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TITLE: A Randomized, Crossover Clinical Trial of Exoskeletal-Assisted Walking to Improve Mobility, Bowel Function, and Cardiometabolic Profiles in Persons with SCI

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14. ABSTRACT

The primary objective was to achieve specific walking velocities and distances using a powered exoskeletal at 12 and 36 sessions over the course of 3 months in people with chronic spinal cord injury (SCI) who were wheelchair users for community mobility. The secondary objectives were to determine if this amount of exoskeletal-assisted walking was effective in improving bowel function and body composition. Exploratory objectives included questions concerning the retention or non-retention of changes, effects of increased physical activity on vagal tone, orthostatic tolerance, lipid profile, endogenous hormone levels, and quality of life. To date (Y5, Y4 with a 1-y NCE) the study has achieved the enrollment goals. The number of participants screened, enrolled and completed were as follows: 104 were consented for screening; 71 were randomized; and 50 participants completed the study. Data has been analyzed for the Primary and Secondary objectives and approximately 75% of the exploratory outcome data has been analyzed. Three manuscripts are in preparation: one for the primary outcome of mobility data and one each for the secondary outcomes of bowel and body composition data. Journal submissions for the three main manuscripts is anticipated by March 2020. Completion of the exploratory outcomes analyses and manuscript submissions will follow in the summer of 2020.

15. SUBJECT TERMS
Exoskeletal Assisted Walking (EAW), Mobility, Bowel Function, Body Composition, Cardiometabolic profile

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1. INTRODUCTION:

Paralysis from traumatic spinal cord injury (SCI) results in an abrupt reduction in the level of daily physical activity. Those with more severe SCI lose the ability to stand and walk, becoming a wheelchair user for mobility. As a result of this sudden and near permanent immobilization, body composition, cardiovascular function, autonomic integrity, and bowel function are but a few of the body systems that are adversely affected. Paralysis from SCI also affects quality of life due to reduced ability to participate in the work force and reduced mobility for community integration. Powered exoskeletal systems provide a new mobility option and appear to have potential therapeutic value for persons with chronic SCI. Phase I trials performed in subjects with non-ambulatory SCI resulted in Food and Drug Administration (FDA) approval in 2011 for institutional use of the powered exoskeleton, ReWalk™ (ReWalk Robotics, Inc., Marlborough, MA) and in 2012 for the Ekso™ (Ekso Bionics, Inc., Richmond, CA). The primary objectives of this proposal were to achieve successful walking at specific velocities and distances and mobility skills in the exoskeletal-assisted walking (EAW) devices over the course of 36 sessions in three months in people with chronic SCI who are wheelchair users for mobility. The secondary objectives were to determine if 36 sessions in three months of EAW was effective in improving bowel function and body composition. The exploratory objectives were to address additional questions about the effects of the increased physical activity from EAW on cardiovascular vagal tone, orthostatic tolerance, lipid profile, total testosterone, estradiol levels, and quality of life (QOL).

2. KEYWORDS:

1) Powered exoskeletons
2) Robotic exoskeletons
3) Paraplegia
4) Tetraplegia
5) Bowel function
6) Body composition
7) Total body fat mass
8) Total body lean mass
9) High density lipoprotein
10) Lipid profile
11) Orthostatic tolerance
12) Total testosterone
13) Estradiol
14) Quality of life
15) ReWalk
16) Ekso

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Major Task 1: Study start-up and continuation administrative functions
Date Completed: 09-Apr-2015

Major Task 2: Study recruitment and enrollment
Date Completed: The last participant was completed on 19-Aug-2019

Major Task 3: Review and complete data acquisition forms, data edits and data entry in

the central database.
Date Completed: 30-Oct-2019

Major Task 4: Review and analyze data
Data analyses began in Dec-2019 and remains ongoing.

Major Task 5: Prepare and write manuscripts. Data analysis for the primary manuscript began Nov-2019 and the writing began Mar-2020. The primary manuscript (Appendix 1) preparation was completed and the manuscript was submitted to *Frontiers in Robotics and AI* on 30-Apr-2020 and was accepted for publication on June 9, 2020.
Additional manuscripts are in preparation with data analyses and writing for the secondary outcomes: 1) bowel/bladder outcomes and 2) body composition. The exploratory outcomes are also in preparation for: 3) autonomic/cardiovascular function, 4) endocrine laboratory values, and 4) quality of life surveys.

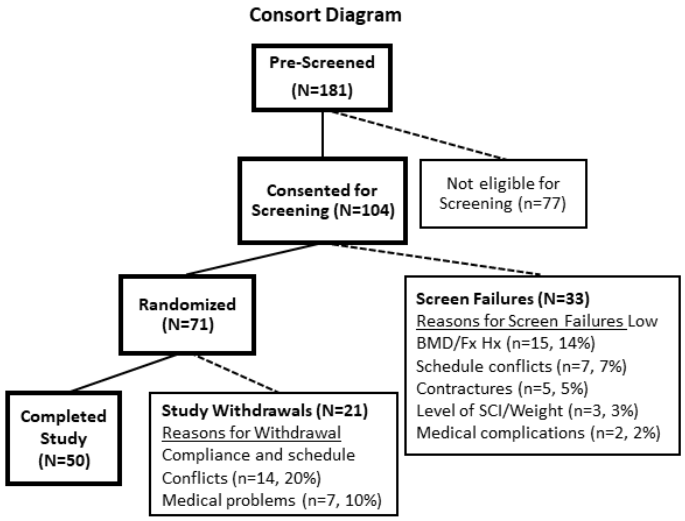
What was accomplished under these goals?

1) The major activities accomplished included the study enrollment and completion of 50 participants, organization of and data input to the central database, analyses of data, abstract presentations, and manuscript writing.

2) The specific objectives accomplished included the completion of administrative start-up for Institutional Review Board (IRB) submissions and approvals for the three study sites and the USAMRDC Human Research Protection Office (HRPO), case report forms for collection of data. Establishment of a central database for the data to be housed for all three study sites. This database was located on the secure and protected VA network at the James J. Peters VA Medical Center (JJPVAMC). Instituting a secure data transfer system for transfer from the sites to the central database. Data cross checking for accuracy with the case report forms for input values. Data analysis for each of the primary, secondary and exploratory outcome variables. Coordinating with the investigators the writing and submitting the primary manuscript. All specific objectives were met as per the Statement of Work (SOW) (Appendix 2).

3) The significant results, major findings and conclusions include the descriptive characteristics of the participants (Table 3, Appendix 1), consort diagram and adverse events (AE) are reported as indicated below. (Note, the Consort Diagram and AEs will be reported in the subsequent secondary outcome manuscripts.

A. Participants were recruited, enrolled and completed from October 2015 to September 2019. A total of 181 potential participants were pre-screened, 104 were eligible to be consented for screening. Of the 104 participants who were screened, 71 were eligible for randomization. The reasons for the 33 screening failures were mostly attributed to low bone mineral density (BMD)/fracture history (14% of total screened participants) or scheduling conflicts (7% of total number screened) due to the time commitment for the 36 sessions. Of the 71 participants who were randomized, 50 completed the study and 21 (30%) withdrew. Compliance and schedule conflicts were the primary reasons for the study withdrawals (Consort Diagram). Of those who completed the study, 26 were in Group 1 (EAW first) and 24 were in Group 2 (UA first).

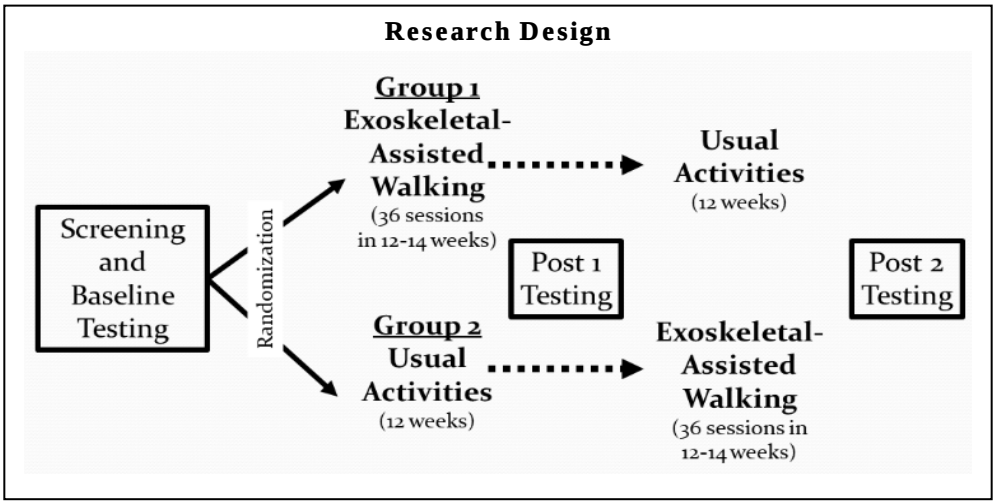


Screen failure percent (%) values were calculated on the total number consented for screening. Study withdrawal percent (%) values were calculated on the total number randomized. N = number; BMD = bone mineral density; Fx Hx = fracture history; SCI = spinal cord injury.

B. The adverse event reporting may be found in the following table. There were eight serious adverse events (SAE); four were possibly related and four were unrelated. Seven of the eight SAEs were resolved and the participants returned to complete the study. One participant was discontinued from the study because the SAE resulted in an unrelated knee fracture due to a fall during an AccessoRide transport. The majority of adverse events (AE) (41 of 75) were related to skin abrasion due to fitting of the devices. These occurred early in the study and with trainer/therapists' better fitting of the devices and experience were minimized. All (but one possibly related) AE were resolved and participants completed the study. The one participant with a "possibly related" AE was diagnosed with a calcaneal fracture of indeterminant age of when the fracture occurred, as such, was likely to have been a pre-existing, undiagnosed foot fracture. Because of this occurrence, a bilateral foot X-ray was added to the screening procedures to rule out potential other undiagnosed foot fractures.

Serious Adverse (SAEs) and Adverse Events (AEs)					
Serious Adverse Events	**Total**	**Relatedness**	**Description/Action Taken**		
Shortness of breath	1	Possibly	Taken to VA ER, medically cleared and discharged, continued in study		
Emotional distress	1	Possibly	Discharged from hospital and cleared, continued in study		
Bowel complications	1	Possibly	Discharged from hospital and cleared, continued in study		
Ankle fracture	1	Possibly	Probable pre-existing, withdrawn from study		
Fall with knee fracture	1	Unrelated	Fall during Access-A-Ride travel, withdrawn from study		
Low blood pressure	1	Unrelated	During UA arm, discharged from hospital and cleared		
Arm numbness	1	Unrelated	During UA arm, discharged from hospital and cleared		
Urinary tract infection	1	Unrelated	Discharged from hospital and cleared		
Total SAEs	8	4 possibly related; 4 unrelated			
Adverse Events	**Total**	**Unrelated**	**Possibly**	**Related**	**Comments**
Skin Abrasion/Bruising	41	1	1	39	All study-related skin abraisons were resolved and participants continued in study
Musculoskeletal/edema	19	4	7	8	All study-related musculoskeletal AEs were resolved and participants continued in study
Calcaneal fracture	1	0	1	0	No hospitalization, indeterminate age of fracture
Falls	6	4	0	2	Four falls during transfers that were unrelated and two falls in the device but no injuries
Urinary tract infection	4	4	0	0	All were unrelated
Other	4	4	0	0	Unrelated miscellaneous medical issues
Total AEs	75	17	9	49	

C. The study design consisted of a two-group, randomized for order of intervention, cross over design. A graphic depiction is displayed in the figure titled “Research Design” below. Group 1 received exoskeletal-assisted walking (EAW) first for 12 weeks then crossed over to usual activity (UA) for a second 12 weeks; Group 2 received UA first for 12 weeks then crossed over to EAW for 12 weeks of training. The EAW arm consisted of EAW training, three sessions per week (4



to 6 hours/week) for 36 sessions. The UA arm consisted of identification of usual activities for each participant and encouragement to continue with these activities throughout the 12-week UA arm. Sub-groups were categorized for duration of injury (≤2years or > 2 years since SCI), neurological deficit (complete tetraplegia, incomplete tetraplegia, complete paraplegia, or incomplete paraplegia) and device used (ReWalk, Ekso). Paired t-tests, repeated measures analyses of variance (ANOVAs) and Chi squared analyses were used to perform the statistical analyses. Results are reported in mean±standard deviation (for the tables and text) or ±standard error (for the figures).

D. The primary aims were related to the walking velocities, distances and mobility skills achieved using the exoskeleton devices by number of sessions and are reported in the primary manuscript (Appendix 1).

i. The major findings were that a total of 50 participants completed 36 sessions of exoskeletal-assisted walking training. At 12 sessions, 31 (62%), 35 (70%) and 36 (72%) participants achieved the ten-meter walk test (10MWT), six-minute walk test (6MWT) and timed-up-and-go (TUG) milestones respectively. By 36 sessions, 40 (80%), 41 (82%) and 42 (84%) achieved the 10MWT, 6MWT, and TUG criteria, respectively.

ii. EAW training conclusions: In conclusions, it is feasible to train chronic, non-ambulatory individuals with paralysis from SCI in performance of EAW sufficiently to achieve reasonable mobility skill outcome milestones. To date and to our knowledge, this is the largest clinical trial completed for an exoskeletal-assisted walking study in persons with SCI. EAW training in either the ReWalk or the Ekso resulted in progressive improvement in walking velocities and distances across the 36 sessions. The rate of improvement in the walking tests was unrelated to DOI, level and completeness of SCI. **This is an important finding because evidence is provided that EAW skill measured by walking velocity and distance is achievable across the spectrum of SCI.** There was high variability in the total number of steps taken in both devices. This may be accounted for by participant motivation, confidence in the device, stamina, or total time attended per session. EAW training was demonstrated to be safe, feasible, and effective within a 36-session training timeline. Most participants improved their walking velocity and distances with the progression of sessions. Subtle differences between the two devices were detected. The observed combination of how the Ekso triggers stepping and higher step clearance allowed participants to walk more successfully during the earlier sessions. Whereas, ReWalk users usually needed more sessions to learn appropriate weight shifting to better trigger stepping and to clear the foot during the swing phase, but once they learned this skill, they walked at faster velocities. More than half of the ReWalk users were able to meet FDA velocity criteria for personal prescription. **Our data suggests that clinical programs can expect success rates of 58% by 12 sessions, 68% by 24 sessions and 78% by 36 session to achieve walking velocity medium and fast milestones of ≥0.25 m/s and ≥0.40 m/s respectively, regardless of level and completeness of injury or device used. The results from this study provide guidelines for estimating the potential of individuals with SCI to achieve proficient and safe EAW skills for institutional and personal use of these devices. These findings provide efficacy and objective data for clinicians to refer to when establishing staffing needs and expected outcomes for patients for exoskeletal-assisted walking programs in their institutions.**

E. A preliminary analyses of the secondary aims and manuscript preparation began in Dec-2019.

i. Bowel function analyses: Overall, for the whole group, there were no significant effects found for changes in patient-reported outcomes for the Bowel Management Difficulties SCI-QOL survey after EAW. **However, for the whole group, the amount of enemas, irrigations, suppositories, oral laxatives or stool softeners, and/or manual digit stimulation was reduced in 12% of the participants after EAW. Additionally, in the whole study group, the amount of daily and weekly time needed for bowel evacuations was reduced in 24% of the participants after EAW.**

a) Post hoc sub-analyses: Because it was noticed by our staff that the newer injured participants were still learning to maximize their bowel management, stratification by the duration of injury (DOI) sub-categories for outcomes of bowel function, showed that those persons injured for more than 2 years demonstrated an improvement trend in the Bowel Management SCI-QOL survey after EAW (51.0±9.5 vs. 48.8±10.2, p=0.1439). Whereas, the newer injured sub-category (DOI<2y) stayed the same or became worse after EAW.

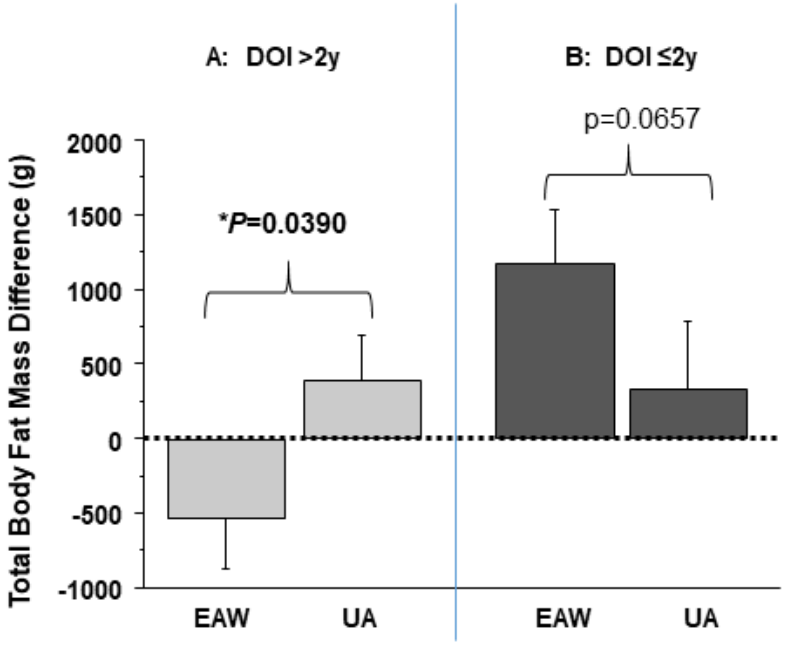
Bowel function conclusions: EAW training had a positive effect about 1/4th of the participants for the patient-reported outcomes for bowel function and management. It appeared that those with newer SCI may still be learning to adjust and become competent with their bowel program, thus negating any effect from the EAW. However, in those with newer SCI, it is not known if the EAW mitigated these untoward bowel function effects. A separate manuscript with the bowel data will be written. Further and more in-depth analyses will be conducted for the full manuscript. This manuscript will also include the bladder data which was an exploratory outcome.

ii. Body composition analyses: Overall for the total group, there were no significant differences found for total body fat mass from pre to post EAW or pre to post UA. There was a trend for EAW to have reduced fat mass and UA to have increased fat mass.

a) Post hoc sub-analyses: Because it has been shown that individuals with SCI continue to gain fat mass for up to two years after injury, a *post hoc* analysis was performed by stratifying the participants on the DOI sub-categories. Those in the DOI>2years demonstrated significant loss after EAW compared to UA in total body fat mass, whereas those in the newer injured

sub-category (DOI≤2y) gained total body fat mass after both conditions (Total Body Fat Mass Figure).

