PROTOCOL TITLE

Randomized Control Trial Comparing Walking Task Specific Training with Stride Management Assist (SMA) Device vs. Functional Task Specific training on Functional Walking Ability in Outpatient Stroke Rehabilitation.

Principal Investigator: Arun Jayaraman, PT, PhD
Department of Physical Medicine & Rehabilitation
Northwestern University
Rehabilitation Institute of Chicago
345 E. Superior
Chicago, IL 60611
Ph: (312) 238-6875
Fax: (312) 238-2081
ajayaraman@northwestern.edu

Sub-Investigator(s): Sangeetha Madhavan, PT, PhD
Department of Physical Therapy
University of Illinois at Chicago
1919 W. Taylor (MC898),
Chicago, IL 60612
(312)3552517
(312) 996-4583
smadhava@uic.edu

Biostatistician: Chaithanya K Mummidisetty
Rehabilitation Institute of Chicago
345 E. Superior
Chicago, IL 60611
(312) 238-1621
(Fax) 238-2081
Email: cmummidise@ric.org

Study Drug/Study Device: **Stride Management Assist designed and developed by Honda R&D Corporation**

Funding Source: Honda R&D Corporation and Max Nader Center Fund

Initial version: [09/04/2013]
Amended: [03/24/2014]

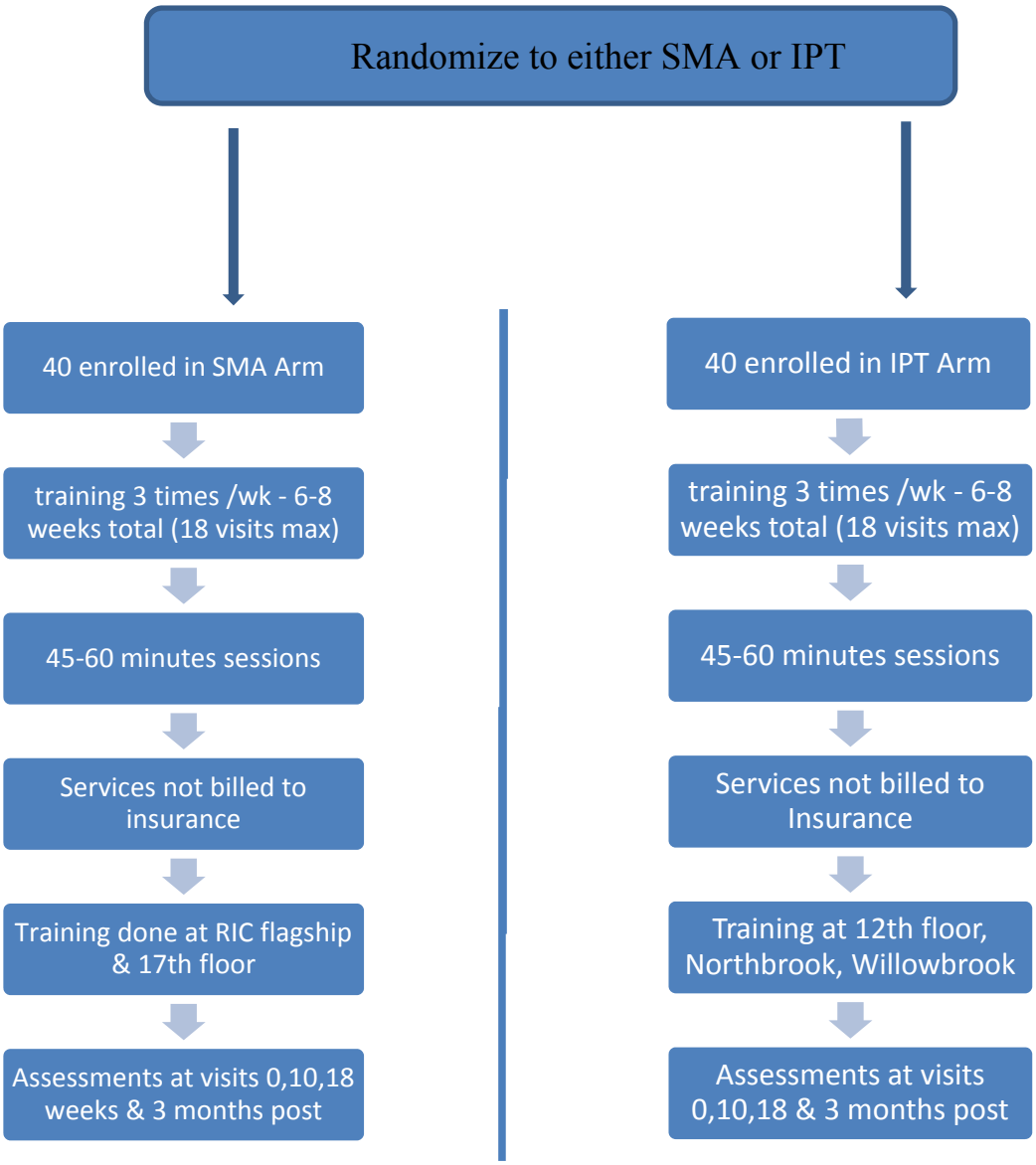
Research Office Address

TABLE OF CONTENTS

STUDY SCHEMA

Design

Individuals with mild-moderate Stroke currently enrolling in out-patient physical therapy can participate in the study.



