Use of a Powered Orthotic Exoskeleton to Promote Mobility Through Improved Squat, Knee Flexion and Loading of the Paretic Leg in Persons with Chronic Stroke

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Abstract:
Veterans who suffer strokes often have disturbances in the ability to walk that reduces independence and quality of life (QOL). Alterations in gait combined with general decreased activity are associated with reduced muscle strength of the paretic leg. This leads to cardiovascular deconditioning and reduced QOL. There is a new and novel battery powered device (Keeogo powered orthotic exoskeleton) that uses motors that assist knee movement while walking, sitting down, and standing up. The Keeogo monitors hip movement to assist the knee, making it simple to learn how to use. If successful, this project will show how this device will help improve the ability to walk and provide evidence to support larger clinical trials in a home and community setting to improve mobility, increase muscle mass and strength in the legs, as well as improve general health and QOL. Lastly, this device could be used to increase motivation and confidence in a person to walk for longer periods of time and distance, providing the ability to walk in places that were previously inaccessible.

Project Summary:
Ninety percent of stroke survivors have clinically significant gait impairments that lead to secondary medical complications, including cardiovascular deconditioning and reduced QOL. Several rehabilitative interventions that increase the level of activity and mobility have been shown to be beneficial. Challenges posed by most of these locomotor gait training interventions require recurring visits to a rehabilitation center. The recent development of novel powered exoskeletons offers a potential mechanism for stroke survivors to improve mobility in the home and community. Although the predominant research using these devices have been in persons with spinal cord injury, there are currently two devices approved by the FDA for use in patients with stroke and additional devices are being developed. The Keeogo powered orthotic exoskeleton is a novel device intended for persons with stroke who can ambulate but have gait impairment. This device consists of a ridged orthotic structure placed over clothing on the legs and batteries to the power motors that assist both knees in gait movement. The system monitors hip movement driven by the user and interprets this movement to apply the appropriate assistance at the knee joint. This unique approach makes learning intuitive, enabling the user only to acclimate to the system rather than learning how to control the device to initiate the desired movement.

This proposal is a randomized controlled pilot study. Fifteen veterans with chronic stroke (>6months) and who retain some ability to take steps but have impaired gait will be recruited. Ten participants will be randomized into the exoskeleton group and 5 into the control group. Both groups will be asked to complete 36 one-hour sessions of ambulation training. The exoskeleton group will train using the Keeogo powered orthotic exoskeleton and the control group will train without using their own conventional aide.

The primary aim is to determine the efficacy of training with this exoskeleton and its ability to improve transfers to standing and sitting as assessed by the five times sit-to-stand test. A secondary aim will be to assess effects of the device during overground ambulation. Outcome measurements to investigate changes of knee range of motion and loading of the paretic limb will be accomplished using an instrumented goniometer; changes in limb loading will be monitored using a foot pressure mapping system; and stepping parameters will be recorded using the GaitRite carpet. An exploratory outcome of changes in energy expenditure during ambulation with and without the powered exoskeleton will be assessed from a 6-minute walking test using a portable metabolic cart. Another exploratory outcome measures of QOL will be determined using the SF-36 and

the Stroke Specific Quality of Life Scale. Additional exploratory outcomes to measure body composition, bone mineral density changes will be assessed using Dual X-ray Absorptiometry (DXA). Additional exploratory outcomes include measuring changes in cortical, corticospinal and spinal excitability in response to brain, spinal and peripheral nerve stimulation (PNS), and brain activation using electroencephalogram (EEG).

Baseline testing for both groups will be performed while ambulating without the device and prior to starting in the training program. The exoskeleton group will repeat testing within the first 3 sessions of the training program. Mid-point assessments will be obtained after 12 and 24 sessions of training. Post assessments will be obtained after 36 sessions of training. Retention will be assessed by repeating the assessments without the exoskeleton after 1 month of stopping the training program.

It is anticipated that longitudinal training with the device will increase number of squats achievable, increase knee flexion during swing, increase loading of the paretic limb, and induce symmetrical stepping. No immediate effect on energy expenditure by the device is expected however, a training effect is expected to demonstrate improvement in the energy cost of ambulation. Any gains observed during this study may not be retained, but as this device has the potential to be used in the home and community environment, justifying a prescription of this device for retention purposes may be warranted. Use of this device may also lead to improvement of QOL.

2. Specific Aims

During ambulation, stroke survivors reduce loading of the paretic lower extremity (LE) by decreasing the amount of weight and time spent loading the limb (1). Alterations in gait combined with general decreased activity are associated with reduced muscle strength of the paretic LE (4). The combination of LE weakness and altered gait can lead to cardiovascular deconditioning and reduced QOL. In effort to increase mobility to a greater extent than that of ambulation with use of typical passive orthotics, powered exoskeletons are being developed to enhance or enable persons with stroke to ambulate thus promoting the use of their paretic limb. These powered devices use motors that power joint rotation to assist the stepping action during ambulation. Learning to ambulate independently in these devices is difficult and lengthy (5, 6). A new powered orthotic exoskeleton, which powers only the knee joint by monitoring volitional movement of the hip joint offers a simple and intuitive approach to assist with ambulation. The range of motion (ROM) of the knee can be adjusted to assist with knee flexion during the swing phase and knee extension during the stance phase of gait. The level of assistance and intuitive activation of this device is hypothesized to promote greater use of the paretic limb in persons with stroke.

The purpose of this pilot project is to investigate the use of a powered orthotic exoskeleton that provides active assistance to the knee joint in persons with impaired gait due to stroke. This pilot project will assess the changes in use of the paretic LE, energy expenditure of walking with and without the powered orthotic exoskeleton, measure longitudinal changes in QOL, bone density, body composition, neuronal excitability, and brain activation. Promoting greater use of the paretic limb in stroke survivors is expected to improve the energy cost of walking and QOL. The results of this work are anticipated to power future investigations of using powered orthotic exoskeletons in the home and community environments to improve ambulatory ability, functional capacity, and thus further improve QOL. The potential for associated benefits for improved cardiovascular function will also be explored in future studies.

Primary Aim: **To determine the change in the ability to squat (LE power) as measured by the Five Times Sit to Stand Test (5xSTS), while wearing and not wearing the powered exoskeleton.**

The 5xSTS is used to determine leg power and an aspect of transfer skill. This test will be used to assess a level of improved function while wearing the device. It will also be used to determine if any training effect is observed after 3 months (36 sessions) of training when not wearing the device.

Secondary Aim: **To determine the efficacy of ambulation training using a powered orthotic exoskeleton on knee ROM and loading of the paretic LE while ambulating over ground with and without the device for 3 months (36 sessions).**
Multiple outcome measures will be used to determine the effect of the powered exoskeleton on a person's gait biomechanics and functional competency. An instrumented goniometer will record knee joint angles during multiple gait cycles to assess changes in knee flexion during the swing phase. Because the powered orthotic exoskeleton provides stability during the stance phase, stepping parameters will be assessed using an instrumented carpet to determine if the paretic limb has more equitable and symmetrical load.

