Transspinal versus Epidural Stimulation for Exoskeletal Assisted Walking after SCI

Protocol-Version 9-05112023

PI: Robert Trainer, MD

Co-investigators: Timothy Lavis, MD, Lance Goetz, MD, Ashraf Gorgey, MPT, PhD, Denise Lester, MD, Adam Klausner, MD, Carrie Peterson, PhD

Table of Contents

Background and Justification

Spinal cord injury (SCI) results in physical impairment and limited mobility, causing survivors to be confined to lifelong wheelchair status with subsequent chronic comorbidities. These comorbidities may include psychosocial, cardiovascular, and metabolic consequences, as well as a significant socioeconomic burden (1-5). The economic burdens for persons with SCI, their families, and society are increasing at an alarming rate, especially with decreasing mortality due to advances in medical interventions (6). Restoring mobility would result in a reduction of many of these SCI associated comorbidities and their associated economic burden (7). Attempts have been made to restore and improve locomotion following SCI including the use of long-leg braces, hip-knee-ankle foot orthoses, functional electrical stimulation, (e.g. Parastep®), and therapist-driven or robotic-driven body weight supported treadmill training. Several of these techniques were considered interventions to counterbalance the changes in body composition, reduce physical activity, and improve lipid and carbohydrate profiles associated with SCI (7-14). Unfortunately, most of these rehabilitation interventions require too high of a metabolic energy demand for individuals with SCI to tolerate long-term walking. This resulted in failure to pursue these interventions or meet the recommended guidelines for improving physical activity after SCI.

Implanted epidural stimulation offers the potential for voluntary control of the paralyzed lower extremity muscles to be activated in order to standup and walk. Several trials successfully demonstrated that an implanted stimulator resulted in evoking muscle potentials in paralyzed muscles of persons with motor complete SCI (C5-T4; AIS A or B). Evoked motor potential was also tested during supine and standing positions using stimulation intensities ranged from 0.5 to 10 V at a frequency of 2 Hz and pulse width of 210-450 μs. The authors reported that epidural electrical stimulation resulted in recruitment in both the proximal and distal leg muscles. Harkema et al. presented a case study of a 23-year old person with paraplegia after 3.4 years of injury. Epidural stimulation was implanted over L5-S1spinal cord segments to stimulate the lumbosacral enlargement. Stimulation amplitudes ranged from 0.5 to 10, frequencies from 5 to 40 Hz with a pulse duration of 210 to 450 μs. The participant showed improvement in voluntary movement, EMG activity, joint angles, foot switch, ground reaction force, and bodyweight during 7 months of training with epidural stimulation. No complications were reported. Huang et al. demonstrated the efficacy of epidural stimulation in two persons with chronic C5-C6 AIS C tetraplegia and T8 AIS C paraplegia during partial body weight supported treadmill training (BWSTT). Epidural stimulation (ES) was placed over T10 to L2 spinal levels with a frequency of 20 to 40 Hz and a pulse duration of 800 μs. The authors reported improvement in bilateral EMG activity of the leg muscles. Epidural stimulation resulted in increase in walking distance and duration via stimulation of the dorsal aspect of the spinal cord. Grahn et al. 2017 described a case of a 26-year old person with a chronic T6 AIS A injury who received epidural implantation. The implantation was followed by 3 weeks of recovery and 8 sessions of volitional motor control over a 2-week period. The authors reported that the participant recovered volitional control over specific muscle activity to produce step-like activity.

Today, applications of epidural stimulation that are currently underway may produce improvement in upper extremity functions, respiration, cardiovascular function and bladder control for persons with SCI. It is expected that technology will be improved to demonstrate implantation and discharge immediately without the need for recovery time that may last for a week or two before starting any training program.

Transspinal stimulation (TS) has also emerged as a highly attractive rehabilitation modality that can similarly activate and neuromodulate the spinal locomotor centers.[45-48] TS has been shown to enhance EMG pattern, depressed motor excitability as measured by H-reflex and facilitate step like activity in both able-bodied and SCI individuals.[47,48] TS uses similar neural pathways as ES. Activation of lumbosacral segments using TS has recently been used in conjunction with exoskeletal assisted walking (EAW+TS) as a neuro-modulatory approach to facilitate stepping and voluntary control of exoskeleton.[45] EAW+TS resulted in continuous stepping with improvements in coordination as well as the autonomic function including cardiovascular and thermoregulation profiles. Another study showed that TS may result in improvements to lower urinary tract functions after SCI.[46]

The department of Veteran Affairs (VA) has almost 46,000 Veterans with SCI. Incorporating epidural stimulation in the rehabilitation of persons with SCI may facilitate restoration of locomotion and ameliorate several health-related secondary complications. We are fortunate here that we have investigators with adequate clinical and training experience to lead the VA in applications of epidural stimulation for persons with SCI. We have recently demonstrated the use of powered exoskeletons to restore ambulation in persons with SCI (41-44). Training may also improve the level of physical activity as well as psychological parameters that are likely to interfere with rehabilitation outcomes.

The purpose of the current study is to determine the feasibility of safely applying epidural stimulation (ES) or transspinal stimulation (TS) to Veterans with SCI. To the best of our knowledge, this will be the first time that these neuromodulation rehabilitation interventions will be conducted in the Department of Veteran Affairs. The intervention will be accompanied by use of a powered exoskeleton (EKSO®) with the hope of facilitating standing and to produce step-like movement in persons with chronic motor complete (AIS A or B) SCI with below C5 level of injury. Cardiovascular performance, as measured by resting blood pressure and heart rate, peak oxygen consumption during walking, energy expenditure, whole and regional body composition assessments will also be measured. We are also going to evaluate the effects of training (EAW+ES) on muscle activation pattern measured by surface EMG and walking parameters including stand-up time, walking time, distance covered, and speed of walking. Finally, we will expand our work to determine the effect of ES or TS on bladder functions in persons with SCI

Name of Epidural Stimulation Device:
Intellis® Platform Spinal Cord Stimulation System

Intended Use:
Electrical stimulation of the lumbar spinal cord to voluntary activate lower extremity muscles to stand up and initiate steps with exoskeleton training in persons with SCI
.
Duration of Study:
1.5 years (3 months of robotic exoskeleton and 6 months and two weeks of intervention and follow-up visits every 3 months up to 9 months).

Study Protocol
Recruitment Plan
We are planning to recruit 10 participants with motor complete SCI (AIS A or B) to participate in the current trial. Five participants will be randomized into the EAW+ES group and the other 5 will be randomized to the EAW+TS. Every effort will be made by the study team to implement a successful recruitment plan, and to avoid any source of coercion during the entire research process.

1-We will develop a timeline to meet our recruitment goals and determine our screen failure rate. The following will be used as recruitment methods:

a. All medical providers will be provided with an inclusion/ exclusion list that allows them to discuss the study with their Participants, if the Participant is interested the PI will be notified.
b. The PI will plan to quarterly present in the SCI grand rounds conference to educate the staff and involve them in the recruitment.

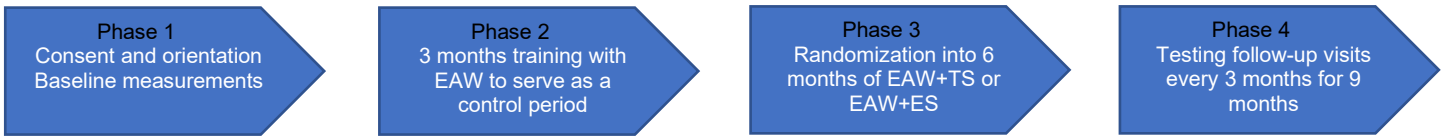
.2-All potential participants will be approached by the PI or a research coordinator after receiving a written medical clearance from their primary care provider of their medical eligibility to participate in the study.

3-The PI and one of our medical personnel will schedule the potential participant and provide a detailed explanation of the study in the presence of one of our medical staff and sufficient time to consider reading the consent form, discuss with relatives and their primary provider. A list of the study benefits and risks will be highlighted.

4-Potential participants will then undergo a detailed medical evaluation for eligibility by a physician coinvestigator.

5- The study is voluntary; all participants will be freely allowed to withdraw from the study at any time point without impacting their medical care or health benefits at the local VA facility.

Study Design. The study design is highlighted in the following figure.
Ten participants with chronic, motor complete (AIS A and B) SCI, aged between 18-70 years, will be randomly assigned to participate into either 6-months of EAW+ spinal cord epidural stimulation (ES; n=5) or EAW+Transspinal (TS; n=5). Following consent each individual will participate in this pilot study for approximately 1.5 year. Initially, participants will undergo 3-months of EAW training (2-3 sessions/week), which will be followed by randomization into either EAW+ES or EAW+TS for an additional 6-months (both: 3 sessions/week). Participants in both groups will also complete a 3-month follow-up visits during which no training will occur up to 9 months. Measurements at baseline (**BL**: prior to EAW) and 3 post-intervention timepoints will occur every 3-months (**P1**: following 3-months of EAW; **P2**: following 3-months of EAW+TS or EAW+ES; **P3**: after completing 6-months of EAW+TS or EAW+ES. For the follow-up visits, visits will be **F1, F2 and F3**: 3, 6 and 9 months after termination of EAW+TS or EAW+ES.



Phase 1:Informed consent, familiarization and baseline measurements (BL)

At this phase, participants will sign a consent form and will undergo a complete study familiarization. Drs. Trainer or Lester will complete direct consenting and answer any clinical questions pertaining to the study. The participant will also undergo a history and physical examination by an SCI physician coinvestigator to determine their medical appropriateness for the study procedures (risk of autonomic dysreflexia, cardiovascular health, etc.) and perform all baseline measurements (see measurements section). To rule out any potential cardiac or pulmonary problems, physical exam will include assessment or pulse ECG assessment, oxygen monitoring and force vital capacity (FVC) testing for subjects who are expected to have some weakness with breathing. Participants will then meet with co-investigator ***Dr. Denise Lester or Dr. Robert Trainer*** (PI of the study) from the Anesthesia/Pain Service to discuss all aspects of the implantation.

