

**Wearable lower extremity exoskeleton to promote walking in persons with multiple sclerosis**

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**Protocol Title:** Wearable lower extremity exoskeleton to promote walking in persons with multiple sclerosis

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**Population:** 15 human subjects

**Number of Sites:** UT Health Motor Recovery Lab at TIRR Memorial Hermann

**Study Duration:** 1 years

**Subject Duration:** 4 weeks

## General Information

Walking impairment is a significant consequence of multiple sclerosis (MS) resulting in substantial limitations of daily activities and compromised quality of life. Energy expenditure of walking is elevated and may contribute to fatigue, which could further lead to a sedentary life style and secondary health deterioration. Thus, developing effective and efficient strategies to promote walking in this population is essential. Recently, wearable lower extremity exoskeleton has been developed to restore ambulation in paralyzed or weak individuals with spinal cord injuries. These exoskeleton robotic devices utilize the user's movements, such as body sway, to initiate externally powered gait and may reduce physical demands required for walking and provide great opportunity for persons with various conditions such as MS to walk independently. Therefore, the purpose of this pilot study is to investigate whether using exoskeleton could promote recovery of walking in persons with MS. Overall, we expect these findings to support that exoskeleton will demonstrate greater efficacy to facilitate walking and can be applied extensively to improve quality of life in MS.

## Background Information

The impaired ability to walk independently is a significant consequence of multiple sclerosis (MS) resulting in substantial limitation in mobility and performance of daily activities, thus restricting full participation and home and community re-integration [1, 2]. Moreover, the energy expenditure of walking is increased [3]. This additional metabolic demand contributes to fatigue, which promotes a sedentary life style that predisposes to secondary health deterioration and compromised quality of life. Gait training/restoration in MS is necessary but often limited due to the progress and severity of the disease and limitations of traditional strengthening exercises. Thus, developing novel strategies to promote independent walking in this population is essential for health promotion. Recently, *wearable* lower extremity robotic exoskeletons (exoskeleton) have been developed to restore ambulation in paralyzed or weak individuals with spinal cord injuries. Different from bodyweight supported robotic-assistance locomotion device integrated into a treadmill (such as Lokomat)[4], exoskeletons are designed to utilize the user's residual active movements, such as body forward and lateral sway, to initiate

externally powered stepping for over ground walking and climbing stairs. Most importantly, the assistance provided by wearable robotic exoskeletons may reduce energy expenditure during walking and allow persons with MS to recover some degree of independent walking that is more efficient. Needless to say, this can have a profound impact on quality of life. Therefore, the purpose of this pilot study is to investigate whether using exoskeleton could promote recovery of walking in persons with MS. We hypothesize that participants will be able to walk with exoskeleton and with minimal to moderate trainer assistance after training (Aim1). We also plan to determine and compare physical and cognitive demands during over ground walking with and without exoskeleton (Aim2). We hypothesize that physical and cognitive demands will reduce (i.e. decrease oxygen cost and shorter reaction time) during over ground walking with exoskeleton and especially after training. The reduced physical and cognitive demands will promote energy conservation and prevent/delay fatigue in over ground walking in this population. *The innovation of this study is this wearable exoskeleton provides a unique opportunity not only to assist a sustained upright posture but also facilitate walking with better energy efficiency in individuals with MS. Overall, we expect these findings to support that exoskeleton will demonstrate greater efficacy to facilitate walking and can be applied extensively to improve quality of life in MS.*

## Objectives

The purpose of this pilot study is to investigate whether using exoskeleton could promote recovery of walking in persons with MS. We hypothesize that participants will be able to walk with exoskeleton and with minimal to moderate trainer assistance after training (Aim1). We also plan to determine and compare physical and cognitive demands during over ground walking with and without exoskeleton (Aim2). We hypothesize that physical and cognitive demands will reduce (i.e. decrease oxygen cost and shorter reaction time) during over ground walking with exoskeleton and especially after training. The reduced physical and cognitive demands will promote energy conservation and prevent/delay fatigue in overground walking in this population. The wearable exoskeleton will be used in this study is Ekso®, by Ekso Bionics, formerly known as eLEGS®.