Secondary Aim**: To determine the energy expenditure of ambulation with and without the powered orthotic exoskeleton at baseline and 3 months (36 sessions) post training.**
A portable metabolic cart will assess oxygen consumption during the two ambulation conditions (i.e., with and without the device) over a 6-minute period. It is anticipated that the baseline comparison test will not show any metabolic changes due to the added weight of the device and negate any metabolic benefit from the motors powering the knee joint movement. However, a training effect over the 3 months (36 sessions) compared to baseline is anticipated due to the participant becoming more comfortable with the device, thus using the paretic LE more effectively.

Exploratory Aim: **To determine the retained function (squatting, knee ROM, paretic LE loading and energy expenditure) 1-month post cessation of training without the device.**
It is not known whether any benefits from training will be retained, but if benefits exist while wearing the device, but are not retained, then long term use may be indicated.

Exploratory Aim: **To determine differences in QOL measurements (SF36 and Stroke Specific Quality of Life Scale [SS-QOL]) over 3 months (36 sessions).**
The mobility portions of the SSQOL and SF36 will be used to determine whether changes in ambulation affect QOL in persons post stroke.

Exploratory Aim: **To determine changes in bone density and body composition (DXA) over 3 months.**
DXA scans of the total body, both hips, and both knees will be used to determine whether any significant changes occur in bone density and body composition.

Exploratory Aim: **To determine changes in cortical, corticospinal and spinal excitability over 3 months.**
Motor responses evoked by noninvasive brain, spinal and PNS will be measured at baseline and after 3 months of training to determine if any significant changes occur in neuronal excitability.

Exploratory Aim: **To determine changes in brain activity (EEG) over 3 months.**
Brain activity will be measured using EEG at baseline and after 3 months of training to determine if any significant changes occur in brain activity.

2a. Research Plan

Background and Significance
In the United States, 90 percent of stroke survivors experience long-term disability associated with mobility impairments (7). Reduced functional use of the paretic leg is associated with reduced weight bearing and time spent on the paretic limb during ambulation. Impaired control of the paretic limb results in alterations in gait mechanics, including reduced knee flexion angle during swing phase and reduced time and load during stance phase of ambulation (1). Difficulty in performing a squatting motion translates into an impaired ability to

perform vital activities such as sit-to-stand and stand-to-sit transfers. These alterations adversely impact overall mobility and is correlated with: cardiovascular deconditioning, impairment of balance, inhibition of motor control, promotion of muscle wasting and weakness on the paretic side. Reduced mobility may compound these associated complications in this compromised population. Therefore, developing strategies such as using a powered exoskeleton to improve ability to stand up and sit down and normalize gait may benefit overall health status and QOL (8).

Repeated training of specific tasks has been shown to produce functional benefits in persons with stroke (9, 10). Performing lower extremity exercises, including different walking tasks and repeated sit-to-stand tasks, has contributed to improved walking speed and endurance (10). A randomized controlled trial enrolled 61 stroke patients into a monitored program to perform functional exercises, i.e. repeated sit-to-stand tests, for 14 days. The results indicate that functional exercises can improve overall mobility in stroke patients ($p=0.002$) (11). Programs that improve basic mobility are believed to translate into improved standard of living (12).

Cardiovascular health and metabolic fitness significantly declines in stroke patients and is thought to be attributed to the decline in weight-bearing mobility. A meta-analysis reported that one third of stroke patients have more than 50% coronary stenosis and 3% are at risk for the development of a myocardial infarction within the first year following a stroke event (13). Existing interventions used to combat cardiovascular and metabolic decline are activity-based and include treadmill gait training and robotic-assistive gait training (14, 15). To our knowledge, specific studies published on the effect of using overground exoskeletal devices on cardiovascular health in stroke patients do not exist. Current reports are concentrated to persons with spinal cord injury (SCI) using a device that fully controls all the movement of the legs (2, 3, 5, 16-19). These studies discuss the activity level necessary to potentially improve cardiovascular health (2, 5). In addition, persons with stroke, who ambulate without a device, require twice the energy cost compared to able bodied controls (20). Therefore, using a powered exoskeleton may allow for longer and more frequent bouts of walking resulting in improved cardiovascular conditioning, even if the device reduces the energy cost of walking (21).

Currently, there is a diverse group of powered exoskeletons available, either commercially or for investigational purposes, that support paretic individuals, depending on the extent of gait/functional impairments (5, 17, 18, 22-25). These devices enable a person with hemiparesis to ambulate overground by appropriately shifting the person's weight and triggering sensors to initiate a step. These devices have also been hypothesized to have a therapeutic effect because improved coordination of muscle activation patterns while ambulating with an exoskeleton has been observed (26). An advantage of these devices over treadmill training is that there is potential for use at home and in the community.

A new and novel type of robotic-device (Keeogo, B-temia, Inc.) was developed to provide powered assistance at the knee for persons with stroke. This device differs from other Food and Drug Administration (FDA) approved devices for individuals with stroke (e.g. Ekso (23) and Indego (22)) in that it only assists the knee joint. This device provides assistance for both knee extension and knee flexion during ambulation, transfers to standing and sitting, in addition to ascending and descending stairs. It is capable of providing up to 40Nm of knee extension and 20Nm of knee flexion which is only a portion of the 50-70Nm of knee extension and up to 20 Nm of flexion used during ambulation (27). As this device isn't able to fully control the movement, it requires the ability of the patient to stand and initiate stepping. The approach the Keeogo uses to monitor the desired movement in order to appropriately provide assistance is different than other exoskeletons. The Keeogo rapidly monitors movement at the hip and, in real-time, provides the partial assistance needed at the knee to take each step. This promotes intuitive learning for the user, minimizing the amount of instruction and practice needed to effectively ambulate. Users have been able to independently ambulate within one session. Other powered exoskeletons require multiple training sessions for the user to achieve independence. This device does not restrict leg movement, so the user can side-step and walk backwards. However, it does not provide assistance during these movements.

Improved ambulation is the most frequently mentioned goal of patients interviewed after stroke (28). The Keeogo powered exoskeleton could potentially be used in any environment including the home and community to augment mobility. It also has the potential to provide rehabilitative treatment as it requires intent to perform the movement and only provides partial assistance. Showing that device that can assist with

ambulation in addition to other challenging tasks such as sitting down, standing up, squatting and other daily activities has the potential to greatly improve the lives of people with residual paresis after stroke. The Department of Veterans Affairs Rehabilitation Research and Development (RR&D) in the Small Projects in Rehabilitation Research (SPiRE) request for applications expressed particular interest in "exoskeleton research, including externally-powered motorized orthoses for stroke…". The proposed work will generate data to support future proposals focusing on long term use in the home and community environment to increase time being mobile, assist with activities of daily living (ADLs), improve QOL, improve cardiometabolic health, reduce muscle atrophy and offer the potential of preventing bone demineralization of the paretic limb in persons with stroke.

Preliminary Studies

The principal investigator (Pierre Asselin) and the co-investigators (Drs. Ann Spungen, Stephen Kornfeld and John Handrakis) have extensive experience using powered exoskeletons, with most of the work having been accomplished in persons with SCI. Our group has published and presented the use of powered exoskeletons on the foot-loading profiles, metabolic demand, ambulation ability and body composition in persons with SCI; our investigators are recognized as international authorities in the study of exoskeletal devices. Since early 2011, our group has trained approximately 200 individuals with SCI to walk using a powered exoskeleton (ReWalk, Ekso and Indego). The following work published by the principal investigator and his co-investigators in SCI mirrors the proposed investigation in stroke survivors for this application.