Phase 2:
Powered robotic exoskeleton (Ekso). Subjects with motor complete SCI will participate in a powered exoskeleton (EKSO) for 2-3 times per week for 12 weeks. The program will involve walking with the robotic suits for 60 minutes per session. Morning and evening sessions will be separated by at least 2 hours. During the training sessions, a member of the research staff will monitor the participant's resting and exercise vital signs (blood pressure and heart rate), participants will perform 10 reps per leg of knee extensions with epidural stimulation for 20 minutes, standing up from their wheelchair or from sitting on a mat using a standard walker for 10 minutes, sitting from a standing position, walking with the robotic exoskeleton for 60 minutes twice a day, and over ground walking. During some of the training sessions, a clear mask will be placed on the participant's face to measure energy using during sitting, standing, walking with a

walker or crutches and recovery from standing and sitting with the robotic suite, this test should not exceed 20 minutes. Pressure sensors will be placed in the sole of the participant's shoes to determine their walking pattern and Surface electromyography (SEMG) will be used to measure the electrical activity of underlying muscle groups placed on the skin (hair will be shaved from surrounding areas). The purpose of this period is to allow each participant to serve as his/her own control. Additionally, it will provide us with information regarding the improvement that may result from using exoskeleton only without using TS or ES. This will serve as a background for any improvement that may be noticed following Phase 3 of the trial.

In a fitting session, hip width, upper leg and lower leg lengths will be measured to appropriately adjust the width and legs of the robotic suit. The Ekso unit will be adjusted to offset for the limited ROM at both hips and knees within 5 and 10 degrees, respectively.

A detailed description of the EKSO device was published elsewhere. The EKSO unit offers a gait training mode with a range of features. Features include a ***first step mode*** in which steps are manually controlled by the therapist, a ***pro-step mode*** that offers complete assistance and pro-step+ mode that provides adaptive and variable assist features. The variable assist feature allows participants to volitionally move their legs and receive the minimal assistance required to complete their stepping. In the first session, all participants will be trained using first step mode until they were able to carefully shift their body weight antero-laterally and achieve quality walking. Participants will then be progressed to either pro-step or pro-step + mode accompanied by two buzzers to cue the subject accurately to complete weight shifting prior to stepping.

During the first 3 months, all participants will undergo training using the adaptive pro-step mode. In phase 3 (next phase), the variable assist feature will allow participants to move their lower extremities with the least assistance required for stepping while using either TS or ES. We will start with 100% swing assistance and it will be dropped down by 5-10% once a participant can generate 80% of his/her steps (i.e. unassisted steps) during a 10-meter walk test. EAW unassisted steps are determined by using the available audible cueing feature. In a slow mode, the audible cueing feature provide subjects with 2.5 seconds to move their leg in a pre-defined trajectory. If the subject is unable to move the legs, the robotic unit will beep and passively move it for them.

Phase 3:
At the beginning this phase, the subjects will be randomized into either 6 months and 2 weeks of ES or TS. The 2 weeks will be used for identifying the stimulation parameters for TS and for implantation procedure in the ES. During this two-week period, the subject will not be exercising.

A. Epidural stimulation (ES; n =5)
This is a 2-step process where temporary implantation precedes permanent implantation when indicated.
The epidural spinal cord stimulation system (Intellis Epidural Stimulator, Medtronic,

Minneapolis, USA) will be used to electrically stimulate the lumbosacral enlargement. During temporary implantation, two 8-electrode lead arrays (please check attached Appendix) will be implanted utilizing fluoroscopic guidance over spinal cord segments T10-L2 (. All operations and procedures of the spinal cord stimulator will be performed by Drs. Denise Lester and Robert Trainer from the Pain service, who are privileged/credentialed to implant and operate the device.

Prior to both temporary and permanent procedures
Hibiclens® (chlorhexidine) soap skin cleanser and Bactroban® (mupirocin) 2% ointment will be given for 7 days prior to the procedure to reduce bacterial colonization of participant's skin and nares. An anesthesia preoperative evaluation will be performed and consent obtained prior to entrance into the operating room. In a rare event when opioids are prescribed for more than 5 days, monitoring will occur according to clinical recommendations.

1. <u>Temporary Implantation.</u>

The participant will be scheduled with either Dr. Lester or Trainer to perform the temporary implantation. After placing the participant in a prone position, the participant will be implanted in a minor procedure room, located on the second floor, under fluoroscopy. A nurse certified in sedation will establish IV access, place standard ASA monitors including noninvasive blood pressure every 5 minutes, Pulse oximetry, continuous EKG, and end tidal co2 from a nasal cannula. Antibiotics (typically ancef 2-3 grams or clindamycin 600-900 mg) will be used at the time of implantation. If sedation is required, small doses of anti-anxiety medications and pain medications (typically versed and fentanyl) can be titrated by the nurse directed by Drs. Lester or Trainer to allow the patient to be conversant and comfortable during the procedure. Through provided 14-gauge epidural needles using X ray guidance and loss of resistance technique the epidural space will be accessed. Next, the leads will be navigated in the epidural space. Drs. Lester or Trainer will test the configuration (i.e. stimulation parameters), in the presence of Medtronic representative, necessary to evoke motor potentials as indicated by visible motor contractions of the paralyzed muscles. The electrodes will be taped and glued to the skin during the temporary implantation procedure as described point-by-point in the attached manual pages 37-39 "securing a lead in a percutaneous trial," to lessen the chance of lead migration.

When comfortable for the participant (typically the next day), they will be scheduled for 3-4 days to perform the process of muscle mapping (i.e. determining the cathodes and anodes as well as the stimulation parameters). Following implantation and for 1 week, the participant will be asked to turn on the temporary epidural stimulation under the guidance of Dr. Denise Lester or Dr. Robert Trainer. EMG activity data from the lower extremity muscles will be collected during lying and sitting as tolerated. During week 1, there will be no use of exoskeleton. The participant will have the dressing changed using the pain service's clinical protocol (Drs. Lester or Trainer; see below for details). Vital signs will be monitored on a daily basis. To perform muscle mapping, we will place EMG electrodes on the major muscle groups (gluteus maximus, gluteus medius, knee extensors and flexors, gastrocnemius and tibias anterior) of the right leg followed by the left leg. The process of mapping will occur in the presence of Dr. Lester or Trainer, a

Medtronic representative and Dr. Gorgey. Either Dr. Lavis or Geotz will be evaluating the patient on a daily basis to ensure that there are no signs of infection or and to ensure no other medical problems have developed. Once the process of mapping has been proven successful, the participant will then be asked; based on their experience and the risks explained whether they would like to proceed with permanent implantation. The participant will have their temporary spinal cord leads removed 7 days later, by Dr. Trainer or Dr Lester. We will be throwing out the temporary leads and place permanent leads. If the temporary implantation did not evoke motor potentials, indicated by visible motor contractions of the paralyzed muscles, they will not to be scheduled for permanent procedure.
If permanent implantation is chosen, the patient will be scheduled in an operating room (OR). Dr. Trainer will perform all surgical implantations.

2- Permanent Implantation and Recovery

For those who are deemed acceptable and willing to have permeant implantation, two 8-electrode arrays of Vectris lead will be implanted, in an operating room, in the presence of an anesthesiologist. Phase 1 of the permanent implantation is identical to the temporary lead trial described but done in the operating room and with the anesthesia provided by an anesthesiologist. The anesthesiologist or a CRNA under his/her direction will establish iv access, place standard ASA monitors including noninvasive blood pressure every 5 minutes, Pulse oximetry, continuous EKG, and end tidal co2 from a nasal cannula. Antibiotics (typically ancef 2-3 grams or clindamycin 600-900 mg) will be used at the time of implantation When sedation is required, small doses of anti-anxiety medications, pain medications, and anesthetics can be titrated by the anesthesia team to allow the patient to be conversant and comfortable during the procedure. Through provided 14-gauge epidural needles using X ray guidance and loss of resistance technique the epidural space will be accessed. Next, the leads will be navigated in the epidural space. Drs. Lester or Trainer will test the configuration (i.e. stimulation parameters), in the presence of Medtronic representative, necessary to evoke motor potentials as indicated by visible motor contractions of the paralyzed muscles. Dr. Trainer will next make an incision in the participant's lower back or their buttock. The generator will then be placed in a pocket of tissue between the muscles and the skin. The leads will be threaded under the skin to a pocket formed and they will be connected to a Medtronic intellis battery. All connections will be checked. Following hemostasis, the wound will be closed in 2-3 layers, dermabond, occlusive dressing and tape will be placed over the wound. A belly band will be provided for patient comfort. Following implant, Drs. Goetz or Lavis will inspect dressings, the insertion site, and monitor vital signs daily and participants will be seen, by Dr. Trainer, within 5-7 days after surgery to change their dressing. The participant will be seen at day 14 and day 30 for wound check and device reprogramming. After implantation, the participant will be ready to undergo rehabilitation for 6 months.

All medical supplies necessary for the procedure will be provided for the scheduled 5 patients. Both Drs. Lester and Trainer will be responsible for inducing motor evoked potentials in the lower extremity muscles.

This will be followed for 2-3 days of resting. During this time, the participant will be trained by Dr. Denise Lester or Dr. Robert Trainer and with the assistance of the Medtronic representative on how to use the epidural stimulation controller to trigger activation of the paralyzed lower extremity muscles.

(Further details regarding surgical device implantation protocol can be found in the Medtronic Surgical Procedure Appendix III)

3 -Training to reinforce standing and stepping

At this phase, Dr. Gorgey and research assistants will be responsible for helping the participants to trigger the paralyzed muscles from supine and sitting using the participant's volitional control ***daily for 3 days per week***. Training will include exoskeleton assisted walking for 3 days/week for a total period of 6 months. Training will occur ***in the morning and in the evening,*** to allow participants enough time to rest, and will not exceed 2 hours per day. Based on the manufacturer's instructions, the participant will be asked to activate his epidural stimulation controller to do the activities listed below:

- Leg extension while seated in wheelchair
- Standing from mat with assistive device (standard walker)
- Standing from wheelchair using exoskeleton
- Stepping during exoskeletal-assisted walking for 60 minutes in the morning and over-ground walking using parallel bars, walker and crutches for 60 minutes in the evening.

