PROTOCOL TITLE:

Incline Training to Personalize Motor Control Interventions after Stroke

PRINCIPAL INVESTIGATOR:

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1.0 Objectives / Specific Aims

Specific Aim 1: Determine the efficacy of motor control deficit guided personalized training on SSWS compared to non-personalized and control interventions. Hypothesis: Individuals receiving walking rehabilitation personalized to their baseline motor control deficit (INCLINE for low Pp and DECLINE for high Pp) will exhibit significantly improved SSWS compared to those receiving non-personalized and control interventions.

Specific Aim 2: Determine the efficacy of motor control deficit guided personalized training on increasing symmetry of Pp compared to non-personalized and control interventions. Hypothesis: Individuals receiving walking rehabilitation personalized to their baseline motor control deficit will exhibit significantly improved symmetry of Pp compared to those receiving non-personalized and control interventions.

Specific Aim 3: Determine if the personalized intervention increase the positive response rate compared to non-personalized and control interventions, and to further advance personalize interventions by identifying factors that predict response. Hypothesis 3.1: A higher percentage of individuals receiving personalized interventions will "respond" than those receiving non-personalized and control interventions. Hypothesis 3.2: Discreet sets of clinical and biomechanical variables will predict responses in those with differing baseline motor control deficits.

2.0 Background

BACKGROUND AND SIGNIFICANCE

Deficits Associated with stroke: Stroke is the leading cause of long-term disability in the United States, affecting approximately 795,000 people each year, with a surviving cohort of nearly 6.5 million.[1] Seventy-three percent of those surviving stroke will have some degree of long mobility deficits,[2] and less than 50% of survivors progress to independent community ambulation.[3] Even among those who achieve independent ambulation, significant residual deficits persist in balance and gait speed, with 60% of persons post-stroke reporting limitations in mobility related to walking.[4,5] Improving walking is the most often stated goal of patients immediately following a stroke[6] and after discharge to the community,[7] and interventions designed to maximize functional ambulation skills are critical to promote activity and social reintegration.[8] The ability to walk an adequate distance at sufficient speed is a critical predictor of mortality, cardiovascular disease, and mobility disability[9] and improving gait function has the potential to improve the quality of life of the 15,000 Veterans who survive stroke annually.[10]

Anterior propulsion is critical for retraining walking: Generation of forces required to propel the body forward during walking is an essential requirement of locomotion.[11] We developed the measure, paretic propulsion (Pp) to quantify this crucial force generation in those with post-stroke hemiparesis and it has emerged as perhaps the most used mechanistic measure of walking performance. Pp describes the contribution of the paretic leg in propelling the center of mass (COM) forward during walking and is defined as the percentage of propulsion performed by the paretic leg.[12] The percentage of propulsion generated by the paretic leg is calculated by dividing the total propulsive impulse (the positive time integral of the anterior/posterior force curve) performed by the paretic leg by the sum of the propulsive impulse performed

by both legs (see Preliminary Studies). Importantly, Pp has relatively little dependence, if any, on walking speed. Propulsion is associated with the muscle activity in the plantarflexors, with increased gastrocnemius and soleus electromyographic activity relating to increased propulsion of the paretic limb.[13] This increased activity in the muscles that contribute to propulsion is also associated with improvements in functional walking tasks, while increased activation in the non-paretic muscles is associated with increased compensatory behavior.[14] In addition, propulsion is improved by increasing the posterior position of the trailing leg relative to the full body center of mass.[15] However, early activation of flexor muscles such as the tibialis anterior and the rectus femoris are inversely related to propulsion, implying that coordination between flexors and extensors is required to optimize the mechanics of propulsion. Kinematically, hip extension increases the anteriorly directed force and is a significant positive predictor of Pp.[16] Since Pp is influenced by many different biomechanical measures, we believe that it represents the coordinated output of the paretic leg. The measure has been used in over 40 examinations of hemiparetic walking and recently therapies have targeted propulsion as a primary outcome[17] and predictor of gait outcomes.[18] This proposal aims to not only expand the use of propulsion to define the motor control deficit but also to indicate an intervention tailored to specifically to that pattern of deficit in order to improve the overall effects of the intervention.

Relevance to the VA: According to the 2014 VA Stroke Quality Enhancement Research Initiative (QUERI), approximately 15,000 VA admissions occur each year for acute ischemic stroke, with a cost approaching $275 million in the first 6 months.[10,19] As the stated mission of the Stroke-QUERI is to "improve care and outcomes for Veterans at risk of ischemic stroke and those who have sustained an ischemic stroke," it is imperative to develop interventions and frameworks to manage care efficiently and optimize outcomes. The VA stroke clinical practice guideline strongly recommends a comprehensive motor recovery program early in stroke rehabilitation "emphasizing progressive difficulties, repetition, and functional task practice."[20] This guideline further suggest that motor recovery interventions, including ambulation interventions, should include cardiovascular fitness and strengthening.[20] In addition, the VA Blueprint for Excellence lists as one of its primary strategies to "advance health care that is personalized, proactive, and patient-driven, and engages and inspires Veterans to their highest possible level of health and well-being."[21] Interventions that are specifically tailored to baseline biomechanical assessments, that are designed to improve force production and cardiovascular status via task-specific training, and are translatable to VA clinics and beyond meet the critical needs of the VA in support of its Veterans with stroke.