Outcome measurements for foot pressures during heel strike, mid-stance and toe off and energy expenditure during ambulation were obtained (2, 3). Measurements of foot pressures were used to determine the loading profile during different phases of gait using the F-Scan system (TekScan, Boston, MA, USA) from 6 participants with SCI and 3 able-bodied controls (3). The SCI subjects used in this analysis participated in the previously mentioned pilot study and ambulated at different skill levels. The able-bodied measurements were obtained during their normal self-selected pace, free of any assistance. Three of the SCI participants needed some level of assistance and three ambulated independently in the device. Data from a distance walked of 10m was analyzed for each step as a percent of the gait cycle. Foot pressures were then calculated as a percent of body weight and averaged throughout the stance phase. Both SCI groups revealed diminished force during heel strike, followed by a gradual increase in limb loading throughout the remainder of the stance phase where the peak force occurred at toe-off (Figure 1). This was different from the able-bodied group that showed the typical loading curve with an initial peak force occurring during heal strike, followed by a dip in limb loading during mid stance and then a second peak force during toe-off (Figure 1). Through observation, the altered gait in both SCI groups was hypothesized to be related to crutch use, where subjects were able to offload part of their body weight onto the crutches. During heel strike the crutches are on the ground to assist with maintaining balance. The toe-off period is when the crutch shift occurs, allowing independent participants to fully load the limb. Those who need assistance, shift their crutches earlier during double-stance, thereby diffusing part of the load to the other leg.

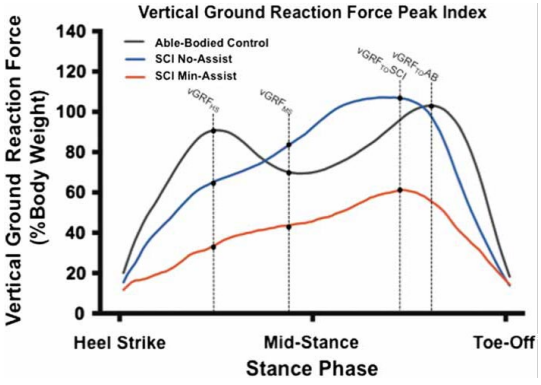

Figure 1: Vertical ground reaction force indexed: heel strike vertical ground reaction force ($vGRG_{HS}$), mid-stance vertical ground reaction force ($vGRG_{MS}$) and toe-off vertical ground reaction force ($vGRF_{TO}AB$ and $vGRF_{TO}SCI$) (3).

Eight participants participated in oxygen uptake (VO_2) measurement after 40 training sessions using a powered exoskeleton (ReWalk) (2). Each participant was asked to wear a mask attached to a portable metabolic system (Oxycon Mobile; Jaeger, Germany) and a 12-lead electrocardiogram that determined VO_2 and heart rate (HR) over one-minute intervals. These measurements were recorded during three phases: 6-minutes of sitting, 6-minutes of standing and 6-minutes of walking. Data within each phase were averaged and analyzed to reveal a significant increase ($p < 0.001$) in VO_2 response (Figure 2) during walking (11.2 ± 1.7 mL/kg/min) compared to

sitting (3.5 ± 0.4 mL/kg/min) and standing (4.3 ± 0.9 mL/kg/min). A similar response was observed in HR values (Figure 3) with a significant increase ($p < 0.001$) observed during walking (118 ± 21 beats per min (bpm)) compared to sitting (70 ± 10 bpm) and standing (81 ± 12 bpm). Prior to this work, many would hypothesize that ambulating with a device providing total assistance of leg movement would not result in a significant increase in energy expenditure, but this was not the case. Similar results have been shown with the Indego (5) and the Ekso (29) exoskeletons, which support that routine ambulation, at this level of VO2 and HR has the potential to decrease adiposity and other associated health-related consequences of paralysis. This work has not been performed using the Keeogo, but as it requires active user input at the knee joint, the user should also an elevated VO_2 and HR which may lead to a similar response.

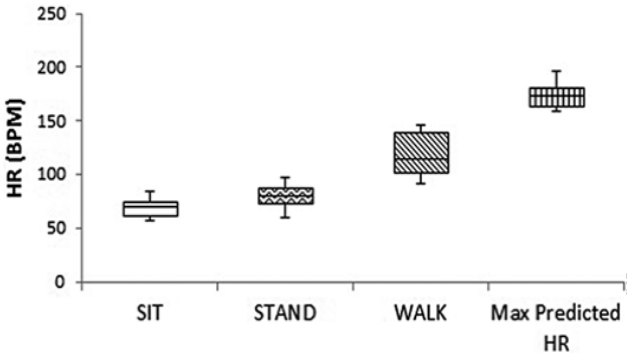

Figure 2: Box plot of oxygen uptake (VO_2) is displayed for each condition (SIT, STAND and WALK) and estimated maximal (Max) predicted VO_2 using predicted equations from leg and arm crank exercises. Significant differences ($p < 0.001$) were found between WALK compared with SIT and STAND (2).

Our group has studied the Keeogo powered orthotic exoskeleton in a preliminary safety trial that focused on adverse events. To date, two persons with stroke walked 10 sessions for a duration of one hour with the assistance of the Keeogo. It was observed that the participants appeared to exert themselves and knee ROM during gait was improved. No adverse events were reported for either participant and the assistance provided was set to less than half of the maximum assistance available. The first participant (right hemiparesis), used 15Nm of flexion and 3Nm for extension on the right leg and no assistance on the left leg. The second participant (right hemiparesis), used 11Nm of flexion and 8Nm for extension on the right leg and 9Nm of flexion and 6Nm for extension on the left leg. The device is able to provide up to 40Nm of knee extension and 20Nm of knee flexion and it is believed that this is the adequate assistance needed for those with stroke. The SPiRE award program is designed to fund small, high-risk projects that lack preliminary data and "develop/refine new intervention and delivery (or in a new setting or for a new population)". The pilot data from the initial study of the ReWalk powered exoskeleton in persons with SCI supported preliminary data for two randomized clinical trials (RCTs). One was funded by the Department of Defense (SC130234) as a three-site, outpatient base study to investigate changes in mobility skills, body composition, bowel function and several other secondary and exploratory outcomes. The other is funded by the VA Cooperative Studies Program (CSP #2003) and is a 15-site RCT to test safety and efficacy for QOL in a four-month home use trial.

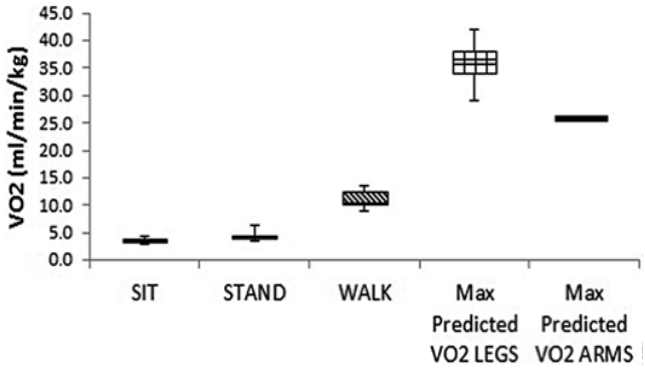

Figure 3: Box plot of heart rate (HR) is displayed for each condition (SIT, STAND and WALK) and estimated maximal (Max) predicted HR. Significant differences ($p < 0.001$) were found between WALK compared with SIT and STAND. BPM = beats per minute (2).

