office B-B322. Since no subjects will receive an implant in this study their information will be destroyed at the end of this study.

62. Record Control Schedule 10-1 indicates all research records must be retained indefinitely. Please indicate where this information will be stored and the safe guards to protect it:

a. Electronic Safeguards:

☐ **No electronic data will be stored**

☐ **VA encrypted laptop**

☐ **Encrypted VA device/media- describe:**

☒ **VA network drive;**

- ☐ **M: drive; whose?**
- ☒ **S: drive**
  - ☒ **Folder access password protected**
- ☐ **Other drive location** *(for example P: drive)*:
  - ☐ **Folder access password protected**

b. Hardcopy safeguards. Two locking barriers must be in place.

☐ **No hardcopy data will be stored**

☒ **Locked Office and Locked File Cabinet**

☐ **Coded by Study Staff**

☐ **De-identified by Privacy Officer or Statistician**

☐ **Other- Describe:**

Facility name, address, and room number where hardcopy or electronic data will be stored:
LSCDVAMC B-B322

Section 8 – Data and Safety Monitoring –Greater than Minimal Risk Study

- For all research that is greater than minimal risk a Data and Safety Monitoring Plan must be developed.
- This is a plan to assure the research includes a system of appropriate oversight and monitoring of the conduct of the study to ensure the safety of subjects and the validity and integrity of the data.

***CHECK BOX IF THIS IS A MINIMAL RISK STUDY ☒ SKIP TO #65**

63. Safety monitoring for this greater than minimal risk project will include:

☐ **Data Safety Monitoring Board:**

☐ **Data Monitoring Committee**

☐ **Other**

- *Attach the plan or provide details including whether committee is independent from the study sponsor, how often it meets, whether written reports are available, etc*

64. Describe the plan for on-site data monitoring by the sponsor, contract research organization (CRO), or other independent body:

- **Research Office must be notified of all on-site monitoring visits.*

65. Conditions that may result in removal of subjects from the research *(check all that apply)*:

☐ **Medical condition unchanged**
☒ **Medical condition worsened**
☒ **Serious adverse event**
☒ **Intolerable complications**
☒ **Pregnancy**
☒ **Investigator's clinical judgment**
☒ **Subject withdrawal**
☒ **Subject uncooperative or noncompliant**
☒ **Study closure by sponsor or FDA**
☐ **Refusal to suspend breast-feeding**
☐ **Other-describe:**
☐ **Not Applicable**

66. If a subject withdraws or is removed from the study, describe the potential risks of early withdrawal and the procedures in place to minimize these risks:

This is a minimal risk study, thus if subjects withdraw or are removed from the study, there should be no added risk to the subject.

Section 9 – FDA-Regulated Drugs/Biologics

NOTE: If this research involves the use of any drugs or biologics, the study is subject to the Food and Drug Administration (FDA) regulations.

- **Documentation of FDA approval for the experimental use of these agents must be provided for review (industry sponsored protocol listing the IND number, letter from the FDA, letter from industry sponsor, or other document and/or communication verifying the IND for this study).**
- All drug/biologic products must be dispensed and tracked through the LSCDVAMC Research Pharmacy.
- An M.D. must be part of the Research Team for all studies that involve the use of a device or drugs.
- The LSCDVAMC Pharmacy and Therapeutics (P&T) Committee must approve: (1) Studies of investigational drugs (2) research involving an FDA-approved drug used in a non-approved manner, and (3) an FDA-approved drug, used as approved, when its use is part of a research protocol.
- **VA Form 10-9012 Investigational Drug Information Record** –must be completed for each drug being evaluated in a research study, regardless of IND status. In addition, the VA Form 10-9012 provides a listing of all authorized prescribers for the study drug(s).

67. Type of Product- check all that apply:

☒ **Not Applicable -No FDA-regulated drugs/biologics involved – Proceed to Section 10**

☐ **Drug**

☐ **Biologic or Other:**

68. Type of Trial *(check as applicable)*:

☐ **Phase I** ☐ **Phase II** ☐ **Phase III** ☐ **Phase IV** ☐ **NA**

Phase I Trials: Initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness; may include healthy subjects and/or patients.
Phase II Trials: Controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks.
Phase III Trials: Expanded controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide adequate basis for physician labeling.
Phase IV Trials: Post-marketing studies to delineate additional information including the drug's risks, benefits, and optimal use.

69. FDA Status of Drugs/Biologics –

*** For drugs, an IND may not be necessary if ALL seven of the following conditions are met:**

1. The drug being used in the research is lawfully marketed in the United States;
2. The research is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;
3. The research is not intended to support a significant change in the advertising for the product;
4. The research does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

5. The research is conducted in compliance with the requirements for IRB review and informed consent (21 CFR parts 56 and 50, respectively);
6. The research is conducted in compliance with the requirements concerning the promotion and sale of drugs (21 CFR 312.7);
7. The research does not intend to invoke 21 CFR 50.24 (Exception from informed consent requirements for emergency research).