INNOVATION

Biomechanical Definition of Motor Control Deficits: We have biomechanically defined post-stroke walking patterns based on Pp: 1) low Pp is the predominant pattern and is associated with increased and early paretic flexor EMG activity, lengthened paretic step length, and decreased paretic hip extension[13,22]; and 2) high Pp pattern is characterized by increased paretic extensor EMG during terminal stance, shortened paretic step length, and prolonged paretic hip extension[13,22] (see Preliminary Studies for how these are defined).[23] This project will focus on the comparison between high and low Pp, as those with symmetric propulsion represents a small portion of the population with post-stroke deficits.

Treatment Determined by Baseline Motor Control Deficit: Our pilot data reveal that the two patterns are most effectively rehabilitated by different treatment strategies: 1) low Pp by walking on an inclined treadmill requiring increased force production and promoting increased and symmetrical hip extension[24,25]; and 2) high Pp by walking on a declined treadmill, limiting hip extension and promoting effective stance to swing transitions, increasing knee flexion, and encouraging improved knee extensor eccentric control.[24,25]

Manipulation of Task Mechanics to Meet Specific Training Goals: Successful uphill walking requires increased force production bilaterally in order to maintain forward progression. Specifically,

spatiotemporal symmetry and paretic hip extension are increased following incline walking post-stroke when the incline is at least eight degrees.[26] Ground reaction forces and joint moments increase with concomitant increases in slope, particularly in the anterior-posterior direction representative of propulsion,[27] and incline walking is associated with increased knee extensor and ankle plantarflexion activity producing the additional propulsion required to step uphill.[28] Gama et al. recently trained individuals post-stroke with body-weight support (BWS) and a 10% incline and compared to a group undergoing level treadmill training with BWS.[29] Incline-trained individuals demonstrated significant improvements over the control group in walking speed ($p=0.002$) and paretic step length ($p=0.02$). However, all individuals trained at the same direction of treadmill inclination.[29]

Although less studied, downslope walking has also been utilized in the training of individuals after neurologic injury. Incline and decline training are both associated with improved endurance, overground walking speed, and dynamic balance control.[30] Randomized controlled trials in individuals with Parkinson's Disease[31] and Multiple Sclerosis[32] demonstrate significant improvements associated with downhill walking in mobility, functional activities, balance, and strength of the knee extensors. This knee extensor strength improvement primarily is associated with improved eccentric control of the knee extensors, and the trailing limb increases negative (eccentric) work production with increased slope of the treadmill.[33] The increased negative work production at the knee is likely associated with the decline training effects of increased knee flexion and improved stance to swing transitions. Electromyographic and kinetic analyses demonstrate an increase in power absorption during downslope walking and increases in extensor activity, representative of increased eccentric control of the knee extensors.[27,34] Downslope walking is also effective in the examination of spinal neurophysiology, demonstrating decreases in spinal level excitability in neurologically healthy adults.[35] In addition, acceleration of the center of mass (see Preliminary Studies) is significantly increased in the transition from stance to swing,[24,25] further indicating the viability of this treatment for individuals with deficits related to decreased knee flexion, poor power absorption, and difficulty transitioning from stance to swing.

Predicting Responders to a Novel Locomotor Rehabilitation Intervention: Many types of locomotor rehabilitation techniques (activity-based therapies,[36] lower extremity strengthening,[37] aerobic conditioning,[38] functional electrical stimulation[39]) produce robust changes in functional outcomes such as increased self-selected walking speed (SSWS). However, no single intervention is shown to be superior in producing these functional changes.[40] In addition, a critical need exists to be able to understand mechanisms associated with recovered function in order to predict responders from non-responders prior to a therapeutic intervention. Currently, mechanistic outcomes are too inconsistently applied to locomotor rehabilitation interventions to draw clear conclusions as to how recovery is generated.[41,42] Recent analyses have begun to examine the patterns of response in rehabilitation participants in an effort to delineate which participants respond to an intervention and how they improve.[43-45] These analyses, however, typically lack a thorough outcome battery that includes broad-based biomechanical and clinical outcome measures. We believe that a full battery of biomechanical and clinical variables will prove crucial for determining a broader set of factors contributing to response to rehabilitation interventions that clinicians can apply to improve decision making regarding intervention selection. This proposal is guided by the overall hypothesis that when provided an intervention tailored to the baseline motor control deficit, there will be fewer non-responders leading to more robust functional effects.