STUDY SUMMARY

Title	Randomized Control Trial Comparing Walking Task Specific Training with Stride Management Assist (SMA) Device vs. Functional Task Specific training on Functional Walking Ability in Outpatient Stroke Rehabilitation.
Short Title	Impairment vs. Functional Walking Training in Sub-Acute and Chronic Stroke (match this to title used it ClinicalTrials.gov)
Protocol Number	STU00085161
Methodology	Randomized Controlled Trial with 2 arms
Study Duration	1 year
Study Center(s)	Single site, multiple clinics within RIC's flagship hospital and it's outpatient clinics
Objectives	Determine if Honda Stride Management Assist vs. traditional Functional Gait Therapy increases Gait speed and function post stroke
Number of Subjects	80
Diagnosis and Main Inclusion Criteria	Cerebrovascular accident (CVA), post 30 days, Gait speed between 0.4 m/s and 0.8 m/s, MMSE > 17, unsupported sitting >30 s, walk at least 10m with up to max assist, follow instructions, physician clearance for participation
Study Product(s), Dose, Route, Regimen	Honda Stride Management Assist device in outpatient physical therapy
Duration of administration	18 Sessions of Outpatient Physical Therapy + 4 Sessions of testing
Reference therapy	Traditional Functional Mobility Training Physical Therapy
Statistical Methodology	Multiple ANOVAs

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Stroke is the leading cause of adult-onset of disability. Recent studies estimate that stroke affects about 795,000 people in the U.S. each year, resulting in a prevalence of over 6.4 million individuals[1,2]. A large proportion of these stroke survivors (up to 80%) experience considerable gait deficits, including reduced walking speeds and asymmetrical walking patterns, limiting their capacity for community ambulation[3]. These mobility deficits are due to a combination of numerous neuromuscular changes following the stroke including: reduced corticospinal drive and control, muscle atrophy and weakness, impaired balance and posture control, abnormal muscle synergies, and visuo-cognitive deficits.

The goal of post-stroke rehabilitation is to reintegrate individuals back to their highest level of function for employment, social and community participation[4]. The return of mobility and walking is a crucial part of this return to function[5]. Gait training has been a major focus of stroke rehabilitation[4], with self-selected walking speed considered to be one of the most important measures of stroke rehabilitation. It is thought to be a predictor of health status, community mobility, social interaction, and overall quality of life. Stroke survivors are currently classified based on their self-selected walking speeds as: non-ambulators (unable to walk), limited household ambulators (<0.4m/s), limited community ambulators (0.4-0.8m/s), and community ambulators (>0.8m/s)[6]. These walking speeds are however significantly lower than those exhibited by healthy controls (1.3-1.5 m/s)[7].

Physical rehabilitation has many methodological approaches to training post stroke. The 2 most commonly applied techniques are task specific training, in this case gait training and impairment based training, which is more focused on balance, and functional deficits. The use of unconstrained robotic exoskeletons may allow gait retraining to be integrated with activities of daily living. However, there are very few studies that looked at the impact of a robotic exoskeleton on walking performance in the mild-moderate-stroke population[8,9]. This study will compare task specific training using a robotic exoskeleton SMA vs. IPT impairment based physical therapy in the outpatient setting for individuals post-stroke.

1.2 Study Agent(s)/Devices Background

The Stride Management Assist (SMA) System is a robotic device developed by Honda R&D Corporation ®, Japan (http://corporate.honda.com/innovation/walk-assist/).

This robotic device assists hip flexion and extension, for each side independently. It is controlled through software run on a tablet. The device weighs 2.8 kgs, and has 2 brushless DC motors running on a rechargeable lithium ion battery. It comes in 3 sizes (small, medium and large). It is worn around like a belt with the motors near the hips and straps on the thighs. The SMA device allows users to increase their stride length by providing assist with the motors in flexion and extension. This device is 1) simple to use in the clinical setting; 2) easily adjustable to alter according to the requirements of each subject; and, 3) can quantify the amount of assistance required to facilitate walking patterns.

1.3 Rationale

There is substantial evidence that post stroke recovery can last for greater than a year[3]. Due to cost pressures, various forms of therapies have been assessed for their effectiveness and efficiency. Task specific training post stroke has been found to be a very effective strategy for gait retraining[10,11]. Impairment based physical therapy is another methodology practiced in clinical settings where the training is based on progressive strength and balance exercise program in the outpatient setting[12]. The SMA group (task specific training) will be trained to simulate the demands of overground walking. The impairment based group will match the SMA group in intensity but will be focused on balance and other functional goals rather than explicitly on walking. The rationale of this study is to assess task specific training with SMA vs. impairment based training. To this end, we will use the Stride Management Assist device by Honda Corporation and compare it to impairment based physical therapy in outpatient sessions.