Based on the success of our pilot study in those with SCI using the ReWalk, we are proposing to perform a parallel pilot study using the Keeogo in Veterans with stroke and to seek funding from the VA RR&D SPiRE mechanism to support these goals. The results of this investigation would support future proposals for investigating benefits from using this exoskeleton in their home and community. Successfully demonstrating improved sit-to-stand and stand-to-sit ability, along with decreasing the metabolic cost of walking would support a hypothesis of using the Keeogo in a home and community environment to improve mobility and ease of performing routine tasks leading to improved QOL. These results would also support future investigations of home and community use that may provide therapeutic

benefit leading to increased use of the paretic limb even while not wearing the exoskeleton. With long-term use of this device, potentially this device could be used to combat muscle and bone loss in the paretic limb.

Research Design and Methods

Participants, Eligibility and Recruitment Strategies: Fifteen persons with stable, chronic stroke (>6 months) will be recruited through the various outpatient clinics that treat Veterans with stroke at the James J Peters VA Medical Center (JJPVAMC). There were approximately 402 unique Veterans with chronic stroke who obtained services during 2018 at the JJPVAMC. This would provide ample potential participants to prescreen 50 Veterans, as outlined in Table 1. It is expected that a portion (n~40) will express interest in signing informed consent, after which further screening will be performed. Candidacy will be determined based on the following inclusion and exclusion criteria: age between 18 and 89; weight under 250lbs, medically stable; and able to stand and initiate steps on their own with walking speed between 0.15-0.75m/s, but with chronic gait impairments such as reduced knee flexion and reduced time spent on the paretic limb during stance phase. A detailed list of the inclusion and exclusion criteria are presented in the Human Subject's section of this application. Because the effects of paralysis from stroke are believed to overpower the effects of age, gender or ethnicity, these demographic characteristics will not be restricted. A total of 15 participants are expected to enroll in the trial, however, to account for attrition, it is expected that 12 participants will complete the trial within the 2-year period.

Table 1: Recruitment efforts

	Year 1				Year 2				Totals
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	
Pre-Screening	10	10	10	10	10	0	0	-	50
Screening	-	7	10	10	10	3	0	-	40
Enrollment	-	3	4	4	3	1	0	-	15
Completers	-	0	2	3	3	3	1	-	12

Randomization: Eligible participants will be randomized into either the exoskeleton group or control group. Block randomization will used with a 2 to 1 ratio to result in 10 participants in the exoskeleton group and 5 participants in the control group (30). This ratio was chosen because future proposals will be focused on home and community use of the device, therefore more pilot data showing safety and feasibility is needed.

Description of Training Sessions: All participants will visit the JJPVAMC for 36 training sessions, 3 times per week for 3 months and will follow the recommendations of the American Heart Association (AHA) and American Stroke Association (ASA) (20). Those in the exoskeleton group will train using the Keeogo powered exoskeleton and those in the control group will train without the exoskeleton using their conventional assistive devices. Training sessions will be progressive, with duration to tolerance for a minimum of 20 minutes and a maximum of one hour. Training will consist of mobility activities affecting daily life including: walking; squatting (or getting in and out of a chair); bending, kneeling or stooping (for picking an item up off of the floor); and ascending and descending stairs. Sessions will be monitored and tailored to the individual, based on their functional ability and to ensure their safety. Exertion will be maintained at a level between 11-14/20 using the Borg scale (31), as per recommended by the AHA and ASA (20). All participants will be allowed to take as many breaks as needed during each session.

Technical Description of the Keeogo™ Powered Orthotic Exoskeleton: Those randomized into the powered exoskeleton group will be using the Keeogo™ (B-Temia Inc., Quebec City, QC, Canada) (32), which is a powered orthotic exoskeleton, designed for users who have difficulty ambulating and/or need assistance with movement of the knee (Figure 4). This device does not restrict movement and only provides assistance at the knee during extension and flexion during ambulation, standing up, sitting down and when ascending or descending stairs. It is not intended for use in those who have complete paralysis of their leg as it requires some active movement to assist with. The Keeogo™ weighs

Figure 4: Keeogo

~15lbs and consists of a combination of soft material and rigid structure that can be adjusted to the person, while attached to both legs.

The motors are attached on the shaft just above the knee and capable of providing various levels of assistance of knee extension (up to 40Nm) and of knee flexion (up to 20Nm) which can be adjusted for each leg independently. This system can assist during ambulation and during concentric and eccentric phases of functional mobility activities (i.e., sit to stand, stand to sit, squatting, lunging and stooping). The device only provides assistance as the user starts to actively perform a movement and does not completely control movement. The user is able to stop the movement, even in the middle of a gait cycle, by volitionally stopping movement of their leg. Therefore, intent to perform the movement is required which will ensure they remain active even if the effort level is diminished because of the assistance provided by the motor.

The system is powered by a lithium-ion battery that can be clipped on the waist belt, making it portable and usable in the home and community. The assistance applied to each leg can be adjusted separately and in two ways. Gross adjustments can be changed by the user at any time using the integrated control unit. The level of assistance is indicated by a colored light emitting diode. Fine tuning the assistance level is accomplished by the trainer using a tablet interface with configuration software.

This device separates itself from the other powered exoskeleton devices (e.g., Indego, Ekso) because it only provides assistance to the knee joint and requires the user to have some ability to ambulate independent of the device. Therefore, the user must be able to initiate the active movement, which will then be enhanced by assistance from the Keeogo. The system assists the knee to enhance user-initiated movements by using kinetic and kinematic data from sensors located at the knee and hip joints to assist in all phases of the gait cycle, i.e. knee flexion and extension in swing phase, knee extension (both eccentric control and concentric assist) in stance phase. In addition to gait, the device assists during other functional lower extremity activities, i.e. squatting motions, kneeling, walking, stair climbing and stand-sit/sit-stand transfers. Keeogo™ has two essential functions: (1) to provide kinematic amplification during the swing phase of gait and (2) to provide stability for the stance phase of gait through knee bracing coupled with non-linear spring-like assistance. Keeogo™ is designed to operate intuitively through automatic sensing and augmenting the user's natural walking movement. The eccentric control assists during the gait cycle at initial contact (loading response), squat (Figure 5), kneel, stand to sit and stairs. The eccentric control applies the torque gradually, thus stabilizing the knee and preventing buckling.

Figure 5: Squatting in the Keeogo

Outcome Measurements and Testing sessions: The timeline for conducting testing sessions is outlined in Table 2. Screening participants and obtaining their medical history and demographics will be obtained once, prior to initiating training. Baseline assessments that do not involve the exoskeleton will be obtained prior to training in both groups. Baseline assessments, which involve the exoskeleton (for the exoskeleton group only) will be obtained during the first three sessions after the participant has been correctly fitted and acclimated to the exoskeleton. Testing will be repeated after training session 36 (3 months) without the exoskeleton for both groups and repeated with the exoskeleton for the exoskeleton group. All participants (control and experimental) will be asked to return 1-month post cessation of training for a follow-up visit where all the outcome measures will be repeated without the exoskeleton for both groups (Table 2) to assess retention of functional gains.