The order of rehabilitation protocol during the 6-month period for both morning and evening sessions is listed below:

1. Resting vital signs including blood pressure and heart rate.
2. 10 reps per leg of knee extension with epidural stimulation (morning session)- for 20 minutes.
3. Train the participant to stand up from his wheelchair or from sitting on the mat using a standard walker (morning session)-10 minutes.
4. Train the participant to volitionally perform controlled sitting from standing position (morning session)-1 or 2 minutes.
5. Train the participant to step/walk using exoskeleton adaptability mode. This mode allows the exoskeleton to gradually lower the assistance provided to the participant based on their performance. We will start with 100% assistance and will drop the support in 5% increments as tolerated until we reach the lowest assistance level possible during walking. The EAW unit provides auditory cueing in forms of beeping once the subject initiates antero-lateral shifting. The unit is equipped with adaptive assistance mode, in this mode, you can have support that range from 0-100%, with 100% means that the unit provides 100% support and assistance to ambulate. Once

the assistance dropped to 95%, this means that the subject can control the unit by 5%, if the subject fails to initiate this level of assistance the unit will beep indicating failure of the subject to initiate stepping. At this point, we will not lower the assistance to ensure subject's safety and prevent any potential falling. To determine this assistance will be dropped from 100% to 95%, researcher will then allow the subject to ambulate for 10 meters and determine the number of steps with and without cueing (i.e. audible sounds). If the subject is capable to generate 80% of his steps without cueing in 10-meter distance, this means that he/she is ready to drop the support from 95% to 90% and so on. Setting the threshold at 80% is arbitrary, but it will provide confidence that with the least assistance subject's safety is ensured and increase his ability to control his legs via epidural stimulation.

6. Overground walking will be implemented to test the ability of the subject to translate exoskeletal assisted walking in motor learning behavior and to determine his ability to generate standing and stepping on his own. We will start with parallel bars and then gradually transition to over-ground ambulation using either a platform walker for below C5 SCI and standard walker for C7 and below.

We have previously tested and published two reports that clearly demonstrated that even a person with C4 AIS A using a platform walker is safe to utilize Ekso with full supervision. For those with C6, we intentionally cuff their hands to either the walker or the crutches during walking. We have examined 2 persons with C6 AIS A and B, both of them appeared to walk with minimal support and guidance using the Ekso. We aware of the fact that the Ekso exoskeleton was cleared by the FDA for institutional use in SCI subjects with C7—T3 ASIA D, and T4-L5 ASIA A-D. Moreover, the Ekso device was cleared for use in patients who have sufficient elbow and shoulder strength to support crutches, a walker, or a cane. Inclusion of subjects with complete SCI at below C5 presents a significant fall risk because subjects are unable to simply grasp assistive devices to mitigate fall risk when inside the exoskeleton. However, we have a developed a fall risk mitigation plan including the followings:

1- Carefully ensuring that they can safely communicate our orders
2- Carefully check the upper and lower extremity intact range of motion.
3- Perform a routine DXA scan for their whole body and determine their T-scores at the hip joints (less than -2.5 SD will be excluded) or bone mineral density (less than 0.6 g/cm2 for distal femur or proximal tibia will be excluded) at the knee joints. This will also facilitate the risk of fracture.
4- Demonstrate they can achieve both sitting and standing balance with minimal support wearing the robotic suit.
5- Monitor their blood pressure and heart rate continuously from sitting and standing to ensure no postural hypotension or sudden dysreflexia of less or more than 20 mmHg at both systolic or diastolic blood pressure measurements.
6- Perform balance training and shifting weight bearing from standing for 20-30 minutes prior allowing patient to perform stepping
7- Operate Ekso at the first step mode for the first session to ensure that we have full control on the unit in case of any emergency.

8- We carefully check the skin for any possible redness or irritations and pad the skin carefully to avoid any skin insult or injury. The patient and his caregiver were also advised to do so for 48 hours.

Plan of actions in case of signs of unsafe changes in blood pressure or heart rate:

1. Every effort will be performed to closely monitor blood pressure and heart rate as highlighted in the protocol (see below)
2. In case of sudden changes, either sudden drop or rise in blood pressure below or above 20 mmHg, any activities will be immediately stopped and the medical doctor (Drs. Lavis or Goetz) will be notified immediately.
3. Prior any activities and to ensure no sign of postural hypotension, participants will be encouraged to drink plenty of fluid to avoid any symptoms of dehydration during exercise.
4. Prior to activities and to ensure no signs of autonomic dysreflexia, participants will be asked to void his bladder and to ensure wearing loose and soft clothes during exercise as well as no tight shoe laces.
5. In case of postural hypotension, the subject will be positioned in a flat position and his legs will be elevated to 30-40 degrees above horizontal and his blood pressure and heart rate will be monitored closely.

B. Transspinal stimulation (TS; n=5)

Transspinal stimulation (TS) has also emerged as a highly attractive rehabilitation modality that can similarly activate and neuromodulate the spinal locomotor centers. TS has been shown to enhance EMG pattern, depressed motor excitability as measured by H-reflex and facilitate step like activity in both able-bodied and SCI individuals. TS uses similar neural pathways as ES. Activation of lumbosacral segments using TS has recently been used in conjunction with EAW (EAW+TS) as a neuro-modulatory approach to facilitate stepping and voluntary control of exoskeleton.[45] EAW+TS resulted in continuous stepping with improvements in coordination as well as the autonomic function including cardiovascular and thermoregulation profiles. Another study showed that TS may result in improvements to lower urinary tract functions after SCI.[46]

Transspinal stimulation will be applied to determine whether participants would be capable to initiate stepping on their own. Transspinal stimulation is a non-invasive procedure using direct current where a large cathode electrode is placed at the thoraco-lumbar region (T9-L2) and the anodes will be placed at both iliac crests. Using the Digitimer stimulator, a direct current will be delivered to activate the central pattern generator (CPG) located at the lower thoraco-lumbar segment of the cord. This may facilitate initiation of stepping in persons with SCI during walking with exoskeleton.

Stimulation parameters that will be utilized based on the subject's level of comfort to avoid triggering autonomic dysreflexia, blood pressure will be monitored regularly every 5 minutes under the supervision of the PI. The stimulation

parameters will be set between 0-100 mA, pulse duration of 1 ms and frequency less than 20 Hz.

Despite the fact that exoskeleton offers the opportunity for persons with SCI to standup and walk; there is no volitional control on their legs (i,e, exoskeleton moves the legs passively). Using transspinal stimulation may facilitate the central pattern generator and allow our participants to initiate stepping on their own. Previous work from other laboratories indicated that TS elicited motor evoked potential as measured by electromyography in the paralyzed muscles. This may provide the opportunity for persons with motor incomplete injury to trigger muscle activation below the level of injury.

Furthermore, combining TS with EAW may increase the metabolic activity of walking and encourage patients to initiate stepping during walking. To test this hypothesis, exoskeleton will set in an adaptive mode and stepping will be set at slow mode (~2.5 seconds), this would provide our participants with 2.5 seconds to initiate stepping. If the participant failed to initiate stepping during this period, the exoskeleton unit will initiate the stepping for them. A research representative will be counting the number of steps initiated by the patient during walking.

Our TS with EAW has been previously approved by our IRB for 12 weeks and we have test 4 participants. After turning the external TS, EMG activity of the paralyzed muscles increased, and the assistance provided by EWA decreased to 55%. Our anecdotal observation indicates that application of TS is safe and easily applied in persons with SCI.
We are hopeful by this pilot trial, we would understand how TS may facilitate activation of the spinal cord locomotor centers and may serve as future simple and cheap alternative for those who do not have access or can afford spinal cord epidural stimulation.

Phase 4: Post-intervention measurements and follow-up visits

Following the 6-month training phase (Phase III of either ES or TS), each participant will undergo post-intervention measurements including gait parameters, body composition assessment and cardiovascular performance by measuring oxygen uptake, and bladder functions (see below). Each participant will be asked to follow-up every 3 months for 9 months to measure changes in body composition using simple anthropometrics, body weight and cardiovascular profile, by measuring oxygen uptake.

For the EAW+ES group, at the end of 9 months training, participants will be given the option of either to keep the implanted ES or to remove it by either Drs. Lester or Trainer. Patient will have the full right to remove the implanted stimulator at any time. At the end of the 6 months training (i.e. following the initial 3 months of EAW training only) and as requested by FDA, all the stimulators have to be turned off and additional approval needs to be considered, have the PI considered to continue working with the participants.

Inclusion/ exclusion criteria

Inclusion

Prior to enrollment in the study, the following inclusion/ exclusion criteria must be attained:

1. A written clearance by the medical doctor to ensure that the participant is safely able to engage in the program.
2. Participants who require assistance with activities of daily living, must have a caregiver or companion with them throughout their participation in the study.
3. Participants will have to be 2 years post-injury with any level of injury below C5 and using wheelchair as the primary mode of mobility. The study is primarily exploratory, and all participants will be between 18-70 years old, men with SCI.
4. Hip width (distance between two greater trochanters), upper leg length (greater trochanter to the lateral aspect of joint line of the knee joint) and lower leg length (lateral aspect of joint line of the knee joint to the bottom of the foot) that can fit the robotic suit.

Exclusion criteria

1. Unhealed fracture in either lower or upper extremities
2. Severe scoliosis, hip knee ROM or flexion knee contractures preventing positioning in an exoskeleton or plantarflexion deformity greater than 20 degrees.
3. High resting blood pressure greater than 140/80 mmHg and or sudden hypotension upon standing as characterized by drop in blood pressure by 20 mmHg especially in persons with tetraplegia.
4. Other medical conditions including cardiovascular disease, uncontrolled type II DM, uncontrolled hypertension, and those on insulin, pressures sores stage 3 or greater, or symptomatic urinary tract infection.
5. Unable to fit in the device for any reason.
6. Taking anti-coagulants or anti-platelet agents, including aspirin if unable to be off this medication for medical reasons.
7. Implanted pacemakers and/or implanted defibrillator devices.
8. Any condition that, in the judgment of the principal investigator or medical provider, precludes safe participation in the study and/or increases the risk of infection.
9. Dual Energy X-ray Absorptiometry (DXA) T-Score less than -2.5. Scans done will include total body, dual hips and knees.
10. Functional upper and lower extremity range of motion (ROM), strength, spasticity and skin integrity will also have assessed prior to enrollment in the program. The Modified Ashworth Scale will be used to ensure safety of the participants prior to engagement in the rehabilitation program. Participants with severe spasticity or limited ROM will be excluded in the trial. This will be done based on the manufacture’s recommendation.
11. Other exclusion criteria include the presence of implanted electrical device, cancer, thrombosis, pacemaker, defibrillator, and this will prevent the participant to participate in trans-spinal optional part of the study. Patients who are currently

on or receive anti-platelet or anti-coagulant medications will be excluded from the trial.