The enhancement of corticospinal excitability may help account for the long-term plasticity and improved motor control in people with stroke. To study this, we will measure corticospinal excitability of the lower limb muscles using Transcranial Magnetic Stimulation TMS. TMS is a safe and non-invasive method that has been widely used to study cognition, brain-behavior relations and the pathophysiology of various neurologic and psychiatric disorders.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To determine the effect on gait speed, as assessed by the 10 meter walk test of the SMA device vs. traditional physical therapy care in an outpatient setting for post stroke individuals.

2.2 Secondary Objectives

2.2.1 To determine the effect on functional walking endurance as assessed by the 6 minute walk test, of task specific training with the SMA device vs impairment based physical therapy in an outpatient setting for post stroke individuals.

2.2.2 To determine the effect on functional balance, as assessed by the Berg Balance Scale, Functional Gait Assessment and Five times sit to stand measure as assessed by the 6 minute walk test, of task specific training with the SMA device vs. impairment based physical therapy in an outpatient setting for post stroke individuals.

2.2.3 To determine the effect on stroke recovery, as assessed by the step counter of task specific training with the SMA device vs. impairment based physical therapy in an outpatient setting for post stroke individuals.

2.2.4 To determine the effect on descending corticospinal drive to the lower limb muscles in training with the Stride Management Assist (SMA) device vs. impairment based physical therapy in an outpatient setting for post stroke individuals.

2.3 Endpoints

The outcome measures will be assessed prior to the start of Outpatient Therapy, after 9 Outpatient PT visits , after 18 sessions and a 3 month follow up testing visit, which will be the endpoints of the study;

3.0 PATIENT ELIGIBILITY

Potential subjects will be recruited from RIC's scheduling for outpatient physical therapy. They will be consented and must fulfill the following criteria:

3.1 Inclusion Criteria

- ≥ 30-days post stroke
- Age: 18-85 Years
- Initial gait speed of > 0.4 m/s and < 0.8 m/s
- Adequate cognitive function (MMSE score >17)
- Subject is willing to be randomized to the control group or the treatment group.
- Ability to sit unsupported for 30 seconds
- Ability to walk at least 10m with maximum 1 person assist,
- Ability to follow a three-step command
- Physician approval for patient participation
- Living in the community post-stroke with ability to travel to the intervention site to participate in the outpatient program and able to perform the HEP program in the residential facility.
- Willing to carry wireless body sensors through the period of the study and to follow-up time period, post inpatient stroke, cardiac, pulmonary, or any other lower extremity physical rehabilitation

- ≥ 90 days post major orthopedic surgery (i.e. hip, knee, and/or ankle joint replacement)
- ≥ 6 months post CABG or cardiac valve procedure
- Able and willing to give written consent and comply with study procedures, including follow-up visits
- Willing to participate in two Transcranial Magnetic Stimulation sessions if they meet compatibility requirement.
- Cannot not be participating in any other structured outpatient or home health physical therapy program

3.2 Exclusion Criteria

- Serious cardiac conditions (hospitalization for myocardial infarction or heart surgery within 3 months, history of congestive heart failure, documented serious and unstable cardiac arrhythmias, hypertrophic cardiomyopathy, severe aortic stenosis, angina or dyspnea at rest or during activities of daily living)
- Severe arthritis or orthopedic problems that limit passive ranges of motion of lower extremity (knee flexion contracture of > 10°, knee flexion ROM < 90°, hip flexion contracture > 25°, and ankle plantar flexion contracture > 15
- Serious medical conditions including myocardial infarction or heart surgery within 3 months, history of congestive heart failure, documented serious and unstable cardiac arrhythmias, hypertrophic cardiomyopathy, severe aortic stenosis, angina or dyspnea at rest or during activities of daily living, Severe hypertension, severe weight bearing pain, life expectancy less than one year
- Preexisting neurological disorders such as Parkinson's disease, Amyotrophic Lateral Sclerosis (ALS), Multiple Sclerosis (MS), dementia
- History of major head trauma, Lower extremity amputation, Non-healing ulcers of a lower extremity, Renal dialysis or end stage liver disease, Legal blindness or severe visual impairment, a history of significant psychiatric illness
- Pacemakers, metal implants in the head region
- History of unexplained, recurring headaches, epilepsy/seizures/skull fractures or skull deficits
- Medications that lower seizure threshold
- History of concussion in last 6 months
- Subject is pregnant, nursing or planning a pregnancy
- Inability to travel 3 times per week for outpatient training programs
- Participating in another clinical trial that, according to the Principal Investigator, is likely to affect study outcome or confound results

4.0 TREATMENT PLAN

4.1 Treatment Sessions

Once subjects have been consented and they meet study inclusion and exclusion criteria, they will be randomly placed into either the SMA group or impairment based (IPT) group. The Physical therapy treatment sessions will follow the guidelines below:

- IPT group
  - Assessment (strength, flexibility, balance, sensation, endurance, transfers, gait). Treatment will be divided into: 15 min balance training, 15 minutes functional mobility (transfers, strength or flexibility training) and 15 min high intensity gait training

- SMA group
  - Assessment (strength, flexibility, balance, sensation, endurance, transfers, gait)
  - Treatment consists of 30minutes high intensity gait training with device, 15 minutes functional mobility with device (eg stairs, ramps, curbs, uneven surfaces, indoors, outdoors)

4.2 Duration of Therapy

The Outpatient physical therapy sessions will last for a maximum of 18 visits per subject.