Table 2: Timeline for testing and training

Schedule of Procedures and Testing										
Week:	**-2 to -1**	**-1**	**1-4**		**4-5**	**5-8**	**8-9**	**9-12**	**12-13**	**16**
Phase	**Pre Screen**	**Screening /Baseline Testing**	**Training**		**Assessments**	**Training**	**Assessments**	**Training**	**Post Assessments**	**1-Month Follow-up**
Chart reviews	x									
Consent	x									
Medical History/ Demographics		x								
Fugl-Meyer		x			x		x		x	x
EEG		x			x				x	x
Neuronal Excitability		x							x	x
DXA		x							x	
QOL(SF36 and SSQOL)		x							x	
Training session number			1-3	3-12		12-24		24-36		
Assessments with out Keogo (both Control and Exoskeleton group)										
5xSTS		x	d	d	x	d	x	d	x	x
Gaitrite		x	w	w	x	w	x	w	x	x
F-Scan		x			x		x		x	x
Energy Expenditure		x			x		x		x	x
Knee range while walking		x	w	w	x	w	x	w	x	x
10mWT		x	d	d	x	d	x	d	x	x
TUG		x	w	w	x	w	x	w	x	x
6MWT		x	d	d	x	d	x	d	x	x
Assessments with Keeogo (only Exoskeleton Group)										
5xSTS			d	d	x	d	x	d	x	
Gaitrite			w	w	x	w	x	w	x	
F-Scan			x		x		x		x	
Energy Expenditure			x		x		x		x	
Knee range while walking			w	w	x	w	x	w	x	
10mWT			d	d	x	d	x	d	x	
TUG			w	w	x	w	x	w	x	
6MWT			d	d	x	d	x	d	x	

Key: w=weekly; d=daily; x=once

The 5xSTS test will be used to address the primary aim of improving participants' squatting ability (LE Strength) (33). This test is performed using a standard free-standing chair with a straight back, solid seat and a seat height of 17 inches. Participants will be instructed with the following statement "By the count of 3, please stand up and sit down as quickly as possible for 5 times. Place your hands on your lap and do not use them throughout the procedure. Lean your back against the chair's backrest at the end of every repetition." The time to complete the test will be recorded and will start once the person back leaves the back rest and stops once the back touches the back rest for the 5th time.

Assessment of gait changes will be performed using the GaitRite Carpet (CIR Systems Inc), the F-scan foot pressure system (Tekscan) and the instrumented goniometer (bendlabs). These measurements will be performed with and without the device. The GaitRite measurement will be obtained by asking each participant to walk over a carpet equipped with sensors, which provide information regarding cadence, step length and time spent on each foot. The F-Scan foot pressure system requires the participant to walk with a disposable insole, which is cut to fit inside their shoe. The disposable insole contains an array of sensors, which provide a continuous pressure profile of each foot during ambulation. This system will measure the percentage of total body weight loaded during the different segments of the stance phase (heel-strike, stance and toe-off) as well as

during the entire gait cycle for each lower extremity. An electronic goniometer will be strapped to each lower extremity for independent and simultaneous measurement and recording of knee ROM.

Testing sessions to assess energy expenditure will be performed. Participants will be asked to wear a face mask attached to a portable metabolic cart (Oxycon Mobile, Vyaire Medical Inc.). Measurements of oxygen uptake (VO_2), heart rate (HR) and respiratory rate (RR) will be assessed and recorded. These measurements will be acquired during 6 minutes of quiet sitting (rest) followed by ambulating at a comfortable, self-selected pace for 6 minutes.

The Fugl-Meyer Assessment Lower Extremity (FMA-LE) will be used as a general score of lower extremity motor and sensory function/post-stroke recovery (34). General changes in QOL will be assessed using the SF36 (35) and SSQOL scales (36).

A Dual X-Ray Absorptiometry (DXA) will be used to determine changes in body composition and bone density. A scan of the total body will be used to view changes in bone mineral content (BMC), lean mass, and fat mass. Scans of both hips, and both knees will be used to compare bone mineral density (BMD).

Motor responses will be measured using surface electrodes placed on the participants skin over key muscles to determine changes in cortical, corticospinal and spinal excitability. These responses will be brought about using either transcranial magnetic stimulation (TMS), transcutaneous spinal cord stimulation (TSCS) or PNS. TMS uses electromagnetic pulses, while TSCS and PNS use a series of electrical pulses. Whether it is stimulation over the brain, spine or peripheral nerve, stimulation causes the targeted muscles to twitch. These twitches are then recorded and compared.

EEG will be used to measure changes in brain activation. A 64 electrode EEG cap will be placed on the subjects head and will record brain activity during a resting state.

Description of Data and Statistical Analyses

The loading profile obtained from the F-Scan foot pressure system will be normalized over the gait cycle as percentage of gait cycle and percentage of body weight for each foot. The total area under the curve will be calculated to obtain a total load on each lower extremity. Peak measurements from heel strike and toe-off will be calculated from the curve along with mid stance where load is typically diminished. Maximum knee flexion angles from 10 continuous steps will be averaged for each limb.

Metabolic measurements (VO_2, HR and RR) will be recorded as averages every minute. Energy cost of distance travelled will be calculated by dividing VO_2 normalized to body weight (ml/kg/min) by the distance traveled (ml/kg/m). The 6 values from the consecutive 1-minute recordings will be averaged for sitting and walking conditions.

Descriptive statistics will be employed for demographic and Fugl-Meyer data. A single group, repeated measures design will be employed in the experimental group to test the within-group effect of using the powered exoskeleton. A two group repeated measures design will be employed to test the between-group differences in outcomes. All outcome measurements will be analyzed using a mixed model ANOVA to determine significant main and interaction effects of group (control, experimental) and time (baseline, session 36, 1-month follow-up). A similar mixed model ANOVA will be used to determine significant main and interaction effects of the two conditions (without [w/o] and with [W] Keeogo exoskeleton) in the experimental group for the 3 time points (baseline, session 36, 1-month follow-up). Post hoc analyses of significant data will be performed using t-tests.

Table 3: Timeline of activities to complete the study

TIME LINE	Year 1				Year 2			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Start-up Activities								
IRB & R&D	x				x			x
Staff Hiring and Training	x							
Purchase Equipment	x							
Database development	x							
Participant Screening		x	x	x	x	x		
Partcipant Enrollment		3	4	4	3	1	0	
Database management		x	x	x	x	x	x	
Abstract writing					x	x	x	
Manuscript writing							x	x

Potential Difficulties and Limitations

The greatest hurdle in conducting investigations with devices is recruiting participants and completing the training as well as obtaining regulatory approval to conduct the study. Feasibility to enroll and complete the 15 participants is

presented in Table 3. We are anticipating enrolling 3-5 participants each quarter. Allocating 2 hours per participant for training sessions (time for set up, breakdown and 1 hour of ambulation training each day), would allow for 3 training sessions daily. This will provide 15 training session time slots per week and allow for up to 5 participants at one time. Assuming 4 participants train simultaneously and require 4 months each to complete the training (3-months training + 1-month follow-up), all 15 participants would complete data collection in 16 months. We have allowed for 3 months of startup and 3 months of closeout giving us a total of 18 months to complete data collection. This timeline allows for delays and downtime including a 2-month buffer to complete data collection. In addition, we have allocated 4 months of work load for the staff for training rather than the only the 3 months required to complete training.