12. Previous allergic reactions or history of allergy to tetracyclines, rifampin or resorbable sutures. Patients with systemic lupus erythematosus will be excluded, because minocycline has been reported to aggravate this condition, or patients with contaminated or infected wounds.

13. Other exclusion criteria may include the followings

- subjects with uncontrolled autonomic dysreflexia
- subjects with concurrent severe neurological injuries other than SCI: MS, CP, TBI, stroke;
- subjects with unresolved deep vein thrombosis (DVT);
- subjects with prosthetic lower limbs;
- subjects with psychiatric or cognitive impairments which will interfere with proper operation of both the spinal cord stimulator as well as the exoskeleton;
- subjects with an unhealed spinal fracture or unstable spine; and
- subjects with known cardiac pathology which precludes safe participation

Screening and Physical Examination

This will include consenting and describing the study events and expectations. Consent to participate will be obtained as described in the Human Participant Protection Section. Informed consent will be obtained prior to the study, after consenting this will be followed by 1-hour history and physical exam that will be done by one of our certified SCI physicians (Drs. Lance Goetz or Timothy Lavis) at the Richmond VA Medical Center. The screening exams including medical evaluations, history and physical, including assessment of inclusion/exclusion criteria previously mentioned. Once the participant is scheduled, a research coordinator will notify the research team to perform testing.

Physical Examination: A physical examination will include the following:

- General appearance
- Time since injury, level of injury and cause of injury
- Weight assessment as well as the weight of the wheel chair and self-reported height
- Vital signs (heart rate, blood pressure and temperature)
- Examination of head, eyes, ears, nose, and throat
- Pulmonary (auscultation of lung fields)
- Cardiovascular
- Abdominal
- Skin
- International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) exam to determine sensory and motor level and impairment classification.

- Modified Ashworth scale
- Penn Spasm Frequency Scale

Methodology
Ten male Veterans with motor complete SCI (AIS A or B) will participate in the current intervention trial for approximately 3 months of EAW + 6 months of either ES or TS (9 months total). The total duration of the trial including the three follow-up visits will be 1.5 years. The trial will demonstrate the feasibility of this rehabilitation approach for Veterans with SCI at McGuire VAMC. This ***feasibility pilot trial will allow three experienced*** teams of investigators to work together including spinal cord injury, chronic pain, and neurosurgery expert researchers. This will ensure our ability to identify the pros and cons of such unique collaboration. The primary goal of this pilot work is to ensure that our procedures are safe and effective for persons with motor complete SCI.

I. Interventions
1.Rehabilitation Protocol (Exoskeleton Training)
Prior to training, participants will be asked to transfer to an adjustable rehabilitation mat. Research personnel, under the direction of Dr. Gorgey, will help fit the participant into the device starting with the shoes-support (distally) and going up towards the trunk (proximally). The software will then be adjusted based on the recommendation from the manufacturer and progressed based on the clinical need for each participant. Every effort will be made to ensure that all straps are snug but not excessively tight to avoid skin irritation or autonomic dysreflexia. Progression in walking time will be based on the participant's performance in the preceding session and his willingness to continue training.

A powered exoskeleton (EKSO®, Ekso Bionics, Richmond, CA, USA) will be used for 5 days/week. The program will involve walking with the robotic exoskeleton for 60 minutes for participants with complete SCI. The exoskeleton offers over-ground ambulation and the ability to gradually decrease the assistance provided to ensure that the participant can control standing and stepping on his own using the epidural stimulation. The variable assist feature will allow participants to volitionally move their legs and receive the least assistance required to complete their stepping. In the first session, all participants will be trained using "first step" mode until they are able to carefully shift their body weight antero-laterally and achieve quality walking. Participants will then be progressed to either "pro-step" or "pro-step +" mode accompanied by two buzzers to cue the participant accurately to complete weight shifting prior to stepping.

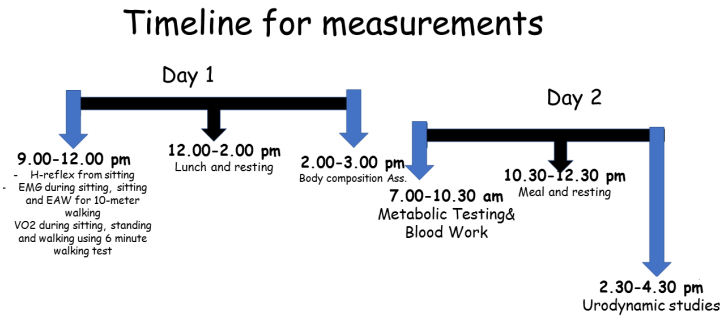
2. Overground ambulation without exoskeleton
Following the exoskeleton session (only for the ES group), the follow-up-visit on the same day will be constructed to provide over ground walking experience. This will start by allowing the subject to stand-up between parallel bars and to do stepping back and forth for 10 feet assisted by a trained physical therapist. Once the subject manages to control standing and stepping between the parallel bars, they will have the opportunity to perform guarded and supervised walking with a therapist and research assistant for 50 feet using a standard roller walker. If the subject is capable to cover the 50 feet, he

will perform supervised and guarded walking with a therapist and a research assistant for 150 feet using bilateral crutches.

3. Epidural stimulation (ES)
This is a 2-step process where temporary implantation precedes permanent implantation (see above regarding the sequence of the events). The epidural spinal cord stimulation system (Intellis Epidural Stimulator, Medtronic, Minneapolis, USA) will be used to electrically stimulate the lumbosacral enlargement. During temporary implantation, one or two 8-electrode lead arrays (please check attached Appendix) will be implanted utilizing fluoroscopic guidance over spinal cord segments T10-L2 (. All operations and procedures of the spinal cord stimulator will be performed by Drs. Denise Lester and Robert Trainer from the Pain service, who are privileged/credentialed to implant and operate the device. Dr. Ashraf Gorgey, MPT, PhD (Sub-I of the study) will be responsible for controlling the epidural stimulator at a low dose and safe range to ensure achieving the study primary specific aims. This will include target mapping of different muscle groups to identify the correct stimulation configurations (location of the cathodes and anodes) and parameters (amplitudes, frequency, and pulse duration).

4. **Transspinal stimulation (TS).**
Transspinal stimulation is a non-invasive procedure where a large cathode electrode is placed at the thoraco-lumbar region (T9-L2) and the anodes will be placed at both iliac crests.[35,36] Using the Digitimer stimulator, a current will be delivered to activate the central pattern generator (CPG) located at the lower thoraco-lumbar segment of the cord using the following stimulation parameters (pulse duration of 1 ms, frequency 30-40 Hz and amplitude necessary to evoke motor potential as determined by EMG activity in the major muscle groups. Considering the pilot nature of the application, we will test the use of different size cathodal electrodes that will be placed between the inter-spinous process T10-T11 and T11-T12 compared to the large thoraco-lumbar electrode that covers T10-L4 spinous processes.

II. Measurements
To reduce subject burden, measurements will be performed over 2-day period for the 10 subjects who will be enrolled in EAW+TS or EAW+ES



Specific aim 1
To determine the impact of 6 months of EAW+TS compared to EAW+ES training on 10-meter walking speed, number of unassisted EAW steps and EMG activity after motor complete SCI.

1. **Primary Outcome Measures**
- Six minute-walk and 10-meter walk distance Tests; Wearing the robotic exoskeleton, the participant will be asked to walk for 6 minutes for measurement of walking speed

and distance (6MWD). Walking time and distance at 10-meter walk test will also be determined. Participants can use either a walker or crutches during testing. The procedure will be done prior to implantation, monthly and every 3 months after implantation or starting of TS up till 9 months and during the follow-up period. The rationale is that six minute-walk and 10-meter walk distance tests will be improved with training. It should be noted that tests will be conducted one-time with the ES or TS off (EAW+ES or TS-off) and another time with the ES on (EAW+ES or TS-on), this will allow each participant to serve as his own control.

- Assistance provided by the exoskeleton; The level of assistance provided to the participant based on his performance will be monitored on weekly basis. We will start with 100% robotic assistance and will drop the support by 5% until we achieve the lowest assistance possible during walking. The drop-in exoskeleton assistance will be determined by the ability of the participant to walk 10-meter distance without stopping.

- Surface electromyography of 12 muscle groups; We will measure the EMG activity from 12 leg muscles and hip, knee, and ankle joint angles during locomotion. We will record bilateral EMG (Delsys Inc. Massachusetts, USA) from the soleus, medial gastrocnemius, tibialis anterior, medial hamstrings, quadriceps, and gluteus maximus muscles unilaterally by bipolar surface electrodes with fixed inter-electrode distance. EMG activity will be measured during the course of the study at different time points (baseline, P1-P3 and F1-F3). Using a digitimer stimulator and while seated, H-reflex of the posterior tibial nerve will also be conducted using a standard procedure to determine the spinal reflexes excitability.

- Two CyberSens Pressure devices will be placed in sole (A custom built pressure sensor device by Dr. Ou Bai at Florida International University). Each device will be installed with three piezo resistive sensors for kinetics, and inertial measurement unit (IMU) for kinematics. The raw signals will be obtained from the three piezo resistive transducers on each foot, while walking withthe EKSO. From the pressure signals on the insole, the following metrics will be extracted: single support time, single support pressure, 1st peak pressure, 2nd peak pressure, time between peaks, loading rate, push off rate. These will then be evaluated to gauge gait symmetry by paired limb consecutive steps. The well-known and widely used Symmetry Index was used for evaluation.

$$\mathbf{SI} = \frac{\mathbf{2(X_l - X_r)}}{\mathbf{X_l + X_r}}$$

$$\mathbf{X_l = Left\ Limb}\frac{\mathbf{Signal}}{\mathbf{Metric}},\ \mathbf{X_l = Right\ Limb}\frac{\mathbf{Signal}}{\mathbf{Metric}}$$

- Following each session, walking time and distance, stepping time and number of steps will be recorded for all participants.

Secondary outcomes for specific aim 2

To determine the impact of EAW+TS compared to EAW+ES for 6 months on cardio-metabolic risk factors as measured by total and regional body composition, oxygen uptake and fasting lipid profile persons with motor complete SCI.