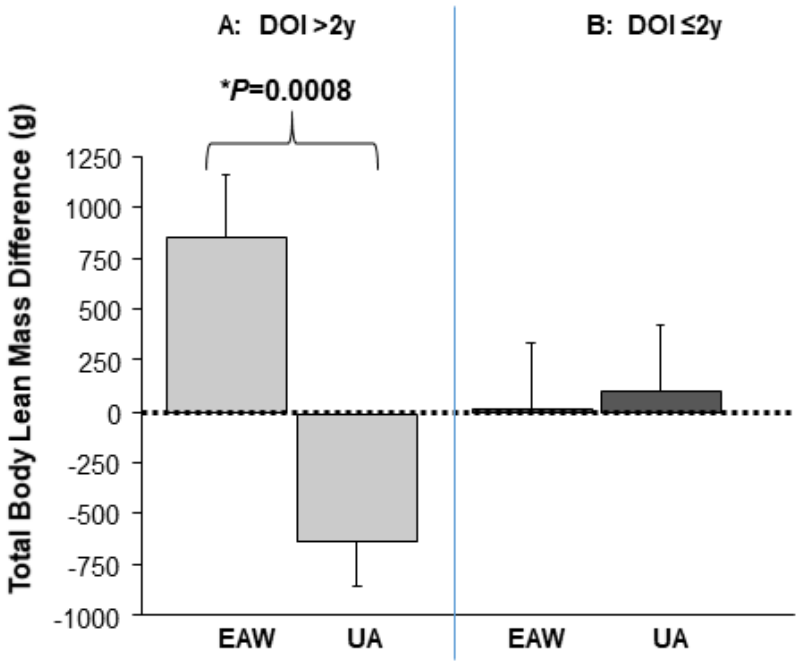
Total Body Fat Tissue Mass Split by Duration of Injury Category Pre and Post Exoskeletal-assisted Walking and Usual Activities



Participants with a duration of injury >2 years (Panel A) or with DOI ≤2 years (Panel B); g=grams; EAW=exoskeletal-assisted walking arm; UA=usual activities arm.

b) Using the same DOI stratification for analysis of **total body lean mass**, those in the DOI>2y sub-category had a significant gain in total body lean mass after EAW compared with their loss after UA. Whereas, those in the newer injured sub-category had no significant change or differences after EAW or UA for total body lean mass (Total Body Lean Mass Figure, below). Additional analyses to determine specific compartment changes will be performed for the body composition manuscript.

Total Body Lean Tissue Mass Split by Duration of Injury Category Pre and Post Exoskeletal-assisted Walking and Usual Activities



Participants with a duration of injury >2 years (Panel A) or with DOI ≤2 years (Panel B); g=grams; EAW=exoskeletal-assisted walking arm; UA=usual activities arm.

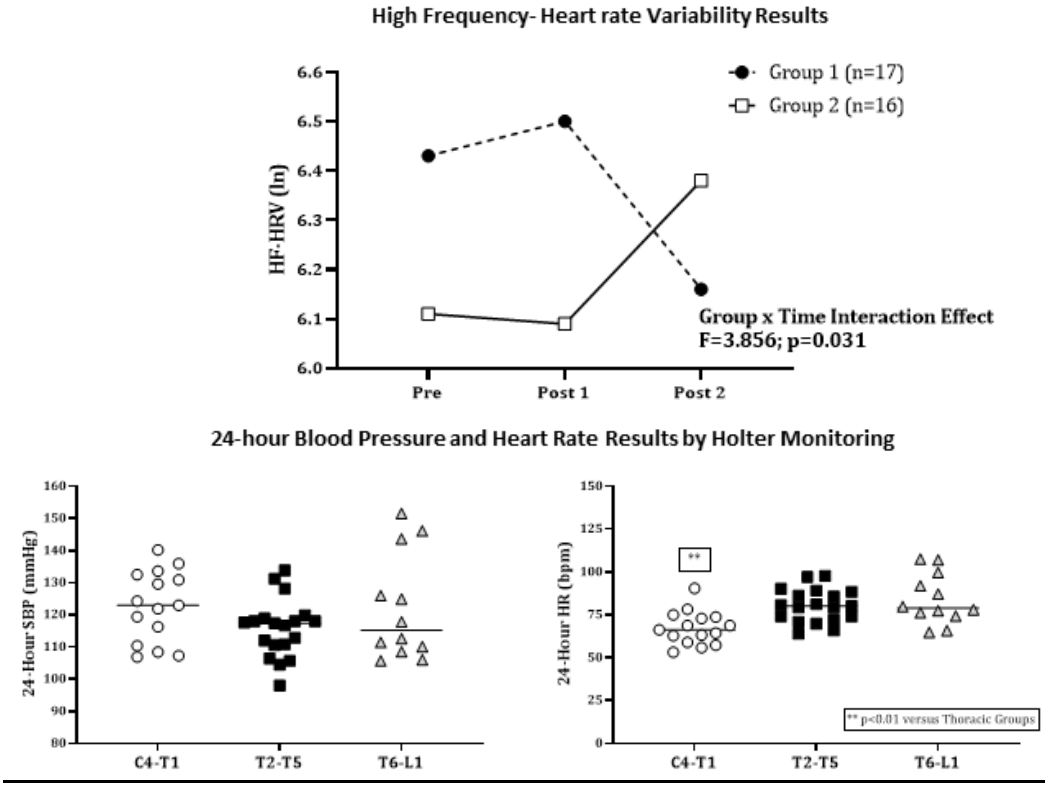
Body composition conclusions: Overall for the total group, there were no significant differences from pre to post EAW found for total body fat or lean tissue masses. However, stratification analyses of splitting the groups by DOI sub-categories showed that those with newer SCI tended to continue to gain fat with no appreciable change in lean tissue mass during both the EAW intervention and the usual activates control arm. However, **those participants with longer duration of SCI in the DOI sub category >2 years, had positive and significant improvements in body compositions with loss of total body fat mass and increases in total body lean mass.** These findings suggest that EAW is associated with improvements is body composition in persons with SCI who have longer durations of injury. Additional analyses of the effects of level and completeness of SCI will be important to ascertain. One important question comes to mind, in those participants with <2 years DOI, we do not know if the increases in fat mass or the losses in lean tissue mass were potentially mitigated by the EAW training. A future, properly designed study would be important to determine the effect of EAW on newly injured persons with SCI.

F. A preliminary analyses of the exploratory aims and manuscript preparation began in Dec-2019.

i. High density lipoprotein cholesterol (HDL-c): Pre and Post EAW HDL-c values were analyzed in 47 participants, blood sample from three participants were not able to be taken during the pre or post status. Twenty-four of 47 (51%) of the participants demonstrated a 2.0 mg/dL improvement in HDL-s after EAW training. An average, these participants had 6.5±3.3 mg/dL increase in HDL-c with a range of 2.0 to 14.0 mg/dL change).

HDL-c conclusions: More than one half of the participants had a clinically meaningful improvement in HDL-c after 36 sessions of EAW.

ii. Cardiovascular function: The data indicate a significant interaction effect for 24-hour high frequency-heart rate variability (HF-HRV, a marker of cardio-vagal tone) (F=3.856; *P*=0.031), such that regardless of test order, 24-hour HF-HRV was significantly increased following EAW compared with the change in 24-hour HF-HRV following UA (+15.8±62.8% vs. -26.9±105.5%; *P*<0.05). (See Figures below: High Frequency-Heart Rate Variability results and 24-Hour Blood Pressure and Heart Rate Results).



Cardiovascular conclusions: The systolic blood pressure and heart rate 24-hour results observed provide preliminary evidence that 36-sessions of EAW may confer beneficial effects on cardiovascular health. The

significance of this finding is that prolonged EAW may reduce cardiovascular disease, which is a leading cause of mortality in the SCI population, and therefore EAW should be promoted.

4) Other Achievements: The primary manuscript is attached (Appendix 1). Once published, a PDF version will be provided to the DOD CDRMP SCIRP. Two secondary manuscripts, and three to five manuscripts about the exploratory outcomes will also be submitted for publication.
    A. The secondary manuscripts include:
        i. The effect of three months of exoskeletal-assisted walking on patient-reported outcomes for bowel and bladder function.
        ii. Changes in body composition for total body fat and lean masses after exoskeletal-assisted walking.
        iii. The data analyses for both of these manuscripts has been completed as of Jun-2020 and both are undergoing writing. We expect to submit these manuscripts in Jul-2020.
    B. The manuscripts from the exploratory aims include:
        i. Changes in autonomic and cardiovascular function (vagal tone) after exoskeletal-assisted walking. Data analysis is completed (May-2020) and manuscript is in preparation.
        ii. Changes in HDL-c, Homeostatic Model of Assessment – Insulin Resistance (HOMA-IR), serum total testosterone and estradiol levels. Data analysis is ongoing and the manuscript is scheduled to begin preparation in Jul-2020.
        iii. Changes in quality of life (QOL) measured by item banks from the SCI-QOL and Patient Reported Outcomes Measurement Information System (PROMIS). Data analysis has not yet begun. We expect to begin this data analysis after we have completed the two manuscripts for the secondary aims, sometime this fall.

What opportunities for training and professional development has the project provided?
Dr. Spungen, the PI, has used this study as an opportunity to provide professional development for three of her junior staff and a staff SCI Physician who was interested in learning and being a part of a research project.

1) Mr. Pierre Asselin is the lead Bio-Medical Engineer and a Co-Investigator on this study. Mr. Asselin used the mentorship and experience from this study to apply for his own funding as a PI and it resulted in a recent approval of a VA RR&D SPIRE funded project using another exoskeleton in a stroke population.
2) Dr. Eun-Kyoung Hong is a Post-doctoral fellow in Dr. Spungen's lab and the database manager for this study. Dr. Spungen has worked one-on-one with Dr. Hong in analyzing, interpreting, writing, and presenting the data at the Academy of Spinal Cord Injury Professionals (ASCIP) in 2017 and 2018 annual meeting in Denver, CO (Appendix 3). Dr. Hong worked very hard on getting the primary manuscript written, in which she is the first author, and submitted for this project.
3) Mr. Steven Knezevic worked as a research coordinator and EAW certified trainer on this protocol. He is also a doctoral candidate at Rutgers University. He will be given the

opportunity to write a manuscript under Dr. Spungen's mentoring. Dr. Spungen has worked one-on-one with Mr. Knezevic in analyzing, interpreting, writing, and presenting the data at the Academy of Spinal Cord Injury Professionals (ASCIP) in 2017 and 2018 annual meeting in Denver, CO (Appendix 3).

a. Additionally, during the study, a high school senior, Mr. David Markowitz, was mentored by Steven Knezevic. The high school student analyzed some of the Quality of Life survey data for his high school senior capstone project.

4) Dr. Stephen Kornfeld, Staff SCI physician at the JJPVAMC and study physician for this protocol. Dr. Kornfeld participated as the medical physician for the study by evaluating the participants for eligibility and reviewing the AEs and SAEs. Dr. Kornfeld also participated in study planning, data review and manuscript writing.
5) Tristan H. Vouga (Doctoral Candidate) at the Faculté des Sciences et techniques de l'Ingénieur, Laboratoire LSRO / Biorob / REHAssist, Programme doctoral en Systèmes Robotiques, École Polytechnique Fédérale de Lausanne (EPFL) pour l'obtention du grade de Docteur ès Sciences. Dr. Spungen was recruited to be a member and examiner on his doctoral thesis and dissertation titled: *Lean Synthesis and Application to Lower-Limb Exoskeletons*. Note, the EPFL in Lausanne, Switzerland is one of the best ranked and most prestigious engineering schools in Europe.

How were the results disseminated to communities of interest?

1) Because of Dr. Spungen's experience and feedback from many users of exoskeletons during this study, she was invited to present and share the knowledge gained about key device features that should be improved upon to several engineering departments at some major universities. These presentations are listed in Appendix 4. Dissemination of user and trainer feedback about the mechanics of the two exoskeletons that were used in this study was vital to those engineering departments that are developing current and future devices.
2) Dr. Spungen was an invited speaker and panel member for the NIH's SCI 2020: Launching a Decade for Disruption in Spinal Cord Injury, Bethesda, MD February 12-13, 2019. At her presentation, she shared the lessons learned, challenges, and the priorities, future applications and directions of EAW in persons with SCI (Appendix 5).
3) Additionally, the study team staff from the Bronx VA attended the Department of Rehabilitation and Human Performance Community-wide Research Day at Mount Sinai Medical Center, NY, NY in 2016, 2017, 2018, and 2019, and the Abilities Research Expo in New Jersey during 2016, 2017, 2018 and 2019 in which information about the study was shared with the consumers and attendees with SCI. The 2020 meetings have been cancelled due to the COVID-19 pandemic.
4) Upcoming presentations and seminars in 2020 (both of which are now to be done in a video/internet/web-based format due to the COVID19 pandemic):
    a. Wearable Robotics 2020, October 13-17, 2020. Special Session Symposium and Workshop Title: Evidenced-based Indications/Contraindications for, and Potential Benefits of, Exoskeletal-Assisted Walking in Persons with Spinal Cord Injury (Appendix 6).
    b. American Association of Physical Medicine and Rehabilitation November 12-15, 2020. Presentation Title: Indications and Contraindications for Exoskeletal-Assisted

Walking in Persons with Spinal Cord Injury Using Evidence-Based Data (Appendix 6.)

5) There has been much concern over potential fragility fractures when using these devices. Our stringent exclusion criteria for bone density and fracture history appears to have been effective in reducing the risk of a fragility fracture when walking in these devices. However, in this study and another one being conducted for home use of the ReWalk through the VA (VA Cooperative Study #2003), the evidence of undiagnosed, pre-existing foot fractures raised concern for additional screening with X-ray, CT or other clinically appropriate method prior to fitting and training an individual with SCI in one of these devices. The study results support that EAW when done properly is safe, with few AEs and no SAEs that were defined as "study-related". The Food and Drug Administration (FDA) will be contacted to let them know that we have completed this study. The FDA and the Department of Veterans Affairs has a memorandum of understanding (MOU) for adverse event and some data sharing. We will contact the FDA to see what, if any, data they may require regarding the AEs or SAEs from this study.

What do you plan to do during the next reporting period to accomplish the goals? This is the Final Report. However, manuscripts will continue to be prepared and be submitted for publication during the current and the next years (2020 and 2021). All published manuscripts will be provided to the sponsor.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project? The principal discipline of this project is the field of rehabilitation for persons with chronic SCI >6 months. Professionals in the rehabilitation field for individuals with chronic SCI include clinicians from SCI medicine, Physiatry, Neurology, Physical Therapy, Occupational Therapy, and Prosthetics and Orthotics (and potentially others). **Findings from this study will serve to expand the knowledge base regarding best screening procedures for safe use of these devices, best procedures for fitting and training, and potential benefits from regular use in a supervised hospital setting. The findings from this study will also serve to inform study designs for future investigation of exoskeletal-assisted walking devices.**

What was the impact on other disciplines? Other disciplines include robotics, mechanical and biomedical engineering. To date (June 2020) it is estimated that more than 150 exoskeletons have been invented and developed to level of a prototype, with only three of them currently having FDA approval. At least six are approved in Europe with the CE Mark (FDA equivalent). Many graduate level students in the engineering and robotics disciplines are not exposed to people with SCI and as such have limited knowledge regarding aspects that are important to consider when designing exoskeletons. It is anticipated that some of the findings from this study will assist the engineering fields to develop better devices that can be used in a broader range of people with SCI and inform the engineers for better overall safety, donning/doffing and walking features.

What was the impact on technology transfer? The exoskeletons used in this study were not invented or modified by our study team. They were already FDA approved and as such our study had no impact on Tech Transfer. Nothing to Report.

What was the impact on society beyond science and technology? We have learned critical lessons about the exoskeleton technology.
These lessons include knowledge that:

1) Not everyone with SCI wishes to use one of these devices;
2) Not everyone who wants to use one is eligible because of contraindications for weight bearing activities such as extreme bone loss, severe spasms and contractures that limit eligible users;
3) Distance from training centers is a barrier.
4) Of those who are eligible and are taught to use them, not everyone becomes a proficient and safe user of the devices;
5) With the same training protocol, some people have better responses than others;
6) Exoskeletons appear to be good for therapy and exercise, but remain limited for mobility (i.e. people still need a wheelchair);
7) Technology (and FDA) requires a companion – which can result in a loss of independence for a self-sufficient person with SCI; and
8) The time commitment for training and/or lack of a companion may limit many would be users. However,
9) **In those who are successful users of these devices, most participants report a high user satisfaction and experience benefits greater than any other intervention that they have experienced since their SCI.**

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change. Specific bone mineral density criteria were applied for the hip and knee based on available information for this study. However, during this study, one participant experienced a calcaneal fracture during the first sessions. It was suggested by the radiologist that the fracture was potentially pre-existing and undiagnosed. In two other (different) studies of exoskeletons a foot fracture during the early sessions were also found and these two appeared to be pre-existing and undiagnosed. As such, an amendment was added for bi-lateral foot X-rays as part of the screening procedures to rule out pre-existing foot fractures. No further fractures occurred during this study.

Actual or anticipated problems or delays and actions or plans to resolve them. Nothing to Report.

Changes that had a significant impact on expenditures. Nothing to Report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents. Nothing to Report.

Significant changes in use or care of human subjects. Nothing to Report.

Significant changes in use or care of vertebrate animals. Nothing to Report.

Significant changes in use of biohazards and/or select agents. Nothing to Report.

6. PRODUCTS:

Publications, conference papers, and presentations

Journal publications:
Acceptance for publication of this manuscript was on June 9, 2020 (Appendix 1).

Manuscript title: Mobility Skills with Exoskeletal-assisted Walking in Person with SCI: Results from a Three Center Randomized Clinical Trial
Journal: Frontiers in Robotics and AI, section Biomedical Robotics
Article type: Original Research
Authors: Eunkyoung Hong, Peter H Gorman, Gail F Forrest, Pierre K Asselin, Steven Knezevic, William Scott, Sandra Buffy Wojciehowski, Stephen Kornfeld, Ann M Spungen
Manuscript ID: 558146
Edited by: Jan Veneman

Manuscripts in preparation

Secondary 1: Bowel outcome data
Secondary 2: Body composition outcome data
Exploratory: Cardio-metabolic profiles, laboratory values and quality of life data

Books or other non-periodical, one-time publications. Nothing to Report.