We do not anticipate long delays obtaining IRB approval because our group has years of experience in submitting and obtaining IRB approval for similar investigations. In addition, we have communication with the FDA stating that the Keeogo device is a 'not a significant risk' (NSR) device (i.e., it does not have potential for serious risk to health, safety, or welfare of a subject). Therefore, the typical hurdle of obtaining an Investigational Device Exemption (IDE) is already completed for research investigation with this device. Another typical challenge associated with longitudinal studies is frequent travel to the VA for 1-hour sessions, several times per week, and for ~4 months. The recruitment effort and participant retention are outlined (Table 1). It is anticipated that about 30% of participants may not be interested or decide not to finish the study. Our previous experience with studies using powered exoskeletons is that retention is not usually an issue. To defray the cost of travel and compensate participants for their additional effort, a stipend will be paid to the participants for each session. The testing sessions do not pose any serious hazard to participants or personnel.

04. Human Subjects

A. Risks to Subjects

Human Subjects Involvement and Characteristics.
This study will recruit 15 people with chronic and stable stroke (>6 months) who are interested in ambulation training using a powered exoskeleton. This study will be conducted at the James J. Peters VA Medical Center (JJPVAMC) therefore recruitment training and testing in this project will require participants to travel to this medical center in the Bronx, NY. The following criteria will be employed for participation:

Inclusion Criteria:

1. Males and females between 18 and 89 years old;
2. Hemiplegia or hemiparesis due to stroke (>6 months);
3. Able to walk between 0.15-0.75m/s
4. Self-reported limitations to mobility and walking activities due to paretic side knee stiffness and loss of range of motion;
5. Weight under 250lbs
6. Desire to increase daily activity levels; and
7. Able and willing to commit to participation and follow directions and communicate basic needs.

Exclusion criteria:

1. Neurological paralysis causing an inability to stand, weight bear or take stepping movements;
2. Fixed contractures resulting in limited range of motion in the hip, knees, or ankles that prevent sitting, standing, walking, and/or squatting activities;
3. Modified Ashworth Scale for spasticity greater than 3 in the lower limbs
4. Able to walk at a normal walking speed (1.4 m/s, 3.2 mph) or better during the 6MWT;
5. Anthropometric incompatibility with the device
    a. Femur length less than 36 cm or greater than 45 cm;
    b. Upper thigh circumference less than 55 cm or greater than 75 cm;

c. Lower thigh circumference less than 27 cm or greater than 40 cm;
d. Calf circumference less than 33 cm or greater than 49 cm;
e. Ankle circumference less than 27 cm or greater than 40 cm;
f. Shin length less than 26 cm;
g. Waist circumference less than 71 cm or greater than 107 cm;

6. Any medical complication or co-morbidity as judged by the study physician to be contraindicated for wearing the device or walking (e.g., cardiovascular disorders, pressure ulcers, open wounds, lower limb vascular disorders, or other medical conditions); and
7. Pregnant or planning to become pregnant (Female participants).

A subset of participants will have MEP recordings using as a result of PNS, TSCS and TMS. The inclusion criteria is the same as previously described. The following is the additional exclusion criteria.

Exclusion criteria:

1. History of seizures, brain tumor, brain surgery, or brain abscess;
2. Use of medications that significantly lower seizure threshold, such as amphetamines, neuroleptics, dalfampridine, and bupropion;
3. History of moderate or severe head trauma (loss of consciousness for greater than one hour or evidence of brain contusion, hemorrhage or depressed skull fracture on prior imaging); Recent (within the last 5 years) brain injury with definite loss of consciousness;
4. History of implanted brain/spine/nerve stimulators, aneurysm clips, ferromagnetic metallic implants, or cardiac pacemaker/defibrillator;
5. Significant coronary artery or cardiac conduction disease;
6. History of bipolar disorder; Active psychosis;
7. History of suicide attempt;
8. History of migraines or reoccurring headaches;
9. Heavy alcohol consumption (greater than equivalent of 5 oz of liquor) within previous 48 hours;
10. Open skin lesions over the face, back, legs, or feet;
11. Unsuitable for study participation as determined by study PI.

In this study, special classes of participants such as pregnant women, prisoners, institutionalized individuals, or other populations that may be considered vulnerable will be excluded from this study except for economically and educationally disadvantaged persons. There are Veterans and military members who are economically, educationally or socially disadvantaged individuals and they will be given the opportunity to participate in this research project. We will not try to identify those who are economically and educationally disadvantaged as the details of this study would not influence their decision to participate. These disadvantaged persons will be given the same treatment as individuals who are not considered to be vulnerable.

Recruitment Methods

Recruitment for this study will comply with the standards of VHA Handbook 1200.05 and is planned to be performed in the following ways:

- Referrals from primary care physicians.
- The investigators have applied for a waiver of HIPAA in order to obtain contact information (name, mailing address and phone number) to mail out study information and follow up on the mailing. This is requested because the investigators would not be able to achieve the recruitment rate needed for this study through other recruitment methods. Participants will be identified using ICD-9 or ICD10 codes to identify patients with stroke who receive care at this facility. The data bases that will be queried will include CPRS, VINCI, CDW and from previous participants that have agreed to be contacted for future studies. Once a list of participants is obtained, recruitment letters/ pamphlets will be mailed. Obtaining this list poses no more than minimal risk to participants and it will be destroyed upon completion of recruitment for this study in order to reduce risk to participants.

- Potential participants that have contacted us previously will be contacted about this study.
- Phone calls will be made to potential participants after initial contact has been made in person or by mailing a recruitment letter.

Sources of Materials.
This research study will not have overlap with the participants clinical procedures or other research studies, therefore no existing specimens, records or data will be used. For the purposes of this investigation, all information and materials obtained from the participant will be used solely for research purposes. No blood or urine specimens will be collected on the participants.

The records that contain PHI that is obtained through the waiver of HIPAA will be stored in electronic format on the VA Network protected by the VA firewall or in hard copies at the JJP VAMC in room 7A-13 in locked cabinets where only authorized personnel will have access. Once recruitment for the study is complete these records will be destroyed.

Other study related material will be stored in locked cabinets in locked rooms at the JJP VAMC in room 7A-13. Electronic files will be stored on the VA network protected by the VA firewall. These records will be maintained according to the requirements for maintaining Federal records according to the VHA Records Control Schedule (RCS) 10-1.

Potential Risks.
The health risks associated with this research study are considered greater than minimal risk. All the risks with this study are associated with the research being conducted and there are no therapeutic risks. As with any investigational study, there may be adverse events or side effects that are currently unknown. In the case of a serious adverse event during the study, hospital emergency personnel will be summoned by study personnel. The following list contains potential risks/and or discomfort related to study procedures:

The risk of falling: This could be caused by loss of control of the ambulation activity by the participant or therapist as well as malfunction of the Keeogo device itself. The risk of falling will be minimized by having experienced research personnel conduct the participant training sessions with assistance as needed and participants will be allowed to use their usual assistive device (cane, walker or other), if needed, when they ambulate with and without the Keeogo. The risk of falling is minimized by excluding individuals with stroke who cannot stand and ambulate.