- Oxygen uptake (l/min), energy expenditure (EE; kcal/min) and body composition will be measured using a portable metabolic cart (COSMED K4b2, Rome, Italy) and dual energy x-ray absorptiometry (iLunar DXA, GE, USA) prior-to and the end of 3, 6 and 9 months of training.

- **Other Outcome Measures**

  Blood pressure and heart rate will be monitored prior to and following all training sessions, and participants will be instructed to communicate any discomfort during training.

Blood pressure and heart rate will be monitored in the following order

- in the sitting position prior to standing;
- after standing up with the device;
- 1-2 minutes after initiation of walking; and
- Immediately after stopping activity when the blood pressure could drop

- Body mass index (BMI) and circumferences: Each participant will be asked to void his bladder contents and then will be weighed on a wheelchair weighing scale. After weighing the participant and his wheelchair (kg-1), he will be helped to transfer to an adjustable mat and his wheelchair will be weighted empty (Kg-2). The weight of each participant will be determined by subtracting (2) from (1) (kg). The height of each participant will be determined at the right side in the supine position. After transferring to the mat, the PI will help each participant to properly align. Two smooth wooden boards will be placed at the participant's head and heels and the distance between them correspond to the height in nearest cm. Every effort will be done to maintain the knees in an extended position. The BMI (Kg/m^2) will be calculated as weight (Kg)/ $height^2$ (m^2). Measurement of WC will be determined in duplicate by identifying the narrowest region of the trunk from sitting and lying positions. A black marker will be used to identify the anatomical site in a sitting position. After normal expiration, a tape measure will be used around the participant's trunk to measure waist and abdominal circumferences. Thigh circumference will also be measured. If the value differs by > 1 cm, a third measurement will be taken.

- Dual energy x-ray absorptiometry (DXA): DXA will be used to measure body composition in SCI individuals, specifically regional and total FM and FFM. Total body and regional (proximal femur, and forearm) DXA scans will be performed using a Lunar Prodigy Advance (GE Lunar Inc., Madison, WI) bone densitometer at the VAMC hospital. We perform testing after lower extremity elevation for at least 30 minutes to minimize fluid shift. All scans will be performed and analyzed by a trained, certified DXA operator using Lunar software version 10.5. The participant will be assisted to lie on a padded table and both legs will be strapped proximal to the knees and the ankles. The arms and legs will be positioned to ensure proper alignment and to lie still for 10 minutes during the period of the scan. After scanning, total and regional (% FM and FFM) will be determined using total and regional DXA software; the coefficient of variability of two repeated scans is less than 3%.

- Resting and Exercise Energy Expenditure (EE); After arriving into the laboratory, the participant will be asked to void his bladder contents. He will then be asked to transfer to the mat using a sliding board before being fitted in the EAW unit. The participant will be then asked to relax in a sitting position for 5 minutes and then a breathing mask will be snugly secured to his face to measure oxygen uptake (l/min) and EE using portable COSMED K4b2 metabolic cart. Resting EE will be collected in a sitting position for 5 minutes to allow sufficient time to recover after transfer to the mat. The EKSO unit will then be placed in standing mode and standing EE will be measured for 5 minutes. EE will be collected for 6 minutes of starting walking, followed by 6 minutes of walking with a walker, and 6 minutes of walking with bilateral crutches. The walking period will be followed by measuring EE during standing (3 minutes) and sitting (3 minutes) recovery periods.

- Walking Index for Spinal Cord Injury II (WISCI II); The Walking Index for Spinal Cord Injury Scale (WISCI 2) has demonstrated a response to change in the Spinal Cord Injury Locomotion Trial (ISCOS 2004) and in clinical validation studies. In scoring the WISCI, the examiner checks the descriptors that apply to current walking performance, and then assigns the highest level of walking performance. In scoring one level, one should choose the level at which the participant is safe as judged by the therapist, with the participant's comfort level described. If devices other than those stated in the standard definitions are used, they should be documented as descriptors. The participant is observed by trained personnel and the WISCI level is recorded on the scale of 0 to 20 at baseline (Baseline WISCI). The participant is observed again at the defined interval (Interval WISCI). The change in score is calculated by subtracting the baseline WISCI from the Interval WISCI, which equals the change in WISCI (Changed WISCI). The scale will be performed at the beginning and at the end of the study (see appendix III).

  Fasting blood samples. Blood will then be collected after an overnight fast for 10-12 hours. After placing a hep-lock IV-line in the antecubital vein. Fasting lipid panel (HDL-C, LDL-C, total cholesterol, and triglycerides) and standard 75-g oral-glucose tolerance challenge will be determined over a three-hour period (30, 60, 90, 120,

180). The hep-lock will be flushed with saline to ensure patency throughout the entire procedure.

Near-infrared spectroscopy (NIRS)
The amount of oxygenated (O_2Hb) and deoxygenated (HHb) in gastrocnemius muscle will be determined prior-to and the end of the 3, 6 and 9 months of training using a portable NIRS unit (Portamon, Artinis Medical Systems). The NIRS probe will be positioned longitudinally on the belly of the muscle of the right leg ~3-5 cm below the popliteal fossa. The probe will be secured by a Velcro strap around the calf. A blood pressure cuff (Hokanson SC-10D, Hokanson, Inc., Bellevue, WA) will be placed proximal to the NIRS probe as high as possible above the knee joint. The blood pressure cuff will be controlled with a rapid-inflation system (Hokanson E20, Hokanson) set to a pressure of 250 mmHg and powered with a 15-gallon air compressor. Resting muscle oxygen consumption will first be measured by inflation of the cuff for 30 seconds. The ischemic calibration, also known as a physiological calibration, is performed to normalize the NIRS signals for every test. It provides a reference point of 0% oxygen saturation in the muscle during a period of arterial occlusion (ischemia) and a reference point of 100% oxygen saturation when the cuff is released. Muscle oxygen consumption (mVO_2) will be determined by the rate of change (i.e. slope) of the HHb signal during walking compared to baseline sitting position. Measurements will be conducted during the 6-minute walk test in conjunction with wearing the mask to measure energy expenditure.

Third specific aim
To determine the effects of EAW+TS compared to EAW+ES for 6 months on parameters of bladder filling and emptying as measured by urodynamic studies.

A multichannel urodynamics system (Laborie) will be used to perform urodynamic studies at baseline and P1-P3. A urethral catheter will be placed, and saline is infused into the bladder. A pressure transducer is also inserted into the bladder and records pressure during filling. The effect of any confounding pressure wave from the abdomen is accounted for by a pressure transducer in the rectum. At Baseline-P3, urodynamic studies will be administered twice with TS or ES off and TS or ES on to distinguish between acute and chronic effects. TS and ES have the potential to create acute effects on extremity motor function and possibly bladder control. This may lead to persistent effects, possibly, by inducing neuroplasticity in the spinal cord.[49,50]

Following implantation, participants will report for 2-3 visits to map the best cathodal and anodal combinations as well as the stimulation parameters for testing bladder functions. Multiple urodynamic parameters will be used to demonstrate TS or ES-induced volitional control at baseline and at timepoints P1-P3.

For this study, only individuals with motor-complete SCI will be recruited. Prior to initiation of treatment a 3-day frequency-volume chart will be completed. This will provide baseline information on bladder capacity. When patients present for baseline urodynamics, in order to standardize fill rates, the initial fill rate will be set to 10% of the

maximum catheterized volume (reported on 3-day void diary) per minute. This will ensure that all bladders are filled at a proportionally equivalent rate. The cystometric capacity will then be defined as the volume at which involuntary contraction with leakage occurs during this first fill and 10% of this cystometric capacity will be used for any subsequent fills in which urodynamic data is collected. This protocol has been used successfully by our urodynamics co-investigator (Dr. Klausner) during his currently funded NIH study investigating novel urodynamic techniques.

The following urodynamic outcome measures will be measured.
Development of volitional voiding: In individuals with motor-complete SCI and baseline urodynamics confirming complete involuntary detrusor contractions, we will evaluate the presence of volitional voiding defined as the presence of any voluntary voiding after the "permission to void" (PTV) command is given.
Time to volitional voiding: We will measure the time from PTV to onset of voluntary voiding.
Voiding efficiency: This is defined as: (voided volume) / (infused volume + post-void residual) and is a standard measure of voiding efficiency.
Suppression of involuntary contractions: In participants with involuntary detrusor contractions, we will measure change in peak pressure of the involuntary contractions to quantify the degree of suppression of involuntary contractions.
Suppression of urinary urgency: If patients report urinary urgency, the ability (yes or no) to suppress involuntary bladder contractions will be assessed and compared.
Alterations of bladder Sensation: The international continence society (ICS) recommends the use of standard verbal sensory thresholds including first sensation of filling, first desire to void, and strong desire to void during urodynamics. In this study will compare the volume at which these verbal sensory thresholds occur at baseline and after TS or ES.
Assessment of Bladder Outlet Obstruction: The ICS nomogram and the Bladder Outlet Obstruction index (PdetQmax – 2Qmax) will be used to compare BOO pre vs. post ES treatment.
Bladder Contractility: Bladder contractility will be assessed using the bladder contractility index defined as PdetQmax + 5Qmax. We have chosen to measure multiple outcome variables, because the aim is exploratory in its nature and we would like to determine what outcome variables are likely to be sensitive to both interventions.

Key points demonstrating scientific soundness of the proposed approach

- Spinal epidural stimulation for locomotion has been previously used in persons with SCI and the listed studies demonstrated safety and feasibly of this approach. Studies have reported improvement in volitional control up to 4 years following implantation. Adopting this rehabilitation strategy in the Department of Veteran Affairs may benefit up to 46,000 individuals with SCI.

- Robotic exoskeletons have been used by our labs for more than 3 years and we have reported its safety in many participants with SCI (kindly check references). The PI has developed the exoskeleton rehabilitation protocol and it will be feasible to

apply in conjunction with epidural stimulation; especially after FDA approval and determine that this is a feasible approach for clinical trial.

- Unlike other programs that implanted epidural stimulation in conjunction with locomotion training or restorative body weight supported treadmill training to restore stepping and locomotion, our program will provide the use of exoskeleton for locomotion purpose. This will provide motivation to our participants to experience independent walking with guarded support from research staff and will further allow us to monitor progress in reducing the assistance provided by the robotic suit in a simple objective way.