4.3 Duration of Follow Up

The study will collect data at 3 points: baseline before entry into therapy session, midway through the therapy session after 9 visits and after 18 visits. There is to be no follow up after the post 18th session testing.

4.4 Removal of Patients from Protocol Therapy

Patients may be removed from therapy if there is a change in medical status. The Principal Investigator may also decide if the patient is unable to continue for any extenuating circumstances to remove the subject from the study, and document the reason for study removal and the date the patient was removed in the Case Report Form.

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

Subjects will be randomized into 2 separate groups, either SMA or IPT. We will enroll 80 subjects, 40 in each group, planning for a 30% attrition rate. These subjects will be recruited when they are referred to RIC's stroke rehabilitation outpatient clinics at RIC's flagship at 345 E. Superior St. 12th floor, or RIC Northshore in Northbrook IL or RIC Willowbrook in Willowbrook, IL. We will also recruit from local physicians or RIC's Clinical Neuroscience Research Registry for subjects who are potential candidates for outpatient physical therapy. They will be directed to a physical therapist who will inform them of the time commitment required and questioned regarding the inclusion/exclusion criteria. Once subjects have agreed to participate in the study, they will come to RIC and be consented at one of the clinics at the Rehabilitation Institute of Chicago. Study staff will explain the study, a written consent form will be signed by the subject and witnessed by study researchers, a copy will be given to the subject and a copy will be kept in the subject's folder in a secure, locked cabinet in the lab's locked office.

After consenting, subjects will undergo a physical evaluation and screening exam by a licensed PT. If they meet study criteria, they will be randomly placed into either the SMA group or the IPT group using a random number generator and they will be entered into the study. Once they are enrolled, baseline outcome measures will be assessed by a blinded research PT.

In addition, subjects will have a baseline measure of their cortical excitability through TMS. This will be conducted at University of Illinois, Department of Physical Therapy. TMS sessions will last approximately 2 hours.

5.2 Procedures during Treatment

After the baseline testing is completed, subjects will begin 18 sessions of PT training in the outpatient clinic with a licensed RIC clinical PT. These sessions will last from 45 to 60 minutes. Their sessions will be recorded in RIC's electronic documentation system Cerner.

A blinded research physical therapist will test the outcome measure at baseline, Mid Testing after Session 9 , at Post Testing after Session 18 and at 3 month follow up testing after Session 18.

IPT group	Baseline TMS	Baseline testing (blinded PT)	Sessions 1-9 3 x wk	Mid Testing (blinded PT)	Sessions 10-18 3 x wk	Post testing TMS	Post testing (blinded PT)	Follow up testing (blinded PT) 3 months post
SMA group	Baseline TMS	Baseline testing (blinded PT)	Sessions 1-9 3 x wk	Mid Testing (blinded PT)	Sessions 10-18 3 x wk	Post testing TMS	Post testing (blinded PT)	Follow up testing (blinded PT) 3 months post

The TMS protocol

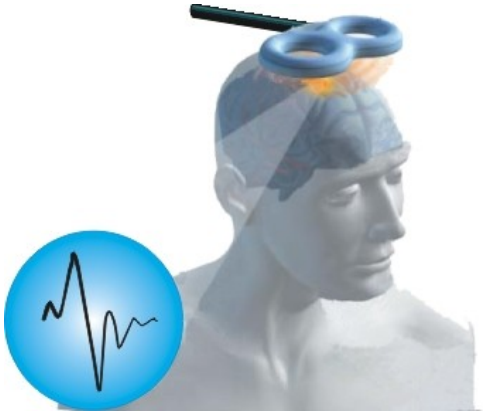
We will test descending corticospinal drive to the rectus femoris, vastus lateralis, lateral hamstrings, tibialis anterior, and medial gastrocnemius muscles. These muscles have the biggest representation in the motor cortex and are most involved during the gait cycle.

Maximum Voluntary Isometric Contractions (MVIC): Before beginning the TMS protocol, an estimate of MVIC will be obtained for each muscle with the subject positioned in sitting on a chair, with the knee joint at 90 degrees of flexion and ankle in neutral position. Manual resistance will be provided by one of the investigators as the subject tries to extend or flex the knee, dorsiflex or plantarflex the ankle. Subjects will then be seated with the feet constrained by flexible 4.0 kg weights placed over the dorsum of each foot. The subject will be given real time feedback of muscle activity to match a target contraction corresponding to 10% MVIC for individual muscles during TMS measurements (details below).

Transcranial Magnetic Stimulation (TMS): TMS is a safe, non-invasive, painless method of brain stimulation that has been widely used to study the physiology of the representations of muscles in the motor cortex in healthy and neurologically disordered individuals[13]. Very short duration (< 1 ms) magnetic pulses are applied via an insulated wire coil placed on the intact scalp overlaying the motor cortical area projecting to a target muscle. Each pulse induces a motor evoked potential (MEP) in a target muscle that can be readily monitored by recording Electromyogram EMG from that muscle. A figure-of-eight or double cone coil is typically used to deliver focal magnetic pulses to a number of scalp sites over the cortical area representing a muscle of interest.