Discomfort, skin pressure/friction, bruising, pain, or unusual swelling caused by the exoskeleton which has the potential to lead to skin breakdown or abrasions. This risk will be minimized by a thorough skin check performed by experienced research personnel at each training session. Adjustments to the device fit and additional padding will be assessed to decrease the risk of skin breakdown as well.

Blood pressure instability during use of the device related to physical activity during testing and training procedures may occur. This risk will be reduced with frequent subjective assessment of participant's symptoms as well as assessment of blood pressure and heart rate prior to training, as necessary during training and following training. Activity will be stopped in the event of instability of vital signs and as recognized by experienced research personnel. Medical clearance will be required prior to any study related activities.

The device itself could malfunction. The device has built-in mechanical stops to limit the devices ability to move through abnormal ranges of motion. In addition, the activities that will be performed with the device will be performed by trained research personnel to monitor device function during use. Participants that use the device in the home environment will have had many hours of prior training to use the system and will be trained to handle any device malfunction.

The DXA scans involve ionizing radiation. We estimate all of these DXA measurements combined will sum up to less than 35 μSv of absorbed radiation. This measurement is minimal even when compared to a routine chest x-ray which has an approximate dose of 60 μSv. In addition, the average person in New York City receives approximately 3000 μSv/year. Therefore, you would have to have all these tests done 100 times to receive an equivalent dose.

Scan Type	Entrance Dose	Effective Dose	Scan Time
Total Body	6 μGy	8.62 μSv	739 sec
Dual Femur	329 μGy	12.3 μSv	212 sec
Knee	34 μGy	2.0 μSv	54 sec

This research may have unknown effects on an unborn child. For female born participants, the study should not be performed during pregnancy (a pregnancy test may be requested). You also agree to avoid becoming pregnant during the study.

There always exists the potential for loss of private information; there are procedures in place to minimize this risk.

There may also be potential risks that are unknown.

Additional risks related to the additional pilot study involving brain, spine and peripheral nerve stimulation:

TMS carries several potential risks. Most of these risks are much greater during application of repetitive TMS, or rTMS (defined as pulses given at a frequency of 1 per second or more frequently), which will not be conducted in this study. There is a small risk of seizure or "convulsive syncope" (fainting with seizure-like movements).

- Before you begin participation in the Study, we will screen you for seizure risk, such as history of prior brain injury, or taking certain medications that raise the risk of seizure. If your seizure risk is too high, you will not be able to participate in the Study.
- Furthermore, the applied stimulus intensity will be kept below 200% of the motor threshold for each muscle. This intensity and pulse frequency fall far within the recommended safe guidelines delineated by TMS experts.

All procedures take place within the JJPVAMC, where there is access to all forms of life-support equipment, medications, and medical personnel. In the unlikely event of a seizure during this study, you should be aware of the implications a seizure could have on your future employment, insurance and eligibility to drive. Since such an event would be considered a response to the procedure and not an underlying disease, a letter documenting that this event does not indicate any underlying disease that could affect your employability, driver's license, or health/life insurability will be provided. If there are any symptoms of dizziness or lightheadedness, which could potentially be warning signs of convulsive syncope, we will halt the procedure immediately, investigate and take steps to end the symptoms. If you feel as though you will pass out. We will lie you down and elevate your legs. Those with previous history of syncope will be assessed for eligibility.

There is a possible but unlikely risk of TMS triggering psychotic or manic symptoms in participants with bipolar depression. This is a very small risk – it is not clearly above the natural rate for these types of symptoms to occur in participants with depression. You will not be able to participate in the study if you have a history of bipolar disease, active psychotic symptoms, or history of suicide attempt.

TMS pulses generate loud auditory clicks. Risk of hearing changes due to the 'click' of the stimulator will be minimized by using earplugs during the experiment. Individuals who complain of hearing loss, ringing in the ears (tinnitus), or ear pressure following completion of TMS will be referred to the appropriate medical care.

While individuals with cochlear implants will be excluded, pre-existing hearing issues will be assessed for eligibility.

Other risks including headache (which may include migraine), local pain, neck pain, toothache, and facial numbness/tingling are possible with magnetic stimulation. These symptoms are much less common using single or double-pulse TMS than rTMS. TMS may cause scalp tingling sensations, pain and toothache that is almost always mild and transient. Neck pain is usually related to the maintaining stationary head posture during the session. These symptoms will be minimized with adequate rest breaks, and acetaminophen (Tylenol) if necessary. Although not known to occur during the type of TMS used in this protocol, we will also monitor for other potential complications such as uncomfortable visual changes. Any complication will result in immediate cessation of the protocol.

The electro-magnetic field generated by TMS exerts forces on ferromagnetic objects such as implanted spine stimulators, deep brain stimulators, vagal nerve stimulators, cardiac pacemakers, cochlear implants, or aneurysm clips. For safety, anyone with such implants will be excluded. Furthermore, jewelry, glasses, and other potentially conducting or magnetic objects worn on the head will be removed during TMS experiments. It is worth noting that chronic exposure to electro-magnetic fields appears safe at levels even greater than those possible with TMS.

The research team has delivered TMS extensively in prior and ongoing IRB-approved clinical studies. A standardized form to assess TMS side effects is used at the end of each TMS session. Single and double-pulse TMS, as well as other precautions and exclusion criteria that we will follow, far exceed guidelines established by TMS experts.

Electrical pulses may be transiently irritating or uncomfortable. Stimulation will be reduced or halted, if a subject is too uncomfortable.

There is a possible but unlikely risk that magnetic or electrical stimulation could cause a heart rhythm problem. However, the stimulation procedure used in this study will not cause current to cross over the heart muscle. Nevertheless, to provide further caution against cardiac damage or rhythm problems, participants who have significant coronary artery disease, cardiac conduction disease, or implanted pacemaker/defibrillators will be excluded. To provide further caution, the procedure will be conducted with continuous vital sign monitoring. Any significant change in blood pressure or oxygen level, associated with symptoms such as sudden shortness of breath, chest pain, or sudden sweating, will lead to immediately cessation, further medical evaluation and treatment.

B. Adequacy of Protection from Risk

Recruitment and Informed Consent.

Potential participants with a history of chronic or stable stroke (>6 months) will be recruited in accordance with Health Information Portability and Accountability Act (HIPAA) from the Medical Service at the James J. Peters VA Medical Center, Bronx, NY, thru IRB approved advertisements, from those who contact the study staff from the ClinicalTrials.gov website, and a clinical referral from physicians at this institution that treat persons with chronic or stable stroke. Upon initial contact with a potential participant, the PI (or designee) will ask the individual what they know or have been told about the study prior to their arrival. After the potential subject reciprocates, the PI (or designee) will give a brief detailed non-scientific explanation of the research study purposes and objectives as well as an overview of the study requirements. Upon completion of this explanation, the PI (or designee) will ask the potential subject if they are still interested in participating. If the potential

subject is agreeable, a meeting time will be arranged to further explain the study, answer questions or address concerns prior to signing the consent forms. During this meeting, the PI (or designee) will read, verbatim, the consent form to the potential subject. After the consent form has been read, the PI (or designee) will ask if the potential subject has any questions, and to reiterate details of the protocol to insure they fully understand the commitments and is aware of their right to withdraw at any time without future prejudice. If there are no further questions, the consent form will be signed by the subject and the investigator. Copies of the signed and completed consent form will be entered in the electronic medical record system and a copy given to the subject. Every effort will be made, within the constraints of the enrollment criteria, to enroll women and persons of diverse ethnicities in the proposed research investigations.