3.0 Intervention to be studied

Intervention

Personalized Intervention: Each participant will be randomized to receive either INCLINE, DECLINE, or CONTROL training. During training, each participant will be asked to walk without an assistive device or ankle-foot orthosis (although an AirCast will be allowed for medial-lateral stability if necessary). For all INCLINE and DECLINE training, individuals will walk for 20 minutes at a 10-degree treadmill tilt, stopping each five minutes for monitoring of vital signs (see "Vital Sign Monitoring" below). As many subjects post-stroke take a beta blocker or other medications that prevent heart rate and blood pressure increases during exertion, a rating of perceived exertion (RPE, must be below "very hard") will also be collected and adverse events will be strictly monitored. For DECLINE training, the treadmill will be tilted to 10 degrees with the belt reversed and the participant facing in the opposite direction. While participants will be allowed to support themselves with the use of handrails for balance as required, they will wear a climbing harness attached to an overhead support system to prevent falls and thus minimize handrail use. Our previous work was completed at 8 degrees of tilt (see Preliminary Studies), based on work by Werner et al. demonstrating that 8 degrees was required to improve gait symmetry and hip extension in patients with stroke.[46] Subsequent reports[29,47] demonstrate that 10 degrees is equally feasible and offers a more intense training opportunity. Individuals will walk at a speed at least 50% of their current overground SSWS, determined at the beginning of each training week, but training as fast as they feel comfortable up to the overground SSWS. Pilot work demonstrated that individuals are not capable of walking on the INCLINE or DECLINE at the overground SSWS secondary to the increased workload associated with the treadmill tilt. Each INCLINE and DECLINE session will be followed by one 6-minute bout of overground walking training as fast as comfortable for each participant focusing on specific gait details targeted in the INCLINE/DECLINE trials (e.g. increased hip extension, increase paretic leg loading, or improved stance to swing transition).

Vital Sign Monitoring: For all training groups, criteria for termination of training include subject complaints of shortness of breath, light-headedness, confusion, severe headache, or dyspnea; onset of angina; excessive blood pressure (systolic BP > 200mm Hg, diastolic BP >110 mm Hg), or drop in systolic BP >10 mm Hg and inappropriate bradycardia (drop in heart rate >15 bpm).[48,49] In addition, we will stop training for a rest break if the RPE exceeds "very hard" (17 on a 6-20 scale).

4.0 Study Endpoints

Outcome Measurement

Paretic Propulsion (Pp): Pp is a quantitative measure of the coordinated output of the paretic leg and is defined as the percentage of propulsion performed by the paretic leg.[12] The percentage of propulsive forces generated by the paretic leg will be calculated by dividing the total propulsive impulse (the time integral of the anterior/posterior force curve) performed by the paretic leg by the sum of the propulsive impulse done by both legs. Importantly, Pp has relatively little dependence, if any, on walking speed. Our instrumented treadmill gives us the ability to measure this quantity in much more detail than would be possible in a conventional gait laboratory because we can easily record a large number of step cycles in a single 30-second trial. Statistics will be run on the absolute deviation from normal (Deviation = |0.5 - Pp|).

Biomechanical Walking Testing: For instrumented treadmill assessments, participants will wear their own low-heeled shoes. A safety harness (Robertson Mountaineering) mounted to the laboratory ceiling will be worn by the participant for protection in the event of loss of balance. Each participant will be asked to walk without an assistive device or ankle-foot orthosis (although an AirCast will be allowed for medial-lateral stability if necessary). Participants will be permitted to practice treadmill walking until they feel comfortable walking without assistive devices, orthotic devices or support from the handrails. During the acclimation period, a trained staff member will offer any support the subject may require. This will continue until the participant feels comfortable enough to begin data collections. Ground reaction force data will be

low-pass filtered with a fourth-order, zero-lag digital Butterworth filter. To optimize capture of steady state data on the treadmill, subjects will walk for approximately 10 seconds to achieve steady state prior to the 30 seconds of data collection (40 seconds per trial). Two trials will be collected at the treadmill self-selected speed and two trials at the fastest comfortable speed. Biomechanical data collections will allow for secondary analyses of associated kinematic and kinetic variables (e.g. force impulse, COMa by gait cycle phase, joint moments/power/work, and joint angles). At baseline testing, post-testing, and at the beginning of *each session*, participants will walk on a 16 ft. long gait mat (GAITRite) to measure SSWS and fastest comfortable walking speed (FCWS) and other spatiotemporal parameters. Subjects will be permitted a practice trial, and then be asked to complete two trials at each speed. A safety harness mounted to the ceiling will protect the subject but will only support their body weight in the case of a loss of balance. Trained study personnel will be present for all testing sessions as needed.

Clinical Assessments: The proposed assessments are standard to most post-stroke intervention trials. As the primary aim of this proposal is to improve functional outcomes using an intervention that is clinically translatable, it is imperative to include assessments routine to clinical rehabilitation. The below measures reflect a battery of body structure and function, activity, and participation measurement to reflect a broad range of clinical assessment across the rehabilitation model (ICF) as has been previously advocated.[50] All clinical assessments will be conducted by a physical therapist evaluator blinded to group allocation (different than the training physical therapist) within the Center for Rehabilitation Research in Neurological Conditions.