## Study Population

We will enroll 15 human subjects who have a diagnosis of MS confirmed by a neurologist. Potential subjects will be referred and recruited from affiliated MS neurology clinics, support group and other community neurologists. We will enroll persons with MS regardless of phenotype without evidence of clinical deterioration for at least 4 months prior to study entry.

Subjects will be enrolled if they meet the following inclusion criteria:

- Age 18 years or older
- Male or non-pregnant female
- Ambulatory with assistive devices (Ambulation status will be determined by the EDSS score)
- With an Expanded Disability Status Scale (EDSS) score [5] between 6 and 7.5 inclusive
- Height and weight are between 160 and 188 cm (5'2" to 6'2"), and less than 100 kg (220 lb), respectively (per exoskeleton manufacturer)
- Able to follow simple 3 step commands
- Able to understand the study procedure and consent form

Subjects will be excluded if they have any of the following exclusion criteria:

- History of severe neurologic injuries other than MS (SCI, CP, ALS, TBI, CVA, etc.)
- Severe comorbidities: active infections, heart, lung, or circulatory conditions, pressure ulcers
- Documented severe osteoporosis affecting the hip and spine
- Severe spasticity in the lower extremities (Modified Ashworth  $\geq 3$ ) or uncontrolled clonus
- Unhealed limb or pelvic fractures
- Skin issues that would prevent wearing the device

- Range of motion restrictions that would prevent subject from achieving a normal, reciprocal gait pattern, or would restrict a subject from completing normal sit to stand or stand to sit transitions.
- Upper extremity strength deficits that limit ability to balance with a front rolling walker or crutches.
- Heterotopic ossification that resists functional range of motion in lower extremities
- Contractures (>15 degrees at the hips or >20 degrees at the knees)
- Psychiatric or cognitive comorbidities resulting in motor planning or impulsivity concerns
- Colostomy
- Non-English speaking

### Study Design and Procedures

This study is designed to investigate whether using exoskeleton could promote recovery of walking in persons with MS. A total of 15 individuals with MS will be recruited for the study. Screening, assessment and treatment sessions will be held at TIRR, Memorial Hermann. Approximately 18 visits over a 1-month period will be required.

Detailed schedule of assessments is shown in Table.

Assessment	Pre Screening/ Screening	Baseline	Exoskeleton Training 5 session/week, 3 weeks, total 15 sessions	Post-treatment (Within a week)
	Visit 1	Visit 2	Visit 3-17	Visit 18
ICF	X			
I/E Criteria	X			
Demographics	X			
Medical History	X			
Mini Mental State Exam		X		X
Muscle strength		X		X
Range of motion		X		X
Barthel Index		X		X
Modified Ashworth Scale		X		X
Quality of life		X		X
Berg Balance Scale		X		X
Timed Up & Go Test		X		X
6-min walk test		X		X
Physical Demand Measure		X		X
Cognitive Demand Measure		X		X
Timed 25 Feet Walk Test		X		X
Physical Demand Measure		X		X
Cognitive Demand Measure		X		X
Exoskeleton training			X	

Borg Rating of Perceived Exertion Scale		X	
Pain scale		X	
Exoskeleton User Feedback			X

#### Recruitment:

Potential subjects will be referred and recruited from TIRR Memorial Hermann hospital and UT Multiple Sclerosis clinic (Dr. John Lincoln, co-investigator) during regularly scheduled appointments. Recruitment will also take place through flyers (see attached) posted at the TIRR Memorial Hermann facilities and the Greater Houston Metropolitan area. We will also post traditional and electrical advertisement on newspapers, the PI website, electronic bulletin boards, research center social media and list-serves. We will also perform targeted recruitment (for participants with MS) at TIRR Memorial Hermann hospital and UT Multiple Sclerosis clinic (Dr. John Lincoln, co-investigator).

Patients will be screened to determine potential eligibility and interest in participation.

#### Pre-screening:

Potential subjects will be screened over the telephone or in person using a survey form which includes a) demographic data; b) basic physical status; c) basic neurological history. The initial telephone or in person screening process will improve the efficiency of the study since it reduces the likelihood of unsuitable participants (i.e., participants meeting exclusion criteria) having to undergo a full screening before being excluded.