Self-adhesive disposable electrodes (Delsys) with an inter-electrode distance of 2 cm will be applied over the muscle bellies of the quadriceps, hamstrings, ankle dorsiflexors and ankle plantarflexors in the lower extremity. A ground electrode will be applied over the patella. Standard skin preparation techniques (light

abrasion and cleansing with alcohol) will be completed prior to application of the electrodes. EMG recordings will be amplified (Delys, Bagnoli EMG), band-pass filtered (10-1000 Hz), and sampled at 5000 Hz. Electromyographic (EMG) activity will be collected from the all the muscles bilaterally. Magnetic stimuli will be delivered via a double cone coil/figure of eight connected to a Magstim 200 unit (Magstim Company, Boston MA). The resting and active threshold for TMS will be determined for each subject. TMS measurements will involve generating motor evoked potentials (MEP) for each muscle from two different coil positions – 2cm on either side of the vertex. Motor evoked potentials (MEPs) at intensities ranging from 70 – 140% active threshold will be generated for each muscle from each coil position. A figure-of-eight or double cone coil will be used to deliver focal magnetic pulses. Resting motor threshold for the muscle of interest in will be defined as the stimulator output intensity that can elicit motor evoked potentials (MEPs) with peak-to-peak amplitude more than 50 μV in four out of eight trials. It will be determined by increasing stimulus intensity in steps of 1% stimulator output. Active thresholds will be determined with the same protocol, however with the subject contracting the muscle of interest to about 10% of maximum voluntary contraction. Subjects will receive approximately 100 – 150 pulses of stimulation. These measures will assist the investigator and co-investigators in generating recruitment curves which will help assess the corticospinal excitability of the ipsilateral and contralateral motor cortex to each lower limb muscle.



The sessions of physical therapy will be customized for each individual based on the group they are placed.

For the IPT group:

Balance IPT OG 15 min	**Dynamic Gait OG IPT 15 min**	**Functional Mobility – IPT OG 15 min**
Sitting balance • Reaching • Perturbations Progress to standing Change stance: • Static • Dynamic • Double limb stance • Romberg • Tandem • Semi-tandem • Unilateral Single limb stance Change surface: • Balance board • Foam cushions, half foam roll • Bosu ball • Balance beam • With/without AFO Dual Tasking: • Ball catch • Cognitive tasks • Reading, visual attention • Perturbations	Change surface/stance: • Level surfaces • Over obstacles • Over compliant surfaces • Tandem walk (forwards/backwards) • With/without AFO Multidirectional walking: • Backwards • Sidestepping • Tandem Dual tasking: • Ball catch • Ball bounce • Cognitive tasks Other: • Increased speed • Pivot turn • Balance beam • Perturbations • Increase distance • Assistive device progression • Reduction in physical assist progression	• Sit to stand transition • Functional up right postures • Reaching • Step up and step down • Stairs • Ramps, curbs • Weights/Theraband • Stretches To customize the program, the therapist may adjust the time between the Balance, Dynamic Gait & Functional Mobility needs of the patient.

For the SMA group:

Dynamic Functional Gait – SMA OG 45 min	ALL training for both groups will be High Intensity Training	Home Exercise Program
Change surface/stance: • Level surfaces • Over obstacles • Over compliant surfaces • Tandem walk (forwards/backwards) • With/without AFO Multidirectional walking: • Backwards • Tandem Dual tasking with gait: • Ball catch • Ball bounce • Cognitive tasks Other Gait challenges: • Increased speed, stopping and starting • Pivot turns • Balance beam • Perturbations • Obstacles • Increased distance • Assistive device progression • Reduction in physical assist progression Functional up right postures • Stairs • Ramps, curbs • Outdoors/community	• Intensity: RPE minimum 12 up to 16 on 6-20 RPE scale • Or HR up to 75% of Age predicted max (220-age) • PT will consider Beta blockers and Ca channel clockers for HR	• Will be customized based on same parameters for both groups: on high intensity gait training • Intensity 12-16 RPE or HR 70% APMHR • Frequency & Duration– initially determined by PT according to pt's functional ability • To work towards 45 min/once a day/at 12-15RPE at d/c

Response Criteria / Outcome Measures:

The following outcome measures will be evaluated for both the groups at testing points at baseline, mid-testing , post-testing and follow-up testing.