- Walking Speed: We will assess SSWS and fastest comfortable walking speed in meters per second over a 16 foot GAITRite walkway. Mean SSWS for individuals post-stroke has been established at 0.84m/s,[51] with excellent test-retest reliability (ICC=0.95 to 0.99) and interrater/intrarater reliability (0.87 to 0.88).[3,52] Minimally Clinically Important Difference (MCID) for SSWS for stroke survivors of 0.16 m/s[53] allows for the clinician to set meaningful walking speed goals, while providing a classification for researchers via cut off scores: <0.4 m/s representing likely limited household ambulators, 0.4-0.8 as limited community ambulatory profile, and >0.8 m/s as community ambulators.[3]
- 6-Minute Walk Test (6MWT)**:** Timed walking tests are primarily a measure of functional capacity.[54] The 6MWT tests populations who present with little functional walking capacity and is validated against the Rivermead Mobility Index (r=0.75) and 10-meter walk time (r=-0.61).[55] The 6MWT has a high intra- and interrater reliability (ICCs = 0.82-0.95).[56] The Minimal Detectable Change (MDC) for individuals with chronic stroke is 120 feet[57] and the MCID is 113 feet.[58]
- Functional Gait Assessment (FGA): The FGA is modified from the Dynamic Gait Index and includes 10 items to assess dynamic balance stability during gait. Each item is scored on a 4-point scale from 0 (poor) to 3 (excellent) with a maximum score of 30. The MDC is 4.2 points,[59] A score 22 or below out of 30 is predictive of falls in older adults (sensitivity and specificity each 85%).[60]
- Fugl-Meyer Assessment of Motor Function: We will utilize the lower extremity (LE FM Assessment) portion of the assessment to characterize our participant sample. The LE FM Assessment is a measure of motor recovery post-stroke and includes measures of reflex, motor control, and coordination with a total score of 34. We will also evaluate separately the 22-point motor sub-score as well as the LE sensory portion.[61]
- Stroke Impact Scale (SIS): The SIS is a stroke-specific outcome measure that includes 59 items covering nine domains: Strength, Hand function, ADL/IADL, Mobility, Communication, Emotion, Memory and thinking, Participation/Role function, and Perceived recovery. Standard error of measurement, MDC, and MCID have been published providing clinicians key metrics to measure the clinical change and significance of the questionnaire.[59] The SIS is responsive to change at 1-3 and 1-6 months[62] (with a greater total responsiveness than the Stroke Specific Quality of Life Scale (SRM

difference =0.36).[59] Test-retest (ICC = 0.7 to 0.92)[62] and interrater/intrarater reliability are all excellent (ICC = 0.82 and 0.80 respectively)[63] with some deviations for specific domains.

- Activities of Balance Confidence: The ABC is a commonly used 16 item subjective measure of confidence in performing various ambulatory activities without falling or experiencing a sense of unsteadiness (falls self-efficacy). Items are graded 0-100% with higher scores representing increasing confidence in functional activities. Standard error of measurement has been published as 6.81 in chronic stroke,[64] whereas the MDC and MCID have yet to be published. A cut-off score of 81.1 can provide some evidence that the patient/subject doesn't have a history of falls.[65] Total score normative data reveals a mean (SD) of 86.3 ±17.3[64] indicating that the average stroke survivor likely has some reduced confidence in their ability to perform ADLs/iADLs without loss of balance. The ABC is designed to be used multiple times on a single patient with excellent 4-week test-retest reliability (ICC = 0.85) including item level metrics (ICC = 0.53-0.93).[64]

5.0 Inclusion and Exclusion Criteria/ Study Population

Subjects: We will recruit 72 individuals post-stroke, specifically targeting Veterans, with persistent motoric disability following a clinical diagnosis of stroke, the most recent no less than six months prior to enrollment. Individuals must present with unresolved propulsion asymmetry ($Pp \leq 0.47$ or ≥ 0.53). Subjects will be aged 25 to 75 years to control for the effects of advanced age on the ability to maintain the effects of motor adaptation training.[66] Participants may be of either gender and will be of diverse ethnic background representing the community. We will also perform a battery of clinical assessments to evaluate degree of function and disability.

Inclusion criteria: 1) 25-75 years of age, 2) stroke ≥ 6 months, 3) residual paresis in the lower extremity (Fugl-Meyer LE motor score <34), 4) ability to walk without assistance at speeds ranging from 0.2 – 1.0 m/s (with a support harness for biomechanical testing); 5) $Pp \leq 0.47$ or ≥ 0.53; 6) Ability to walk on a treadmill without orthotic or assistive device using overhead harness system; 7) provision of informed consent, and 8) written approval from the primary physician (see attached sample of Medical Approval Cover Letter).

Exclusion criteria will be: 1) history of congestive heart failure, unstable cardiac arrhythmias, hypertrophic cardiomyopathy, severe aortic stenosis, angina or dyspnea at rest or during ADLs; 2) History of COPD or oxygen dependence; 3) Pre-existing neurological disorders or dementia; 3) History of major head trauma; 5) Legal blindness or severe visual impairment; 6) Severe arthritis or other problems that limit passive ROM; 7) History of DVT or pulmonary embolism within 6 months; or 8) Severe hypertension with systolic >200 mmHg and diastolic >110 mmHg at rest.

