Mobility and Therapeutic Benefits resulting from Exoskeleton Use in a Clinical Setting (SC140121 Study 1)

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Experimental Protocol

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1.0 Background

Currently in the United States, about 270,000 individuals live with SCI; roughly 12,000 new such injuries occur in the nation annually [1]. One of the most significant impairments resulting from SCI is loss of mobility. Surveys of persons with SCI indicate that mobility concerns are among the most prevalent [2], and that chief among mobility desires is the ability to stand and walk [3]. In addition to limiting access to places inaccessible by wheelchair, the inability to stand and walk impedes social inclusion and often results in a depressive psychological impact. As importantly, loss of legged mobility results in substantial secondary adverse health effects: pressure-induced skin complications; increased incidence of pain, muscle spasticity, urinary tract infections and increased body-mass index (BMI) impaired digestive, lymphatic and vascular functions; and decreased bone mineral density (BMD), respiratory, and cardiovascular capacities [4-6]. The collective effect of such impairments is a substantial decrease in quality of life and substantial increase in health care costs for individuals with SCI.

Recently, powered lower limb exoskeletons have emerged onto the landscape of rehabilitative interventions for people with spinal cord injuries (SCI). These devices have the potential to provide substantial health benefits, promote neurological and functional recovery, and allow community ambulation for individuals with SCI. Nevertheless, studies have yet to be conducted to substantiate these potential benefits.

2.0 Hypotheses, Aims, and Study Outline

Prior Studies regarding Efficacy of Exoskeletons

Given the relatively recent availability of lower limb exoskeletons, little has been published on the potential health and therapeutic benefits of exoskeleton walking for non-ambulatory individuals; however, a pilot study was conducted of such walking, with 12 individuals with motor-complete thoracic-level SCI. Although that study's primary objective was to establish the safety and efficacy of the device for purposes of mobility, it anecdotally found improvements in pain, bowel and bladder function, spasticity, and emotional well-being [7]. Another small study of exoskeleton walking involving 6 subjects with motor-complete paraplegia found that all participants sustained a significant loss of fat tissue mass after 20-60 hours of use [8]. Since fat tissue mass increases the propensity for diabetes and cardiovascular disease [9], such a reduction may decrease predisposition towards these conditions.

Studies of supported standing indicate a number of health benefits for non-ambulatory individuals with SCI, including improvements in well-being, circulation, bowel and bladder function, skin integrity, and sleep, in addition to reduction in spasticity and pain [10-12]. The investigators hypothesize that, if such benefits can be derived from the stationary nature of a standing frame, substantially more dramatic health benefits can result from walking with a lower limb exoskeleton, since an exoskeleton provides a similar upright weight-bearing posture, but also provides lower limb and coordinated upper body movement, as well as cyclic weight bearing shifts from one leg to the other. Since an exoskeleton also provides mobility, and thus utility, it has the potential for much greater frequency and duration of use, relative to a standing frame, and greater dosing will likely increase the benefits of upright weight bearing.

Hypotheses

The proposed study is intended to inform the hypotheses that (1) regular dosing of exoskeleton walking will provide health benefits to non-ambulatory and poorly-ambulatory individuals with SCI, including decreased pain and spasticity, improvements in bowel and bladder function, decreased body-mass index (BMI), enhanced well-being; (2) regular dosing of exoskeleton walking will facilitate neurological or functional recovery in some

individuals with SCI, particularly those with incomplete injuries; and (3) the level of mobility enabled by a lower limb exoskeleton is commensurate with the walking speeds, distances, and surfaces required for community ambulation.