If the subject passes the pre-screening, the details of the study specific procedures will be reviewed with the subject. Subjects will be given an opportunity to review the information and ask questions. Once they have decided they are interested in participating in the study, they will sign the informed consent. Once informed consent is obtained, a letter to request approval to participate in the study will then be sent to the subject's physician (either neurologist or primary care physician). The subject's physician will verify the following medical status of the subject: subject's Expanded Disability Status Scale (EDSS) score, absence of clinical deterioration during the previous 4 months, non-pregnancy status of all females. After the research team receives the approval letter, the subject will be enrolled and baseline session will be scheduled. Each enrolled subject will be assigned an identification number.

#### Screening

Once physician clearance has been obtained, a screening visit will be scheduled. The screening visit will include an assessment of subject's flexibility in their arms and legs (range of motion), tension or resistance movement (spasticity) in arms and legs, strength in arms and legs, and physical measurements of hips and legs to ensure subject is able to safely fit into the robotic device. This visit will last about 30-45 minutes.

#### Baseline Functional Assessment:

After being medically cleared, screening visit completed and subject meets all inclusion criteria, the subject will be contacted to schedule an appointment for functional evaluations to quantify their motor impairment levels prior to training.

#### Outcome Measures

Subjects will perform the following measures before exoskeleton training and after training:

1. Barthel Index: This test measures the ability of a person with a neuromuscular or musculoskeletal disorder to care for him/herself. It is a 10-item questionnaire wherein each item is rated based on the

level of assistance required to complete the activity/item (with higher scores representing more functional independence).

2. Mini Mental State Examination: Folstein Mini Mental State Examination (MMSE) provides information about orientation, attention, learning, calculation, delayed recall, and construction.
3. Muscular Strength test: we will measure lower extremity muscle strength using force gauge such as handheld dynamometer. Subjects will lie down or sit on an examination table during testing based on the tasks. Subject will be asked to produce force to against the force gage at their maximal efforts for few times. Verbal encouragement will be provided for motivation. One minute or more resting time will be provided between trials.
4. Range of Motion: we will measure range of joint motion of bilateral hip, knee and ankle joints. Subject will lie down on an examination table. We will move the joint in the desired directions (flexion-extension, abduction-adduction, internal-external rotation) and we will measure the angle between start and stop position.
5. Modified Ashworth scale for spasticity: This test measures spasticity in patients with lesions of the Central Nervous System by testing resistance to passive movement about a joint with varying degrees of velocity. Scores range from 0-4, with 6 choices (i.e., 0, 1, 1+, 2, 3, 4), with 0 indicating normal muscle tone, and 4 indicating very high spasticity. This test has good reliability for determining spasticity levels in lower limbs after MS. During this test, subject will sit or lie down on a examination table. The examiner will move the tested joint several times.
6. Quality of Life Questionnaire: subject will fill out Multiple Sclerosis Quality of Life-54 (MSQOL-54). MSQOL-54 is a self-report questionnaire and a multi-dimensional health-related quality of life measure that includes the Health Status Questionnaire (SF-36) and 18 items for MS-specific issues such as fatigue and cognitive function.
7. Berg Balance Scale: A 14-item objective measure designed to assess static balance and fall risk in adult populations, with maximum summed score of 56 (higher scores represent better functional outcome). This task will be formed without using exoskeleton at pre-assessment and post-assessment.
8. Timed Up and Go Test: this task involves subject to stand from the standard chair, walk straight for 3 meters, turn around, walk back to the chair and sit down with shoes and assistive devices if any. A standard chair with arm rests will be place at the start of the testing course. A mark will be placed on the floor at the 3 meter distance. Subject will be asked to perform the task as fast as possible without losing their balance. One research member will stand next to the subject to monitor the subject performance to prevent falls. The time to complete the task will be measured and recorded. Subjects will also have recording of electromyography in the lower limbs i.e., sensors will be placed on the skin of the legs and thighs (4 on each leg) to non-invasively record muscle activity during walking. Additional sensors i.e., goniometers will be placed on the skin to non-invasively record joint angles of the hip, knee and ankle on each leg. These will be attached to the skin using hypoallergenic tape. This task will be formed without using exoskeleton at pre-assessment and with and without exoskeleton at post-assessment.