Other publications, conference papers, and presentations. Please refer to Appendix 4 for a total list of presentations. The following were presented within the reporting year:

- International Spinal Cord Society (ISCoS) Annual Meeting 2019 Exoskeleton Workshop Tuesday, November 5, 2019, Location: Risso8, Nice, France
  - Results from a randomized clinical trial of 36 sessions of exoskeletal-assisted walking in persons with chronic SCI – Dr. Ann M. Spungen, Principal Investigator
  - Walking Measure Results – Dr. Gail F. Forrest, Co-Investigator
  - Cardiovascular Autonomic Results – Dr. Jill M. Wecht, Co-Investigator
  - Body Composition and Lipid Profile Outcomes (Preliminary analyses) – Dr. Peter H. Gorman, Co-Principal Investigator
- NeuroScience 2019, Society for NeuroScience (SfN), Tuesday, October 22, 2019, Location Chicago, IL
  - Basic-Translational-Clinical Roundtable Session Exoskeletons and Robotics for Neurorehabilitation
    - Mobility skills and health-related outcomes from a clinical trial of exoskeletal-assisted walking in persons with chronic spinal cord injury – Dr. Ann M. Spungen
- École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland; 9/24/2019 - Exoskeletal-Assisted Walking for Persons with Paralysis from Spinal Cord Injury
- Swiss Paraplegic Center Nottwil, Switzerland; 9/24/2019 - Exoskeletal-Assisted Walking for Persons with Paralysis from Spinal Cord Injury

Website(s) or other Internet site(s) Nothing to report.
Technologies or techniques Nothing to report.
Inventions, patent applications, and/or licenses Nothing to report.
Other Products Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project? Please see chart below:

Bronx Veterans Medical Research Foundation (BVMRF)		Status
Name:	**Ann M. Spungen, EdD**	No change
Project Role:	Principal Investigator	
Nearest person month worked:	1.20	
Contribution to the Project:	Principal Investigator	
Funding Support:	JJPVAMC	
Name:	**Pierre K. Asselin, MS**	No change
Project Role:	Co-Investigator	
Nearest person month worked:	1.20	
Contribution to the Project:	Biomedical Engineer	
Funding Support:	VA RR&D Center	
Name:	**Stephen D. Kornfeld, DO**	No change
Project Role:	Co-Investigator	
Nearest person month worked:	0.60	
Contribution to the Project:	Site physician	
Funding Support:	JJPVAMC SCI Service	
Name:	**Jill M. Wecht, EdD**	No change
Project Role:	Co-Investigator	
Nearest person month worked:	0.36	
Contribution to the Project:	Autonomic and orthostatic expertise	
Funding Support:	JJPVAMC	
Name:	**William A. Bauman, MD**	No change
Project Role:	Co-Investigator	
Nearest person month worked:	0.36	
Contribution to the Project:	Endocrine and body composition expertise	
Funding Support:	JJPVAMC	
Name:	**Steven Knezevic, MS**	No change
Project Role:	Lead Research Coordinator	
Nearest person month worked:	6.00	
Contribution to the Project:	Study Coordinator, site primary trainer	
Funding Support:	BVMRF and VA RR&D Center	
Name:	**Eun-Kyoung Hong, PhD**	No change
Project Role:	Study Database Manager	
Nearest person month worked:	9.00	
Contribution to the Project:	Database developer/manager, trainer	
Funding Support:	BVMRF	
Name:	**Denis Doyle-Green**	No change
Project Role:	Research assistant	
Nearest person month worked:	6.00	
Contribution to the Project:	Assistant trainer and phlebotomist	
Funding Support:	BVMRF	

University of Maryland Rehabilitation Orthopedic Institute (UMROI)		Status
Name:	**Peter H. Gorman, MD, PhD**	No change
Project Role:	Co-Principal Investigator	
Nearest person month worked:	0.60	
Contribution to the Project:	Site PI and study physician	
Funding Support:	UMROI	
Name:	**Paula R. Geigle, PhD, PT**	No change
Project Role:	Co-Investigator	
Nearest person month worked:	0.60	
Contribution to the Project:	Site physical therapist	
Funding Support:	UMROI	
Name:	**William Scott, MA**	No change
Project Role:	Research coordinator	
Nearest person month worked:	3.00	
Contribution to the Project:	Primary trainer	
Funding Support:	UMROI	
Name:	**Rebecca Webb, PT**	No change
Project Role:	Site research coordinator	
Nearest person month worked:	3.00	
Contribution to the Project:	Trainer, physical therapist	
Funding Support:	UMROI	

Kessler Foundation Research Center (KF)		Status
Name:	**Gail F. Forrest, PhD**	No change
Project Role:	Co-Investigator	
Nearest person month worked:	1.20	
Contribution to the Project:	Site PI, Biomedical engineering	
Funding Support:	KF	
Name:	**Leigh Ann Martinez**	No change
Project Role:	Site research coordinator	
Nearest person month worked:	12.00	
Contribution to the Project:	Recruitment, IRB paperwork	
Funding Support:	KF	
Name:	**Steven C. Kirshblum, MD**	No change
Project Role:	Site physician	
Nearest person month worked:	0.36	
Contribution to the Project:	Site physician	
Funding Support:	Kessler Institute for Rehabilitation	
Name:	**Sandra Buffy Wojciehowski, DPT**	No change
Project Role:	Site Physical Therapist	
Nearest person month worked:	4.00	
Contribution to the Project:	Trainer, physical therapist	
Funding Support:	KF	
Name:	**Jonathan Augustine**	No change
Project Role:	Research assistant	
Nearest person month worked:	4.00	
Contribution to the Project:	Trainer	
Funding Support:	KF	
Name:	**Erica Garbrini, PT**	No change
Project Role:	Physical therapist	
Nearest person month worked:	6.00	
Contribution to the Project:	Primary trainer, physical therapist	
Funding Support:	KF	
Name:	**Christopher Cirnigliaro, MS**	No change
Project Role:	Study assistant	
Nearest person month worked:	2.00	
Contribution to the Project:	Body composition assessments	
Funding Support:	VA RR&D Center	

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

The PI has been awarded several new grants which are listed below. All new and pending projects either represent an outgrowth of this DOD study or do not have any overlap with the design or outcomes that were studied herein.

OTHER SUPPORT (as of January 2020)

SPUNGEN, Ann M.

ACTIVE

I21RX001734 C (PI: Bauman, Co-PI: Spungen) 07/01/2016 – 6/30/2021 2.40 calendar
VA Rehabilitation Research and Development Service, B2020-C Total $4,500,000
Title: National center for the medical consequences of spinal cord injury
The major goals of this project are to study the secondary medical consequences of SCI. The specific aims are divided into the following five main programs: Endocrine, Pulmonary, Cardiovascular/Autonomic, Gastrointestinal and Molecular. Auxiliary programs include Physical Activity and Neurorehabilitation.
Role: Co-PI

CS#2003 (Chair: Spungen, Ann) 10/01/2015 – 09/30/2021 2.40 calendar
VA Cooperative Studies Program Total $40,000,000
Title: Exoskeletal-assisted walking in persons with SCI: impact on quality of life
The major goals of this project are to demonstrate that Veterans with chronic SCI of ≥ six months duration who are medically stable and are wheelchair users for indoor and outdoor mobility as their standard of care (SOC) plus use of an exoskeletal-assisted walking device in their home and community environments will have clinically meaningful net improvements in the Mental Component Summary of the Veterans Rand-36 and in patient-reported outcomes for the SCI-QOL bladder, bowel, and pain item banks compared with those who use only SOC for home and community mobility
Role: Chair/PI

17833 (PI: Spungen) 08/01/2019 – 07/31/2022 1.20 calendar (no salary support)
NYS DOH Total $159,204
Title: Effects of incorporated exoskeletal-assisted walking in SCI acute inpatient rehabilitation
The purpose of this study is to conduct a prospective, randomized control trial in two groups to determine if EAW training incorporated in AIR is feasible, safe and efficacious approach to facilitating functional independence and reducing pain and inflammatory response in those with SCI who are candidates for locomotor training.
Role: PI

CSCR13IRG013 (PI: Forrest, Gail) 2014 – 2017/20 (3-year no-cost extension) 0.60 calendar
New Jersey DOH/NY State Commission Total $180,000 (VA site only)
Title: Non-ambulatory SCI walk using a robotic exoskeleton: effect on bone and muscle
The major goals of this project are to examine the effectiveness of exoskeleton-assisted over ground walking (5 hours per week, 100 sessions, 20 weeks = 100 hours) to induce positive changes in muscle volume and structure of the lower limbs for non-ambulatory persons with SCI and to define changes in bone mineral density, bone structure, and biochemical markers of bone metabolism with intensive exoskeleton assisted walking.
Role: Co-Investigator

DOH01-PART3.C34461GG (PI: Bauman) 05/2019 - 04/2022 0.60 calendar
NYS Spinal Cord Injury Research Board
Title: Abaloparatide to Improve Bone Mineral Density and Architecture in Subacute SCI
Description: To determine whether 12 months of treatment with anabolic agent in persons with motor-complete SCI results in a significant retention of sublesional bone mass.
Role: Co-Investigator

VA RR&D Bauman (PI) 03/2020 – 02/2023 0.60 calendar
IIR Merit Review
Title: Romosozumab to Improve Bone Mineral Density and Architecture in Chronic SCI
Description: To determine whether 12 months of romosozumab administration in persons with chronic (3 to 10 years post SCI) motor-complete SCI will result in a significant increase in sublesional bone mass, and to determine if a sequential treatment with denosumab preserves or extends skeletal gains achieved with romosozumab.
Role: Co-Investigator

(PI: Spungen, Ann M) 01/31/2021 to 07/30-2025 1.8 calendar
Craig H Neilsen Foundation Total $597,000
Title: Combination drug therapy to prevent bone loss in persons with acute SCI
A clinical trial will be conducted in 30 participants with motor-complete SCI who are >6 months injured. Eligible participants will be randomized to receive 12 months of romosozumab followed by 12 months of denosumab (intervention group, n=15) or 24 months of placebo (control group, n=15). The primary goal is to maintain ≥70% of bone at the knee in ≥80% in the intervention group at 24 months compared to bone at the knee at baseline (before medications have been started). Secondary goals include maintaining ≥80% of bone at the knee and hip at 12 months and ≥70% of bone at the hip at 24 months compared to bone at these respective skeletal sites at baseline. Delayed Start due to COVID-19 pandemic
Role: PI

What other organizations were involved as partners?
Bronx Veterans Medical Research Foundation, James J. Peters VA Medical Center Bronx, NY

Additional financial support was provided by: The James Lawrence Kernan Endowment Fund and a philanthropic gift from Dr. Bert Glaser at the Baltimore site, University of Maryland Orthopaedic and Rehabilitation Institute Baltimore, MD

Kessler Foundation West Orange, NJ

All listed significantly supported this work by providing space for the study and extra salary support for study staff during the final year of the no cost extension (NCE).

8. SPECIAL REPORTING REQUIREMENTS

- COLLABORATIVE AWARDS: N/A
- QUAD CHARTS (Appendix 7)

9. APPENDICES:

Appendix 1. Primary Manuscript

From: Frontiers Robotics and AI Editorial Office <roboticsandai.editorial.office@frontiersin.org>
Sent: Tuesday, June 9, 2020 9:59 AM
To: Spungen, Ann M. (BRX)
Subject: [EXTERNAL] Frontiers: Congratulations! Your manuscript is accepted - 558146

Follow Up Flag: Follow up
Flag Status: Flagged

Dear Dr Spungen,

Frontiers Robotics and AI Editorial Office has sent you a message. Please click 'Reply' to send a direct response

I am pleased to inform you that your manuscript Mobility Skills with Exoskeletal-assisted Walking in Person with SCI: Results from a Three Center Randomized Clinical Trial has been approved for production and accepted for publication in Frontiers in Robotics and AI, section Biomedical Robotics. Your manuscript is currently being prepared for publication. The provisional version of the abstract or introductory section is currently available online. Please do not communicate any changes at this stage. You will be contacted as soon as the author proofs are ready for your revisions.

Manuscript title: Mobility Skills with Exoskeletal-assisted Walking in Person with SCI: Results from a Three Center Randomized Clinical Trial
Journal: Frontiers in Robotics and AI, section Biomedical Robotics
Article type: Original Research
Authors: Eunkyoung Hong, Peter H Gorman, Gail F Forrest, Pierre K Asselin, Steven Knezevic, William Scott, Sandra Buffy Wojciehowski, Stephen Kornfeld, Ann M Spungen
Manuscript ID: 558146
Edited by: Jan Veneman

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Best regards,

Your Frontiers in Robotics and AI team

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Mobility Skills with Exoskeletal-assisted Walking in Person with SCI: Results from a Three Center Randomized Clinical Trial

EunKyoung Hong[1,2], Peter H. Gorman[3], Gail F. Forrest[4,5], Pierre K. Asselin[1,2], Steven Knezevic[1], William Scott[6], Sandra Buffy Wojciehowski[4,7], Stephen Kornfeld[1,2], Ann M. Spungen[1,2,8*]

[1]Spinal Cord Damage Research Center, James J. Peters VA Medical Center, Bronx, NY, USA

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[4]Kessler Foundation, West Orange, NJ, USA

[5]Rutgers New Jersey Medical School-Rutgers University, Newark, NJ, USA

[6]Department of Neurology, University of Maryland School of Medicine, and VA Maryland Healthcare System, Baltimore, MD, USA

[7]Craig Hospital, Englewood, CO, USA

[8]Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

*** Correspondence:**
Ann M. Spungen, EdD
Ann.Spungen@va.gov

Keywords: Exoskeletal Assisted Walking, Mobility Walking Test, 10MWT, 6MWT, TUG, FDA

Abstract

Background: Clinical exoskeletal-assisted walking (EAW) programs for individuals with spinal cord injury (SCI) have been established, but many unknown variables remain. These include addressing staffing needs, determining the number of sessions needed to achieve a successful walking velocity milestone for ambulation, distinguishing potential achievement goals according to level of injury, and deciding the number of sessions participants need to perform in order to meet the Food and Drug Administration (FDA) criteria for personal use prescription in the home and community. The primary aim of this study was to determine the number of sessions necessary to achieve adequate EAW skills and velocity milestones, and the percentage of participants able to achieve these skills by 12 sessions and to determine the skill progression over the course of 36 sessions. **Methods**: A randomized clinical trial (RCT) was conducted across three sites, in persons with chronic (≥6 months) non-ambulatory SCI. Eligible participants were randomized (within site) to either the EAW arm first (Group 1), three times per week for 36 sessions, striving to be completed in 12 weeks or the usual activity arm (UA) first (Group 2), followed by a crossover to the other arm for both groups. The 10-meter walk test (s) (10MWT), 6-minute walk test (m) (6MWT), and the Timed-Up-and-Go (s) (TUG) were performed at 12, 24 and 36 sessions. To test walking performance in the exoskeletal devices, nominal velocities and

distance milestones were chosen prior to study initiation were used for the 10MWT (≤40s), 6MWT (≥80m) and TUG (≤90s). All walking tests were performed with the exoskeletons. **Results**: A total of 50 participants completed 36 sessions of EAW training. At 12 sessions, 31 (62%), 35 (70%) and 36 (72%) participants achieved the 10MWT, 6MWT and TUG milestones respectively. By 36 sessions, 40 (80%), 41 (82%) and 42 (84%) achieved the 10MWT, 6MWT, and TUG criteria respectively. **Conclusions**: It is feasible to train chronic non-ambulatory SCI individuals in performance of EAW sufficiently to achieve reasonable mobility skill outcome milestones.

1 INTRODUCTION

Paralysis resulting from spinal cord injury (SCI) often leads to a reduction in mobility and an associated decrease in daily physical activity. In addition, SCI also leads to other secondary adverse consequences related to body composition (1-3), cardiovascular function (4, 5), autonomic integrity (6, 7), and bowel function (8-10). The combination of reduced mobility and secondary consequences of SCI leads to a reduced quality of life (11-15).

Devices classified by the Food and Drug Administration (FDA) as "powered exoskeletons" (16) have become commercially available and enable individuals with motor paralysis to stand and walk over ground. These devices employ use of a ridged external frame for bracing the lower extremities and trunk. Rechargeable battery powered motors are then used to power movement of the hip and knee joints. Just as able bodied walking requires the ability to maintain balance and perform weight shifting (17), powered exoskeleton assisted ambulation requires the same. These movements are measured by sensors in the device that trigger motors to power movement at the hip and knee joints. Consecutive weight shifting must be completed by actively maintaining balance on the stance leg so that the swing leg can clear the floor appropriately. Subsequent weight shift onto the contralateral side continues to trigger the device to take steps. Over ground balance maintenance and weight shifting are assisted through use of crutches or a walker. The execution of this exoskeletal-assisted walking (EAW) movement places demands on the neuromuscular and sensory systems of the user, increasing oxygen consumption when compared to able bodied ambulation (18, 19). The additional metabolic activity required to ambulate with these devices has the potential to provide a cardiovascular exercise challenge and thereby improve cardiovascular health (20). However, since this technology remains relatively new, many aspects of its use by persons with SCI have yet to be determined.

Due to limitations with current available systems, not all persons with SCI are able to successfully achieve EAW (walking velocity of ≥0.40 m/s over 10 meters and 6-minute walk distance ≥110 m with minimal assistance or less). Some users may manage to take steps but require a significant amount of assistance to accomplish this. Therefore, identification of basic skills during early sessions in order to predict who would be potential responders, that is successful and independent users of the device in the home and community after completing a training program, would be important. The purpose of this study was to document the number of sessions necessary to achieve adequate EAW skills and velocity milestones, to document the proportion of participants who achieved successful EAW skills by 12 sessions, and to determine the skill progression over the course of 36 sessions.

2 METHOD

2.1 Recruitment

This study was approved by the Institutional Review Boards (IRB) of the three collaborating clinical sites, namely the James J. Peters VA Medical Center (JJPVAMC), Bronx, NY, Kessler Institute for Rehabilitation/Kessler Foundation (KIR/KF), West Orange, NJ, and the University of Maryland,

Baltimore IRB for the University of Maryland Rehabilitation and Orthopaedic Institute (UM Rehab and Ortho), Baltimore, MD). In addition, the Department of Defense Congressionally Directed Medical Research Program (DOD CDMRP) IRB approved the total study. Several recruitment strategies were employed. The study physicians at each site were the primary source of identifying potential participants. In-services at each site were provided to educate other staff physicians about this study for referrals. Additionally, at each site IRB-approved flyers and brochures were distributed. Physician-referred potential participants, as well as those responding to IRB approved advertisements or the clinicaltrials.gov website listing (NCT02314221), were informed about the details and eligibility for the study. The targeted study population with chronic SCI (≥6 months) who were non-ambulatory and therefore used wheelchairs for mobility. The inclusion/exclusion criteria of this study are described below (**Table 1**).

INSERT **Table 1.**

2.2 Protocol

Participants were screened for eligibility after signing the informed consent form. Screening tests for eligibility included a complete history and physical examination incorporating the following: the International Standards for Neurological Classification of SCI (ISNCSCI) examination to determine level and completeness of injury, range of motion at the hips, knees and ankles bilaterally, Ashworth spasticity examination in the lower extremities, standing orthostatic tolerance test, and bone mineral density (BMD) scanning of bilateral knees (proximal tibia and distal femur) and hips (femoral neck and total hip) by Dual Energy X-ray Absorptiometry (DXA). Exclusion criteria for the BMD measurements have been described (**Table 1**).

Eligible participants were randomized within site to one of two groups for 12 weeks (three months): Group 1 received EAW first for 12 weeks then crossover usual activity (UA) for a second 12 weeks; Group 2 received UA first for 12 weeks then crossover to EAW for 12 weeks of training. The EAW arm consisted of EAW training, three sessions per week (4-6 h/week) for 36 sessions. The UA arm consisted of identification of usual activities for each participant and encouragement to continue with these activities throughout the 12-week UA arm. This study employed a randomized, crossover design with an EAW intervention arm and an UA arm which was designed to serve as a control arm for the secondary outcomes of the clinical/medical variables. The results are beyond the scope of the present manuscript and will be presented in a future work. As such, the UA arm was not intended to be used as a control comparison for the mobility outcome measures.

INSERT **Figure 1.**

Two powered exoskeleton devices (**Figure 1**) were used in this study, namely the ReWalk™ (ReWalk Robotics, Marlborough, MA) (21) and the Ekso™ (Ekso Bionics, Richmond, CA) (22). These powered exoskeletons were chosen because they were the only devices commercially available and FDA approved for use within rehabilitation centers at the time of study development. In addition, the ReWalk has been FDA approved for home and community use based on certain user characteristics and achievements within a supervised rehabilitation center (spinal injury level T7 to L5, walking velocity of ≥0.4 m/s over 10 meters and 6 minute walk distance ≥110 m) (23). Both devices have functional similarities, such as the required concurrent use of Lofstrand crutches or a wheeled walker in the case of the Ekso, and the need for the user to shift their weight in order to trigger sensors that in turn motor the hip. However, there are some notable differences in the devices' specifications such as the stepping pattern and the design such as the footplate. The maximum documented velocities for the devices are 0.80 m/s for the ReWalk and 0.45 m/s for the Ekso (21, 22). The Ekso device has a rigid back that provides thoracic support to accommodate participants who have less trunk stability such as

those with a low cervical (C) or high thoracic (T) level of injury. The footplate of Ekso has a sensor to detect weight shifts and assist with triggering the hip motors. The foot trajectory of the Ekso follows a semi-elliptical trajectory with a higher step height for foot clearance, leading to a marching style gait pattern. In the Ekso, depending on the functional abilities of the user, the level of device assist could be selected from the adaptive, maximal or fixed mode (22). In response to the participants' functional abilities, variable assistance constantly adapts motor output or a fixed level of assistance could be set for participants. The ReWalk gait paradigm is more of a swing pattern minimizing the step height but requiring more controlled balance to successfully achieve reciprocal stepping (21, 24). Thus, the ReWalk powered exoskeleton was chosen primarily for participants with injury levels at T3 and below who could perform weight shifting and clear each of the feet during stepping. Those with higher cord lesions and less trunk stability were more able to utilize the Ekso powered exoskeleton. Although choice of which device was commonly distributed based on level and completeness of injury, device selection was somewhat variable depending on the participant's preference and the clinical judgment of the study team. Both devices were used at JJPVAMC and Kessler, and the ReWalk was only used at UM Rehab and Ortho. Study-related serious adverse event (SAE) and adverse event (AE) tracking occurred throughout the study.