Study Outline

Study 1, as described herein, will assess the three hypotheses, i.e., health benefit, neurological recovery, and mobility benefits, in the context of regular dosing of exoskeleton walking in a clinical setting. These studies will be conducted at three study sites, Vanderbilt University Medical Center in Nashville TN, the James A. Haley Veterans Hospital in Tampa FL, and the Mayo Clinic in Rochester MN. All study sites will conduct an identical study protocol. The study will involve 24 non-ambulatory and poorly-ambulatory individuals with incomplete and complete SCI (i.e., 8 subjects at each site). In this study, "poorly ambulatory" is defined as persons with functional independence measure (FIM) gait score of 2 to 6 who may be able to walk short distances with or without braces and stability aid, or may be able to walk with assistance of one person, but whose primary means of mobility is a manual or power-operated wheelchair. Of the 24 individuals, half will be individuals with motor-complete injuries (i.e., American Spinal Injury Association Injury Scale, AIS, A or B), and half with motor-incomplete injuries (i.e., AIS C or D). As described subsequently in the Study Procedures section, the study will assess the therapeutic and functional effects of exoskeleton walking over an 8-week period of treatment, where the treatment consists of 3 walking sessions per week, each approximately 1.5 hours in duration for a total of 24 walking sessions. Therapeutic effects will be assessed via a number of measurements recorded primarily at study start, at the 4-week study midpoint, at the 8-week completion of treatment, and in a follow-up session, 8 weeks following the conclusion of treatment. Among the primary measurements to be used to assess secondary health benefits are dual-energy X-ray absorptiometry scans (DXA) to assess bone mineral density (BMD); Modified Ashworth scale (MAS) ratings and Spinal Cord Injury Spasticity Evaluation Tool (SCI-SET) to assess effect on spasticity; body mass to assess BMI; and a self-report questionnaire to assess effect on pain, spasticity, bowel and bladder function, skin, and well-being. Neurological effects for non-ambulatory subjects will be assessed via neurological examination and the functional reach (FR) test. Neurological effects for poorly-ambulatory subjects will additionally be assessed via the Functional Independence Measure gait score (FIM-G), the Walking Index for Spinal Cord Injury II (WISCI-II), the Ten Meter Walk Test (10MWT), and the Timed Up and Go (TUG) test, all measured while the subject is not wearing the exoskeleton. The level of mobility provided by the exoskeleton for both motor-complete and motor-incomplete injuries will be assessed by use of the FIM-G, WISCI-II, 10MWT, Six-Minute Walk Test (6MWT), TUG test, and Borg Rating of Perceived Exertion (BRPE), all measured while the subject is wearing the exoskeleton.

3.0 Description of Intervention: The Indego Exoskeleton

This study will employ the Indego exoskeleton (Parker Hannifin Corp), shown in Fig. 1, which is a lower limb exoskeleton that incorporates powered movement of both hip and knee joints, in addition to built-in ankle-foot-orthoses (AFOs) at both ankle joints, which provide ankle support and stability, and also transfer the weight of the exoskeleton to the ground. The Indego exoskeleton requires use of a stability aid, such as a rolling walker or set of forearm crutches. The exoskeleton enables individuals with SCI to stand, walk, and sit, and provides nominal walking speeds between approximately 0.3 and 0.6 m/s. An SCI subject is shown walking with the exoskeleton in Fig. 2. All exoskeleton walking conducted in this study will be conducted with the (contact guard) assistance of a trained physical therapist, as shown in Fig. 2.

Fig 1. Indego exoskeleton to be used in proposed study.

Fig. 2. SCI subject (T11 AIS A injury) walking with Indego exoskeleton, with assistance from physical therapist.

FDA Status and Device Safety

A recent study of the safety and efficacy of the Indego exoskeleton on 40 spinal-cord-injured individuals, conducted at five rehabilitation hospitals in the US, formed the basis of a 510(k) application for FDA approval of the exoskeleton. The five hospitals conducting the FDA trials were the Shepherd Center (Atlanta GA); Craig Hospital (Denver CO); the Rehabilitation Institute of Chicago (Chicago IL); Rusk Rehabilitation Hospital (New York NY); and Kessler Rehabilitation Hospital (West Orange NJ). The 510(k) application was submitted in early August 2015, and is currently under review at the FDA. The clinical evaluation report submitted with the 510(k)

application is included as an attachment with this protocol. The following discussion describing device safety was excerpted from page 38 of that report:

> Over the 10 month course of the Indego clinical trial completed at the time of this filing, 40 subjects each completed the 27 sessions already described. These subjects included men and women with a wide range of characteristics. The height of the subjects ranged from 5'1" to 6'3" (155 cm to 191 cm), weight from 115lbs to 231lbs (52 kg to 105 kg), SCI level from L2 AIS C to T3 AIS A, age from 18 to 64, and time since injury from 5 months to 23 years.
>
> All Adverse Events (AE's) were recorded during this study. An AE is defined as: "… any undesirable clinical experience (any sign, symptom, illness, abnormal laboratory value or other medical event) that occurs in a subject (or an event that worsens during the course of the study) and that could possibly be associated with the investigational product, procedure or medications required by this protocol." A Serious Adverse Event (SAE) is defined as: "… an event that is fatal or life-threatening, results in persistent or significant disability, requires intervention to prevent permanent impairment, results in hospitalization (or prolongation of hospitalization) or results in congenital anomaly or malignancy."
>
> Out of 1,237 total study sessions completed as of July 17, 2015, there were 44 trial- related Adverse Events and 0 Serious Adverse Events. Of the 44 trial-related AE's, 19 were known to be device related. These 19 included minor instances of bruising, redness, abrasion, and swelling, as well as one instance of a rolled ankle. The causes of these events were all determined to be related to improper fitting or improper padding, except for one case of minor abrasion which was related to a padding malfunction.

Of particularly relevance for this study, no serious adverse events occurred during the 1,237 study sessions completed with the Indego during the 10-month FDA study trial.

<u>IRB Determination of NSR in Previous Studies</u>
Although a 510(k) application was submitted to the FDA in August 2015, due to the lengthy process entailed in the de novo FDA process, it is unlikely FDA approval will be issued in advance of the study start date. The investigators note, however, that all five of the IRBs at the aforementioned study sites involved in the FDA trials determined the exoskeleton to be non-significant risk (NSR).

Additionally, the Vanderbilt IRB has reviewed a number of prior related studies (since 2009) involving the Indego exoskeleton, and predecessors to it. In every case, the intervention has been determined to be non-significant risk (NSR), including active studies IRB no. 150089 and 140856, and former studies 091519 and 120343. The determination of NSR has additionally been substantiated by the fact that no injuries or serious adverse events have occurred during any of those studies, which collectively encompass hundreds of hours of exoskeleton use over a period of several years, and with approximately ten to fifteen different SCI subjects of varying injury levels.

4.0 Inclusion/Exclusion Criteria

<u>Inclusion Criteria:</u>
- Age 18 years or older.
- Size and limb proportions capable of fitting in the exoskeletal device :
  - Height between 1.55 m (5 ft, 1 in) and 1.92 m (6 ft, 3 in).
  - Femur length between 37.5 cm (15 in) and 43.125 cm (17.25 in).

  - Body mass no greater than 114 kg (250 lb).
- Non-ambulatory or poorly-ambulatory. In this study, "non-ambulatory" is defined as a person who cannot walk, or is classified with a Functional Independence Measure (FIM) Gait score 1; "poorly ambulatory" is defined as a person with FIM Gait 2- 6, who may be able to walk short distances with or without braces or stability aid, or may be able to walk with assistance of one person, but whose primary means of mobility is a manual or power-operated wheelchair.
- Sufficient upper extremity strength and coordination to balance using a appropriate stability aids, such as a rolling walker or forearm crutches, during exoskeleton walking.
- Present with SCI and NLI C5 or lower, with AIS A, B, C or D (as per the International Standard for Neurological Classification of SCI, ISNCSCI), who are non-ambulatory or poorly ambulatory.
- Chronic SCI: at least 6 months post-injury, and preferably post-injury more than 1 year.
- Sufficient bone health for walking with full weight-bearing without undue risk of fracture, as determined by each subject's personal medical doctor, and approved by each site's medical supervisor.
- Passive range of motion (PROM) at shoulders, trunk, upper extremities and lower extremities within functional limits for safe gait and use of appropriate assistive device/stability aid.
- Skin intact where interfacing with robotic device.
- MAS for spasticity score 3 or less in lower extremities.
- Blood pressure and heart rate within established guidelines for locomotor training:
  - At rest: systolic 150 mmHg or less, diastolic 90 mmHg or less, heart rate 105 bpm or less.
  - During exercise: systolic 180 mmHg or less, diastolic 105 mmHg or less, heart rate 145 bpm or less.
- Ability to tolerate an upright standing position for 20 min, passive or active, without being lightheaded or having a headache.
- Sufficient responsiveness to FES in the quadriceps, hamstrings, tibialis anterior, and gastrocnemius, as defined by MMT in response to stimulation of 3 or greater on a 5-point MMT scale. Note that this is specifically for Study 2, but is included in Study 1 in order to economize study resources regarding enrollment, training, and assessment, as previously discussed.
- Access to a wireless internet connection. Note that is required only for Study 3, but is included in Study 1 in order to economize study resources regarding enrollment, training and assessment, as previously discussed.