9. 6-minute walk test: Subjects will be asked to walk back and forth in a hallway with or without assistive device (consistent among assessment visits) for 6 minutes. The objective is to cover as much space as possible in 6 minutes. Subjects can slow down or stop to rest if they feel like, but should start walking when they feel they are able. Electromyography sensors will also be placed on the skin of the leg and trunk muscles to measure muscle activity. A research team member will walk behind the subject to prevent loss of balance during the test. This task will be formed without using exoskeleton at pre-assessment and with and without exoskeleton at post-assessment. In this tasks, we will measure physical demands and cognitive demand in separate trials or sessions:
  - A. Physical demands measures: Physical demands during walking with and without EKSO will be determined by oxygen cost. Oxygen cost will be calculated from oxygen consumption as the product of gait speed and body weight [10]. Oxygen consumption will be collected on a breath-by-breath basis measured by a portable metabolic system (K4 b2 Cosmed). Prior to the testing, the system will be calibrated using room air and reference gas mixture [11]. During the testing, the subject will wear a face mask and a heart rate monitor at all times and will be asked to breathe normally. The portable device will be carried by the subject at where it will not interfere with the walking (i.e. upper back or waist).
  - B. Cognitive demands measure: Cognitive demands during walking with and without exoskeleton will be determined by reaction time using a dual-task paradigm [12]. Dual-task paradigm is commonly used to quantify the cognitive (i.e. attentional) resources allocated during a motor task such as walking and usually entails reciting the alphabet or counting backwards [13]. However, this specific measurement is limited by structural issues involving respiration, vocal responses or motor action of the upper limb (push a button) for which there are shared execution pathways with locomotion [14, 15] could interfere with the primary motor task, despite not being caused by competing demands for limited attentional resources. Thus, we chose a simple reaction task (RT), in which the response will be biting on a pressure sensor to make the response pathways as independent as possible from the motor pathways of locomotion [12]. Subjects will with and without EKSO (use same assistive device) at their preferred speed. The secondary RT task consists of biting a pressure transducer placed in the mouth in response to an unpredictable sensory (will not cause pain) electrical stimulation applied by an electrode on the back of the neck [12] without changing walking speed and pattern. The stimulation intensity will be adjusted for each individual before data collection. Shorter RT indicates that reduced amount of attentional resources are required.
10. Timed 25 Feet Walk Test (T25-FW): this task will ask the subject to walk for 25 feet at comfortable pace. Subjects will wear their exercise or walking shoes and are allowed to use assistive device such as cane or walker if necessary. The start and finish line of the 25 feet test course will be marked with tape on the floor. Additional 5 feet at the end of start and finish will be used for subject to turn around. A chair will be provided next to the start area so the subject may rest. During the test, the subject will walk at his/her comfortable pace without losing balance followed by walking at maximal pace. Resting periods will be provided between trials. One trial for each pace will be performed. Trial will be repeated if subject cannot finish the task due to fatigue or loss of balance. A research team member will walk next to the subject for safety. The time to complete the tasks will be recorded. We will place markers on the skin of the legs and trunk and the marker data will be recorded by motion capture system. Electromyography sensors will also be placed on the skin of the leg and trunk muscles to measure muscle activity. This task will be formed without using exoskeleton at pre-assessment and with and without exoskeleton at post-assessment. A research team member will walk behind the subject to prevent loss of balance during the test. This task will be formed without using exoskeleton at pre-assessment and with and without exoskeleton at post-assessment. In this tasks, we will measure physical demands and cognitive demand in separate trials:
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11. Exoskeleton satisfaction questionnaire: After completion of exoskeleton training sessions subjects will complete a survey of 9 questions regarding their experience with the exoskeleton and any feedback they would like to provide.

### Exoskeleton Training

Subjects will participate in individualized training sessions using Ekso®. Each training session will last up to 60 minutes, 5 days per week for 3 weeks, for a total of 15 sessions.

During the training, subjects will wear a lower extremity exoskeleton robotic walking device. Subjects will participate in individualized treatment sessions which may include: sit to stand, static and dynamic standing balance, weight shifting, walking, turning, and stand to sit. Each training session will last up to 90 minutes (60 minutes of training with 30 minutes for setup, don/doff of device) and training will be held 5 days per week for 3 weeks with a total of 15 sessions.