Provide the following information for <u>each</u> drug/biologic used in this study:

Trade and Generic Name	**Manufacturer**	FDA Approved	**Product use consistent with product labeling**	**IND Required***	**IND Number**	**IND Sponsor or Holder****

70. **When the PI holds the IND, complete the following:

i. The PI has reviewed the Guidance on Requirements of the Sponsor and the Investigator as Sponsor

☐ **Yes**

ii. As the PI, you will comply with the regulatory responsibilities of a sponsor

☐ **Yes**

71. Drug Information for each drug listed in the protocol -check as applicable

☐ **Approved Drugs**

☐ **Not Approved**

- **Attach VA Form 10-9012 Investigational Drug Information Record for each drug used in the protocol**
- **Attach Package Insert or PDR monograph – copy ready, 8.5 x 11 for each drug listed in the protocol**
- **Attach Investigator's Brochure**

72. Provide a detailed description of how FDA-regulated drugs/biologics will be stored, secured, dispensed, administered, tracked, and returned.

Section 10 – FDA-Regulated Devices

This section should be completed for a medical device that is the <u>subject</u> of a clinical study designed to evaluate the effectiveness and/or safety of the device.

- An investigational device may be an FDA approved device that is being studied for an unapproved use or efficacy. This also includes an approved device that is being studied for an unapproved or approved use in a controlled, randomized, or blinded clinical trial.

- Documentation of FDA approval for the experimental use of the device must be provided for review (industry sponsored protocol listing the IDE number, letter from the FDA, letter from industry sponsor, or other document and/or communication verifying the IDE for this study).

Device Risk Determination:

Significant Risk (SR) Device is an investigational device that: (1) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject, or (2) is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; or (3) is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Non significant Risk (NSR) Device is a device other than a significant risk device.

The IRB is required to document the basis for risk determination based on the proposed use of a device in the research by considering the nature of the harm that may result from the use of the device. FDA has the ultimate decision in determining SR and NSR.

An M.D. must be part of the Research Team for all studies that involve the use of a device.

The Environment of Care Committee (EOC) must approve all research that involves electrically line-operated devices, which have leads or electrodes and will come in contact with human subjects.

73. Type of Product-check all that apply:

☒ **Not Applicable -No FDA-regulated devices involved – Proceed to Section 11)**

☐ **An FDA regulated device will be used BUT not with intent of studying safety or efficacy** *(Proceed to Section 11)*

☐ **Device**

74. List the device-include name and manufacturer:

75. FDA Regulatory Status of the Device:

☐ **FDA Approved Device**

- **A device approved by the FDA for distribution, marketing, sale to, and use by, the public for the study's indication.**

☐ **New Indication of an FDA Approved Device**

- **A device NOT approved by the FDA for distribution, marketing, sale to, and use by, the public for the indication used in the study.**

☐ **Investigational - Investigational Device Exemption (IDE)**

- **An FDA designation that permits a manufacturer to lawfully ship an unapproved device for use in a research study.**

Provide the following:

a. **IDE Number:**

b. **IDE Sponsor or Holder:**

If the PI holds the IDE, complete the following:

i. **The PI reviewed the Guidance on Requirements of the Sponsor and the Investigator as Sponsor**

☐ Yes

ii. As the PI, you will comply with the regulatory responsibilities of a sponsor

☐ Yes

c. FDA or Sponsor Device Risk Determination

☐ Non-Significant Risk

☐ Significant Risk

d. Attach documentation of FDA approval for the experimental use of the device (industry sponsored protocol listing the IDE number, letter from the FDA, letter from industry sponsor, or other document and/or communication verifying the IDE for this study).

☐ Humanitarian Use Device (HUD)

- An FDA designation for a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. For more information about Humanitarian Use Devices see the HRPP SOP manual on the R&D website.

Provide the following:

a. HUD Number:

b. HUD Sponsor or Holder:

c. Include a copy of the FDA letter granting Humanitarian Use Device (HUD) status.

☐ 510(k) Status –

- A device determined by the FDA to be "substantially equivalent" to an existing device that is legally marketed in the U.S. Until a 510(k) device is approved, it is still considered investigational.

a. Provide the name of an equivalent device and sufficient documentation to justify 510(k)

76. Attach device information (i.e., brochure, device label)

77. Provide a detailed description of how FDA-regulated devices will be stored, secured, dispensed, administered, tracked, and returned.