<u>Exclusion Criteria:</u>

- Heterotopic ossification that, in the opinion of the site medical supervisor, would place the subject at undue risk for fracture.
- Inability to follow instructions.
- Colostomy bag.
- Women who are pregnant or attempting to become pregnant during the course of the study. Note that a pregnancy test will be required and must be negative for all women prior to enrolling in the study, and will be additionally required and must be negative every four weeks during the course of the study protocol.
- Any disease, concomitant injury, or condition that interferes with the performance or interpretation of the protocol- specified assessments.
- Insufficient availability to complete study.
- Any other issue which, in the opinion of the investigators or medical supervisor, make the subject unsuitable for study participation.

5.0 Enrollment

Eight subjects will be recruited from the clinical practices and surrounding communities for each of the three data collection sites. Subjects will be enrolled if they satisfy the inclusion/exclusion criteria outlined above, and agree to the 18 week commitment for the study. Investigator patient lists, therapist and physician referrals, and medical record search engines will all be used to recruit potential subjects. In addition, subjects will be identified during outpatient clinical visits by study investigators. Subjects will be identified through lists and medical records. Once enrolled, subjects will be reimbursed $25 per visit for their involvement, in addition to receiving mileage and parking reimbursement for travel to and from their trial sites.

6.0 Study Procedures

Design:
This study will include 24 non-ambulatory or poorly-ambulatory individuals with chronic SCI, i.e., at least 6 months post-injury, 12 with complete and 12 with incomplete SCI, to assess the mobility and therapeutic benefits resulting from exoskeleton use in a clinical setting. Changes in physiological and neurological status will be assessed via measurements taken pre-, mid-, and post- the 8-week intervention, as well as 8 weeks post-treatment. At all study sites, subject enrollment will begin following IRB approval, with 8 subjects enrolled at each of the 3 sites. Following IRB approval and enrollment, the study is expected to occur over an 18-month period. The treatment for each subject will consist of 31 sessions spanning 18 weeks in total, comprising a combination of 4 assessment, 3 training, and 24 treatment sessions. The 24 treatment sessions each consists of approximately 1 hour of walking in the exoskeleton, although 1.5 hours are allotted to account for donning/doffing, measurement of vital signs, skin checks, etc., and will be delivered 3 times per week over an 8-week period.

Intervention
The intervention will be carried out identically at all sites and will be comprised of 31 sessions at the subjects' trial site, including 4 assessment sessions (pre, mid, immediately post treatment, and 8 weeks post-treatment), 3 exoskeleton fitting/training sessions, and 24 intervention sessions. The interventions at each site will be administered by a PT experienced in locomotor training for individuals with SCI. Parker Hannifin will provide exoskeleton-specific training at each site, in order to ensure safe, effective implementation and use of the exoskeletons. A summary of each session's activity and measurements follows:

- Session 1: Informed consent and pre-treatment health and neurological assessment, including PT evaluation and Dexa Scan (x-ray picture of the bone) of the distal femur and proximal tibia locations, and drawing about 2 teaspoons (9.5 mL) of blood to check A1C (measures the amount of hemoglobin in the blood that has glucose attached to it) and Lipid Panel to measure cholesterol levels (lasting 4 hrs).
- Sessions 2-4: Exoskeleton fitting, adjustment, and training sessions (3 sessions per week lasting 1.5 hours per session)
- Sessions 5-16: Exoskeleton treatment consisting of walking in the exoskeleton during a 1.5-hr session, with breaks as needed, and with sit-to-stand, turning, and stand-to-sit maneuvers as appropriate (3 sessions per week lasting 1.5 hours). Note that sessions 15 and 16 are additionally used for assessment of the mobility provided by the exoskeleton.
- Session 17: Mid-treatment health and neurological assessment (lasting 3-4 hours).
- Sessions 18-29: Exoskeleton treatment consisting of walking in the exoskeleton during a 1.5-hour session, with breaks as needed, and with sit-to-stand, turning, and stand-to-sit maneuvers as appropriate (3 sessions per week lasting 1.5 hours per session). Note that sessions 28 and 29 are also used for assessment of the mobility provided by the exoskeleton.