The training intensity and frequency is adapted from our ongoing research protocol for Spinal Cord Injury (SCI) robotic exoskeleton locomotion training (unpublished data, HMSC-13-0536). These SCI participants with paraplegia (either motor incomplete or complete SCI) can stand and walk with assistance devices (walker or canes) prior to the training and are able to walk with exoskeleton with moderate trainer assistance for at least 100 meters on a level surface at the end of 15 training sessions. Therefore we think this training intensity and duration will apply in individuals with MS who can stand and walk with assistance devices. Initial training will be focused on static and dynamic standing balance and weight shift training with EKSO. This will progress to more difficult activities, such as transitioning from sit-to-stand and stand-to-sit, walking, and turning depending on each subject's capability. A trainer will always be present during the training sessions to provide varying levels of assistance. As a subject's skill with the powered exoskeleton improves, the need for trainer assistance will be proportionately reduced. The level of assistance will be quantified by 4 categories of trainer-assisted efforts: (1) maximal assistance – both hands on the pelvic band of the device for significant and frequent weight shift and balance support to the participant; (2) moderate assistance–both hands on the pelvic band or other part of the device for occasional weight shift and/or balance support to the participant; (3) minimal assistance—one hand on the device for infrequent balance support; and (4) close contact guard/no assistance–no hand on the device, but is near enough to be able to provide assistance if necessary [6]. To monitor safety and fatigue, we will ask all subjects periodically during training sessions about their perceived

exertion using Borg Rating of Perceived Exertion Scale (RPES) [7]. Training will be stopped if a subject reports a level of 17 or greater, and will only be resumed after rest.

#### Assessment of participant status after each training session:

Additionally, for every session, participant's physical comfort will be monitored for documentation of safety. Pain, discomfort, fatigue will be assessed at the start and end of each experimental session on a 11-point visual analogue scale ranging from 0 (none) to 10 (worst). Physical and cognitive demand assessment data will be recorded as well. The progress note will also document experimental session details (e.g., task performed, date, time etc.). The data collected through this survey will help monitor safety and comfort of using device on a session-by-session basis throughout the training period.

All collected assessment data forms will be de-identified and only include the coded-name for each participant.

#### Photography and Videotaping:

A portion of the assessment and training sessions will be photographed and videotaped for scientific publications and presentations. Subjects' consent will be required to perform any photography and videotaping. Subject identity will be protected in any published photography and videotaping placing a black square across subject's face.

### **Data and Safety Monitoring**

We will use following strategies to prevent some expected events for this study:

#### 1) Loss of confidentiality or privacy

Information obtained for this study will be kept private to the extent allowed by law. However, research information may be shared with the University of Texas Health Science Center at Houston Institutional Review Board (IRB), the research physician investigator, the research staff and others who are responsible for ensuring compliance with laws and regulations related to research.

The study will be performed at The Institute for Rehabilitation and Research (TIRR) Memorial Hermann in the physical therapy gym. All data collection records will be locked in the Study Coordinator's office in a locked file cabinet. The only data entered electronically will be de-identified data. All computers are password protected and therefore, only authorized persons have the access to the electronic files saved in computers and will adhere to TIRR MEMORIAL HERMANN standards.

#### 2) Loss of saved electronic data after a computer crash

All original data will be maintained on paper data collection forms. De-identified data may be entered into computer for data analysis. A standard procedure of electronic file backup is established and enforced by the PI. All file backups are routinely performed in the local hard drive.

However, if there are other unanticipated problems which occur during and after data collection: the original paper version of the data will be maintained in the locked file cabinet.

#### 3) Muscular soreness or fatigue

Borg Rating of Perceived Exertion Scale (Borg) will be administrated periodically throughout the intervention sessions. Subject will be provided with rest period as needed, in particular if BORG rating  $\geq 17$ .

#### 4) Loss of balance or fall from testing

One research team member will remain next to the subject as long as the subject is donned in the exoskeleton robot to prevent loss of balance or fall whether sitting or standing. If a fall or significant loss of balance occurs, one staff physician will be notified immediately. All adverse events will be reported per CPHS protocol.