2.3 Training Sessions

Generally, within the first two sessions, standing balance skills were practiced and achieved prior to progression to walking skills. Walking skills began with unloading the right foot (both devices use the right leg to take the first step). Shifting weight onto the right foot and unweighing the left foot was the next step in the progression of walking. Continuous walking resulted from serially performance of the anterior-lateral diagonal shift onto the contralateral limb. Because this was an entirely new skill for the participants, mobility outcomes were not measurable at time 0 (baseline). It was important to determine how many participants could achieve successful EAW skills by 12 sessions to prove or disprove clinical relevance and to project progression by 36 sessions. Participants were asked to perform EAW sessions three times/week for 12 weeks. During each session, heart rate (HR), blood pressure (BP), total steps and rating of perceived exertion (RPE, by the Borg scale: from 6 to 20) (20, 25) were monitored. Additional details of the training program were presented previously (24, 26). Missed sessions (due to transportation, weather, etc.) were added on to the length of the training period when possible in order to achieve a total of 36 sessions. A modified Functional Independence Measure (FIM) was used to assess how much physical assistance from the trainer was provided to participants in order to complete mobility skills. The FIM scale (7: Complete Independence, 6: Modified Independence, 5: Supervision, 4: Minimal Assist, 3: Moderate Assist, 2: Maximal Assist, 1: Total Assist, 0: Activity does not occur) (27, 28) for level of assistance during EAW was used and ranged from 0 to 6. While a score of 7, complete independence, is a part of the FIM scale, it is not applicable for this study as all participants required the use of the exoskeleton, thus negating the ability of complete independence (27, 28).

2.4 Outcome Measures

A variety of walking assessments were employed to assess an individual's functional independence (29, 30). The 10-meter walk test (10MWT), which measures the time in seconds (s) taken to walk 10 meters, is a short distance performance measurement to determine functional mobility and vestibular function (31, 32). The six minute walk test (6MWT) is a submaximal exercise test that measures the distance in meters (m) traversed over six minutes and provides cardiopulmonary and musculoskeletal functional capacity information (32, 33). The timed-up-and-go (TUG) is the time from the starting in a seated position to stand-up, walk ten feet, turn around, walk back ten feet, and sit down. This

measurement was performed to assess fall risk and ability to balance and maneuver the device during the sit-to-stand and stand-to-sit procedures (32, 34). During all walking tests, level of assistance, balance maintenance, weight shifts, reciprocal stepping and functional mobility were observed and recorded. The three walking test measurements were performed during the 12th, 24th and 36th sessions.

2.5 Data Analysis

All statistical tests were set *a priori* at alpha = 0.05. Descriptive statistics and frequency distributions were used to describe the demographic data. All statistics analyses were completed using SPSS 23.00 or higher. The continuous variables were reported in mean plus or minus standard deviation. Total steps over 36 sessions and average of steps were calculated to determine participants' overall performance during this study. Because of differences in characteristics of devices, number of steps and velocity were categorized by devices. With each walking outcome (10MWT, 6MWT, and TUG), achievement of the hypothesized goals during the EAW intervention were reported as categorical data and presented as percent occurrence with 95% confidence intervals (CI). The hypotheses for significant positive changes at session 12 verses session 36 for the EAW walking tests were as follows: at session 12, 10% of participants would complete the 10MWT in ≤40 s and 20% of the participants would complete the 6MWT of ≥80 m and TUG in ≤90 s; at session 36, 70% of participants would complete the 10MWT in ≤40 s and 6MWT of ≥80 m and 60% of participants would perform the TUG in ≤90 s. Additional analyses were performed according to skill level of completing the 10MWT, 6MWT and TUG categorized by slow, medium, and fast velocity sub-groups. The velocity sub-groups were defined post hoc after the review of data starting with using the FDA criteria as the minimum velocity for "fast" and thus representing those with the greatest skill levels in the devices. The "medium" velocity was defined as those who could walk at speed and distance ranges that demonstrated some proficiency with the devices, and "slow" were those who were minimally able to use the devices. The velocities and distances by category for each walking test are provided (**Table 2**). To determine significant main effects, the mobility skills were evaluated for the three different time points using a repeated measure analysis of variance (ANOVA). Post hoc analysis were performed using paired t-tests to determine significance between sessions 12 and 36 for progression of participant performances on the mobility outcomes. Additionally, the TUG criterion was analyzed further and compared to the established FDA criteria for the 10MWT (speed ≥0.40 m/s) and 6MWT (distance ≥110 m).

INSERT **Table 2**.

Due to differences in characteristics of level of injury with residual muscle function, participants were sub-grouped according to the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI): Motor Complete Tetraplegia (C1-C8; American Spinal Injury Association impairment scale (AIS) A&B); Motor Incomplete Tetraplegia (C1-C8; AIS C&D); Motor Complete Paraplegia (T1-T12; AIS A&B); and Motor Incomplete Paraplegia (T1-T12; AIS C&D). A mixed model ANOVA was performed to determine significant main and interaction effects for the neurological classifications with respect to time (12, 24, and 36 sessions), number of steps per session block and mobility test (10MWT, 6MWT and TUG). Post hoc analyses were performed using a paired t-test to compare performances of walking assessments from 12 to 36 sessions within the level and completeness sub-groups.

3 RESULTS

3.1 Participants

A total of 50 individuals (average age 39±14years) completed 36 sessions of EAW training. Demographic information for gender, height, weight, duration of injury, level of injury, ISNCSCI classification and device used are summarized (**Table 3**).

INSERT **Table 3.**

The proportion of males (76%) and females included in this study corresponds with reported proportion of males (about 78%) and females in the United States SCI population (35). More individuals with paraplegia participated in this study mainly due to the need of arm and hand function in order to safely use crutches or a walker to maintain balance. Most participants with injury level of T3 or lower used the ReWalk and participants with injury level higher than T3 used the Ekso. However, there were some participants that were thought to be better suited for the other device. This resulted in a total of 28 participants that trained in the ReWalk and 22 that trained with the Ekso (**Table 3**).

There were no probably study related SAEs, but there were four possibly related SAEs. There were 49 total study-related AEs which included 39 skin abrasions/bruising, eight musculoskeletal/edema, and two falls. All study-related skin abrasions and musculoskeletal AEs were resolved, and participants continued in study. There were two falls during EAW, but no injuries occurred. Participants had appropriate HR and BP responses throughout the training sessions. RPE's during training ranged from very, very light (7) to very hard (17). There were no HR or BP-related AEs during EAW.

3.2 Total Steps Results

There were no order effects for Group 1 (immediate) versus Group 2 (delayed therapy) for total steps and for any of the walking test results. Descriptive statistics were used to determine mean and standard deviation for the cumulative total number of steps for all sessions. The average number of steps per session by session 36 for all participants (N=50) regardless of the device were 51,065±17,836 and the average steps per session were 1,420±491. The cumulative total number of steps taken across all sessions for all participants split by device is presented in relation to the fastest walking velocity achieved by 36 sessions (**Figure 2A**). The number of steps taken per session increased over all sessions for both devices. Participants who used the ReWalk took significantly less steps per session during the first 12 sessions than participants who used the Ekso. However, during the last 12 sessions (sessions 25-36) participants who used the ReWalk were able to take more steps per session than those who used the Ekso. Ultimately, participants who used the Ekso took more total overall steps than those who used the ReWalk. The first 6 sessions were pilot sessions where the participants were introduced to the device and had the actual training. The linear regressions of ReWalk (r^2=0.0956, y=27.90x+931.24) and Ekso (r^2=0.082, y=16.62x+1267.96) were performed with steps only on sessions 7-36. (**Figure 2B**, **Table 4**).

INSERT **Figure 2**, and **Table 4**

3.3 10 Meter Walk Test (10MWT) Results

At session 12, 92% of the participants performed the 10MWT in ≤60 s (≥0.17 m/s). Participants were able to perform the 10MWT with an average of 38.6±14.8 s by 12 sessions. The fastest 10MWT at 12 sessions was 20.0 s and the slowest was 83.4 s. By 36 sessions, 82% of the participants (compared with 62% at session 12) were able to perform the 10MWT in ≤40 s (≥0.25 m/s). The average 10MWT across all participants was 36.3±14.6 s by 24 sessions and 32.1±12.6 by 36 sessions. With 36 sessions of EAW training, 17 of 50 participants (34%) fulfilled the FDA 10MWT requirement (≥0.40 m/s) for personal use prescription (**Table 5**, **Table 6**).

INSERT **Table 5, and Table 6**

3.4 Six Minute Walk (6MWT) Test Results

Thirty-five participants (70%) were able to walk a distance equal or greater to 80 meters in 6 minutes by 12 sessions. Twenty-six participants (52%) achieved successful EAW training with or without minimal assistance by 12 sessions. Forty-eight participants (96%) were able to walk more than 50 meters (≥0.14 m/s) in the 6MWT and the average 6MWT was 99.8±35.1 m at 12 sessions. By 24 sessions, about half of the participants (24 participants, 48%) were able to meet FDA requirements for the 6MWT (≥110 m). By 36 sessions, 41 (82%) participants accomplished a 6MWT of ≥80 m (≥0.22 m/s). The average 6MWT was 111.9±42.6 m by 24 sessions and 125.3±40.4 m by 36 sessions. At 36 sessions of EAW training, 33 of 50 participants (66%) fulfilled the FDA requirement for the 6MWT (110 m) for personal use prescription (**Table 5, Table 6**).

3.5 Timed Up and Go (TUG) Test Results

At session 12, 46 participants (92%) performed the TUG in 120 s and 36 participants (72%) performed the TUG in less than 90 s. By Session 36, 84% of the participants were able to perform the TUG in less than 90 s (**Table 5, Table 6**).

3.6 Combined Walking Test Result Reporting

The number and percent of participants who were categorized by slow, medium, and fast walkers, their progression into the more skillful category over the three timepoints (sessions 12, 24, and 36) and number of participants who met FDA velocity criteria with categorized level of injuries are presented (**Table 5**). With 36 sessions of EAW training, 15 of 50 participants (30%) who used the ReWalk succeeded in achieving both of FDA speed requirements for personal use prescription (10MWT within 25 s or ≥0.40 m/s and 6MWT ≥110 m or ≥0.31 m/s). Those fifteen participants met the FDA requirement by 24 sessions. (**Table 5**).

The overall performance results from the different walking assessments at the three time points, the change in performance with additional training sessions and the range of speeds achieved respectively are presented (**Table 6**). A repeated measures ANOVA with a Greenhouse-Geisser correction determined that the mean of 10MWT, 6MWT, and TUG differed statistically between time points (10MWT: ($F(1.841, 88.372)$ 13.921, $p<0.0005$), 6MWT ($F(1.849, 88.734)=34.830$, $p<0.0005$), and TUG ($F(1.597, 68.665)=13.749$, $p<0.0005$). Paired-sample t-tests were conducted to compare the performance of tasks with the number of sessions. There were no significant differences in the 10MWT and the TUG from 12 to 24 sessions. However, there were significant differences in all mobility assessments, 10MWT, 6MWT and TUG from 24 to 36 sessions. There were also significant differences from 12 to 36 sessions. The mean values for the 10MWT (s), 6MWT (m), and TUG (s) walking assessments are presented (**Table 6**). The average results of all participants' walking velocities and distances from 12 to 36 sessions were significantly improved (**Table 6**).

Using the walking velocity, participants were divided into three sub-groups: slow, medium, and fast. The results of the TUG showed most of participants (82%) falling into the medium and fast velocity sub-groups at session 12. This improved with further training, as 86% of participants fell in the fast category at session 36. It was hypothesized that 20% of participants at 12 sessions and 60% of participants at 36 sessions would be able to perform the TUG in in ≤90 s. However, more than two thirds of participants (72%) accomplished TUG criterion at session 12 and 90% of participants did at session 36 in ≤90 s. Using the walking velocity from the 10MWT, the average TUG was calculated for the three velocity sub-groups and presented (**Table 7**).

INSERT **Table 7.**

3.7 Comparison between Devices

Due to the different characteristics between the ReWalk and Ekso, the results from the 10MWT, 6MWT and TUG were significantly different by device. By session 36, the fastest participant in the ReWalk performed the 10MWT in 16.6 s and slowest in 47.5 s, whereas in the Ekso the fastest was 21.0 s and the slowest was 63.7 s (**Table 4**, **Figure 3A**).

3.8 Effect of Neurological Deficit

Change in walking test performance was independent of neurological deficit. As mentioned previously, participants were divided by four neurological deficit sub-groups: Complete Tetraplegia (n=4); Incomplete Tetraplegia (n=10); Complete Paraplegia (n=27); and Incomplete Paraplegia (n=9). There were no significant differences between groups in terms of improvements from 12 to 36 sessions on the 10MWT (one-way ANOVA ($F(3, 45)=2.555$, $p=0.067$)), 6MWT(one-way ANOVA ($F(3, 45)=1.150$, $p=0.339$)), and TUG (one-way ANOVA ($F(3, 41)=1.115$, $p=0.354$)). Within level and completeness sub-groups, paired t-tests were used to compare the performance of tasks from 12 to 36 sessions. Overall, those with complete tetraplegia walked shorter distances in the 6MWT and took more time for the 10MWT and TUG at session 12. Participants with complete paraplegia performed the best among the sub-groups for 10MWT and 6MWT at session 12. From sessions 12 to 36, those with complete tetraplegia demonstrated no significant change in the 10MWT and 6MWT, however, there was significant improvement on TUG ($p=0.019$). All walking assessments were significantly improved from 12 to 36 sessions in the sub-groups of incomplete tetraplegia (10MWT: $p=0.020$, 6MWT: $p=0.011$, TUG: 0.046) and complete paraplegia (10MWT: $p=0.001$, 6MWT: $p<0.000$, TUG: $p=0.002$). Both those with incomplete tetraplegia and complete paraplegia demonstrated improvement in the TUG ($p=0.015$). Each sub-group's results of the walking tests are reported at 12, 24, and 36 sessions (**Figure 3B**).

INSERT **Figure 3.**

Using the average of the highest achieved number of steps per session block (between 1-12, 13-24, 25-36) split by tetraplegia/paraplegia and device, a repeated measures ANOVA with a Greenhouse-Geisser correction determined that the number of steps differed statistically between session blocks ($F(1.336, 66.477)=39.868$, $p<0.0001$). However, there were no significant differences among groups (tetraplegia/paraplegia and device) in term of number of steps from session block 1-12 (one-way ANOVA ($F(3, 46)=0.507$, $p=0.679$)), session block 13-24 (one-way ANOVA ($F(3, 46)=0.364$, $p=0.779$)), and session block 25-36 (one-way ANOVA ($F(3, 46)=0.437$, $p=0.728$)) (**Figure 4**).

INSERT **Figure 4.**

Regardless of device there was a positive relationship between the total cumulative number of steps taken during the 36 sessions and the maximum 10MWT velocity achieved. ReWalk users had a stronger relationship than those who used the Ekso ($p=0.0028$ vs. $p=0.093$) (**Figure 5**).

INSERT **Figure 5.**

4 DISCUSSION

More than half of the participants succeeded in achieving hypothesized milestones of ≤40s for the 10MWT, ≥80m for the 6MWT and ≤90s for TUG using EAW by session 12 and more than 80% of the participants achieved them by session 36. The rate of improvement in the walking tests was unrelated

to the level, completeness, or duration of SCI. These findings indicate that improving the skill level of using these devices as measured by walking velocity and distance is achievable across a broad spectrum of SCI level and completeness. Among neurological sub-groups, there were no significant differences in improvements on walking assessments. However, there were different outcomes. Participants with complete paraplegia performed better than participants with complete tetraplegia for all walking assessments (10MWT, 6MWT, and TUG) during all time points, but there were no differences between incomplete tetraplegia and incomplete paraplegia by session 36. This was expected, as those with lower levels of injury retain more residual motor control over their body, allowing them to control thoracic movements in the device, and translating into a better ability to perform exoskeletal ambulation. All participants in the complete tetraplegia sub-group used the Ekso for this study. Participants with lower level injury more often were placed in the ReWalk group. The study was not designed to determine differences in the mobility test outcomes between the Ekso and ReWalk groups. However, the faster walking velocities in the ReWalk may have been due to differences in level and completeness of injury as well as differences between the devices' engineering characteristics.

It may not be practical for clinicians to provide 36 sessions of EAW training due to limitations in payment for physical therapy visits, especially for personal prescription (i.e. use in the home and community). However, participants who met FDA criteria (10MWT: speed ≥0.40 m/s and 6MWT: distance ≥110 m) mastered weight shifting while standing and clearing the foot for stepping within 24 sessions. Nine participants achieved this by session 12, and 15 achieved it by session 24, and continued to meet these criteria at session 36. Future investigations focused on the different characteristics of the participants that would eventually obtain the skill needed to pass the FDA criteria should be explored. This could then be used to formulate a basic screening test to identify participants most likely to achieve the skills needed to pass the FDA criteria. Although the number of covered physical therapy visits vary depending on insurance, in general there is a cap at about 20 visits for Medicare and Medicaid patients. Our data suggest that the "sweet spot" for achieving the FDA criteria for most individuals falls between 12 and 24 visits, and is in alignment with current Center for Medicare and Medicaid Services (CMS) reimbursement guidelines.

There was high variability in the total number of steps taken in both devices. This may be accounted for by participant motivation, confidence in the device, stamina, and/or total time attended per session. All participants walked more steps with the progression of sessions. On average, Ekso users took more total cumulative steps than ReWalk users. However, the average number of steps during later sessions and within session 36 for ReWalk users were higher than those for Ekso users. Overall, the ReWalk users were faster than the Ekso users. While the participants who used the ReWalk were generally able to walk faster, this device was limited to those individuals with a greater amount of trunk stability (based on ISNCSCI level) and strong enough hand grasp to use crutches without any type of assistance. Greater trunk stability and strength likely improved balance and made the performance of weight shifting easier. Our findings suggest that the Ekso is easier to learn to use than the ReWalk initially, but once learned, the ReWalk user has more flexibility to control velocity and achieve faster walking speeds. The Ekso users increased the number of steps per session early in training with many reaching near their peak steps by session 12, and then they plateaued. On the other hand, the ReWalk users initially had less steps per session, but progressively increased by 36 sessions. This is likely a design feature, since the Ekso can provide more hip and knee flexion assistance than the ReWalk, making it easier to learn to use the device. Ekso users were able to achieve higher number of steps early and continue to steadily increase stepping throughout session progression. ReWalk use requires more trunk control over the device to successfully take steps and has a higher initial learning curve to achieve proper posture, weight shifting and stepping for many participants.

Even with the limitation of the device characteristics, there were two Ekso users in the sub-group of incomplete tetraplegia who met the fast walking velocity criteria. While these two Ekso users were daily power wheelchair users and had cervical levels of SCI, they were functionally able to walk slowly without the exoskeleton but with an assistive device such as a walker and with physical assistance from another person. Remarkably, these two Ekso users met all hypothesized criteria of nominal velocity and distance by session 12. Although the ReWalk requires trunk stability and strong enough hand grip to use the crutches, in the incomplete tetraplegia sub-group, there was one person who used the ReWalk and met the fast walking criteria (i.e., the FDA personal use criteria). In contrast, only three of the nine participants with low paraplegia made the FDA criteria in the sub-group of incomplete paraplegia who used the ReWalk. One participant with low paraplegia who used the ReWalk was partially able to meet FDA criteria (6MWT: distance ≥110 m), although the person had performed all hypothesized study criteria of nominal velocity and distance by session 12.