- Session 30: Post-treatment health and neurological assessment, within 3 days of session 29, including Dexa Scan (x-ray picture of the bone) of the distal femur and proximal tibia locations, and and 2 teaspoons (9.5 mL) of blood to check A1C (measures the amount of hemoglobin in the blood that has glucose attached to it) and Lipid Panel to measure cholesterol levels (lasting 3-4 hours).
- Session 31: Follow-up health and neurological assessment, including Dexa Scan (x-ray picture of the bone) of the distal femur and proximal tibia locations, and 2 teaspoons (9.5 mL) of blood to check your A1C (measures the amount of hemoglobin in the blood that has glucose attached to it) and Lipid Panel to measure cholesterol levels, 8 weeks following session 30 (lasting 3-4 hours).

Women of child bearing potential will have a urine pregnancy test at baseline, and in sessions 17, 30 and 31.

Outcome Measures

The various measures employed in Study 1 are summarized below:

Measures assessing physiological (i.e., health) effects:

- DXA: Assessment of changes in BMD over treatment course. Scans will be taken at the distal femur and proximal tibia locations.
- Spasticity rating: MAS, used to assess changes in degree of spasticity over course of treatment. Physical Therapy will assign a gross MAS score for the upper and lower extremities immediately after exoskeleton use as well as on the following day, in order to characterize acute and non-acute effects of exoskeleton use on spasticity.
- SCI-SET: 7-day recall self-report questionnaire that takes into account the effects of spasticity on daily life in people with SCI. Subjects will complete SCI-SET at treatment-start, at mid-point, immediately post-treatment, and at an 8-week post-treatment follow-up.
- Weight: Subjects will be weighed pre-treatment, at treatment midpoint, following treatment, and at an 8 week post-treatment follow-up.
- Subject self-report health questionnaire, including questions regarding pain, spasticity, bowel and bladder function, skin, and well-being.

Measures assessing neurological or functional recovery:

- International Standard for Neurological Classification of SCI (ISNCSCI, R2011). Neurological exams will assess status of neurological recovery. Since inclusion criteria restrict inclusion to chronic injury (i.e., at least 6 months post-injury, preferably at least 1-year post-injury), significant changes in neurological testing would presumably be a result of treatment. This exam will include manual muscle testing (MMT) for subjects with incomplete injury.
- For subjects who are poorly-ambulatory: FIM gait score, WISCI-II rating, 10MWT, and TUG test, all while the subject is not wearing the exoskeleton.
- FR test will be performed while subject is sitting to assess potential changes in trunk control and/or strength.
- Borg Reported Percieved Exertion Scale (BRPE)

Measures assessing level of mobility enabled by the exoskeleton to include the following, all measured while subject is using the exoskeleton:

- The 10MWT as a measure of gait speed.
- The TUG test measures ability to independently sit, stand, walk, turn, and return to sitting. The TUG test will be used as a measure of mobility independence.

- The 6MWT measures gait speed over a six-minute period. This test provides a controlled measure of endurance, and provides a secondary measure of gait speed.
- The BRPE measures perceived exertion during walking and will be assessed in this protocol during the 6MWT.

Additional measures taken during each session will include:

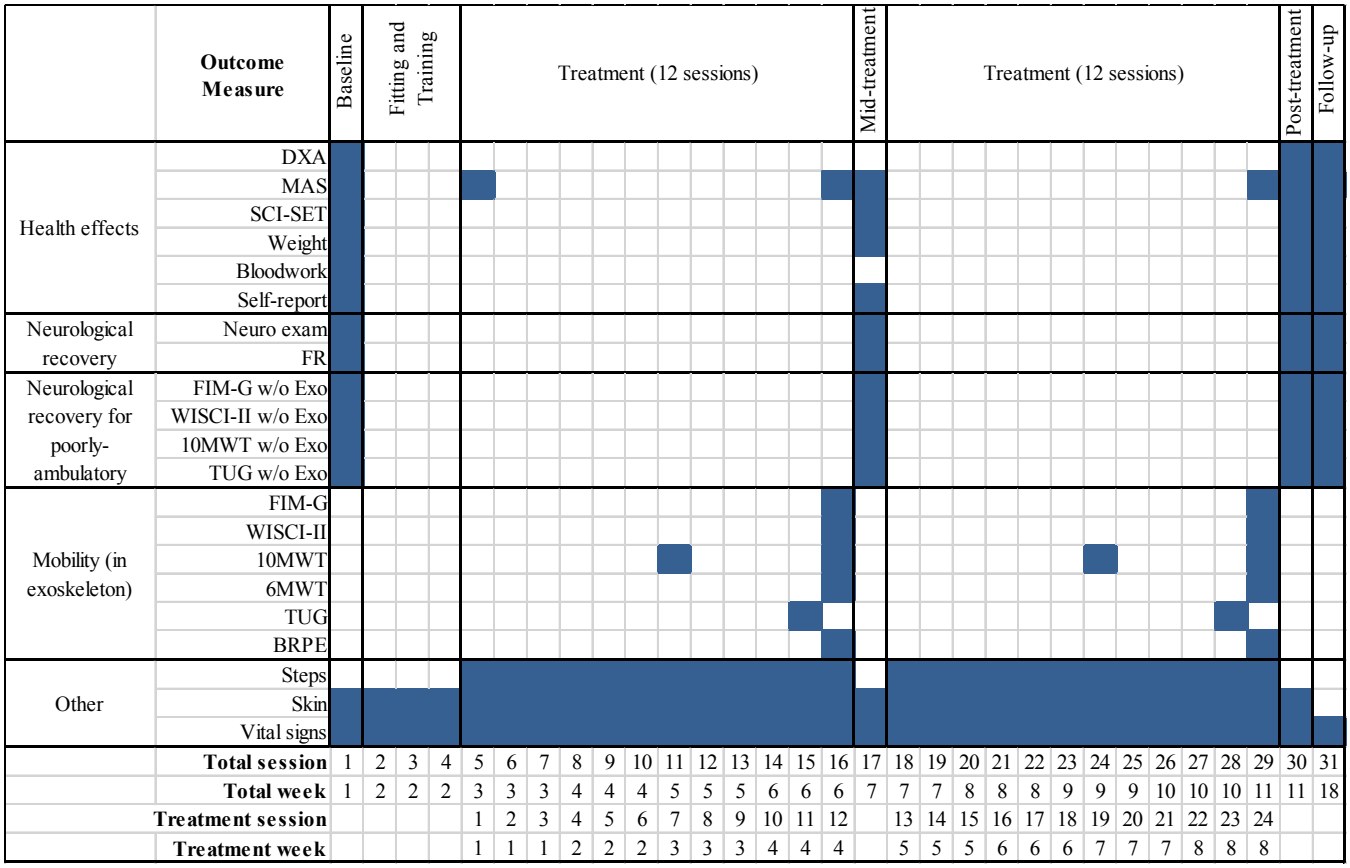
- Vital signs at start of each session (blood pressure and heart rate)
- Number of steps taken during each training session (measured by exoskeleton)
- Monitoring of skin integrity at exoskeleton contact points, following each session

Schedule of Assessments

The study will include 4 primary assessments characterizing health and neurological effects of exoskeleton use, in addition to 2 primary assessments characterizing level of mobility provided by the exoskeleton. The assessments characterizing potential health include DXA, MAS, SCI-SET tests, weight, and a self-report questionnaire. The assessments characterizing potential neurological or functional recovery include the MMT and FR tests, and for poorly-ambulatory subjects, also include the FIM-G, WISCI-II, 10MWT, and TUG tests, all performed without the exoskeleton. This battery of assessments is expected to require 3-4 hours, and will occur 4 times during the study as follows: pre-treatment (at study start, session 1), mid-treatment (after 4 weeks of treatment, session 17), post-treatment (after 8 weeks of treatment, session 30), and 8 weeks post-treatment (session 31). Note that DXA will not be measured at mid-treatment, in order to mitigate associated costs, since an 8-week interval is a short enough period of time relative to characteristic time scales associated with changes in BMD. Note that treatment will not occur on these assessment days, i.e., the exoskeleton will not be used on these days. Finally, the MAS will be administered on these 4 days, and also on 3 additional days, each immediately following exoskeleton use associated with a treatment session, at the start, mid-point, and end of treatment.

In addition to assessment of health, neurological and functional status, additional assessments will be performed to characterize the level of mobility provided by the exoskeleton. These assessments include the FIM-G, WISCI-II, 10MWT, 6MWT, TUG, and BRPE tests, all performed while the subject is wearing the exoskeleton. The battery of mobility assessments will occur within the standard treatment sessions at treatment midpoint (i.e., after 4 weeks of treatment, during sessions 15 and 16) and at treatment end (i.e., after 8 weeks of treatment, during sessions 28 and 29). Note that the TUG test is performed on a separate day from the other assessments, to mitigate the number of tests to complete in a single session. Note also that the 10MWT will be administered once during each quarter of treatment, since the test is informative and easily administered, and thus will not substantially disrupt a session of typical exoskeleton treatment.