Statement of Inclusion of Women and Minorities in Research: This research will include women and minorities to the extent reflected by composition of the population in Charleston, SC and its surrounding areas. There are no exclusion or inclusion criteria which would exclude or preclude women or minorities from participating in this study.

Targeted/Planned Enrollment Table

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	5	5	10
Not Hispanic or Latino	31	31	62
Ethnic Category: Total of All Subjects *	36	36	72
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	2	2	4
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	16	16	32
White	18	18	36
Racial Categories: Total of All Subjects *	36	36	72

6.0 Number of Subjects

Sample Size Determination and Statistical Approach: A total of 72 individuals post-stroke will be recruited for this study. We are assuming an attrition rate of 20% resulting in a final sample size of 60 for statistical analyses, ideally 10 in each combination of baseline group (low and high Pp) and intervention (INCLINE, DECLINE, and CONTROL training). 10% is consistent with attrition rates from previous trials of locomotor rehabilitation conducted by our group,[43] but we have chosen a more conservative rate of 20% based on the novelty and intensity of the intervention. There will be two strata of 30 individuals each with baseline low Pp and high Pp, respectively. From those strata, using block randomization, the subjects will be equally randomized into the INCLINE, DECLINE, and CONTROL training (10 in each training cell).

7.0 Setting

The research will be done at the MUSC/VA Rehabilitation Research space located at 77 President St. Charleston, SC 29425. The following labs will be utilized:

Locomotor Energetics and Assessment Laboratory (LEA): The LEAis a 988 square foot laboratory located in the College of Health Professions Research Building on the campus of Medical University of South Carolina. The laboratory is a shared resource of the college and is supported in part by the Department of Health Sciences and Research. The laboratory is located in the same building as the offices of the PI, Co-I and staff. It features equipment capable of collecting kinematic, kinetic, electromyographic, strength, and metabolic data. A substantial investment in improving the capabilities of the laboratory will be funded by the startup funds of the PI. The motion analysis laboratory is adjacent to a small workshop available for the construction, repair, and alteration of simple mechanical devices.

The Locomotor Rehabilitation Laboratory (LRL): is a state-of-the-art treatment laboratory, designed to offer a full range of locomotor interventions for those with impaired walking secondary to neurologic injury. The LRL is an 808 square foot laboratory located on the second floor of the College of Health Professions Research Building, Room C-213. The laboratory houses a ZeroG mobile body weight support system (only the 6th one installed nationally) designed to create a permissive environment for retraining walking ability not only over a treadmill, but also over level ground and environmental obstacles. Research participants will have access to a Woodway split-belt treadmill, for training cardiovascular endurance as well as lower extremity strength and power. Additional assessment capabilities include: 8 camera Phase Space Motion Capture system, Delsys Wireless EMG system, and Biodex Dynamometer. The research will focus on a multi-faceted approach to locomotor recovery after neurological injury, initially targeting stroke and spinal cord injury. The overall goal is to understand and improve clinical decision making relative to locomotor interventions.

Motor Performance Laboratory (MPL): The MPL is an approximately 914 ft2 room located in the College of Health Professions Research Building, Room C102. The primary focus of the MPL is to investigate the neural and muscular mechanisms underlying muscle function in people with neurological conditions, such post-neurological injury i.e. stroke or spinal cord injury and/or healthy controls. An additional focus is the development of effective interventions to counteract these neuromuscular impairments and improve overall function, activity, and participation. Research participants will have access to a Woodway treadmill, a Precor elliptical trainer, Shuttle Systems jump trainers (MVP and 2000), recumbent and upright bikes, NUSTEP Recumbent Stepper, Full metabolic and EKG cart, and passive safety rail and harness system all aimed at improving and measuring lower extremity function and physical function.

The Functional Neuro-Stimulation Laboratory (FNSL): The FNSL is located on the 2nd floor of the College of Health Professions Research Building on the campus of Medical University of South Carolina. FNSL studies use electromagnetic approaches as either research tools investigating neuroscience questions or as investigational or FDA approved treatments for brain diseases. Techniques actively being used by FNSL researchers and their collaborators include transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS)

8.0 Recruitment Methods

Subject Recruitment: Participants for this program will be recruited from the Ralph H. Johnson VA Health Care Systemand the Medical University of South Carolina (MUSC). The Ralph H. Johnson VAHCSand MUSC share core facilities through a memorandum of understanding which provide a unique environment from which to recruit participants. The combination of the Ralph H. Johnson VAHCS and the MUSC Stroke Program sees over 60 new stroke patients per month and all patients are routinely screened for eligibility to our various research studies. Potential participants will be given information while inpatient and again when they are seen for follow up in the outpatient clinic. We currently have an IRB-approved existing recruitment database through the Ralph H. Johnson VAHCS (IRB# 43107 “VA Stroke Rehabilitation Research Database”, Cence, PI). This database is initially populated with an existing patient registry kept by Neurology Service which includes approximately 500 post-stroke patients seen at the Ralph H. Johnson VAHCS or one of the 5 affiliated community-based outpatient clinics (CBOC’s). Of these, approximately 350 meet the age criteria for enrollment in the proposed study (excluding duplicates from our MUSC registry, see below). Ongoing recruitment is expected to add 5-8 more subjects each month.