In summary, most participants who were unable to meet the fast walking velocity criteria were high level paraplegic individuals or were Ekso users. Unexpectedly, three participants with tetraplegia achieved the FDA criteria even with the severity of their neurological deficit. Based on these results, selection of the proper device should not solely be defined by neurological deficit, but other factors such as user preference, comfort and fit, and skill ability as determined by a short trial of devices. Although it is recognized that the number of sessions during training may be limited to policies of third-party payers or government insurance coverage, when possible, the duration and number of individualized EAW mobility training sessions should be determined by participants' stamina, motivation, residual function, and strength, and not just the level or completeness of the SCI.

To minimize trainer support and help the user gain reasonable independence, it is important to establish appropriate goal setting and time management for EAW mobility training. When personal prescription is the goal, an efficient EAW mobility skills training should be implemented. Following guidelines already established by our group, an effective exoskeleton training program necessitates all components of appropriate candidate selection, proper fitting of the device, a steady skill progression plan, and provision of participant assistance on areas of the body with intact sensation (24). As was the case in a previous report, we used these guidelines for this study. For the effective training program, sufficient education of the elements of EAW must be included. Upon completion of a training program, the user should be able to identify the safe environments for device use and operate the device in simulated or actual use environments representative of indicated environments and use (36). One of the most important elements is using the devices in actual environments such as noisy or crowded hallways, door navigation, and in spaces where turning is required. The EAW walking tests have been previously reported as reliable for testing achievements in mobility during the walking sessions and were accurate predictors of functional independence in the home and community (37). Our data confirm the reliability of these tests. There are no specific FDA criteria for the TUG although it is important to measure. The TUG is an essential skill because users must be proficient at standing up, walking, turning and sitting down. Our hypothesized minimal criteria for TUG success were ≤120 s by session 12 and ≤90 s by session 36 sessions. These criteria were easy to achieve compared to 10MWT and 6MWT. According to our average TUG data set of 10MWT, the TUG criterion to ≤75 s by session 12 and ≤60 s by session 36 sessions would be more discriminative. Thus, TUG ≤60 s would be suggested as a benchmark for skill proficiency. This more stringent TUG criterion could be used to support a skill level needed to take the device home, as it encompasses additional skills and is not solely focused on walking speed.

5 CONCLUSIONS

EAW training was demonstrated to be safe, feasible, and effective within a 36-session training timeline. Most participants improved their walking velocity and distances with the progression of sessions. The observed combination of how the Ekso triggers stepping and higher step clearance allowed participants to walk more successfully during the earlier sessions. Whereas, ReWalk users usually needed more sessions to learn appropriate weight shifting to better trigger stepping and to clear the foot during the swing phase, but once they learned this skill, they walked at faster velocities. More than half of the ReWalk users were able to meet FDA velocity criteria for personal prescription. Our data suggests that clinical programs can expect success rates of 58% by 12 sessions, 68% by 24 sessions and 78% by 36 session to achieve walking velocity medium and fast milestones of ≥0.25 m/s and ≥0.40 m/s respectively, regardless of level and completeness of injury or device used. The results from this study provide guidelines for estimating the potential of individuals with SCI to achieve proficient and safe EAW mobility skills for institutional and personal use of these devices.

6 CONFLICT OF INTERST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

7 FUNDING

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551 **Table 1. Enrollment Criteria**

Enrollment Criteria
Inclusion criteria: 1. Males and females, between 18-65 years old; 2. Traumatic or non-traumatic tetraplegia or paraplegia >6 months in duration; 3. Unable to ambulate faster than 0.17 m/s on level ground with or without an assistive device and are wheelchair-dependent for mobility; 4. Height 160 to 190 cm (63-75 in or 5'3" to 6'3" ft) 5. Weight <100 kg (<220 lb) 6. Able to hold the Lofstrand crutches or wheeled walker; and 7. Able to sign informed consent. *Exclusion criteria:* 1. Diagnosis of neurological injury other than SCI including: a. Multiple sclerosis, Stroke, Cerebral Palsy, Amyotrophic lateral sclerosis, Traumatic Brain injury, Spina bifida, Parkinson's disease, or b. Other neurological condition that the study physician considers in his/her clinical judgment to be exclusionary; 2. Severe concurrent medical disease, illness or condition; 3. Lower extremity fracture within the past 2 years; 4. Dual Energy X-ray Absorptiometry (DXA) results indicating a t-score below -3.5 at the femoral neck or the total proximal femur bone and knee bone mineral density (BMD) <0.60 gm/cm2; 5. Diagnosis of heterotopic ossification of the lower extremities which affect range of motion or proper BMD measurements; 6. Significant contractures defined as flexion contracture limited to 35º at the hip and 20º at the knee; 7. Untreated hypertension (SBP>140, DBP>90 mmHg); 8. Symptomatic orthostatic hypotension during standing that does not resolve after attempts at upright posture that were made over several days, and standing by the participant is deemed to pose a health risk, as determined by a physician, because of symptomatic orthostatic hypotension; 9. Systemic or peripheral infection; 10. A medical diagnosis in the patient chart of atherosclerosis, congestive heart failure, or history of myocardial infarction; 11. Trunk and/or lower extremity pressure ulcers; 12. Severe spasticity (defined by an Ashworth score of 4.0 across a lower extremity joint or clinical impression of the study physician or physical therapist); 13. Significant contractures defined as flexion contracture limited to 25º at the hip and knee; 14. Diagnosis of heterotopic ossification of the lower extremities which affect range of motion or proper measurement of BMD measurements; 15. Psychopathology documentation in the medical record or history of that may conflict with study objectives; 16. Pregnancy and/or lactating females. 17. Brain injury with score on mini-mental status examination less than 26 18. Diagnosis of coronary artery disease that precludes moderate to intense exercise; 19. Deep vein thromboses in lower extremities of less than 6 months duration; 20. Other illness that the study physician considers in his/her clinical judgment to be exclusionary.

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554 **Table 2. Exoskeletal-assisted Walking Velocity Categories for each of the Walking Tests**

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EAW Category	10MWT	6MWT	TUG
Slow	<0.25 m/s	<80 m	≥120 s
Medium	≥0.25 and <0.40 m/s	≥80 and <110 m	≥90 and <120 s
Fast	≥0.40 m/s	≥110 m	<90 s
10MWT=10-minute walk test, 6MWT=six-meter walk test, TUG=timed up and go, m/s=meters per second, m=meters, s=seconds			

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557 **Table 3. Demographic and Spinal Cord Injury Characteristics of the Total Study Group**

	Count (N) and Percent (%)		Demographic Characteristics				SCI Characteristics				
			Age	Height	Weight	Body Mass Index	Duration of Injury	Motor Complete (AIS A/B)		Motor Incomplete (AIS C/D)	
Category	N	*%*	Years	cm	kg	kg/m^2	Years	n	*%*	n	*%*
All	50	*100*	38.68±14.15	174.14±10.33	72.80±13.44	23.94±3.65	4.69±5.18	31	*62*	19	*38*
Males	38	*76*	39.87±14.78	178.00±8.52	76.80±11.67	24.24±3.44	5.37±5.63	26	*52*	12	*24*
Females	12	*24*	34.9±11.68	161.93±4.07	60.14±10.80	22.97±4.25	2.55±2.46	5	*10*	7	*14*
Para	36	*72*	37.44±12.68	173.85±10.08	72.16±13.40	23.83±3.80	4.99±5.78	27	*54*	9	*18*
Tetra	14	*28*	41.86±17.50	174.90±11.31	74.45±13.93	24.22±3.36	3.93±3.22	4	*8*	10	*20*
Males-Para	28	*56*	39.21±13.31	177.53±8.04	74.92±12.53	23.74±3.58	5.77±6.27	22	*44*	6	*12*
Males-Tetra	10	*20*	41.70±19.01	179.32±10.10	82.06±6.88	25.64±2.72	4.25±3.31	4	*8*	6	*12*
Female-Para	8	*16*	31.25±8.01	160.97±3.83	62.48±12.41	24.12±4.75	2.26±2.16	5	*10*	3	*6*
Females-Tetra	4	*8*	42.25±15.59	163.83±4.40	55.45±4.93	20.66±1.74	3.12±3.28	0	*0*	4	*8*
DOI > 2 years	26	*52*	38.15±13.39	174.97±8.60	74.79±12.98	24.37±3.67	7.85±5.55	16	*32*	10	*20*
DOI ≤ 2 years	24	*48*	39.25±15.20	173.25±12.05	70.65±13.87	23.47±3.65	1.28±0.54	15	*30*	9	*18*
ReWalk Para	27	*54*	35.63±11.07	174.32±9.77	72.59±13.38	23.88±4.04	5.73±6.43	20	*4*	7	*14*
ReWalk Tetra	1	*2*	31	188.96	84.37	23.88	5.00	0	*0*	1	*2*
Ekso Para	9	*18*	42.89±16.15	172.44±11.46	70.86±14.16	23.67±3.14	2.79±2.14	7	*14*	2	*4*
Ekso Tetra	13	*26*	42.69±17.92	173.89±11.10	73.69±14.19	24.24±3.49	3.85±3.33	4	*8*	9	*18*

Values represent means and (standard deviations); SCI=spinal cord injury; AIS=American Spinal Injury Association Impairment Scale; cm=centimeters; kg=kilograms; m=meters; G1=Group 1; G2=Group 2; Para=paraplegia; and Tetra=tetraplegia; EAW=exoskeletal-assisted walking; UA=usual activities; DOI=duration of SCI; ReWalk or Ekso user for the study as indicated.

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559 **Table 4. Walking Test Results by Devices (ReWalk and Ekso)**

Walking Test	Unit	Session 12		Session 24		Session 36	
		ReWalk	Ekso	ReWalk	Ekso	ReWalk	Ekso
10MWT	mean±SD (s)	29.51± 7.80	50.08±13.59	26.89±7.53	48.37±12.41	25.61±7.89	40.02±12.87
	Min - Max (s)	19.98-46.17	29.90-83.43	17.80-46.60	24.70-70.58	16.58-47.50	21.03-63.68
	mean±SD (m/s)	0.36±0.09	0.21±0.06	0.40±0.10	0.22±0.06	0.42±0.11	0.27±0.08
6MWT	mean±SD (m)	119.50± 32.68	74.78±18.01	136.85±38.50	80.05±20.93	148.44±32.99	96.79±28.94
	Min - Max (m)	59.70-168.40	43.75-112.70	40.70-196.40	46.53-141.80	65.40-206.60	54.60-162.00
	mean±SD (m/s)	0.33±0.09	0.21±0.05	0.38±0.11	0.22±0.06	0.41±0.09	0.27±0.08
	FIM 1 to 3 (n, %)	10 (38%)	9 (47%)	8 (30%)	4 (18%)	2 (7%)	2 (9%)
	FIM 4 to 5 (n, %)	14 (54%)	10 (53%)	14 (52%)	18 (82%)	15 (56%)	19 (86%)
	FIM 6 (n, %)	2 (8%)	-	5 (18%)	-	10 (37%)	1 (5%)
TUG	mean±SD (s)	67.17±15.25	90.33±18.33	69.69±33.82	81.95±24.11	53.41±11.24	72.22±20.47
	Min - Max (s)	43.72-108.78	64.90-134.37	34.59-155.24	39.05-144.60	35.15-81.50	42.61-103.38
	FIM 1 to 3 (n, %)	12 (52%)	17 (89%)	14 (58%)	12 (54%)	7 (27%)	7 (33%)
	FIM 4 to 5 (n, %)	10 (43%)	2 (11%)	8 (33%)	10 (46%)	12 (46%)	13 (62%)
		1 (5%)	-	2 (9%)	-	7 (27%)	1 (5%)
Total Steps by Sessions	mean±SD (#)	11,789±5,421	14,357±5,186	28,788±12,441	32,760±9,892	50,475±19,393	53,685±13,645
	Min - Max (#)	3,620-21,459	4,963-21,516	8,925-47,493	13,163-48,352	21,005-85,125	22,633-74,772
Grouped Total Steps[1]	mean±SD (#)	11,789±5,421	14,357±5,186	16,999±7,455	18,403±5,078	209,52±8,246	20,925±4,544
	Min - Max (#)	3,620-21,459	4,963-21,516	5,025-28,820	8,200-28,431	9,338-38,677	9,470-27,767
Steps within Session	mean±SD (#)	1,173±594	1,256±345	1,426±593	1,538±430	1,718±731	1,601±349
	Min - Max (#)	210-2,300	423-1,835	427-2,511	389-2,556	143-3,689	745-2,108

10MWT=ten meter walk test in meters (m); 6MWT=six-minute walk test in seconds (s); TUG=timed up and go in seconds (s); SD=standard deviation; m/s=meters per second; Min=minimum values achieved; Max=maximum value achieved; n=number and %=percent of participants who achieved the criteria; Com=motor complete; Tetra=tetraplegia; Inc=motor incomplete; Para=paraplegia; FDA=Food and Drug Administration; and FIM=Functional Independence Measure. Shaded areas indicate the FIM scores (FIM definitions are reported in Table 4) for 6MWT and TUG walking tests at 12, 24 and 36 sessions. Not all participants had a FIM score recorded during Sessions 12, 24, and 36.
[1]Grouped Total Steps were defined as grouped sessions: 1-12, 13-24 and 25-36.

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561 **Table 5. Number and Percent of Participants by Walking Velocity Categories**

	Outcomes	Velocity and Distance Categories	12 sessions n (%)	24 sessions n (%)	36 sessions n (%)
10MWT	**Primary**	≥0.17 m/s	46 (92%)		
	Primary	≥0.25 m/s	31 (62%)		41 (82%)
		Slow: <0.25 m/s	21 (42%)	16 (32%)	10 (20%)
		Medium: ≥0.25 to <0.40 m/s	16 (32%)	18 (36%)	22 (44%)
		Fast: ≥0.40 m/s	13 (26%)	16 (32%)	17 (34%)
	ReWalk Users Only Met FDA Velocity and Distance Criteria (10MWT: ≥ 0.40 m/s and 6MWT: ≥110 m)	Total (n=28)	9 (32%)	15 (54%)	15 (54%)
		Com Tetra (n=0)	n/a	n/a	n/a
		Inc Tetra (n=1)	1 (100%)	1 (100%)	1 (100%)
		Com Para (n=20)	6 (30%)	11 (55%)	11 (55%)
		Inc Para (n=7)	2 (29%)	3 (43%)	3 (43%)
6MWT	**Primary**	≥50 m	48 (96%)		
	Primary	≥80 m	35 (70%)		41 (82%)
		Slow: <80m	16 (32%)	14 (28%)	8 (16%)
		Medium: ≥80 to <110m	18 (36%)	12 (24%)	8 (16%)
		Fast: ≥110 m	16 (32%)	24 (48%)	33 (66%)
		FIM ≥4	26 (52%)	37 (74%)	45 (90%)
TUG	**Primary**	≤120 s	48 (96%)		
	Primary	≤90 s	36 (72%)		45 (90%)
		Slow: ≥120s	1 (2%)	5 (10%)	0 (0%)
		Medium: ≥90 to <120s	10 (20%)	5 (10%)	5 (10%)
		Fast: <90s	36 (72%)	38 (76%)	43 (86%)
		FIM ≥4	13 (26%)	20 (40%)	33 (66%)

10MWT=ten meter walk test in meters (m); 6MWT=six-minute walk test in seconds (s); TUG=timed up and go in seconds (s); SD=standard deviation; m/s=meters per second; Min=minimum values achieved; Max=maximum value achieved; n=number and %=percent of participants who achieved the criteria; Com=motor complete; Tetra=tetraplegia; Inc=motor incomplete; Para=paraplegia; and FDA=Food and Drug Administration. slow, medium, and fast velocity sub-groups. The velocity sub-groups were defined post hoc after the review of data.
Shaded areas indicate the Primary outcome results for each of the walking tests at 12 and 36 sessions. The FDA criteria was applied only to the ReWalk users because the Ekso is not indicated for personal use.

Modified Functional Independence Measurement (FIM) Scoring Key:
1 = Total Assist (performs less than 25% of task)
2 = Maximal Assist (performs 25% to 49% of task)
3 = Moderate Assist (performs 50%-74% of task)
4 = Minimal Assist (performs 75% or more of task)
5 = Supervision (cuing, coaxing, prompting)
6 = Modified Independence (no assistance, user may require extra time)
7 = Complete Independence (timely, safely, no assistance, no devices), albeit, not applicable in this study

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563 **Table 6. Walking Test Assessment Results**

Sessions		12	24	36
10MWT	mean±SD (s)	38.56±14.80	36.34±14.60	32.08±12.59 ¥Ŧ
	mean±SD (m/s)	0.30±0.11	0.32±0.12	0.36±0.12 ¥Ŧ
	Min - Max (s)	20.0-83.4	17.8-70.6	16.6-63.7
6MWT	mean±SD (s)	99.83±35.07	111.86±42.61 *	125.25±40.37 ¥°
	mean±SD (m/s)	0.28±0.10	0.31±0.12 *	0.35±0.11 ¥°
	Min - Max (s)	43.8-168.4	40.7-196.4	54.6-206.6
TUG	mean±SD (s)	78.01±20.28	75.31±30.10	62.03±18.55 ¥°
	Min - Max (s)	43.72-134.37	34.59-155.24	35.15-103.38

SD=standard deviation; m=meters; WT=walk test; min=minutes; TUG=timed up and go; sec=seconds; and m/s=meters per second. Sessions 12 vs.24: *$p<0.0001$; Sessions 12 vs. 36: ¥$p<0.0001$; and Sessions 24 vs. 36: Ŧ$p=0.0008$, °$p<0.0001$.

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566 **Table 7. Average TUG by Velocity sub-groups of 10MWT Speed**

			TUG					
			Session 12		Session 24		Session 36	
			N	mean±SD	N	mean±SD	N	mean±SD
10 MWT	≤0.25m/s	Slow	20	89.61±19.75	16	87.84±24.43	10	83.25±16.76
	0.25≤Speed≤0.4	Medium	15	74.93±18.40	17	76.24±32.01	23	59.48±16.43
	≥0.4m/s	Fast	12	62.53±9.84	15	60.88±28.77	15	51.80±10.32
10MWT=ten-meter walk test in meters, TUG=timed up and go in seconds, SD=standard deviation, m/s=meters per second. TUG was defined/calculated by the velocity sub-groups of 10MWT at 12, 24, and 36 sessions.								