The scheduling of assessment for each subject is provided in the chart below.



Schedule of Treatment and Outcome Measures Associated with Study 1

Data Analysis

Table 1 lists the relationships between the outcome measures and each hypothesis. Given that each patient is in a chronic stage of injury (i.e., spontaneous changes in health and neurological status are unlikely or minimal), the investigators assume that any statistically significant change in the outcome measures between pre- and post-treatment will have resulted from treatment. Since all measures are quantitative, including the self-report and SCI-SET, testing the respective hypotheses entails testing the extent to which the pre- and post-treatment means, of respective measurements across all subjects, are different. As such, the investigators will employ paired-sample t-tests to test the extent to which pre- and post-treatment means are statistically different, by employing a 95% confidence level in the analysis, unless results indicate a more appropriate confidence level for a given set of data. In addition to using paired t-tests for validating differences in means, and establishing associated confidence levels in those differences, analysis of variance (ANOVA) methods will be employed when determining statistical significance of differences in means between multiple data sets, with 95% confidence levels. Specifically, ANOVA will be used when assessing differences in means between pre-, mid-, post-, and 8-week follow-up measurements. In addition to analyzing results across all subjects, more meaningful results will be provided by separating the subject population into appropriate groups, such as: motor-complete and motor-incomplete individuals; non-ambulatory and poorly-ambulatory ones; individuals with tetraplegia and those with paraplegia; persons with upper paraplegia and those with lower paraplegia; etc. For example, measures associated with walking while not wearing the exoskeleton will only be recorded for poorly-ambulatory individuals; neurological recovery is not expected for individuals with motor-complete injuries (while perhaps possible, such recovery is not hypothesized here); and individuals with tetraplegia are less likely to achieve walking speeds and levels of independence commensurate with community ambulation, relative to individuals with paraplegia. For these groups, ANOVA techniques will be employed to assess differences in

means between groups, in order to indicate and validate differences in outcomes. Software packages facilitating statistical analysis will be employed, including IBM SPSS 22 and MATLAB 2014. Note that a clinical statistician is among the key study personnel associated with this proposal, as outlined in the attached organizational chart.

TABLE 1: Hypotheses and measures associated with Study 1

Hypothesis	Method of Measurement/Testing
Decreased BMI	Body mass (weight) at baseline, treatment midpoint, post-treatment, and at 8 week post-treatment follow-up
Changes in BMD	DXA at baseline, post-treatment, and at 8 week post-treatment follow-up
Improved bowel and bladder function	Self-report at baseline, treatment midpoint, post-treatment, and at 8 week post-treatment follow-up
Reduced spasticity	MAS and SCI-SET at baseline, treatment midpoint, post-treatment, and at 8 week post-treatment follow-up
Reduction in pain	Self-report at baseline, treatment midpoint, post-treatment, and at 8 week post-treatment follow-up
Enhanced well-being	Self-report at baseline, treatment midpoint, post-treatment, and at 8 week post-treatment follow-up
Neurological recovery (complete SCI)	ASIA neurological exam and FR at baseline, treatment midpoint, post-treatment, and at 8 week post-treatment follow-up
Neurological recovery (incomplete SCI)	ASIA neurological exam, FR, and MMT at baseline, treatment midpoint, post-treatment, and at 8 week post-treatment follow-up
Functional recovery (poorly-ambulatory)	FR, MMT, FIM-G, WISCI-II, TUG, 10MWT, and BRPE at baseline, treatment midpoint, post-treatment, and at 8 week post-treatment follow-up
Community mobility	FIM-G, WISCI-II, TUG, 10MWT, and 6MWT and BPRE relative to published recommendations for community ambulation

7.0 Risks of Investigational Devices

Risks:
See section 3 of this document. As stated in that section, following over 1200 hours of exoskeleton walking with 40 subjects with SCI, no serious adverse events occurred. As such, risks to subjects are expected to be minimal.