Clinical Performance Outcome Measures:

1. **6 Minute Walk Test:** The 6MWT measures the distance a subject can walk indoors on a flat, hard surface in a period of 6 minutes, using assistive devices, as necessary. The test is a reliable and valid evaluation of functional exercise capacity and is used as a sub-maximal test of aerobic capacity and endurance. The minimal detectable change distance for people with sub-acute stroke is 60.98 meters.[14]

2. **10 Meter Walk Test:** The 10mWT assesses walking speed in meters per second over a short duration. Changes in gait speed that result in a transition to a higher category of ambulation classification resulted in better function and quality of life[15]. In the 10mWT, subjects are directed to walk at their self-selected and maximum safe speed with the effects of acceleration and deceleration minimized (by adding 1 meter at the beginning and at the end of the course to isolate the subject's steady state speed). Any assistive device and orthotic should be kept consistent and documented. It should also be documented whether the gait is tested at "preferred walking speed" or "fastest walking speed". The 10mWT has been validated for the stroke population and is accepted as a responsive, functional measurement of the patient's ability to ambulate over short distances such as those typical to a household setting. A small meaningful change for people with stroke is 0.06 meters/second; a substantial meaningful change is 0.14 meters/second14. A speed of <0.4 and >.08 m/s is an exclusion in the study.

3. **Berg Balance Scale (BBS):** The BBS is a 14-item objective measure designed to assess static balance and fall risk in adult populations and is a well-accepted measure in the stroke literature. The functional activities that are assessed include sitting and standing balance during transfers, altered base of support, reaching, turning, eyes open and closed. Each item is scored from 0 to 4 points. The maximum score is 56 points. A score from 0 to 20 represents balance impairment, 21 to 40 represents acceptable balance, and 41-56 represents good balance. The minimal detectable change score for individuals with acute stroke is 6.9 points[16] and 4.66 points in chronic stroke[17].

4. **5 Times Sit to Stand Test (5xSST):** The 5xSST is used to measure functional lower extremity strength during the transitional movement of sit to stand. The individual is timed in moving from the start position of sitting, arms across chest, in a standard chair without armrests to fully standing five times. The minimal detectable change in individuals with chronic stroke is 3.6 seconds.[18]

5. **Gait Analysis:** A quantitative means of assessing gait function in adults post-stroke based on spatiotemporal parameters of gait. The GaitRite® system is an electronic walkway with integrated sensors and is considered a reliable and valid means of assessing gait changes poststroke.

6. **Functional Gait Assessment (FGA):** The FGA is a 10-item test for assessing postural stability during various walking tasks. It includes 7 of the 8 items from the original Dynamic Gait Index, and 3 new items, including "gait with narrow base of support," "ambulating backwards," and "gait with eyes closed." The FGA demonstrates excellent concurrent validity with the Berg Balance Scale for individuals with stroke.[19] The maximum score is 30 points; minimal detectable change for chronic stroke is 4.2 points.[20]

7. **Fugl-Meyer Assessment of Motor Recovery after Stroke (FMA):** The purpose of the FMA is to evaluate and measure recovery in post-stroke hemiplegic patients. There are five domains assessed on a 3 point ordinal scale from 0-2. “0” is equal to “cannot perform”, “1” is equal to “performs partially”, and “2” is equal to “performs fully. The domain for lower extremity motor function will be used. It has been found to be reliable and valid in assessing individuals with stroke with a minimal clinically important difference of 10 points for the lower extremity motor scores.[21]

Self-Reported Measures:

8. **Modified Falls Efficacy Scale (mFES):** The mFES is a 14 item self-report survey that assesses an individual’s perception of balance and stability during indoor and outdoor activities of daily living. The mFES is a 10 point numerical rating scale with higher scores indicating higher confidence in the performance of the activity.

9. **Activities- specific and Balance Confidence Scale (ABC):** The ABC is a 16-item self-report questionnaire that measures confidence in performing various ambulatory activities without falling. Items are rated on a scale ranging from 0-100, with zero representing no confidence and 100 representing complete confidence. It has good to excellent reliability and adequate construct validity, correlating with the BBS and 10mWT.[22]

10. **Stoke Impact Scale (SIS):** The SIS is a validated measure of the impact of stroke on overall physical and cognitive function. This 59-item patient-based questionnaire assesses eight domains of stroke recovery: strength, mobility, communication, emotion, memory and thinking, participation, activities of daily living/instrumental activities of daily living (ADL/IADL) and hand function. An additional question requires the patient to rate their stroke recovery on a scale from 0 to 100. This measure instructs subjects to answer the question based on the period of time two-four weeks prior to the questionnaire.

11. **Community Participation Indicators (CPI):** The CPI is an eighty-item self-report questionnaire that assesses the individual’s satisfaction with their community participation.

12. **Visual Analog Scale or Numeric Pain Rating Scale:** The 0-10 rating scale for pain is used to gain a subjective report of the intensity of a person’s pain. Zero represents “no pain” and ten represents “the most intense pain imaginable”. A meaningful change would be plus or minus 3 points.

13. **Patient Health Questionnaire-9 (PHQ-9):** The PHQ-9 is a 9-item self-report screening assessment for depression. It is the depression module of the Diagnostic and Statistical Manual (4th edition). Each item is scored from 0-3; total scores may be 0-27, with higher scores representing increased severity of depression.

14. **Stroke Specific Quality of Life (SSQoL):** The SSQoL is a self-report questionnaire that is accepted as a reliable and valid way to assess health-related quality of life specific to stroke survivors. Subjects respond to 49 questions in 12 domains: mobility, energy, upper extremity function, work/productivity, mood, self-care, social roles, family roles, vision, language, thinking, and personality. Each item is rated on a 5-point Likert scale, with higher scores indicating better functioning. Domains scores (un-weighted average of item scores) and a summary score (un-weighted average of all 12 domain scores) are computed.