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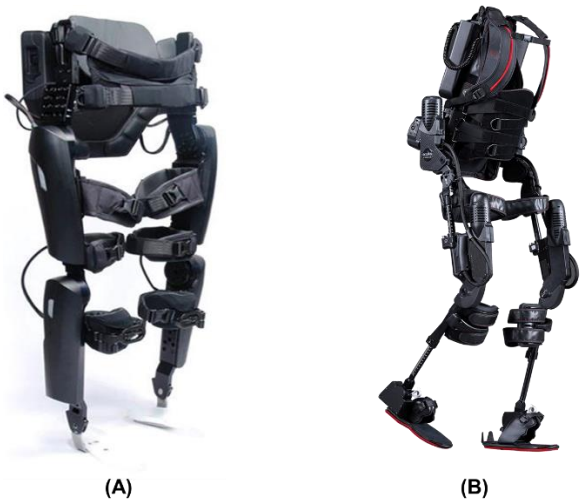

Figure 1. Exoskeletons used in this study: (A) ReWalk (ReWalk Robotics, Inc. Marlborough, MA, USA) and (B) Ekso GT (Ekso Bionics, Richmond, CA, USA)

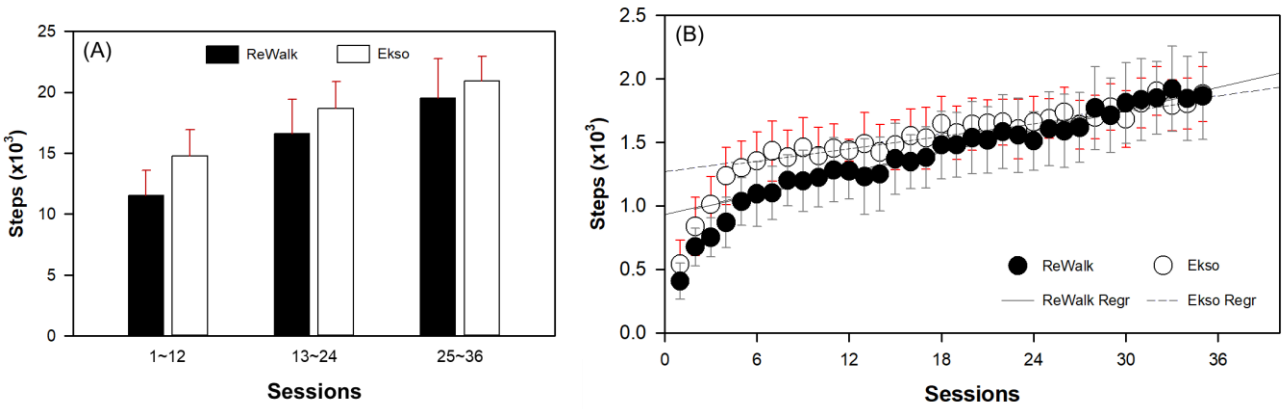

Figure 2. Results of average steps per session block (A) and by session (B) split by device. Both those using the ReWalk (r^2=0.0956, y=27.90x+931.24) and Ekso (r^2=0.082, y=16.62x+1267.96) took more steps during later sessions. Since the first 6 sessions were pilot sessions where the participants were introduced to the device, the linear regression models were performed with data from sessions 7 to 36. The Ekso users increased the number of steps per session by 6 to 12 sessions then plateaued, whereas, the ReWalk users initially had less steps per session, but progressively increased by 36 sessions.

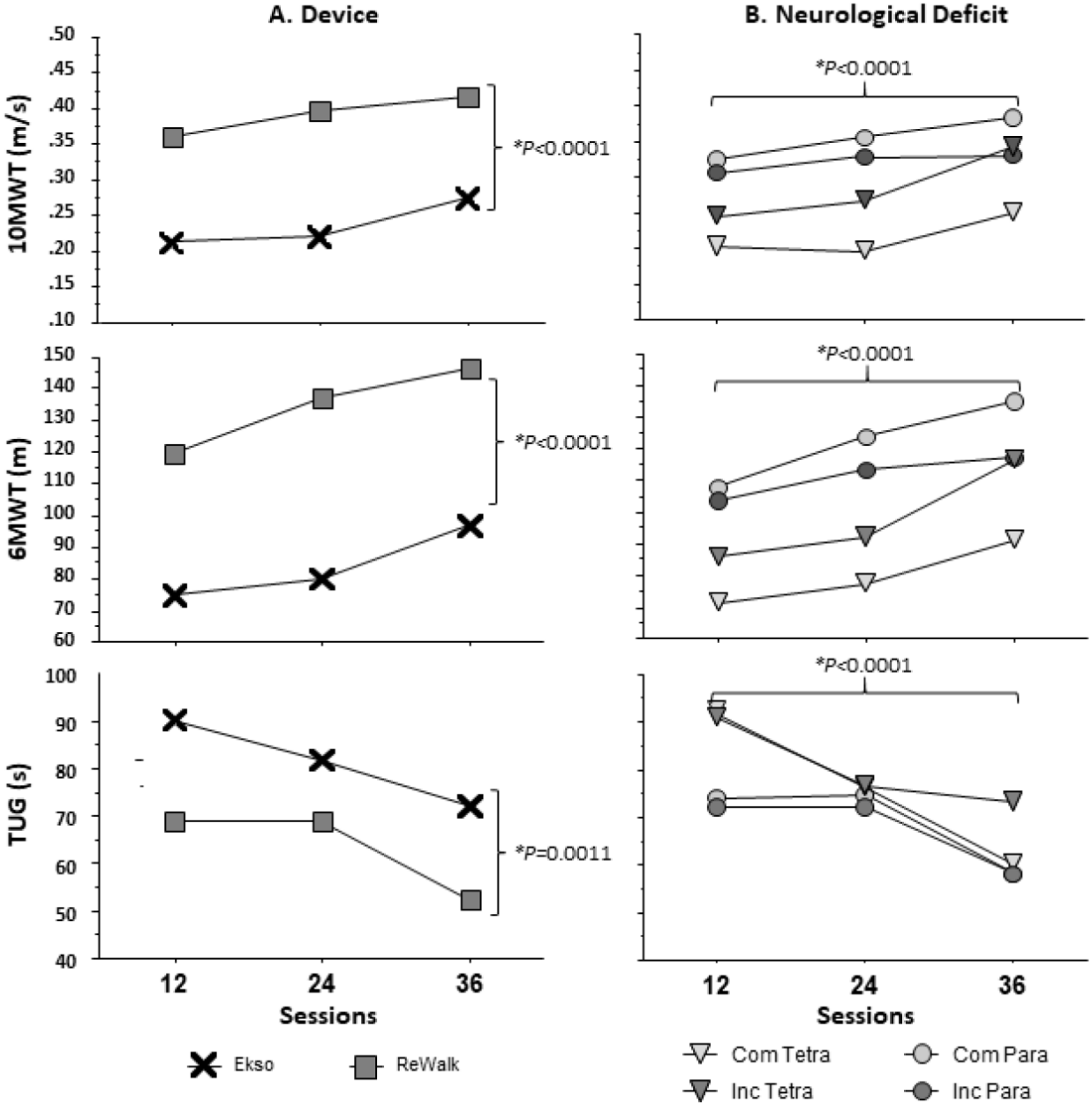

Figure 3. Results of Walking Tests across 12, 24, and 36 sessions by (A) device and (B) neurological deficit. Neurological deficit: Com Tetra (Motor Complete Tetraplegia); Inc Tetra (Motor Incomplete Tetraplegia); Com Para (Motor Complete Paraplegia); and Inc Para (Motor Incomplete Paraplegia). The main effects for neurological deficit (ANOVA: 10MWT (F(3, 46)=2.568, p=0.658), 6MWT (F(3, 46)=2.267, p=0.0933), TUG (F(3,46)=0.946, p=0.4263) were not significantly different, but the main effects for sessions and device (10MWT: p<0.0001, 6MWT: p<0.0001, TUG-12: p=0.0006, TUG-24: p=0.1299, TUG-36: p<0.0001) were statistically significant for each walk test as shown.

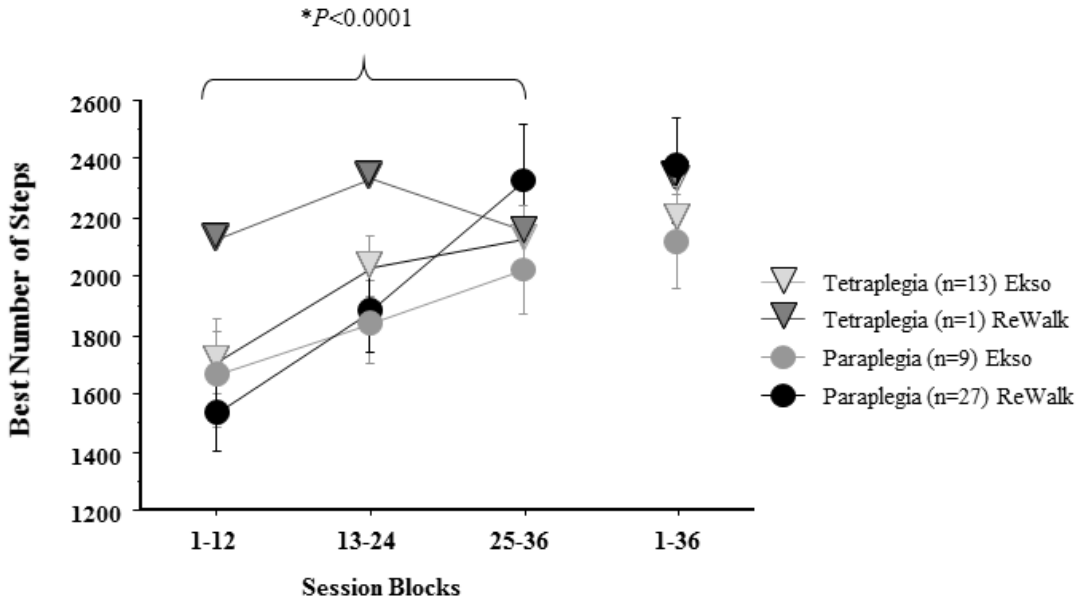

Figure 4. The average best number of total steps in a session block by level of SCI by device. The mean±standard error of the best number of total steps/sessions achieved during each 12-session block by Tetra (Tetraplegia), Para (Paraplegia) and by device (ReWalk, Ekso) are reported. The overall best number of steps in a single session is reported for 1-36. The number of steps significantly increased by session block, but no significant effects were found for combination of Tetra/Para and Device.

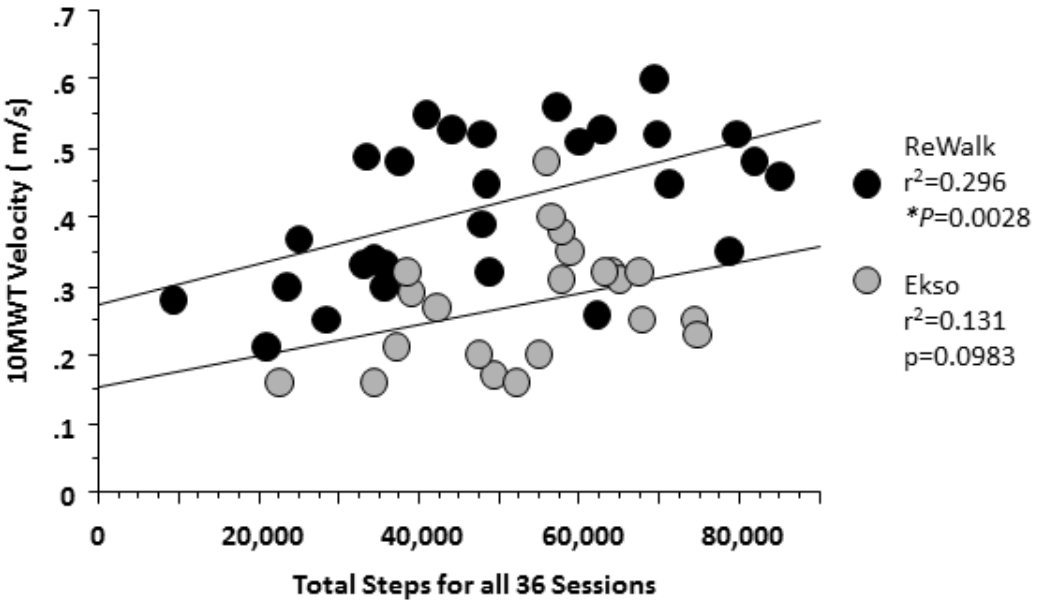

Figure 5. Relationship between the total steps and 10MWT velocity at 36 session by Device. At 36 sessions, participants using either device showed that with more steps taken there was an associated increase in 10MWT velocity. A significant relationship was noted for those who used the ReWalk (r^2=0.296, p=0.0028) and a trend for those who used the Ekso (r^2=0.131; p=0.0983).

Appendix 2. Statement of Work (SOW)

Table 1. Statement of Work	Timeline (months)	Percent Completed	Date Completed
Major Task 1: Study start-up and continuation administrative functions			
Subtask 1: Prepare Regulatory Documents and Research Protocol	1 to 3	100%	30-Dec-14
If Applicable, coordinate with Sites for CRADA* submission	n/a	n/a	n/a
If Applicable, coordinate with Sites for material transfer agreements (MTAs) or clinical trial agreements (CTAs) submission	n/a	n/a	n/a
If Applicable, coordinate with Sites for nondisclosure agreements (NDAs).	n/a	n/a	n/a
If applicable, indicate time required for submission and exemption of an Investigational Device Exemption (IDE) application to the U.S. Food and Drug Administration	1 to 3	100%	30-Dec-14
Refine eligibility criteria, exclusion criteria, screening protocol	1 to 3	100%	30-Dec-14
Finalize consent form & human subjects protocol	1 to 3	100%	30-Dec-14
Coordinate with Sites for Local IRBs** protocol submission	1 to 3	100%	30-Dec-14
Coordinate with Sites for University IRB** review	1 to 6	100%	30-Dec-14
Coordinate with Sites for Military 2nd level IRB** review (ORP/HRPO)	1 to 6	100%	30-Dec-14
Submit amendments, adverse events and protocol deviations as needed	As needed	100%	19-Aug-19
Coordinate with Sites for annual IRB** report for continuing review	Annually	100%	30-Sep-19
*Milestone Achieved: Local IRB** approval at BVMRF, UMROI, and KFRC*	3	100%	30-Mar-15
*Milestone Achieved: HRPO*** approval for all protocols and local IRB** approvals.*	6	100%	30-Mar-15
Subtask 2: Coordinate with Sites for job descriptions design	1 to 3	100%	30-Dec-14
Advertise and interview for project related staff	1 to 3	100%	30-Dec-14
Coordinate for space allocation for new staff	1 to 3	100%	30-Dec-14
Coordinate with Sites for hiring and training of staff	1 to 6	100%	30-Dec-14
Coordinate with Sites for providing standard training procedures among exoskeletal-trainers	1 to 6	100%	30-Dec-14
Milestone Achieved: Research staff hired and begin staff training	6	100%	30-Dec-14
Subtask 3: Facilitate and Coordinate with Sites for hiring, training, supervision and fidelity checks as needed for study participant attrition	6 to 48	100%	30-Dec-14
Coordinate multi-site training meeting for exoskeletal training, walking assessments standardization, data collection paper forms, data collection web-based forms, and use of log record	3 to 6	100%	9-Apr-15

Table 1. Statement of Work	Timeline (months)	Percent Completed	Date Completed
PI, Lead Engineer and Study Coordinator travel to Sites for staff training of procedures	3 to 6	100%	9-Apr-15
Coordinate multi-site training meeting for standardization of SCI QOL and bowel function assessments	3 to 6	100%	9-Apr-15
Coordinate multi-site training meeting for blood draw procedures (fasting condition, amounts, tubes, mailing to Quest Diagnostics)	3 to 6	100%	9-Apr-15
Coordinate multi-site training meeting for orthostatic tolerance test and Holter monitor assessment	3 to 6	100%	9-Apr-15
Coordinate with Sites for training to maintain 100% concordance with Study protocol	6 to 48	100%	9-Apr-15
Milestone Achieved: Maintained trained Study staff throughout duration of the clinical trial	6 to 48	100%	9-Apr-15
Major Task 2: Study recruitment and enrollment			
Subtask 1: Begin participant screening and consenting process	6 to 7	100%	11-May-15
Milestone Achieved: Participant #1 consented, randomized and enrolled at each Site	6 to 7	100%	14-Aug-15
Subtask 2: Randomize the first 4 participants at each respective Site	7 to 15	100%	22-Sep-15
Complete participant baseline evaluations	7 to15	100%	10-Oct-15
Complete participant weekly and monthly evaluations	7 to 15	100%	1-Apr-16
Complete participant post evaluations	7 to 15	100%	1-Apr-16
Milestone Achieved: 12 participants consented, screened, randomized, and enrolled for the study	7 to 15	100%	22-Sep-15
Subtask 3: Randomize the next 8/6/4 participants at each respective Site	16 to 24	100%	1-Oct-16
Complete participant baseline evaluations	16 to 24	100%	1-Oct-16
Complete participant weekly and monthly evaluations	16 to 24	100%	1-Mar-17
Complete participant post evaluations	16 to24	100%	1-Mar-17
Milestone Achieved: 30 participants consented, screened, randomized, and enrolled for the study	16 to 24	100%	1-Mar-17
Subtask 4: Randomize the next 8/6/4 participants at each respective Site	25 to 33	100%	1-Dec-17
Complete participant baseline evaluations	25 to 33	100%	1-Dec-17
Complete participant weekly and monthly evaluations	25 to 33	100%	1-Feb-18
Complete participant post evaluations	25 to 33	100%	1-Feb-18
Milestone Achieved: 48 participants consented, screened, randomized, and enrolled for the study	25 to 33	100%	1-Feb-18
Subtask 5: Randomize the next 8/4/4 participants at each respective Site	34 to 42	100%	1-Apr-18
Complete participant baseline evaluations	34 to 42	100%	1-Apr-18
Complete participant weekly and monthly evaluations	34 to 42	100%	19-Aug-19
Complete participant Post 1 evaluations	34 to 42	100%	19-Aug-19
Complete participant Post 2 evaluations	34 to 42	100%	19-Aug-19

Table 1. Statement of Work	Timeline (months)	Percent Completed	Date Completed
Milestone Achieved: 64 participants consented, screened, randomized, and enrolled for the study	34 to 42	100%	1-Apr-18
Subtask 6: Complete training and testing of any remaining participants at each respective Site	43 to 45	100%	19-Aug-19
Complete participant weekly and monthly evaluations	43 to 45	100%	19-Aug-19
Complete participant post evaluations	43 to 45	100%	19-Aug-19
Milestone Achieved: All participants at each respective Site completed	43 to 45	100%	19-Aug-19
Major Task 3: Review/complete data forms, data edits and entry			
Subtask 1: Ongoing review of data entry	7 to 45	100%	30-Sep-19
Subtask 2: Ongoing review of adverse and serious adverse	6 to 45	100%	30-Sep-19
Subtask 3: Ongoing data edits for missing values	7 to 45	100%	30-Sep-19
Subtask 4: Ongoing review for data entry errors	7 to 45	100%	30-Sep-19
Subtask 5: Complete all data entry	43 to 45	100%	30-Sep-19
Milestone Achieved: Data entry is completed in the data base	45	100%	30-Sep-19
Major Task 4: Review and analyze data			
Subtask 1: Review of data / analyze data	7 to 15	100%	1-Oct-15
Review data for problems	7 to 15	100%	1-Oct-15
Make necessary protocol adjustments (if needed)	7 to 15	100%	1-Oct-15
Perform sub analyses of walking tests and activity logs in first 12 participants	15 to 16	100%	1-Dec-15
Milestone Achieved: Data reviewed for necessary adjustment	7 to 15	100%	1-Oct-15
Subtask 2: Analyze preliminary data for primary outcomes	24 to 38	100%	30-Oct-19
Perform sub analyses of walking tests and activity logs in the first 20 to 38 participants	24 to 38	100%	30-Oct-19
Subtask 3: Submit abstracts with preliminary data for primary outcomes for national meetings	24 to 38	100%	30-Oct-19
Milestone Achieved: Abstract presentations of preliminary data	28 to 38	100%	30-Oct-19
Subtask 4: Analyze preliminary data for secondary outcomes	24 to 40	100%	30-Oct-19
Perform sub-analyses of body fat mass in the first 30 to 48 participants	24 to 36	100%	30-Oct-19
Subtask 5: Analyze preliminary data for exploratory outcomes	24 to 40	100%	30-Oct-19
In Group 1, perform sub analyses of body fat mass at 3 months follow-up in first 15 to 24 participants	24 to 40	100%	30-Oct-19
Perform sub analyses of blood pressure tests and Holter monitor in the first 30 to 48 participants	25 to 36	100%	30-Oct-19
Perform sub analysis of lipids, and endocrine outcome variables in the first 30 to 48 participants	25 to 36	100%	30-Oct-19

Table 1. Statement of Work	Timeline (months)	Percent Completed	Date Completed
Perform sub analyses of SCI-QOL and bowel function assessments in first 30 to 48 participants	25 to 36	100%	30-Oct-19
Major Task 5: Prepare and write manuscripts			
Subtask 1: Prepare and write manuscripts on full data set of participants	43 to 48	50%	Ongoing
Prepare and write manuscript of the primary outcomes	43 to 48	50%	Ongoing
Prepare and write manuscript of the secondary outcomes	43 to 48	50%	Ongoing
Prepare and write manuscripts for the exploratory outcomes	43 to 48	50%	Ongoing

Appendix 3. ASCIP Presentations (2017 and 2018)

Patient-reported bladder management improvements after exoskeletal-assisted walking

EunKyoung Hong, PhD[1]; Steven Knezevic, MS[1]; Pierre Asselin, MS[1]; Christopher M. Cirnigliaro, MS, CEP, CBDT[1]; Stephen Kornfeld, DO[1,2,5]; Peter H. Gorman, MD[3]; Gail Forrest, PhD[4]; William A. Bauman, MD[1,5,6]; Ann M. Spungen, EdD[1,5]

[1]Spinal Cord Damage Research Center, James J. Peters VA Medical Center, Bronx, NY; [2]Spinal Cord Injury Service, James J. Peters VA Medical Center, Bronx, NY; [3]University of Maryland Rehabilitation Research Center, University of Maryland Rehabilitation and Orthopedic Institute, Baltimore, MD; [4]Kessler Foundation, West Orange, NJ; [5]Departments of Rehabilitation Medicine, Icahn School of Medicine at Mount Sinai, New York, NY; [6]Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY

Background: People with spinal cord injury (SCI) have difficulties with bladder management [1-3]. Depending on level and completeness of SCI, the bladder may be spastic, flaccid or a combination, resulting in time consuming care and unwanted voiding accidents or leakage between catheterizations. The SCI-QOL Physical-Medical Health Domain has a short form for Bladder Management Difficulties [4]. The influence of physical activity on bladder management and function in persons with SCI is largely unknown. The purpose of this study was to determine the effect of the three months of Exoskeletal Assisted Walking (EAW) on bladder management/function in people with chronic SCI.