Section 11 – Genetic Testing and Discovery of Genetic Information (DNA)

78. Does the research involve genetic testing or DNA/RNA extraction?

☒ No genetic testing (*Proceed to Section 12)*

☐ Yes- complete the following:

a. Describe the purpose of the genetic testing component of the study

- *Is it to establish risks, associations, or prevalence?*

b. **Describe whether the test is a standard test already in clinical use or a new or experimental laboratory study**

c. **Describe the accuracy of the test**

- *Sensitivity, specificity, reliability, validity, and variability*

79. Does an abnormal test result indicate that the subject:

☐ **Has a specific condition**

☐ **Is at risk for a specific condition**

☐ **May be at risk for a specific condition**

☐ **Has, is, or may be at risk for some other outcome**

☐ **Other** *(describe):*

80. Does a normal test result indicate that the subject

☐ **Is not at risk for a specific condition**

☐ **Is at a lower risk for a specific condition**

☐ **Is at a population risk for a specific condition**

81. Is there a risk of discovery of other results such as non-parentage or other genetic conditions?

☐ **No** ☐ **Yes- please explain:**

82. Will test results produce information on anyone (e.g. a first-degree relative) besides the subject?

☐ **No** ☐ **Yes- please explain:**

83. To whom and in what manner will genetic information be reported?

84. Will genetic counseling be made available to subjects?

☐ **No** ☐ **Yes- indicate who will conduct the counseling and whether there are any additional charges:**

85. Will DNA samples be stored?

☐ **No** ☐ **Yes--describe where, how, and for how long the samples will be stored:**

86. Who will own the DNA samples?

87. Will there be any subsequent analysis of the DNA samples?

☐ **No** ☐ **Yes- describe the purpose of the subsequent analysis and whether there will be dissemination of any new information:**

88. Describe how samples will be handled if the subject withdraws consent for further participation:

89. Will the samples be distributed to other investigators?

☐ No ☐ Yes- please explain:

90. Describe the provisions to maintain the confidentiality of research data, especially in cases where data can be linked to individual subjects:

Section 12 – Tissue Collection/Storage/Banking*

It is VA policy to ensure that human biological specimens, as well as the linked data collected as part of research projects conducted by VA investigators in VA facilities or approved off-site locations, are maintained at *VA approved tissue banks or VA-sponsored tissue banks.

See VHA Directive 2000-043 "Banking of Human Research Subjects' Specimens" for more information and also visit http://www.research.va.gov/programs/tissue_banking/default.cfm

Human biological specimens (specimens).

- **Human biological specimens are materials, such as blood, urine, tissue, organs, hair, nail clippings, buccal swabs or any other materials that are derived from human subjects and are either collected specifically for research purposes or as residual specimens from diagnostic, therapeutic or surgical procedures.**

91. *Does the research involve storage or banking of human specimens or identifiable private information for use in future studies? *(check all that apply)*

☒ **No** *(proceed to Section 13)* ☐ **Yes-describe status of VA approved or VA sponsored facility:**

☐ **Storing or banking identifiable private information**

☐ **Storing or banking human specimens**

Please provide the following information:

a. **What identifying information will be required?**

b. **What are the foreseeable uses of the specimens (e.g., research, pharmaceutical products, production of cellular lines for various uses, etc.)?**

c. **What is the VA approved or VA sponsored location/institution where the information and/or specimens will be stored?**

d. **How long will the information and/or specimens be stored?**

e. **Is the storage facility an on-site or off-site location?**

f. **Will subjects be able to request that their specimen and/or information be withdrawn from the bank or repository?** *(explain)*

Section 13 – Children as Research Subjects

Research involving children must not be conducted by VA investigators while on official duty or at VA or VA-approved offsite facilities unless a waiver has been granted by the CRADO (See VHA Directive 2001-028 "Research Involving Children" for more information.

92. Do you plan to enroll children as research subjects?

☒ **No** *(Proceed to Section 14)*

☐ **Yes- Age range of subjects:**

93. Category of Research *(Check the box next to the category of research you believe your research falls under. The IRB will make a final category determination during review.)*:

☐ **Research involving minimal risk (the probability & magnitude of harm or discomfort anticipated are not greater than those ordinarily encountered in daily life or during routine physical or psychological tests.)** *(46.404)*

☐ **Research involving greater than minimal risk but of potentially direct benefit to the subject.** *(46.405)*

☐ **Research involving greater than minimal risk and no prospect of direct benefit to the subject but likely to yield generalizable knowledge about the subject's disorder or condition.** *(46.406)*

☐ **Research not otherwise approvable which presents an opportunity to understand, prevent or alleviate a serious problem affecting children/decisionally impaired adults.** *(46.407)*

94. Do you anticipate enrolling minors who are wards of the state?

☐ **No** ☐ **Yes**

95. Permission of parents or guardian *(check one only)*:

☐ **The permission of each child's parents or guardian will be sought unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child (required for categories 46.406 and 46.407 above in item 104).**

☐ **The permission of only one parent will be sought (acceptable for categories 46.404 or 46.405). If marked, provide justification:**

96. Assent of Children *(check one only)*:

☐ **The assent of each child who is capable of providing assent based on age, maturity, and psychological state will be sought.**

☐ **The assent of each child will not be sought because the capability of all of the children in this study population is so limited that they cannot reasonably be**

consulted. Explain why the capacity is so limited, e.g., age, maturity and/or psychological state:

☐ **The assent of each child will not be sought because the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research. Explain what the direct benefit may be and why it is only available in the context of the research:**

Section 14 – Other

97. Please describe any other study procedures not referenced in the previous sections:

☒ **Not applicable**