The MUSC Stroke Program holds Joint Commission's Certificate of Distinction for Primary Stroke Centers which recognizing centers that make exceptional efforts to foster better outcomes for stroke care. The MUSC Stroke Program alone sees over 50 new stroke patients per month and routinely screens all patients for eligibility to our various research studies. In addition, since the proposed research investigates

stroke recovery, it will have access to resources at the NIH-funded Center of Biomedical Research Excellence (COBRE) in Stroke Recovery at MUSC. Dr. Bowden is a currently a junior investigator in this center and will be able to access the Clinical and Translation Tools and Resources (CTTR) Core for subject recruitment support. The CTTR Core provides recruitment resources through a bioinformatics-enabled database registry via a separate IRB approved database (IRB# 37803 "RESTORE"). Currently, there are 682 post-stroke subjects (93 veterans), 560 of whom are ≤ 75 years old, in our database registry and recruitment is expected to add 3-5 more subjects each week. Thus, with such a large cohort of stroke patients, we should have no difficulty in recruiting the subjects required to address our aims.

The study coordinator will obtain contact information from the recruitment database(s) and will make initial contact via the telephone. If they meet inclusion criteria as capable of being obtained over the phone, potential participants will be requested to come in person to the research laboratories where they will participate additional testing as allowed by the database IRB (Pro00037803 or Pro00043107). The participant will engage in the consent process in a privated area in the research space, and consent may be obtained by the PI, the study coordinator, or a member of the investigative team.

9.0 Consent Process

The consent process will take place in the labs or private office of the study coordinator at the time of the subjects' visit. The PI, Co-PI's, investigators and study coordinator are experienced in consenting subjects. At least one of these study personnel will be onsite to review the consent document with the subject and answer any questions. The subject will be asked to document his or her consent in writing on the informed consent document. The process will occur in privacy in one of several labs listed in the protocol.

The participant will be given the opportunity to discuss the protocol and ask any questions that they may have. After the conversation, the participant will be given the opportunity to consent or not. The PI, the study coordinator, or members of the research team may obtain consent.

10.0 Study Design / Methods

This proposal seeks to develop a theory-based clinical decision-making framework for the training of walking recovery after stroke based on how different biomechanical patterns of walking illustrate distinct motor control deficits. 72 individuals with unresolved propulsion asymmetry after chronic stroke (greater than six months post-stroke, so additional natural recovery is not expected) will be evaluated to determine their baseline level of Pp: low Pp ($\leq$ 0.47) and high Pp ($\geq$ 0.53) (0.47 to 0.53, equal to 3 standard deviations around the mean for healthy controls). Individuals will be randomly assigned to one of three intervention groups (INCLINE, DECLINE, or CONTOL training), and we will recruit into each training group an equal number of 10 individuals with low or high Pp (Figure 6). Each participant in INCLINE training will walk four 5-minute bouts at the at the highest speed they can tolerate for 5 minutes (up to SSWS and at least 50% of SSWS) on a 10% up-sloped treadmill followed by 6 minutes of level overground walking at the pace that they can maintain (breaks are allowed as necessary while the clock continues to run). INCLINE training will focus on increasing force production and promoting increased and symmetrical hip extension. Those in DECLINE training will also walk with the same number of bouts, intensity, and overground walking as INCLINE on a 10% down-sloped treadmill, limiting hip extension, and promoting effective stance to swing transitions through increased knee flexion and eccentric control of the knee. During the 6-minute walk, each participant will focus on specific gait details targeted in the INCLINE/DECLINE trials (e.g. increased hip extension, increase paretic leg loading, or improved stance to swing transition. CONTROL participants will walk four 5-minute bouts at their SSWS on a flat treadmill followed by 6 minutes of level overground walking at the SSWS, controlling for equal time of walking activity. Placement into the INCLINE, DECLINE, or CONTROL training groups will be randomized based on a computerized randomization by the study statistician. Each individual will complete 12 sessions (three times a week for four weeks). Clinical and biomechanical outcome measures will be collected pre- and post-training and after a one-month follow-up period. In addition, we will collect a battery of clinical outcome measures before and after training. Spatiotemporal variables (including SSWS) will be collected before and after each session. All clinical and biomechanical assessments will be conducted by an evaluator blinded to training group allocation.