Protection Against Risk.
The PI will oversee the conduct of data collection and will review all aspects of the data's quality during and immediately after data collection on a per subject basis. Efforts to minimize the previously described potential risks will be done by using a "Clinician Fitting Checklist" that will be provided to all study staff to ensure proper device fitting and training of staff to use the device properly. The checklist verifies placement of the device and that the appropriate device settings are being used. Completion of the fitting checklist will be performed prior to each training session; fit will be re-verified prior to performance of outcome assessments. In addition, the study physician will be available to field any questions that the participants may have regarding the study device, its effects, or their experiences. In the event of unexpected or expected adverse event, a report to the IRB will be completed in accordance with local policy. During the annual continuing review, the frequency and type of adverse events from the preceding year (and study duration) are reviewed. Under special circumstances, the IRB may request that the consent form be modified to reflect new potential risks or side effects. During our acute study, no participants exhibited or expressed any sign or symptom of an unanticipated side effect.

All research protocols, informed consent forms, and case report forms are subject to random and/or planned annual audit and continuing review by the IRB and Research and Development Committee, which are accredited by the Association for the Accreditation of Human Research Protection Programs, Inc. The minimum number of procedures is being performed to effectively address the research objectives

Study participation can be terminated at any point during the investigation at the request of the participant or the PI. To minimize a breach against privacy after the time of consent, each subject will be assigned a code (unique subject identification number). Any data collected (digital and paper) pertaining to the study will be referenced and stored under this code. Digital data will be stored in a password-protected database on the VA network protected by the VA firewall. This firewall and encrypted network is protected by centralized antivirus software that is updated daily to prevent loss or compromise of data with malware. No raw or processed data are maintained on individual computers, or hard drives that may be lost or stolen. Every VA facility stores user's data on a local data center network that is backed up daily. Paper data will be stored in a locked file cabinet of the respective institutions. Study documents signed by the participant will have no reference to the participant number. A single digital key containing the name, contact information, and study coded number for all participants enrolled will exist for study administration and monitoring purposes only and be kept in a separate password protected database on the VA network behind the firewall. The PI and designated study staff will be the only individuals to have access to the password.

In the event of an unexpected adverse event during a study visit, appropriate medical intervention and care will immediately be sought in accordance with VA policies. A further explanation of adverse event reporting is provided in the subsequent section.

This research does not involve pregnant women, human fetuses and neonates, prisoners, children or individuals with diminished mental capacity. The possibility exists that economically or socially disadvantaged individuals

will participate in this study. The economic or social circumstances of an eligible participant are not relevant to our investigation. However, we appreciate that a proportion of enrollees may satisfy the criteria. We will not ask an individual to disclose this information, but offer the explanation that economically or socially disadvantaged individuals will be given the same treatment as individuals who are not considered to be vulnerable. For all participants, (a) the study will be explained in its entirety, (b) the terms of the consent form will be explained prior to obtaining the individual's signature, and (c) individuals will be given the opportunity to ask questions prior to signing the consent form.

C. Potential benefits of research to subjects and others.

It is possible that enrolled participants may derive no direct benefit as part of their participation in this study. However, some of the participants may experience improvement in their gait and tolerance of overground ambulation. Abnormal clinical findings from the study will be shared with individual participants so they can follow up with their primary care physician. Some participants may derive personal satisfaction knowing that their involvement in the proposed study may contribute to science and clinical care, subsequently helping other individuals.

The anticipated or potential derived benefits outweigh the perceived and/or known risks of the study procedures. The associated risks for the study are considered greater than minimal risk however, they pose no known major long-term health risks. The information derived from this study may show benefits to improved gait that may lead to improvements in body composition and associated improvements in quality of life.

D. Importance of knowledge to be gained.

Ensuring safety is a high priority, therefore, the following Data and Safety Monitoring Plan will be implemented. Adverse events and device malfunctions will be monitored on a session to session basis. All adverse events for all study participants including those that are anticipated or unanticipated will be recorded and submitted to the IRB in a timely and complete fashion. This safety information assists study management in identifying any untoward medical occurrence, thereby allowing: a) protection and safety of study participants, b) a greater understanding of the overall safety profile of the study treatments and therapeutic modalities, c) improvements in study design or procedures, and d) compliance with regulatory requirements. The PI will be responsible for reviewing the accuracy and completeness of all reported events, compliance with VA policies for reporting adverse events (AE), serious adverse events (SAE), Unanticipated Adverse Device Effects (UADE), and closely monitoring research participants at each study visit for any new SAEs. Any serious adverse event may lead to the change in study procedures to avoid any future occurrence of similar type of events. If any findings that may affect the participants' health or welfare, their primary care physician (PCP) will be notified of these findings.

The goals of this study have been outlined in the research plan. Weekly staff meetings will be scheduled to ensure study timeline and safety goals are met such as: IRB approval, database management and participant recruitment goals, participant compliance, adverse events, scheduling, etc. In the event there are some participants that are not reliable and are inconsistent with study appointments, the PI will have the ability to withdraw them from the study and they will be replaced.

The inclusion of women, minorities and/or children.
Every effort will be made, within the constructs of the inclusion and exclusion criteria, to identify and enroll women and persons of minority background in the proposed research investigation. Women, although comprising 50.7% of the total population in the United States, represent only 10% of Veterans. Under these circumstances, we do not anticipate an equal proportion of women to enroll in this investigation and realistically expect a similar proportion of women to participate in the project. The racial and ethnic background of the

participants located in the Bronx, NY are predominantly Caucasian, African American and Hispanic and the equality of the demographics may be skewed to those ethnicities. This study will not include children and the minimum age for participation is 18 years.

Appendix – List of Abbreviations

5xSTS	Five Times Sit to Stand Test
ADL	Activities of daily living
AHA	American Heart Association
ASA	American Stroke Association
bpm	Beats per minute
CDMRP	Congressionally Directed Medical Research Program
CSP	Cooperative Studies Program
DOD	Department of Defense
DXA	Dual energy x-ray absorptiometry
EEG	Electroencephalogram
FDA	Food and Drug Administration
HR	Heart rate
IDE	Investigational Device Exemption
JJPVAMC	James J Peters VA Medical Center
kg	Kilogram
m	Meter
min	Minute
ml	Milliliter
LE	Lower extremity
NCS	Neurological Clinical Specialist
Nm	Newton meter
NSR	Not a Significant Risk
PNS	Peripheral Nerve Stimulation
QOL	Quality of Life
RCTs	Randomized clinical trials
ROM	Range of motion
RR	Respiratory rate
SCI	Spinal cord injury
RR&D	Rehabilitation research and Development
SPiRE	Small Projects in Rehabilitation Research
SS-QOL	Stroke Specific Quality of Life Scale
TSCS	Transcutaneous Spinal Cord Stimulation
TMS	Transcranial Magnetic Stimulation
VO2	Oxygen uptake
W	With
w/o	Without

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