Design: A two-group, crossover study design was employed. **Methods**: Fourteen participants with SCI were randomized to either EAW or usual activity (UA) first followed by crossover to the other intervention. Participants received 36 sessions of EAW over 12 weeks followed or proceeded by 12 weeks of UA. Patient-reported outcomes from the bladder SCI-QOL questionnaire (PRO bladder) were performed three times (baseline, at crossover, and after completion). A five-point decrease was considered to be clinically meaningful. The data was analyzed using Wilcoxon Signed Rank test and paired T-Tests. **Results:** The mean age of all participants was 42±16 years and the average duration of injury was 5±5 years. There were four with tetraplegia and ten with paraplegia. A greater proportion of participants reported a clinically meaningful change in bladder management (50% vs. 14%, p=0.059) across their EAW intervention compared with their UA. Across the EAW intervention arm, there was an overall average of 3.1±3.4 points improvement (55.5±7.2 vs. 52.3±7.3, p=0.008) in the PRO bladder. There were no clinical differences between the tetraplegic and paraplegic individuals' responses.

Conclusion: Thirty six sessions of EAW was associated with improved bladder management. These improvements included less interference with sleep, worry about an accident, limits to independence, and less time for bladder management functions. This preliminary work has implications for unexpected urologic quality of life improvements associated with EAW.

Support: Department of Defense/CDMRP SC130234 Award: W81XWH-14-2-0170 and National Center for the Medical Consequences of SCI (B9212-C, B2020-C), James J. Peters VA Medical Center

References:

1. Costa, P., et al., *Quality of life in spinal cord injury patients with urinary difficulties.* European Urology, 2000. **39**(1): p. 107-113.

2. Benevento, B.T. and M.L. Sipski, *Neurogenic bladder, neurogenic bowel, and sexual dysfunction in people with spinal cord injury.* Physical Therapy, 2002. **82**(6): p. 601.

3. Walter, J.S., et al., *A database of self-reported secondary medical problems among VA spinal cord injury patients: its role in clinical care and management.* JRRD, 2002. **39**(1): p. 53.

4. Tulsky, D.S., et al., *Development and psychometric characteristics of the SCI-QOL Bladder Management Difficulties and Bowel Management Difficulties item banks and short forms and the SCI-QOL Bladder Complications scale.* JSCM, 2015. **38**(3): p. 288-302.

Learning Objective: To determine the effect of EAW on bladder management.

Increased serum high density lipoprotein after 36 exoskeletal-assisted walking sessions.

Steven Knezevic, MS[1]; Pierre Asselin, MS[1]; EunKyoung Hong, PhD[1]; Christopher M. Cirnigliaro, MS, CEP, CBDT[1]; Stephen Kornfeld, DO[2]; Peter H. Gorman, MD[3]; Gail Forrest, PhD[4]; William A. Bauman, MD[1,2,4,5]; Ann M. Spungen, EdD[1,5];

[1]Spinal Cord Damage Research Center, James J. Peters VA Medical Center, Bronx, NY; [2]Spinal Cord Injury Service, James J. Peters VA Medical Center, Bronx, NY; [3]University of Maryland School of Medicine, University of Maryland Rehabilitation and Orthopedic Institute, Baltimore, MD; [4]Kessler Foundation, West Orange, NJ; 5Departments of Medicine and Rehabilitation Medicine, Icahn School of Medicine at Mount Sinai, New York, NY

Background: Previous reports have shown that in persons with spinal cord injury (SCI), 64% with tetraplegia and 60% with paraplegia, had high density lipoprotein cholesterol (HDL-c) levels that were below 40 mg/dL; an independent risk factor for cardiovascular disease (CVD). As a result, persons with SCI have an increased risk for the development of CVD, which is one of the leading causes of death in the SCI population. Increased physical activity is an important factor associated with raising HDL-c levels. The effect of exoskeleton-assisted walking (EAW) on the lipid profile (LP) for serum total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL-c) and HDL-c was examined.
Design: Prospective observational study in participants with chronic SCI.
Methods: Fifteen participants with SCI were recruited for study. Participants trained in the exoskeleton for 36 one-hour sessions in 12 weeks. Fasting blood samples were collected to determine serum HDL-c levels before and after completion of the 36-training sessions. Fasting serum samples were sent to Quest Diagnostics Laboratory for analysis using an automatic assay analyzer. For purpose of this work, a minimally clinically significant change was considered to be ≥2.0 mg/dL. Absolute values and a pre-post percent change were used to determine a clinically significant change.
Results: Greater than half **(**8 of 15) of the participants demonstrated a change ≥2.0 mg/dl in serum HDL-c levels. In the majority, HDL-c improved by an average of 6.5±4.4 mg/dL (ranging from 2.0 to 14.0 mg/dL). Although not statistically significant, those who had an improvement in serum HDL-c level walked for an average of 10,195 more steps than those who had no change (45,200±13,883 vs. 55,395±21,802, ns). No other significant changes were noted in the other lipid variables of TC, TG, and LDL-c.
Conclusion: The present study suggests that EAW of 3x a week for 12 weeks provides sufficient activity to favorably impact HDL-c levels in approximately half of those studied. Identifying successful methods to promote increased physical activity, improve serum HDL-c levels, and thus, reduce CVD risk would be anticipated to result in a healthier lifestyle and greater longevity in persons with SCI.

Support: DOD/CDMRP Award: W81XWH-14-2-0170/SC130234; VA RR&D National Center for the Medical Consequences of Spinal Cord Injury (B9212-C, B2020-C), James J. Peters VA Medical Center.
References:

- Bauman, W. A., et al. "Depressed serum high density lipoprotein cholesterol levels in veterans with spinal cord injury." *Spinal Cord* 30.10 (1992): 697-703.
- Bauman, W. A., and A. M. Spungen. "Coronary heart disease in individuals with spinal cord injury: assessment of risk factors." *Spinal Cord* 46.7 (2008): 466-476.
- Brenes, Gilbert, et al. "High density lipoprotein cholesterol concentrations in physically active and sedentary spinal cord injured patients." *Archives of physical medicine and rehabilitation* 67.7 (1986): 445-450.

Learning Objectives: Identify the practical applications of exoskeletons as therapeutic and clinical rehabilitation tools.

FDA exoskeletal-assisted walking velocity: Who can get there?

EunKyoung Hong, PhD[1,2]; Steven Knezevic, MS[1]; Pierre Asselin, MS[1-3]; Stephen Kornfeld, DO[1-3]; Peter H. Gorman, MD[4]; Gail Forrest, PhD[5]; and Ann M. Spungen, EdD[1,2,6]

[1]Spinal Cord Damage Research Center, James J. Peters VA Medical Center, Bronx, NY; [2]Department of Rehabilitation Medicine, Icahn School of Medicine at Mount Sinai, New York, NY; [3]Spinal Cord Injury Service, James J. Peters VA Medical Center, Bronx, NY; [4]University of Maryland School of Medicine, University of Maryland Rehabilitation and Orthopedic Institute, Baltimore, MD; [5]Kessler Foundation, West Orange, NJ; [6]Departments of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY

Background: Clinical exoskeletal-assisted walking (EAW) programs have been established throughout the country. There are many unknown challenges to set up these programs such as: addressing staffing needs; determining the number of sessions to achieve the walking velocity milestone for ambulation; and the FDA criteria for personal use prescription in the home and community with these devices. The purpose of this study was to determine the proportion of participants who achieved successful EAW velocities at 12 and 36 sessions. **Design:** A three-site, multi-center, on-going interventional study in participants ≥6 months post SCI is being performed. **Methods**: To date, 29 participants completed 36 sessions of EAW training, three sessions per week (4-6 h/week) in a 12-week period. The 10 meter walk test (seconds) (10MWT), 6-minute walk test (meters) (6minWT), and the timed-up-and-go (seconds) (TUG) are reported at 12 and 36 sessions. A nominal velocity and distance milestones of 0.25m/s (V_N) for 10MWT and at least 90m (D_N) in 6min were chosen by other studies [1] as a minimal safe speed of ambulation. For personal use prescription, the FDA requires 0.40 m/s (V_{FDA}) and 110m (D_{FDA}). **Results:** The mean age and duration of injury of all participants were 40±14 years and 4±4 years, respectively. By 12 sessions: for the 10MWT, 16 of 29 (55%) participants succeeded V_N and 5 (17%) achieved V_{FDA}; 12 (41%) accomplished D_N and 6 (21%) D_{FDA}; 20 participants (69%) performed the TUG test in <90s. By 36 sessions: 22 (76%) accomplished V_N and 8 (28%) V_{FDA}; for the 6minWT, 22 (76%) accomplished D_N and 19 (66%) D_{FDA}; and the TUG had 20 (69%) participants in <90s. **Conclusion**: More than one-half of the participants achieved V_N and less than one-fifth, achieved V_{FDA} by 12 sessions, the proportion of participants to achieve these same goals were greater by 36 sessions. It may not be practical for clinicians to provide 36 sessions of EAW training. Therefore, when personal prescription is the goal, an EAW basic mobility skills screening test should be developed to identify those participants most likely to achieve FDA skill criteria in a feasible number of sessions as per the resources of the clinic setting and the availability of the client. **Support**: Department of Defense/CDMRP SC130234 Award: W81XWH-14-2-0170 and National Center for the Medical Consequences of SCI (B9212-C, B2020-C) at the James J. Peters Veterans Affairs Medical Center.

References:

1. Louie, D.R., J.J. Eng, and T. Lam, *Gait speed using powered robotic exoskeletons after spinal cord injury: a systematic review and correlational study.* Journal of neuroengineering and rehabilitation, 2015. **12**(1): p. 82.

Walk Test	Criteria	12 Sessions	36 sessions
		n (%)	n (%)
10MWT	≥0.25 m/s	16 (55%)	22 (76%)
	≥0.40 m/s*	5 (17%)	8 (28%)
6minWT	≥90 m	12 (41%)	22 (76%)
	≥110 m*	6 (21%)	19 (66%)
TUG	<90 s	20 (69%)	25 (86%)

* FDA criteria for Personal use

Learning Objective:

The audience will learn about three walking tests that are used in EAW

The audience will learn the walking skills achieved in 12 sessions

The audience will learn about the resources for conducting an EAW program for FDA personal use criteria.

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Category - Robotics and exoskeletons

HDL-c changes after 50,000 steps in a powered exoskeleton.

Steven Knezevic, MS1; EunKyoung Hong, PhD1; Pierre Asselin, MS1; Christopher M. Cirnigliaro, MS, CEP, CBDT1; Stephen Kornfeld, DO2; Peter H. Gorman, MD3; Gail F Forrest, PhD4; William A. Bauman, MD1,2,4,5; Ann M. Spungen, EdD1,5

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Background: Serum high density lipoprotein cholesterol (HDL-c) levels below 40 mg/dL (an independent risk factor for cardiovascular disease) have been reported in 64% of persons with tetraplegia and 60%, with paraplegia. As a result of this lipoprotein abnormality, as well as other risk factors, persons with spinal cord injury (SCI) have an increased risk for the development of cardiovascular disease (CVD), which is one of the leading causes of death in the SCI population. Increased physical activity is an important factor to increase serum HDL-c levels. Previously, we reported HDL-c levels in 15 participants after 36 sessions of exoskeletal-assisted walking (EAW). We now report on 12 additional (N=22) participants after 36 sessions of EAW.
Design: Prospective, three-site (ongoing) interventional study in participants with chronic SCI.
Methods: Twenty-two participants with chronic SCI have completed the study to date. Participants trained in the exoskeleton for 36, one-hour sessions over a 3 month period. Fasting blood samples were collected to determine serum HDL-c levels before and after completion of the training sessions. Serum samples were sent to Quest Diagnostics Laboratory for analysis using an automatic assay analyzer. The absolute change of the serum HDL-c value in a given participant was used to determine a clinically significant change. The minimal significant change accepted for clinical significance was ≥2.0 mg/dL.
Results: Eleven of 22 (50%) participants had an increase in serum HDL-c of ≥2.0 mg/dL after the EAW intervention (mean±SD = 7±4 mg/dL). Additionally, participants who completed ≥50,000 total steps, 64% (7 of 11) versus 36% (4 of 11) demonstrated a clinically significant change in serum HDL-c levels. In those who completed ≥50,000 total steps, HDL-c improved by an average of 3.5±6.0 mg/dL (range: 2.0 to 14.0 mg/dL) and had slightly more number of steps per session than those who did not have a clinically significant change (1,475±541 vs. 1,230±575 steps, p=0.26). No significant changes were noted in the serum triglycerides or low density lipoprotein cholesterol.
Conclusion: In the majority of persons with chronic SCI, EAW of at least 50,000 steps performed in 3 sessions a week, for 12 weeks, resulted in favorable changes in the serum HDL-c. The observed increase in serum HDL-c would be anticipated to reduce the risk for the development of CVD.
Support: DOD/CDMRP Award: W81XWH-14-2-0170. VA RR&D National Center for the Medical Consequences of Spinal Cord Injury (B9212-C, B2020-C), James J. Peters VA Medical Center.

References:

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- Bauman, W. A., and A. M. Spungen. "Coronary heart disease in individuals with spinal cord injury: assessment of risk factors." *Spinal Cord* 46.7 (2008): 466-476.
- Brenes, Gilbert, et al. "High density lipoprotein cholesterol concentrations in physically active and sedentary spinal cord injured patients." *Archives of physical medicine and rehabilitation* 67.7 (1986): 445-450.

Learning Objectives: To identify the effect of exoskeletal-assisted walking on the lipoprotein profile in persons with chronic SCI.

Appendix 4. Invited Presentations 2016-2019

INVITED LECTURES/PRESENTATIONS

	Date	Type	Institution	Topic
1	11/5/2019	Exoskeleton Workshop	International Spinal Cord Society (ISCoS) Annual Meeting 2019, Nice, France	Results from a randomized clinical trial of 36 sessions of exoskeletal-assisted walking in persons with chronic SCI
2	10/22/2019	Invited Roundtable Panelist & Chair	Society for Neuroscience (SfN) Annual Meeting, Chicago, IL	Exoskeletons and Robotics for Rehabilitation
3	9/24/2019	Invited Speaker	École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland	Exoskeletal-Assisted Walking for Persons with Paralysis from Spinal Cord Injury
4	9/24/2019	Invited Speaker	Swiss Paraplegic Center Nottwil, Switzerland	Exoskeletal-Assisted Walking for Persons with Paralysis from Spinal Cord Injury
5	3/13/2019	Invited Speaker	Department of Biomedical Engineering, Stevens Institute of Technology, Hoboken, NJ	Exoskeletal-Assisted Walking for Persons with Paralysis from Spinal Cord Injury
6	2/13/2019	Invited Panelist	NIH SCI 2020: Launching a Decade for Disruption in Spinal Cord Injury Research	Session 6: Technological Facilitation; Prosthetic and Robotic Interventions and Therapies Across the Spectrum of mild/moderate/severe SCI (NIBIB/NCMRR/NINDS)
7	10/18/2018	Invited Speaker	4th International Symposium on Wearable Robotics (WeRob2018), Pisa, Italy	Update from on-going exoskeletal-assisted walking clinical trials in chronic and acute spinal cord injury
8	10/12/2018	Invited Speaker	Robotics, Rehabilitation and Caregiving, Brecia, Italy	Exoskeletal-assisted walking for persons with Spinal Cord Injury
9	6/19/2018	Invited Presentor	VA Office of Research and Development Science Fair for Congress, Rayburn Building, Capitol Hill, Washington, DC	Exoskeletal Technologies for people with walking impairments
10	5/2/2018	Workshop Co-Leader	American Spinal Injury Association Annual Scientific Meeting, Rochester MN	Craig H. Neilson Foundation sponsored workshop on Bowel and Bladder Assessments for SCI
11	4/24/2018	Invited Speaker	U.S. Army Natick Soldier Research, Development & Engineering Center (NSRDEC) and will be held at the Lord Community Center at NSRDEC in Natick, MA	Office of the Under Secretary of Defense for Research and Engineering (OUSD R&E), Department of Defense (DoD) Exoskeleton Technical Interchange. "Exoskeletal-assisted walking for persons with Spinal Cord Injury"

INVITED LECTURES/PRESENTATIONS

	Date	Type	Institution	Topic
12	2/13/2018	Invited Speaker	VA Breakout at American Academy of Orthotists & Prosthetists Annual Meeting, New Orleans, LA	Exoskeletal-assisted walking for persons with paralysis: What we know and don't know
13	11/28/2017	Invited Speaker	Grand Rounds, Department of Rehabilitation Medicine Icahn School of Medicine at Mount Sinai, NY, NY	Exoskeletal-assisted walking for persons with paralysis: What we know and don't know
14	11/5/2017	Invited Speaker	The 2017 International Symposium of Wearable and Rehabilitation Robotics (WeRob2017), Houston, TX	Advising the organizing committee on the scientific content of the symposium and reviewing abstracts for platform and poster presentations.
15	10/24/2017	Invited Speaker	Internationa Spinal Cord Society Annual Scientific Meetg, Dublin, Ireland	Exoskeletal-Assisted Walking in Acute Inpatient and Chronic Outpatient Spinal Cord Injury Rehabilitation.
16	9/3/2017	Invited Speaker	ASCIP 2017 by: ASCIP Program Committee, Denver, CO	Donald Munro Lecture: Exoskeletal-assisted walking for persons with paralysis: What we know and don't know
17	2/24/2017	Invited Speaker (via Skype)	ReWalk International Conference 2017 sponsored by: Fondazione Teresa Camplani Casa di Cure Domus Salutis, Italy	Tools for clinical, functional and instrumental evaluation of effects of ReWalk on human functioning
18	11/5/2016	Invited Plenary Speaker	American Association of Anatomists NY Regional Meeting, Columbia University, NY, NY	Exoskeletal-assisted walking for persons with Spinal Cord Injury
19	10/26/2016	Invited Investigator	Department of Defense, Congressionall Directed Medical Research Program, Invited Investigators Meeting, Fort Deitrick, MD	A Randomized, Crossover Clinical Trial of Exoskeletal-Assisted Walking to Improve Mobility, Bowel Function, and Cardiometabolic Profiles in Persons with SCI
20	10/25/2016	Invited Subject Matter Expert (SME)	US Senate, Russell Building, Capitol Hill, Washington, DC	Senate Veterans Affairs Committee Roundtable on exoskeleton suits
21	09/4-7/2016	Invited Panelist	Academy of Spinal Cord Injury Professionals (ASCIP) 2016 Educational Conference, Nashville, TN	Point - Counter Point Panel: Exoskeleton devices: when is the best time to use and who is best for the prescription of these devices?