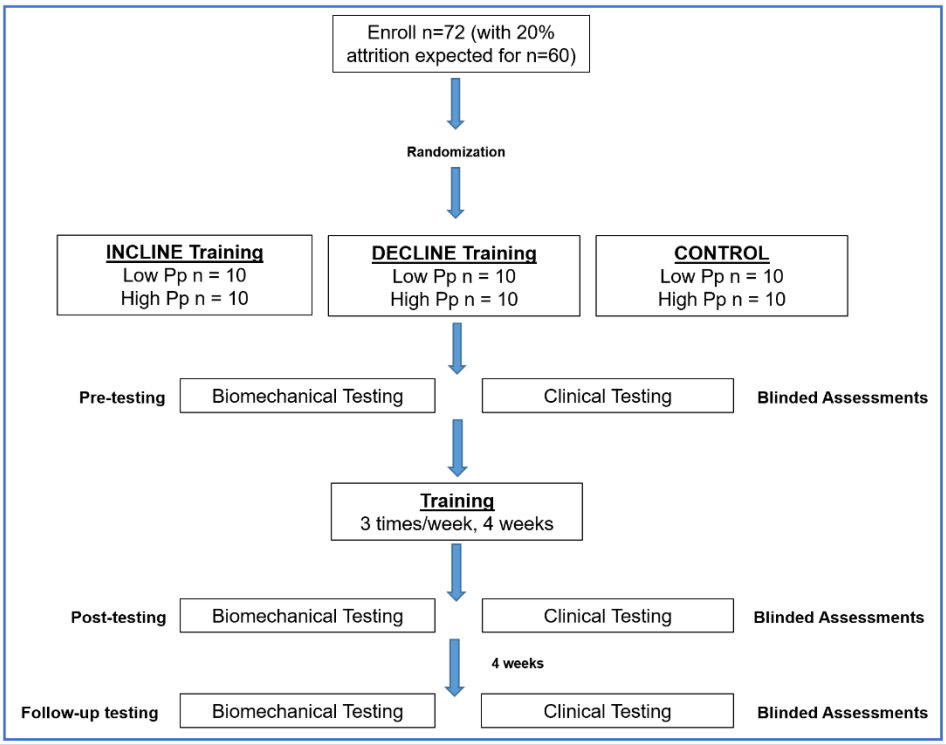

Figure 6. Study design and flow of assessments and training.

11.0 Data Management

As a clinical trial, the details of this project will be entered into clintrials. Clinical data from assessment sessions will be recorded on hard copies (stored in a locked file cabinet in the Ralph H. Johnson VAHCS rehabilitation research space) and entered into a RedCAP electronic database by the project coordinator immediately after each session. These data will be de-identified for further analysis. Only the PI will have

access to de-identified data. Gait data will be analyzed using a custom MATLAB program, automatically populating a LabView Data Viewer from which customized data may be retrieved. The research coordinator will check the data entry, and pool all data into a group-wide de-identified spreadsheet. All data from training sessions will also be analyzed and stored using an automated MATLAB program. All electronic data will be stored on a secure server that is backed-up nightly. Upon completion of all Aims, the de-identified spreadsheets and group assignment list will be shared with the statistician for analysis. The de-identified dataset will be available for sharing with other investigators, and this trial will be registered in the NIH-supported registry.

Sample Size Determination and Statistical Approach: A total of 72 individuals post-stroke will be recruited for this study. We are assuming an attrition rate of 20% resulting in a final sample size of 60 for statistical analyses, ideally 10 in each combination of baseline group (low and high Pp) and intervention (INCLINE, DECLINE, and CONTROL training). 10% is consistent with attrition rates from previous trials of locomotor rehabilitation conducted by our group,[43] but we have chosen a more conservative rate of 20% based on the novelty and intensity of the intervention. There will be two strata of 30 individuals each with baseline low Pp and high Pp, respectively. From those strata, using block randomization, the subjects will be equally randomized into the INCLINE, DECLINE, and CONTROL training (10 in each training cell). The power analysis was based on our pilot training data for INCLINE and DECLINE combined compared to CONTROL. For the power analysis, we used a repeated measures model with an AR(1) correlation value of 0.45 which we obtained from the pilot data. With an average standard deviation of 0.35 (also obtained from the pilot data) and 80% power, with 10 subjects per group we will be able to detect a difference of at least 0.20 between the intervention groups and CONTROL group. A log transformation was applied to achieve normality. Also, we will longitudinally evaluate speed at each session. We will therefore conduct a repeated measures 2-way ANOVA and test the relevant hypotheses using contrasts in a Bonferroni post-hoc analysis. We will include an adjustment for baseline Pp group, intervention group, time, and their interactions. Depending on the within subject correlation across time (which we anticipate to be high) this could also provide additional power. Therefore, in a secondary analysis we will be able to examine several covariates, including the sub-types mentioned above. For each Aim, each variable will be assessed utilizing a repeated measures analysis of variance (baseline Pp, group and time) to evaluate the interaction between baseline Pp, group and time as well as the main effects of treatment for each group and group assignment at each time point. Since pilot data required a log transformation of SSWS, we will assess the final SSWS outcome for normality and perform a transformation if necessary. All power estimates were conducted by a biostatistician (Dr. Ramakrishnan) using PASS 2008 (NCSS, Kaysville, Utah). Spaghetti plots and descriptive statistics regarding HR, BP, and RPE responses to INCLINE and DECLINE training will be reported prior to formal analyses. Patterns of attrition between the 2 groups will also be compared.

Dr. Ramakrishnan will be the unblinded statistician who will track the trial to ensure adverse events are not disproportionately harmful to any one group of participants. After every adverse event, a report will be prepared by Dr. Ramakrishnan and shared with the team and the MUSC IRB. All serious adverse events will be analyzed by the investigative team and the MUSC Institutional Review Board. Serious adverse events are defined as 1) being unexpected; 2) related to a subject's participation in research; and 3) that subjects are at greater risk of harm than was previously recognized. If > than 10% in each cell have a serious adverse event, we will evaluate the circumstances and decide if the event was caused by a particular treatment. If a majority of team or the IRB decides that the adverse event was related to intervention, subsequent randomizations will be stopped.