15. **TMS:** will assist researchers in generating recruitment curves which will help assess the corticospinal excitability of the ipsilateral and contralateral motor cortex to each lower limb muscle.
16.

5.3 Time and Events Table

	Consent, Baseline	Sessions 1-9	Mid Testing	Sessions 10-18	Post Testing	Follow up
Inclusion Exclusion	X					
Informed Consent	X					
History and PE	X					
SMA protocol or IPT protocol		X		X		
Clinical performance measures	X		X		X	X
Self-Reported Measures	X				X	X
TMS	X				X	X

5.4 Removal of Subjects from Study

5.4.1 Patient voluntarily withdraws from treatment

5.4.2 Patient withdraws consent (termination of treatment and follow-up);

5.4.3 Patient is unable to comply with protocol requirements

5.4.4 Patient demonstrates change in medical condition

5.4.5 Patient experiences adverse event that makes continuation in the protocol unsafe;

5.4.6 PI judges continuation in the study would not be appropriate;

5.4.7 Patient becomes pregnant

6.0 ADVERSE EVENTS

6.1 Potential risks

6.1.1 The risk of falling: This could be caused by loss of control of the training activity by the participant or therapist as well as malfunction of the SMA device itself. The risk of falling will be minimized by having RIC licensed PT personnel conduct the participant training sessions with manual assistance, gait belt, assistive devices such as cane or a walker as needed. This risk is similar to that during any clinical outpatient physical therapy session.

6.1.2 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 RIC's experienced licensed physical therapy personnel at each session. Adjustments to the sizing and placement of

additional padding will be assessed to decrease the risk of skin breakdown as well.

6.1.3 The device itself could malfunction. The device delivers 6-8 Nm (Newton-meter) of torque, which give a gentle assist to movement. In the event of device malfunction, this force will be absent and the subject will be given with physical assistance if required, and the patient will be able to safely transfer out of the device, if required. Research engineers will ensure that the device has been maintained according to specifications and the software is always in working order.

6.1.4 Muscle soreness from exercises during therapy sessions. All subjects will work with RIC's licensed physical therapy personnel and will be initiated with testing and therapy sessions with simple activities, progressing on to more dynamic, complex activities when it is clear that they are safe and acclimated to the protocol being used. To manage this, subject will be provided with adequate rest periods and subjects will be monitored by questions regarding discomfort.

6.1.5 Risks associated with TMS:

There are certain populations who have a risk of seizures following TMS. Individuals will be screened using the TMS safety checklist. Single pulse TMS has been deemed to "carry little risk beyond occasionally causing local discomfort" in healthy adult populations (Anand and Hotson 2002). Our stimulation procedures follow published safety guidelines. Seizure activation is extremely unlikely with the single pulse low numbers of stimulation proposed in the current investigation.

A small number of people find TMS uncomfortable, particularly at high intensities of stimulation. If subjects report feelings of discomfort stimulation intensity will be reduced or, if not feasible, testing will be terminated. The "clicking" noise associated with stimulation may also be uncomfortable for some individuals. All subjects will be provided with protective ear-plugs during stimulation.

There is a possibility that a subject could develop muscle soreness or fatigue from holding a tonic contraction. If shoulder, wrist or leg pain occurs as a result of the experiment, we will withdraw the subject from the study. During testing, there is also a possibility that a subject may experience irritation due to the nerve stimulation or EMG electrodes or electrode gel**.**

7.0 DEVICE INFORMATION

7.1 Device

- Other names for the device: Walking Assist Device with Stride Management System
- Classification - type of device: Walking Assist Device
- Mode of action: This device is a light weight design with 2 DC motors can generate torque up to 6 Nm, worn around hips and thighs to provide assistance during walking.

- Storage and stability: Weighs 2.8 kgs and easy to store in a cabinet
- Protocol dose: 45-60 min sessions ,3x/week for 6-8 weeks
- Preparation: Belt like device to be worn around hips and thighs
- Availability: Provided by Sponsor (free of Charge)

8.0 STATISTICAL CONSIDERATIONS

8.1 Study Design/Study Endpoints

This proposed study is a randomized control trial to compare Task Specific Training with SMA and Impairment based Physical Therapy on Functional Walking Ability in Outpatient Stroke Rehabilitation setting.

8.2 Sample Size and Accrual

A total enrollment of 80 subjects is estimated for this study. Each enrolled subject is randomly assigned to either one of the groups (SMA or IPT; 40 participants per group). A detailed description of study procedures and study endpoints are provided in section of 5.0

8.3 Data Analyses Plans

The outcome measures for each subject (listed in Section 5.2) are recorded during 0^{th}, 10^{th} and 18^{th} session of the training cycle and at 3 month follow up visit. Photographs and video without individual subject's faces will be recorded as this device is not commercially available yet and dissemination of accurate information will be assisted by showing how the device operates when donned and used by subjects Outcome measures are compared with in the subject and across the subject pools for statistical significant differences using Multiple ANOVAs. All the statistics will be performed at 90% confidence level.