#### 5) Possible skin irritation

Local irritation, bruising, swelling, or temporary discomfort following wearing of the exoskeleton may occur. Prior to donning the exoskeleton subject's skin will be inspected by a licensed Physical Therapist for baseline, and compared after doffing. Any differences will be recorded and followed up with the study physician accordingly. All adverse events will be reported per CPHS protocol.

#### 6) Bone Fracture

Subjects will be assessed using the SCI Bone Health Screen, their scores will be reviewed with the subject and an informed consent will be signed. All subjects will be cleared by study physician prior to enrollment in the study. The risk of fracture to the subject is no greater with the use of exoskeleton than conventional weight bearing and walking therapy.

#### Statistics

Descriptive analyses will be used for Aim 1. For Aim 2, outcome measures will be analyzed using separate paired t-test (exoskeleton vs. no-exoskeleton walking). We also plan to plot the trend at pre-and post- training for all outcome measures for each subject (without exoskeleton). Significant level will be set at .05.

This is a pilot study therefore no data is available to calculate sample size. The reason to enroll 15 subjects is based on the limited funds awarded to this project. We anticipate that the data from this study will allow for performance of power analysis to determine effect size and sample size for future studies.

#### Ethics

The study will be performed under the prevue and in accordance with the rules set by the Committee for the Protection of Human Subjects (UT IRB). Potential subjects will be identified by physiatrists working in the outpatient clinic and/or on the inpatient wards at The Institute for Rehabilitation and Research (TIRR) Memorial Hermann. Once identified, the potential subjects will be approached and asked if they wish to discuss a study utilizing exoskeletons (Robotic suits worn on the outside of the body) to help people with incomplete spinal cord injury achieve a better gait pattern (better walking). It will also be explained that choosing not to inquire further about the study will in no way jeopardize the relationship with anyone at TIRR or in the Memorial Hermann system. Once the potential subject agrees he/she will be introduced to either the Principal Investigator or the Study Coordinator. Once the potential subject agrees to discuss the study, the individual and anyone that the potential subject wishes to accompany him/her will go into a private room to discuss the contents of the consent form with either the Principal Investigator or the Study Coordinator. After the consent is reviewed in its entirety, and after allowing ample time for questions, either the Principal Investigator or the Study Coordinator will give the potential subject time to discuss the study with whomever the potential subject cares to discuss the study with. If the subject agrees to enroll in the study, the Study Coordinator or Principal Investigator will review the informed consent form with the subject in its entirety.

#### Data handling and record keeping

The subject's name and demographic information will be collected prior to testing. Each subject will be assigned an identification number which will be used from this point forward. All measurements will be stored according to the identification number. The Study Coordinator's locked office contains a locked file cabinet in which research materials are kept. All computers are password protected and only authorized persons have the access to the electronic files saved in computers. Paper data will be stored in the Study Coordinator's office in a locked file cabinet. Access to the file cabinet will be given to the Primary Investigator and authorized team members. All electronic data stored on the hard drive of the desktop machine will be password protected and available only to the authorized research team members. Identifiable data will be stored for 5 years after

the study is completed. Stored files will be deleted from the portable hard drive after 5 years as well. Identifiable data will be shredded at the end of 5 years after the completion of the study.

## Quality control and assurance

To ensure research integrity, standard written procedures for all tests will be established by the Principle Investigator and the Study Coordinator who will then assess each team member's competence for research conduction on a regular basis. Therefore, the testing protocol will be consistent throughout the entire data collection for this study. All outcome measures (pre and post-test) will be performed by a single masked investigator to ensure consistency with performance of the outcome measures and to maintain an un-biased perspective.

## Publication Plan

The results of this study will be used for presentation at national conferences and publications in peer-reviewed journals. The publications will be provided without cost to the study participants.

## ATTACHMENTS

1. Physician clearness letter
2. Phone Screening Form
3. Case Report Forms (pre and post-test outcome measures)
4. Barthel Index
5. MMSE
6. Quality of life measure
7. Berg Balance Scale
8. BORG Rate of Perceived Exertion Scale

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