12.0 Provisions to Monitor the Data to Ensure the Safety of Subjects (if applicable)

Informed consent will be obtained by the on-site R&D IRB approved VA research staff (i.e. research therapist, research assistant, investigator, coordinator, or other associated trained staff) in a private room located at the Center for Rehabilitation Research in Neurological Conditions (CNNRC), Dept. of Health Sciences and Research, MUSC, 77 President Street, MSC 700, Charleston, SC.2nd Floor, Room C214 and 213 (designated VA space through MOU between MUSC and VA).

All hard copies of signed consent forms and associated data (intake form) will be stored in a locked office located on the 2nd floor, Room C213, north wall, in a badge access and secure building at the Medical University of South Carolina (77 President Street, Charleston, SC, designated VA space through a Memorandum of Understanding between MUSC and VA).

13.0 Risks to Subjects

Potential Risks: There are no significant risks to the subjects in the proposed training methods. The risks to individuals participating in this study are no greater than the risks when providing conventional physical rehabilitation services to an individual after stroke. The same precautions and safety guidelines will be taken that are provided in patient care in rehabilitation settings. The rehabilitation program should not present a risk for the patient but could result in muscle soreness and/or joint stiffness but these symptoms should not persist more than a few days. There is a minimal risk for muscle strains during the testing and training. The locomotor assessments used in the proposed study are routine, clinical assessments of gait used in physical therapy clinics and rehabilitation facilities. The GAITRite system has been used to assess walking performance with no adverse reactions or report of discomfort. The experimental protocol to be used in this portion of the proposal involves minimal risk, and is considered standard clinical practice. During all treadmill walking trials and training sessions, a safety harness will be worn and a trained staff member will be present to provide assistance in the event of loss of balance. During training, individuals will be allowed to use a small amount of body weight support (≤ 20% of body weight) to facilitate independent walking. The harness will be designed to eliminate the consequences of falling as the device "catches" the subject should they trip or stumble. The presence of this device affords comfort and diminishes the "fear of falling" in subjects.

Dr. Ramakrishnan has been granted permission to break the blind of the data to ensure that randomization to each group is not harmful to the participants. This plan is thoroughly described in the Research Plan and Human Subjects sections. All serious adverse events will be analyzed by the investigative team and the MUSC Institutional Review Board. Serious adverse events are defined as 1) being unexpected; 2) related to a subject's participation in research; and 3) that subjects are at greater risk of harm than was previously recognized. If greater than 10% in each cell have a serious adverse event, we will evaluate the circumstances and decide if the event was caused by a particular treatment. If a majority of team or the IRB decides that the adverse event was related to intervention, Dr. Ramakrishnan will stop randomizing that patient profile into that group.

Protection Against Risk: A licensed physical therapist will be present in the building during all treatment sessions. In addition, during all treadmill walking trials, a safety harness will be worn to provide assistance in the event of loss of balance. The research staff will closely monitor the subject to ensure their comfort. Any adverse events will be recorded and monitored as required by our Institutional Review Board. In the event of an adverse medical event, standard facility emergency procedures will be followed and proper personnel notified. The PI on this proposal is a licensed physical therapist with over 22 years of experience in the development and implementation of exercise interventions. On-site medical services will be available in the event of adverse events to the subjects. Subjects will be able to terminate the training or testing sessions at their request at any time without prejudice. Minimization of risk will be accomplished by monitoring vital signs every 5 minutes within prescribed criteria for termination of the training session. We will follow the American College of Sports Medicine criteria for terminating an exercise session which

includes: subject complaints of light-headedness, confusion, or dyspnea; onset of angina; excessive blood pressure changes (systolic BP greater than 220 mmHg, diastolic BP greater than 110 mmHg); and inappropriate bradycardia (drop in heart rate >10 beats per minute).

Confidentiality: All records regarding participation in this study will be kept in locked file cabinets in the appropriate laboratories and/or offices, and stored on password-protected computers/servers in the offices and laboratories of the PI's research team. There will be no direct link to participant identifying information (other than subject code) without access to a password-protected computer containing the identifying information linking information to a given subject. Access to linked identifiers is limited to research personnel intimately involved with the human subjects. All data and records acquired from subjects is for research purposes only and will be kept confidential and maintained in a secure database identifiable only by subject code. The results of the study may be published for scientific purposes; however, subjects' identities will not be revealed and data will not be traceable to any individuals in any resultant publications. The information gathered during this study will be kept confidential to the extent permitted by law.

14.0 Potential Benefits to Subjects or Others

Subjects with who participate in this study may see improvements in their functional ability, but any benefit cannot be guaranteed. Others may benefit from advancement of scientific knowledge. Given the minimal risks involved and the potential for improved functional capacity, the potential benefits of participation make the potential risks reasonable

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