9.0 STUDY MANAGEMENT

9.1 Data Management and Monitoring/Auditing

Subjects' records will be kept completely confidential. Data will be collected and kept confidential and compliant with HIPPAA requirements. Research data will be de-identified and stored in locked cabinets in the lab with access only to research staff. Electronic data will be de-identified and kept on secure, password protected files and password protected computers.

9.2 Record Retention

Study documentation will be collected and kept confidential and compliant with HIPPAA requirements. Photographs and video without recording individual subject's faces will be recorded as this device is not commercially available yet and dissemination of accurate information will be assisted by showing how the operates when donned and used by subjects. Data will be held for 3 years after the study is completed and published.

10.0 REFERENCES

[1] H. S. Kaye, et al., "Mobility Device use in the united states. Disability Statistics Report (14) Washington, D.C.: U.S. Department of Education, National Institute on Disability and Rehabilitation Research," 2000

[2] C. f. D. Control. (July 2013). Fast-Stats-Cerebrovascular Accident or Stroke.

[3] K. J. Sullivan, et al., "Effects of task-specific locomotor and strength training in adults who were ambulatory after stroke: results of the STEPS randomized clinical trial," Phys Ther, vol. 87, pp. 1580-602, Dec 2007.

[4] J. P. Wood, et al., "'Getting back to real living': A qualitative study of the process of community reintegration after stroke," Clinical rehabilitation, vol. 24, pp. 1045-56, 2010.

[5] H. S. Jorgensen, et al., "Recovery of walking function in stroke patients: the Copenhagen Stroke Study," Arch Phys Med Rehabil, vol. 76, pp. 27-32, Jan 1995

[6] A. Schmid, et al., "Improvements in speed-based gait classifications are meaningful," Stroke; a journal of cerebral circulation, vol. 38, pp. 2096-100, 2007

[7] R. W. Bohannon, "Comfortable and maximum walking speed of adults aged 20-79 years: reference values and determinants," Age Ageing, vol. 26, pp. 15-9, Jan 1997

[8] Shimada et al: The Use of Positron Emission Tomography and [18F] Fluorodeoxyglucose for Functional Imaging of Muscular Activity During Exercise With a Stride Assistance System

[9] Shimada et al: Effects of an automated stride assistance system on walking parameters and muscular glucose metabolism in elderly adults

[10] Dean CM, Shepherd RB.: Task-related training improves performance of seated reaching tasks after stroke: a randomized controlled trial. Stroke 1997;28:722–728

[11] French B, Thomas LH, Leathley MJ, Sutton CJ, McAdam J, Forster A, Langhorne P, Price CI, Walker A, Watkins CL: Repetitive task training for improving functional ability after stroke. Cochrane Database Syst Rev 2007;(4):CD006073

[12] Nadeau SE et al: Effects of Task-Specific and Impairment Based Training Compared With Usual Care on Functional Walking Ability After Inpatient Stroke Rehabilitation: LEAPS Trial. Neurorehabilitation and
Neural Repair 27(4) 370–380.

[13] Anand, S. and Hotson, J. (2002), 'Transcranial magnetic stimulation: neurophysiological applications and safety', *Brain Cogn,* 50 (3), 366-86

[14] Perera S, Mody S, Woodman RC, Studenski SA. Meaningful change and responsiveness in common physical performance measures in older adults. J Am Geriatr Soc. 2006 May;54(5):743-749.

[15] Schmid A, Duncan PW, Studenski S, Lai SM, Richards L, Perera S, Wu SS. Improvements in speed-based gait classifications are meaningful. Stroke. 2007. 38(7):2096-2100.

[16] Stevenson TJ. Detecting change in patients with stroke using the Berg Balance Scale. Aust J Physiother. 2001;47(1):29-38.

[17] Hienqkaew V, Jitaree K, Chaiyawat P. Minimal detectable changes of the Berg Balance Scale, Fugl-Meyer Assessment Scale, Timed Up and Go, gait speeds, and 2-minute walk test in individuals with chronic stroke with different degrees of ankle plantarflexor tone. Arch Phys Med Rehabil. 2012;93(7):1201-1208.

[18] Mong Y, Teo TW, Ng SS. 5-repetition sit-to-stand test in subjects with chronic stroke: reliability and validity. Arch Phys Med Rehabil. 2010;91:407-413.

[19] Thieme H, Ritschel C, Zange C. Reliability and validity of the functional gait assessment (German version) in subacute stroke patients. Arch Phys Med Rehabil. 2009;90(9):1565-1570.

[20] Lin JH, Hsu MJ, Hsu HW, Wu HC, Hsieh CL. Psychometric comparisons of 3 functional ambulation measures for patients with stroke. Stroke. 2010;41(9):2021-2025.

[21] Shelton FD, Volpe BT, Reding M. Motor impairment as a predictor of functional recovery and guide to rehabilitation treatment after stroke. Neurorehabil Neural Repair. 2001;15(3):229-237.

[22] Botner EM, Miller WC, Eng JJ. Measurement properties of the activities-specific balance confidence scale among individuals with stroke. Disbil Rehabil. 2005;27(4):156-163.