Potential benefits:
The intent of the study is to characterize potential health and mobility benefits provided by the exoskeleton. As such, there is no clearly-established medical evidence of health benefits resulting from exoskeleton walking. Despite this, the investigators hypothesize that subjects will experience improvements in well-being, circulation, bowel and bladder function, skin integrity, and sleep, in addition to reductions in spasticity and pain. Moreover, subjects with incomplete SCI may experience neurological and/or functional improvement.

Regarding the general population of individuals with SCI, if exoskeleton use substantially mitigates the prevalence of secondary impairments, as hypothesized herein, these devices could substantially decrease the cost of health care for individuals with SCI. If such use is found to facilitate neurological and/or functional recovery for patients with motor-incomplete injuries, the intervention could have a substantial impact on improving rehabilitative outcomes for large numbers of individuals.

8.0 Clinical Monitoring Plan and Reporting of Adverse Events

Good clinical practice monitoring: Each site will employ an independent medical monitor, who will review the study protocol prior to each study; observe the initial treatment session of the first subject in each study; and be apprised of any AE at any site in the study.

Safety monitoring: Safety monitoring and oversight will be performed by each respective site PI. All PIs will have the authority temporarily or permanently to discontinue a particular protocol and/or the involvement of a given subject, if deemed necessary or appropriate for the safety of the subject. If any concern or unexpected issue is identified with one subject that could be of potential risk or concern to other subjects, action will be taken by the data and safety monitoring team to address, mitigate, and/or eliminate such risk from the study. Any AE will be reported immediately, i.e., within 24 hours, to the site study coordinator and site PI. The site PI and site medical monitor will determine if any action is required to resolve the AE. The site PI will also report the AE to the site IRB, and to the lead site study coordinator and PI.

Risk management and emergency response:
Risks will be managed by employing the following safety and oversight measures:

- A licensed PT will directly supervise all sessions.
- A safety gait belt or overhead harness will be utilized at the discretion of the supervising PT.
- Blood pressure and heart rate will be monitored throughout each session to ensure vital signs fall within the recommended ranges for locomotor training activity.

Any AE will be reported immediately, i.e., within 24 hours to the site study coordinator and site PI. The site PI and site medical monitor will determine if any action is required to resolve the AE. The site PI will also report the AE to the site IRB, and to the lead site study coordinator and PI. Each site PI will have the authority to temporarily or permanently discontinue a particular protocol and/or the involvement of a given subject, if deemed necessary or appropriate, for the safety of the subject. If any concern or unexpected issue is identified with one subject that could be of potential risk or concern to other subjects, the data and safety monitoring team will take action to address, mitigate, and/or eliminate such risk from the study.

If determined by study personnel or the medical monitor that an injury occurred as a direct result of the tests or treatments involved in this study, each respective site will cover the cost of immediate medical care provided at that site to treat the injury. Neither the study, nor each site, will be responsible for the costs of additional care.

9.0 Study Withdrawal/Discontinuation

Subjects can choose to discontinue participation in the study at any time. If the investigators feel that the safety of the participant, or others, is compromised for any reason during the study, that subject will be withdrawn from the study.

10.0 Privacy/Confidentiality Issues

All data, dexa scans, videos, and photographs recorded during this study will be held in a secured location at the trial site. Data will continue to be held until the study researchers deem the data is no longer scientifically relevant, at which point the data will be destroyed. All data will be de-identified prior to publication.
The research team will take photographs and record videos of participants throughout this study. The participants entire body including their face will be included. The purpose of the photographs and videos is to help participants

learn more about the device as well as to provide information to the researchers and for other participants in this or other studies. The photographs and videotapes may also be used for scientific publications, meetings of scientists, public formats for nonscientific groups. Participants will be given the option to have or not have their photographs or videos shared outside of this study. Photographs and videos will be securely stored at the particpants site. If partiicpants have agreed to allow photographs or videos chared outside of this study they will be transferred using Vanderiblt's secure file transfer or via RedCap.

11.0 Follow-up and Record Retention

The data collected in the study will be maintained in a RedCap database. Key study personnel at each site will have a user id and password and will have access to only their data. Vanderbilt will have access to all data at all sites. Data will continue to be held until the study researchers deem the data is no longer scientifically relevant, at which point the data will be destroyed.

12.0 References

[1] National SCI Statistics Center, Spinal cord injury facts and figures at a glance, https://www.nscisc.uab.edu/, 2013.
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