- Although the method of implantation is invasive and requires skilled intervention, our study team (Drs. Lester and Trainer) are experts in implanting epidural stimulation for pain management and they perform on average 3-4 implantation procedures per month. This procedure is FDA approved for pain management. We have provided an IDE from the FDA for the same device to be use3d in the manner described.

- Stimulation parameters will be adjusted and controlled by Drs. Lester and Trainer (with the help of a Medtronic specialist) to ensure the participant ’s safety and ability to elicit motor evoked potentials sufficient to trigger movement, standing and stepping.

- Performing this procedure for locomotion will not be any different from implantation for pain management.

- Successful completion of this procedure will provide persons with SCI an opportunity to stand-up. This will decrease the overall seated time in wheelchairs. Seated time has been shown to be an independent risk factor for mortality in the general population. Moreover, it will provide a further avenue for improving levels of physical activity by allowing participants to initiate or take steps on their own. It is well established that persons with SCI are considered the lowest on the spectrum of physical activity and searching for ways to improve their physical activity may prevent secondary health comorbidities including type II diabetes mellitus, obesity, metabolic syndrome and cardiovascular disease after SCI.

Discussion of increased risks and how these will be minimized.
Every effort will be made to minimize potential risks. There will be strict adherence to the inclusion & exclusion criteria of the protocol. Appropriate health screening and strict compliance with the established exclusion criteria will minimize attrition due to medically related causes. Participants will be closely monitored by study personnel at all visits. All participants will be provided with 24-hour contact information for the investigator and instructed to call for any concerns. Unscheduled visits may be performed if required for evaluation of safety. If a participant has an adverse event, more frequent visits may be necessary. Please see ***the attached Memo from the study team*** to ensure that our participants will be safe and every effort will be made to minimize risk of infection or any other study related adverse events. In event of infections, this will be treated as an

event of special interest to the study team and it will be reported immediately to the IRB within five business days.

What may present a risk?	Possible Risk/Side Effect	How often has it occurred?
Pressure wound from skin irritation during exercise	Break in your skin creating a wound requiring daily wound care.	Occasionally occurs, but no more so than usual activities.
Risks associated with transfers	Fall	Unlikely
DXA	This research study will require you to have 4 DEXA scans which involves exposure to radiation in the form of X-rays. This radiation exposure is not necessary for your medical care and is for research purposes only. All radiation increases the risk of developing cancer in the future. The total amount of radiation that you will receive in this study is equal to about 3 extra weeks of exposure from natural background radiation. The McGuire VA Medical Center Radiation Safety Committee has reviewed the use of radiation in this research study and has approved this use as involving acceptable risk and necessary to obtain the research information desired. Please tell your doctor if you have taken part in other research studies or received any other medical care recently involving radiation	Unlikely
Fluoroscopy radiation	Cancer from Radiation	Unlikely
Falls during exercise	Falls could occur during training which requires careful stabilization of the patient in the exoskeleton unit or during over ground training.	Rarely occurs

Risk of Fracture	SCI is commonly accompanied with bone weakness and weight bearing on the subject's limbs while may expose them to the risk of fracture ambulating may increase their risk of bone fractures	Rarely
Autonomic Dysreflexia	headache, pounding in the head, ringing in the ears, dizziness, blurry vision, sweating, anxiety, flushing, tightness in the chest, stuffy nose, heart flutters, or difficulty breathing.	Rarely occurs
Epidural stimulation	Infection, lead migration, scarring, Hemorrhage and epidural abscess. Infection risk from implantation rarely occurs and less than 2.5%. Lead migration can occur in up to 5% of the cases and requires re-implantation.	Rarely occurs
Infection, inflammation or abscess formation	Risk of infection may occur at any time during temporary or permanent implantation	Rarely occurs
Anesthesia and surgical procedures	Nausea, vomiting, and pain where an injection is given. Although rare, severe complications include: injury to blood vessels, drug reactions, bleeding, blood clots, loss of sensation or limb function, infection, paralysis, stroke, brain damage, heart attack, and death.	Rarely occurs
Failure to use MRI	Implanted stimulator can function with magnetic resonance imaging (MRI).	Rarely occurs
Device Malfunction	It is possible that the implanted device may experience malfunction or migration of the leads, intermittent stimulation, pain at neurostimulator site, programmer or data transmission problems or malfunction of the leads.	Rarely occurs

Risk of Medications	All medications associated with the current trial can cause allergic reactions, rashes, nausea, vomiting, feeling of light-headed and upset stomach.	Rarely occurs
Risk of using external electrical stimulation	Light-headedness, shortness of breath, altered heart rate, autonomic dysreflexia, muscle soreness at the neck and back, shoulder, arms and hands.	Rarely occurs
Risk of using exoskeleton for 9 months	Continuous use of exoskeleton may result in skin abrasion or breakdown, strain ligaments, falls, fracture.	Rarely occurs
Risk of blood draws	Pain, bleeding, bruising and infection at the site where the needle goes in, fainting, or light-headedness.	Rarely occurs
Risk of Opioids and anesthesia	For opioids, drowsiness, mental fog, nausea, addiction and constipation. For anesthesia, you may develop allergies, nausea, vomiting, chills, confusion for a few days and a sore throat caused by a breathing tube.	Rarely occurs
Risks associated with Urodynamics and Fosfomycin	Small risks of infection, auto dysreflexia (AD), sudden high blood pressure, possible headache, sweats, blurred vision, stuffy nose, diarrhea, nausea, dizziness and nervousness.	Rarely occurs
Risks associated with taking antibiotics	Possible allergic reaction, mild with a rash or hives, or severe, with difficulty breathing and low blood pressure.	Rarely occurs

- **<u>Protection of skin integrity during training</u>**
  Skin will be closely checked following each training to ensure skin integrity. If a pressure wound develops, the participant will be asked to avoid any further skin irritation and be kept off the pressure wound until it heals.

- **Protection from risk associated with transfers:**

  To minimize risk, an investigator will be available to assist in all transfers and provide a slide board or any other assistive devices needed.

- **Protection from risk associated with dual energy x-ray absorptiometry (DXA) Scan**
  To minimize risk, only the required scans will be performed. Testing will be performed early in the day and after lower extremity elevation for at least 30 minutes to minimize lower extremity edema. An overhead lift system is installed in the exercise lab to ensure safe transfers on and off scanner.

- **Protection from fluoroscopy**
  This research study will require the use of fluoroscopic imaging which involves exposure to radiation in the form of X-rays. This radiation exposure is not necessary for your medical care and is for research purposes only. All radiation increases the risk of developing cancer in the future. The total amount of radiation that you will receive in this stud is equal to about 6-12 extra weeks of exposure from natural background radiation. The McGuire VA Medical center Radiation safety Committee has reviewed the use of radiation in this research study and has approved this use as involved acceptable risk and necessary to obtain research information desired. Please tell your doctor if you have taken part in other research studies or received any other medical care recently involving radiation.

  A possible health problem seen with radiation exposure is the development of cancer later in life. This extra cancer risk is higher at younger ages and for girls and women. The extra lifetime risk of dying of a fatal cancer due to the radiation exposure from this research is very low. At such low radiation exposures, scientists disagree about the amount of risk. These estimates are very uncertain, and there may be no extra risk at all.

- **Protection from Falls during exercise**
  Falls could occur during training which requires careful stabilization in the exoskeleton unit. This rarely occurs, and a well-trained research assistant will be working with the patient at all time to ensure his safety during walking with the exoskeleton. The exoskeleton is also equipped with safety features that allow the unit to protect the patient from falling and going straight from walking to stand still mode.

- **Protection against risk of Fracture**
  Every effort will be taken to minimize possible bone fracture; DXA scan will be performed as detailed earlier prior to enrollment in the trial. Persons with T-score less than -2.5 SD at the hip joints or with bone mineral density less than 0.6 gm/cm^2 at the knee joints will be excluded from the trial.

- **Protection from Autonomic Dysreflexia**
  Blood pressure will be monitored closely during the entire intervention as detailed earlier in the protocol. Any significant rise in blood pressure greater than 20 mmHg above resting blood pressure, the intervention will be ceased immediately and a medical provider will be notified. The blood pressure will be continuously monitored and exercise/walking will not be permitted unless there is a clearance from the medical team.

- **Protection from risk epidural stimulation infection**
  There is a real risk of epidural abscess which can involve surgery, scarring and prolonged IV antibiotics. The risk of infection with implanted epidural stimulators reported in the scientific literature is quite low, approximately 2.45%. The investigative team for this study will take careful measures to monitor for signs and symptoms of infection, including:

  1. Daily inspection of dressings and insertion site.
  2. Daily interview of subjects for symptoms.
  3. Daily vital signs monitoring (including temperature, heart rate, blood pressure, respirations, and pain level).

  - **Preoperative:** After consenting, the pre-operative procedures will be determined by either Dr. Lance or Dr. Lavis during the physical exam and will be documented in CPRS for Drs. Trainer or Lester to access prior working with the subject.

  1. Decreased medical co-morbidities such as diabetes, immunosuppression and dental disease. Hemoglobin A1c must be <8 and no immediate dental procedures being planned.
  2. Preoperative screening and decolonization for Staphylococcus aureus carriers with mupirocin intranasal swab bid for 7 days, chlorhexidine wash daily x 7 days.
  3. Smoking cessation or reduction
  4. Appropriate hair removal

  - **Peri-procedure:**

  1. Appropriate agent for skin antisepsis. Ancef 2-3 grams unless there is a penicillin allergy, in which case clindamycin 600-900 mg iv x 1 is utilized.
  2. Wide skin preparation and drape.
  3. Limiting traffic in the operating room.
  4. Limiting procedure time.

  - **Post Procedure:**

  1. Occlusive dressing for at least 48 hours with attention to tape allergies and skin irritants. An occlusive dressing with impregnated chlorhexidine is our current standard.

2. Daily inspection of dressings and insertion site. Daily interview of subjects for symptoms. Daily vital signs monitoring (including temperature, heart rate, blood pressure, respirations, and pain level).
3. All patients will be seen in the pain clinic within 3 days of permanent trial lead insertion for changing of occlusive dressing, inspection of the site, review of systems and evaluation of patient condition and vital signs. Bandages will be changed at the 7-day visit. Permanent trial leads will be placed in the operating room, and a permanent battery will be placed if indicated in the operating room on day 7. A tyrex pouch will be used for full implantation which is an antibiotic coated pouch (minocycline and rifampin) currently used in implants performed by Dr Trainer.
4. Continued education regarding fever and warning signs of early infection. Infectious disease consultation will be obtained if any signs or warning signals of infection are present.

- **Protection against failure to use MRI**
  It is recommended to turn off the epidural stimulation before any MRI scans and consult the medical provider before conducting MRI.

- **Protection against Device Malfunction**
  It is possible that the implanted device may malfunction or migration of the leads or malfunction of the leads. The manufacture will be notified immediately and they will be able to replace the malfunction device. The clinicians will be also and notified and the stimulator will be tuned off until the problem will be resolved.

- **Protection against using the exoskeleton for 9 months**
  Regularly check skin on a daily basis, having 2 trained persons working with patient to ensure safe ambulation, properly customize the unit to the patient's physical characteristics to minimize shear during walking.

- **Protection against risks of blood draws**
  Blood draws will be performed by a licensed registered nurse. To ensure a clear heplock line, the nurse will infuse the line with saline after each blood draw.

- **Protection against risks of medications**
  All medications associated with the current trial can cause allergic reactions, rashes, nausea, vomiting, feeling of light-headed and upset stomach. Our clinicians will take history of prior reactions against using antibiotics and monitor the patient closely during the course of the trial to ensure that they would not develop any adverse events related to the use of medications. A pre and post-operative evaluation, including labs, EKG, and a drug screening, will be completed to protect against risks of anesthesia and opioids. Participants will remain awake during the procedures, as minimal anesthesia is needed and will be administered by a boardcertified Anesthesiologist.

- **Protection against the risks associated with Urodynamics**

Because urodynamic studies involve placing a catheter into the urethra, and possibly removing your old one if present, there is a small risk of infection. A single dose of an antibiotic drink called Fosfomycin is given prior to this procedure to minimize the risk of infection.

- **Protection against the risks associated with taking antibotics**
  We will check to make sure that the participant is not allergic to Fosfomycin.

Participants will be monitored for any changes in baseline health. Their SCI provider will be notified of any changes that may require attention. An adverse event is any experience that has taken place during research project, which, in the opinion of the investigators, was harmful to a participant participating in the research, increased the risks of harm in the research, or had an unfavorable impact on the risk/benefit ratio. Adverse events will be monitored throughout the study via exams, vital signs, laboratory tests, review of medical charts, and verbal concerns voiced by the participant or an associated friend or family member. Any adverse event will be documented in their file. Files will be reviewed for adverse events, protocol violations, and reasons for dropouts/withdrawals every ten days. The PI will provide the McGuire VA IRB with an annual summary of adverse events. All serious adverse events (SAEs), such as those that are life-threating or involve hospitalization, will be promptly reported to the McGuire IRB within five business days. SAE is defined as the unexpected medical occurrence associated with the implantation procedure that may lead to death, life-threatening medical condition, inpatient hepatization for or longer than 24 hours, persistent or significant incapacity or substantial disruption of the ability to conduct normal daily activities.

During the study and at the completion of this study, all participants will continue to receive their usual health care from their assigned SCI provider and/or other providers within our outside VHA. When study procedures begin, the importance of reporting any perceived problem, adverse event or change from baseline health will be stressed to the participants. Examples will be given to the participant of potential problems requiring immediate medical attention and potential problems requiring a phone call to the coordinator. Above all, it will be stressed to the participant that direct phone access to the study staff 24hrs/day is available and that if it is ever any doubt or concern on the part of the participant about any problem a call should be made. At the completion of this study all participants will continue to receive their health care from their assigned SCI provider or other provider of participants' own choice. All participants will be identified by an assigned number and their initials. Participants' research charts will be kept in the PIs office which is locked inside a locked file cabinet. Only study staff listed on the Personnel List will have access to participant study records and medical information. A master sheet of the full names will be kept in a locked file in the PIs office. All completed study files will be stored in the PI’s SCI research office 1V-129. At the end of 4-year period, all records will either be stored in the SCI Research Exercise Laboratory locked room or sent to Dunmar Storage Facility for space issues per direction of McGuire Research Institute.

Photographs, audio, and/or video recordings, of research participants who agree, will be captured and used in future presentations, to share knowledge about the study.

Description of this device

The Intellis Platform Spinal Cord Stimulation System is manufactured by Medtronic (Medtronic Neuromodulation-Minneapolis, USA).

The Intellis Spinal Cord Stimulation system has been FDA cleared (Pre- Market Approval PMA) for chronic pain management in persons with Spinal Cord Injury.

The Intellis™ implantable neurostimulator is powered by proprietary Overdrive™ battery technology. It is designed to overcome limitations with current SCS systems and is optimized for the increased energy demands of High Dose (HD) therapy. The Intellis platform uses a tablet with wireless programming and a neurostimulator that can record participant activity around the clock.

The Intellis system has two main sets of components

1- External components for Intellis:

- Model 97715/97716 Wireless External Neurostimulator

  The Medtronic Model 97715/97716 Wireless External Neurostimulator (ENS) is part of a neurostimulator system used for intraoperative testing during lead placement and for trial stimulation outside of the operating room. The Medtronic Model 97715/97716 Wireless External Neurostimulator is a disposable, sterile, single-use device equipped with BLUETOOTH® wireless technology.
  (A detailed description and a list of all labels are in the attached manual-Appendix-II)

- Model 97745 Patient Controller.

  The controller is a hand-held device that allows to turn the neurostimulator on and off and check the neurostimulator battery status. It is also used to adjust some of the stimulation settings.
  (A detailed description and a list of all labels are in the attached manual-Appendix-II)

- Model 375003 Boot for Wireless External Neurostimulator

  The external neurostimulator boot is a nonsterile, single-use accessory used to secure the Model 97725 Wireless External Neurostimulator to Participant 's skin with an adhesive pad during trial stimulation.
  (A detailed description and a list of all labels are in the attached manual-Appendix II)

- Model 97755 Recharger

The Medtronic Model 97755 Recharger is designed to charge Medtronic rechargeable neurostimulator.
(A detailed description and a list of all labels are in the attached manual-Appendix II)

- Model 8880T2 Communicator
  The Model 8880T2 Communicator is intended for use by clinicians to use in conjunction with the clinician tablet and clinician programmer app for communication with Medtronic neuromodulation medical devices.
  The communicator is handheld and battery-operated. Communication between the communicator and a
  clinician tablet can occur wirelessly using BLUETOOTH® technology or wired using the USB connector cable.
  (A detailed description and a list of all labels are in the attached manual-Appendix II

2- Implanted components for Intellis:

- Model 977D260 Vectris™ 1x8 Compact Trial Screening Lead Kit
  The Medtronic Vectris 1x8 Compact Model 977D260 Trial Screening Leads is part of a neurostimulator system. The lead has electrodes on the distal end; the proximal (connector) end fits into an 8-conductor connector. A stylet has been inserted into the proximal end of the lead to aid in positioning. *(A detailed description and a list of all labels are in the attached manual-Appendix II).*

Data Monitoring Plan

The principal investigator will monitor and review the protocol as well as data collection on a monthly basis to evaluate participant safety, data quality, and study progress and execution. The principal investigator will review the protocol for any major concerns prior to implementation. The data monitoring board will have the option to request stopping or cessation participants' enrollment and all research procedure, if deemed necessary. The PI will also assess the performance of overall study operations and any other relevant issues, as necessary. The DSMB is responsible to oversee the safety of the research and report observations/findings to the IRB on an annual basis. They will review all unanticipated problems involving risks to subjects or others associated with the protocol and provide an independent report of the event to the IRB. They may discuss the research protocol with the investigators; shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report; and shall have the responsibility to promptly report their observations and findings to the IRB.
A letter will be drafted from the DSMB and will be attached with the annual summary report to the IRB. Elements in the letter will include the followings:

- Evidence of study-related adverse events
- Evidence of efficacy according to pre-established statistical guidelines, if appropriate;

- Data quality, completeness, and timeliness
- Performance of individual center (VAMC)
- Adequacy of compliance with goals for recruitment and retention
- Adherence to the protocol
- Factors that might affect the study outcome or compromise the confidentiality of the trial data (such as protocol violations)
- Factors external to the study such as scientific or therapeutic developments that may impact participant safety or the ethics of the study.

The Data Safety Monitoring Board (DSMB) will include

Sean McAvoy, MD
SCI Physician
Richmond VA Medical Center, Richmond VA
(804) 675-5586
Sean.McAvoy@va.gov

Jeffrey Tubbs, MD
SCI Physician
Richmond VA Medical Center, Richmond VA
(804) 675-5455
Jeffrey.Tubbs@va.gov

David X. Cifu, MD
Associate Dean of Innovation and System Integration
Herman J. Flax, MD Professor and Chair,
Department of Physical Medicine and Rehabilitation
Virginia Commonwealth University School of Medicine
804-828-4231
David.cifu@vcuhealth.org

References

1. Harkema, S., Gerasimenko, Y., Hodes, J., Burdick, J., Angeli, C., Chen, Y., Ferreira, C., Willhite, A., Rejc, E., Grossman, R.G., Edgerton, V.R., 2011. Effect of epidural stimulation of the lumbrosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: a case study. The Lancet 377: 1938-1947.
2. Gerasimenko, Y., Roy, R.R., Edgerton, V.R., 2008. Epidural stimulation: Comparison of the spinal circuits that generate and control locomotion in rats, cats, and humans. Experimental Neurology 209: 417-425.
3. Alam, M., Garcia-Alias, G., Jin, B., Keyes, J., Zhong, H., Roy, R.R., Gerasimenko, Y., Lu, D.C. Edgerton, V.R., 2017. Electrical neuromodulation of the cervical spinal cord facilitates forelimb skilled function recovery in spinal cord injured rats. Experimental Neurology 217: 141-150.
4. Alam, M., Garcia-Alias, G., Shah, P.K., Gerasimenko, Y., Zhong, H., Roy, R.R., Edgerton, V.R., 2015. Evaluation of optimal electrode configurations for epidural spinal cord stimulation in cervical spinal cord injured rats. Journal of Neuroscience Methods 247: 50-57. Https://doi.org/10.1016/j.jneumeth.2015.03.012
5. Becker, D., Gary, D.S., Rosenzweig, E.S., Grill, W.M., McDonald, J.W., 2010. Functional electrical stimulation helps replenish progenitor cells in the injured spinal cord of adult rats. Experimental Neurology 222: 211-218. Https://dx.doi.org/10.1016/j.expneurol.2009.12.029
6. Gerasimenko, Y., Gorodnichev, R., Puhov, A., Moshonkina, T., Savochin, A., Selionov, V., Roy, R.R., Lu, D.C., Edgerton, V.R., 2015. Initiation and modulation of locomotor circuitry output with multisite transcutaneous electrical stimulation of the spinal cord in noninjured humans. Journal of Neurophysiology 113: 834-842. Https://doi.org/10.1152/jn.00609.2014
7. Kocina P. Body composition of spinal cord injury adults. Sports Med 1997;23(1):48–60.
8. Bauman WA, Spungen AM. Carbohydrate and lipid metabolism in chronic spinal cord injury. J Spinal Cord Med 2001; 24(4): 266-277.
9. Bauman WA, Spungen AM. Coronary heart disease in individuals with spinal cord injury: assessment of risk factors. Spinal Cord 2008; 46(7): 466-476.
10. Dolbow DR, Gorgey AS, Daniels JA, Adler RA, Moore JR, Gater DR Jr. The effects of spinal cord injury and exercise on bone mass: a literature review. Spinal Cord. 2012; 50(11):170-1.
11. Gorgey AS, Dolbow DR, Dolbow JD, Khalil RK, Castillo C, Gater DR. Effects of spinal cord injury on body composition and metabolic profile - part I. J Spinal Cord Med. 2014;37(6):693-702.
12. Strauss D, DeVivo M, Shavelle R, Brooks J, Paculdo D. Economic factors and longevity in spinal cord injury: a reappraisal. Arch Phys Med Rehabil. 2008;89(3):572-4.
13. Dobkin B, Apple D., Barbeau H. et al., Weight-supported treadmill vs over-ground training for walking after acute incomplete SCI, Neurology 66 (2006), 484–493.

14. Barbeau H. Locomotor training in neurorehabilitation: emerging rehabilitation concepts, Neurorehabil Neural Repair 17 (2003), 3–11.
15. Giangregorio LM, Hicks AL, Webber CE et al., Body weight supported treadmill training in acute spinal cord injury: impact on muscle and bone, Spinal Cord 43 (2005) 649–657.
16. Hornby TG, Zemon DH and Campbell D. Robotic-assisted, body-weight-supported treadmill training in individuals following motor incomplete spinal cord injury, Phys Ther 85 (2005), 52–66.
17. Maxwell JL, Granat MH, Baardman G. and Hermens HJ. Demand for and use of functional electrical stimulation systems and conventional orthoses in the spinal lesioned community of the UK, Artificial Organs 23(5) (1999), 410–412.
18. Ambrosia RD, Solomonow M and Baratta R. Current status of walking orthosis for thoracic paraplegics, Iowa Orthopaedic Journal 15(174–181) (1995).
19. Gorgey AS, Poarch H, Miller J, Castillo T, Gater DR. Locomotor and resistance training restore walking in an elderly person with a chronic incomplete spinal cord injury. NeuroRehabilitation. 2010;26(2):127-33.
20. Gorgey AS, Poarch H, Harnish C, Miller JM, Dolbow D, Gater DR. Acute effects of locomotor training on neuromuscular and metabolic profile after incomplete spinal cord injury. NeuroRehabilitation. 2011;29(1):79-83.
21. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc 2007;39(8):1423–34.
22. Evans N, Wingo B, Sasso E, Hicks A, Gorgey AS, Harness E. Exercise Recommendations and Considerations for Persons with Spinal Cord Injury. Arch Phys Med Rehabil. 2015; 96(9):1749-50.
23. Buchholz AC, McGillivray CF, Pencharz PB Physical activity levels are low in free-living adults with chronic paraplegia. Obes Res 2003;11(4):563–70.
24. Buchholz AC, Martin Ginis KA, Bray SR, Craven BC, Hicks AL, Hayes KC, Latimer AE, McColl MA, Potter PJ, Wolfe DL. Greater daily leisure time physical activity is associated with lower chronic disease risk in adults with spinal cord injury. Appl Physiol Nutr Metab. 2009 Aug;34(4):640-7.
25. Hicks AL, Martin Ginis KA, Pelletier CA, Ditor DS, Foulon B, Wolfe DL. The effects of exercise training on physical capacity, strength, body composition and functional performance among adults with spinal cord injury: a systematic review. Spinal Cord 2011; 49 (11):1103–1127.
26. Hetz SP, Latimer AE, Buchholz AC, Martin Ginis KA; SHAPE-SCI Research Group. Increased participation in activities of daily living is associated with lower cholesterol levels in people with spinal cord injury. Arch Phys Med Rehabil. 2009 Oct;90(10):1755-9.
27. Gorgey AS, Gater DR Jr Prevalence of obesity after spinal cord injury. Top Spinal Cord Inj Rehabil 2007;12(4):1–7.
28. Gorgey AS, Caudill C, Sistrun S, Khalil RE, Gill R, Castillo T, Lavis T, Gater DR. Frequency of Dietary Recalls, Nutritional Assessment, and Body Composition Assessment in Men With Chronic Spinal Cord Injury. Arch Phys Med Rehabil. 2015;96(9):1646-53.

29. Gorgey AS, Gater DR Regional and relative adiposity patterns in relation to carbohydrate and lipid metabolism in men with spinal cord injury. Appl Physiol Nutr Metab 2011;36(1):107–14.
30. Miller LE, Zimmermann AK, Herbert WG. Clinical effectiveness and safety of powered exoskeleton-assisted walking in patients with spinal cord injury: systematic review with meta-analysis. Medical devices (Auckland, NZ). 2016;9:455.
31. Sale P, Russo EF, Russo M, Masiero S, Piccione F, Calabrò RS, Filoni S. Effects on mobility training and de-adaptations in subjects with Spinal Cord Injury due to a Wearable Robot: a preliminary report. BMC neurology. 2016 Jan 28;16(1):1.
32. Evans N, Hartigan C, Kandilakis C, Pharo E, Clesson I. Acute cardiorespiratory and metabolic responses during exoskeleton-assisted walking overground among persons with chronic spinal cord injury. Top Spinal Cord Inj Rehabil. 2015;21(2):122-132.
33. Kozlowski AJ, Bryce TN, Dijkers MP. Time and effort required by persons with spinal cord injury to learn to use a powered exoskeleton for assisted walking. Top Spinal Cord Inj Rehabil. 2015;21(2):110-121.
34. Zeilig G, Weingarden H, Zwecker M, Dudkiewicz I, Bloch A, Esquenazi A. Safety and tolerance of the ReWalk exoskeleton suit for ambulation by people with complete spinal cord injury: a pilot study. J Spinal Cord Med. 2012;35(2):96-101.
35. Yang A, Asselin P, Knezevic S, Kornfeld S, Spungen AM. Assessment of in-hospital walking velocity and level of assistance in a powered exoskeleton in persons with spinal cord injury. Top Spinal Cord Inj Rehabil. 2015;21(2):100-109.
36. Hartigan C, Kandilakis C, Dalley S, et al. Mobility outcomes following five training sessions with a powered exoskeleton. Top Spinal Cord Inj Rehabil. 2015;21(2):93-99.
37. Asselin P, Knezevic S, Kornfeld S, et al. Heart rate and oxygen demand of powered exoskeleton-assisted walking in persons with paraplegia. J Rehabil Res Dev. 2015;52(2):147-158.
38. Kressler J, Thomas CK, Field-Fote EC, Sanchez J, Widerström-Noga E, Cilien DC, Gant K, Ginnety K, Gonzalez H, Martinez A, Anderson KD, Nash MS. Understanding therapeutic benefits of overground bionic ambulation: exploratory case series in persons with chronic, complete spinal cord injury. Arch Phys Med Rehabil. 2014 Oct;95(10):1878-1887.e4
39. Fineberg DB, Asselin P, Harel NY, Agranova-Breyter I, Kornfeld SD, Bauman WA, Spungen AM. Vertical ground reaction force-based analysis of powered exoskeleton-assisted walking in persons with motor-complete paraplegia. J Spinal Cord Med. 2013 Jul;36(4):313-21.
40. Gorgey AS. Exercise awareness and barriers after spinal cord injury. World J Orthop. 2014 Jul 18;5(3):158-6.
41. Gorgey AS, Wade R, Sumrell R, Villadelgado L, Khalil RE, Lavis T. Exoskeleton Training May Improve Level of Physical Activity After Spinal Cord Injury: A Case Series. Top Spinal Cord Inj Rehabil. 2017;23:245–255.
42. Gorgey A, Sumrell R, Goetz L. Exoskeletal assisted rehabilitation after spinal cord injury. In: Atlas of Orthoses and Assistive Devices., editor. 5th ed. Canada: Elsevier; 2018. pp. 440–447.

43. Gorgey AS. Robotic exoskeletons: The current pros and cons. World J Orthop. 2018 Sep 18;9(9):112-119.
Lester RM, Gorgey AS. Feasibility of robotic exoskeleton ambulation in a C4 person with incomplete spinal cord injury: a case report. Spinal Cord Ser Cases. 2018 Apr 27;4:36.
44. Gad P, et al. Weight Bearing Over-ground Stepping in an Exoskeleton with Non-invasive Spinal Cord Neuromodulation after Motor Complete Paraplegia. Front Neurosci. 2017; 8;11:333.
45. Gad P.N., et al. Non-invasive Neuromodulation of Spinal Cord Restores Lower Urinary Tract Function After Paralysis. Front Neurosci. 2018; 29;12:432.
46. Murray LM, Knikou M. Transspinal stimulation increases motoneuron output of multiple segments in human spinal cord injury. PLoS One. 2019;14(3):e0213696.
47. Murray LM, Tahayori B, Knikou M. Transspinal Direct Current Stimulation Produces Persistent Plasticity in Human Motor Pathways. Sci Rep. 2018 Jan 15;8(1):717.
48. Herrity AN, Williams CS, Angeli CA, Harkema SJ, Hubscher CH. Lumbosacral spinal cord epidural stimulation improves voiding function after human spinal cord injury. Sci Rep. 2018 6;8(1):8688.
49. Hubscher, C. H. et al. Improvements in bladder, bowel and sexual outcomes following task-specific locomotor training in human spinal cord injury. PloS one 2018; 13, e0190998.