INVITED LECTURES/PRESENTATIONS

	Date	Type	Institution	Topic
22	8/3/2016	Invited Speaker	VHA Prosthetics Leadership Board (Web-based presentation)	Overview: Cooperative Studies Program and CSP #2003
23	7/12/2016	Invited Speaker	Rehabilitation Engineering & Assistive Technology Society of America (RESNA) and Nat. Coalition for Assistive and Rehab Tech (NCART) Promoting Access to Assistive Technology 2016 Conference, Arlington, VA	Panel: Research as the Key to Improving Assistive Technology
24	5/11/2016	Invited Speaker	Current Advances in SCI Research Symposium, Dept. of Neurological Surgery Rutgers New Jersey Medical School, State University of New Jersey, Newark, NJ	Exoskeletal-Assisted Walking for Persons with Spinal Cord Injury: Lessons Learned to Date
25	4/29/2016	Invited Speaker	VISN 4 Medical Grand Rounds, VA Pittsburgh Health Care System, Pittsburgh, PA	Exoskeletal-assisted walking for persons with paralysis: What we know to date.

Appendix 5. NIH SCI2020 Presentations Slides

SCI 2020: Launching a Decade for Disruption in Spinal Cord Injury Research

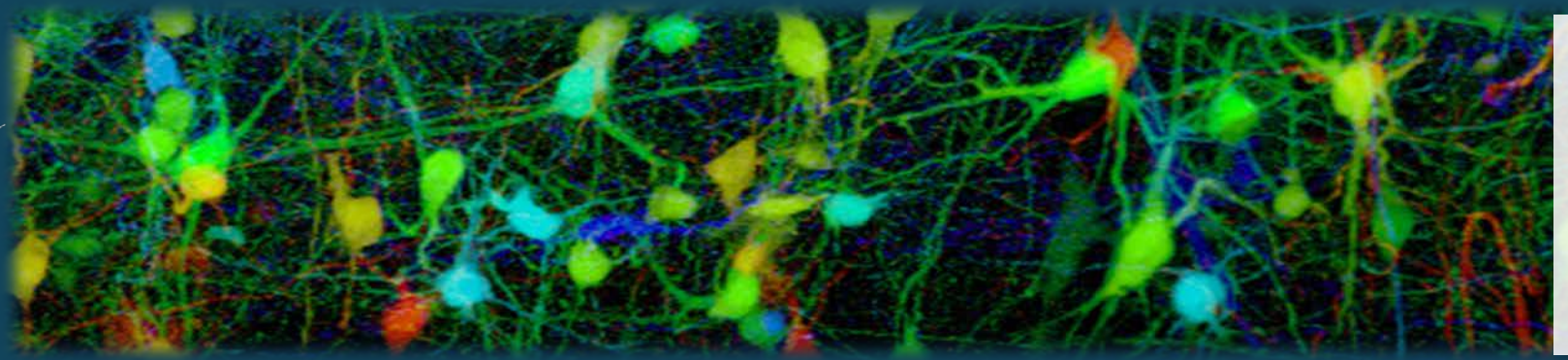
February 12-13, 2019 Bethesda MD

Overview of Science and Status of Exoskeleton Technology for SCI

Ann M. Spungen

James J. Peters VA Medical Center, Bronx, NY

Icahn School of Medicine at Mount Sinai, NY, NY



National Institutes of Health

Session # 6 - Disclosures

- **No industry support**
- **Peer-reviewed funding:**
  - VA RR&D National Center for the Medical Consequences of Spinal Cord Injury(PI: Spungen) (B9212-C, B2020-C).
  - VA CSP Exoskeletal-Assisted Walking in Persons with SCI: Impact on Quality of Life, (Chair: Spungen) (CS#2003).
  - DOD CDMRP Clinical Trial A Randomized, Crossover Clinical Trial of Exoskeletal-assisted Walking to Improve Mobility, Bowel Function and Cardio-Metabolic Profiles in Persons with SCI (PI: Spungen; Co-PI Peter Gorman) (W81XWH-14-2-0170, SC130234).
  - NJCSCR Non-ambulatory SCI Walk Using a Robotic Exoskeleton: Effect on Bone and Muscle (PI: Gail Forrest) (CSCR13IRG013).

OVERVIEW AND STATUS

2010 Exoskeletons for overground walking debut in the U.S.

2014 FDA created a new Class 2 for exoskeletons for SCI.

First device was approved for institutional and personal use.

2015 CDMRP/DOD funded a 3-site hospital-based RCT (40 completed, 11 to be completed May 2019).

VA CSP funded a 6-site home-use RCT.

2016 Two more devices for overground walking received FDA market clearance for institutional use; one also for personnel use.

VA SCI Services approved exoskeletons for clinical prescription.

VA CSP added 4 sites to ongoing RCT.

2018 VA CSP added 5 sites to ongoing RCT; VA CSP #2003 15-site RCT (101 S's randomized to date, enrollment ends in September 30, 2021).

2019 Nearly 50 papers published to date on exoskeletons for SCI.

OVERVIEW AND STATUS

Most papers report walking velocities, gait characteristics and engineering aspects

Published Research findings:

- Reduced body fat mass & increased lean mass (Spungen et al, *Topics in Spinal Cord Injury Rehabilitation* 2013; Karelis et al, *Journal of Rehabilitation Medicine 2017*)
- Weight bearing in the device is near 100% of total body weight (Fineberg et al *J Spinal Cord Med.* 2013;)
- Seated forward and lateral stability was improved (Tsai et al, *WeRob* 2017)
- Positive energy expenditure (Asselin et al, *J Rehabil Res Dev.* 2015; Evans et al, *Topics in Spinal Cord Injury Rehabilitation* 2015; Lefeber et al, *Assistive Technology,* 2017)
- Walking velocity ranges 0.20 to 0.72 m/s (Yang et al, *Spinal Cord Inj Rehabil.* 2015)
- Neuromuscular activation, body mechanics and postural control (Ramanujam et al, *WeRob* 2018; Gad et al, *Frontiers in Neuroscience* 2017)

No significant bone changes have been reported to date.

LESSONS LEARNED

- ✓ **Not everyone with SCI wishes to use one of these devices.**
- ✓ **Not everyone who wants to use one is eligible:**
  - **Contraindications for weight bearing activities such as:**
  - **extreme bone loss, severe spasms and contractures limit eligible users.**
- ✓ **Distance from training centers is a barrier.**
- ✓ **Of those who are eligible and are taught to use them, not everyone becomes a proficient and safe user of the devices.**
- ✓ **With the same training protocol, some people have better responses than others.**
- ✓ **Exoskeletons appear to be good for therapy and exercise, but remain limited for mobility (i.e. people still need a wheelchair).**
- ✓ **Technology (and FDA) requires a companion – which can result in a loss of independence for a self-sufficient person with SCI.**
- ✓ **Time commitment for training and lack of a companion limits many would be users.**
- ✓ **In those who are successful users of these devices, most users have high satisfaction.**

PRIORITIES, FUTURE APPLICATIONS & DIRECTIONS

(Reported from users, researchers and clinicians)

Safety as the priority; improve the technology for:

- Use on stairs
- Decreased time and staff needed for training
- Minimized need for a companion
- Minimize need for crutches/walkers
- Better walking on ramps/uneven surfaces
- Stopping ability
- Walking speed
- Portability

Use in daily life for:

- Community mobility
- Variable walking speeds
- Extended battery life
- Wearable under clothes
- Ability to toilet in the devices

Potential use for ambulation therapy after:

- Epidural stimulation, Brain Computer Interface, Stem cell therapy, or
- Other interventions that require significant hours of walking rehabilitation.
  - Need for improved variable gait assistance

CHALLENGES

Who are best candidates and for which device(s)?

How much training is needed to become proficient?

What tests should be used to define proficiency?

Will these devices be used in the home/community?

What is the dosing level to get positive changes and to maintain them for any of the health- or medical-related outcomes?

Can these devices be used safely and effectively in acute inpatient rehabilitation to prevent or mitigate secondary adverse changes from SCI?

Appendix 6. Upcoming presentations

American Academy of Physical Medicine and Rehabilitation (AAPM&R) Annual Assembly 2020 Abstract (November 12-15, 2020)

CONTROL ID: 001

TITLE: Indications and Contraindications for Exoskeletal-Assisted Walking in Persons with Spinal Cord Injury Using Evidence-Based Data

AUTHORS: Ann M. Spungen, Pierre K. Asselin, Eun-kyoung Hong, Karen Jones, Peter H. Gorman, Gail F. Forrest, Kousick Biswas, and William A. Bauman

INSTITUTIONS: 3 Rehabilitation/Medical Centers and 15 VA Medical Centers

PRESENTATION TYPE: Abstract

CURRENT CATEGORY: General Rehabilitation

ABSTRACT BODY:

Objective: To report eligibility screening and participant completion/withdrawal results from two different multicenter trials for exoskeletal-assisted walking (EAW) and the associated complications/successes in conducting this research.

Design: Descriptive report of two separate randomized controlled trials.

Setting: Outpatient medical centers.

Participants: Spinal cord injury (SCI) >6 months and wheelchair use for mobility. One investigation included 50 participants over 3 sites and the other investigation included 100 participants over 15 sites.

Interventions: 36 sessions of EAW and 20-30 sessions of EAW followed by 4 months of home-use of a powered exoskeleton

Main Outcome Measures: Number and reasons for screen failures and withdrawals; number and types of adverse events.

Results: In the 3-site trial: 104 were consented/screened, 71 were randomized and 50 completed 36 sessions of EAW. Of the screen failures (33/104), the top 5 causes were: 1) low bone mineral density (BMD) or fracture history (15/104, 14%), 2) schedule conflicts (7/104, 7%), 3) contractures (5/104, 5%), 4) level of SCI or weight (3/104, 3%) and 5) medical complications (2/104, 2%). The reasons for withdraws (21/71, 30%): compliance/schedule conflicts (14/71, 20%) and medical problems (7/71, 10%). In the 15-site trial (to date): 294 were consented/screened, 38 declined to continue, 100 were randomized and 151 screen-failed. Reasons for screen failures were: 1) fracture history/low BMD (75/294, 25.5%), 2) contracture/spasticity (37/294, 12.6%), 3) anthropometric/weight (29/294, 9.9%), 4) failed EAW basic skills test (23/294, 7.8%), 5) medical complications (21/294, 7.1%), 6) level of SCI/neurological status (19/294, 6.5%), 7) no companion/home not suitable (n=16 5.4%), and 8) physician discretion (7/294 2.4%).

Conclusions: The most frequent contraindications found for EAW were fracture history or low BMD. Using standardized screening for hip and knee BMD measurements across all sites, no study-related long bone fractures occurred; but two calcaneal fractures presented during first training sessions.

Level of Evidence - Abstract Submission Role: Level I

Financial Disclosures: None

The International Symposium

on Wearable Robotics

October 13-16, 2020

Title of the proposed Special Session

Evidenced-based Indications/Contraindications for, and Potential Benefits of, Exoskeletal-Assisted Walking in Persons with Spinal Cord Injury

Abstract (1974 of 2000 max. characters)

Introduction: Persons with spinal cord injury (SCI) have adverse secondary medical and quality of life changes as a result of immobilization. A person with SCI who has completed rehabilitation after injury and is unable to ambulate receives a wheelchair as standard of care for mobility. Powered exoskeletons are a technology that has become available (mainly for research purposes) in the USA since 2010. They offer an alternate form of mobility by providing an external framework for support and computer controlled motorized hip and knee joints to assist with standing and overground ambulation. Restoration of ambulatory function and the potential for the subsequent improvement of health has long been a goal of SCI rehabilitation research. The use of powered exoskeletons may offer a partial solution to this problem. Three studies (ClinicalTrials.gov Identifiers: NCT02314221, NCT02658656, NCT02324322) have been underway to determine the safety and efficacy of the use of these devices in chronic SCI. *Methods:* Data from these three clinical trials will be reviewed. In the populaiton with chronic SCI: 50 participants have been completed for 36 sessions, 160 participants have been randomized to a four-month home-use trial, and 12 participants have completed 100 sessions. *Purpose:* The goals of this Special Session are to report the findings from these trials as evidenced-based data on the following topics: 1) Eligibility criteria for screening successes and failures. An emphasis on the importance of bone mineral density and fracture screening, case reports of fractures and serious advers events from these studies will be presented and discussed; 2) Training approaches, number of sessions and recommended modifications for the devices; 3) Biomechanical attributes, walking and mobility skills achieved and characteristics of successful users; and 4) Systemic immune and medical/health responses to overground walking in these devices.

Topics

Safety and efficacy of the use of exoskeletons in persons with spinal cord injury

Invited Speakers (at least 4 speakers)

1. Ann M. Spungen, EdD, Professor, Department of Rehabilitation and Human Performance, Icahn School of Medicine at Mount Sinai, NY, NY and James J. Peters VA Medical Center, Bronx, NY, USA
2. Gail F. Forrest, PhD, Associate Professor, Rutgers New Jersey Medical School, Director, Center for Spinal Stimulation; Associate Director Center for Mobility Engineering and Rehabilitation. Kessler Foundation, NJ, USA

3. Pierre K. Asselin, MS, Assistant Professor, Department of Rehabilitation and Human Performance, Icahn School of Medicine at Mount Sinai, NY, NY and James J. Peters VA Medical Center, Bronx, NY, USA
4. Ona Bloom, PhD, Professor, The Feinstein Institue for Medical Research; Zucker School of Medicine at Hofstra Northwell, NY, USA
5. Peter Gorman, MD MS, Associate Professor, Department of Neurology, University of Maryland School of Medicine and Chief, Division of Rehabilitation Medicine, University of Maryland Rehabilitation and Orthopaedic Institute, Baltimore, MD, USA

Invited Papers (at least 4 papers)

1. Ann M. Spungen, EdD, **Title: Indications and contraindications for exoskeletal-assisted walking in persons with spinal cord injury.** Icahn School of Medicine at Mount Sinai, NY, NY and James J. Peters VA Medical Center, Bronx, NY, USA
2. Gail F. Forrest, PhD, **Title: The biomechanical attributes, walking and mobility skills achieved and characteristics of successful exoskeletal-assisted walkers.** Rutgers New Jersey Medical School and Kessler Foundation, NJ, USA
3. Pierre K. Asselin, MS, **Title: Training approaches, number of sessions and recommended modifications for the devices.** Icahn School of Medicine at Mount Sinai, NY, NY and James J. Peters VA Medical Center, Bronx, NY, USA
4. Ona Bloom, PhD, **Title: The impact of exoskeletal-assisted walking on systemic inflammation.** Zucker School of Medicine at Hofstra Northwell, NY, USA
5. Peter Gorman, MD, **Title: Medical/health-related responses to exoskeletal-assisted walking: responders vs. non-responders.** University of Maryland School of Medicine and University of Maryland Rehabilitation and Orthopaedic Institute, Baltimore, MD, USA

Organizers

Ann M. Spungen EdD, Peter Gorman MD MS, Pierre Asselin MS, and Gail Forrest PhD

Contact

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Appendix 7. Quad Chart

A Randomized, Crossover Clinical Trial of Exoskeletal-assisted Walking to Improve Mobility, Bowel Function and Cardio-Metabolic Profiles in Persons with SCI

Insert ERMS/Log Number and Task Title (Unknown)
SC130234

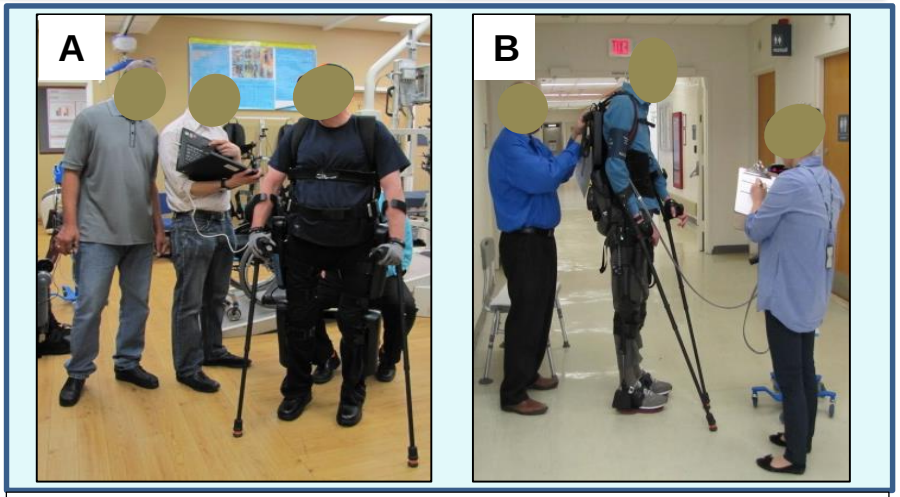
PI: Dr. Ann M. Spungen **Org:** Bronx Veterans Medical Research Foundation **Award Amount:** $1,555,889

Study/Product Aim(s)

The **primary objectives** are to achieve successful walking skills in the exoskeletal-assisted walking devices for an extended period of time and at specific velocities and distances over the course of 36 sessions in three months in people with chronic SCI who are wheelchair dependent for community mobility. The **secondary objectives** are to determine if this amount of walking is effective in improving bowel function and body composition.

Approach

A two-group, Phase III randomized clinical trial (RCT) is being performed using a crossover design with an exoskeletal-assisted walking intervention. Group 1 serves as the intervention follow-up to assess retention/non-retention of change due to the intervention on the outcome variables. Group 2 will serve as a lead-in to assess stability of the outcome variables prior to the intervention.



Panel A – Participant with motor incomplete paraplegia (T4, AIS A) walking in the ReWalk exoskeleton. Panel B - Participant with motor incomplete tetraplegia (C5, AIS D) walking in the Ekso exoskeleton.

Timeline and Cost

Activities	FY 16	17	18	19
Text (12 participants enrolled)	Completed			
Text (30 participants to be enrolled)		Completed		
Text (48 participants to be enrolled)			Completed	
Text (64 participants to be enrolled)				Completed
Estimated Budget ($K)	**$352**	**$371**	**$381**	**$263**

Updated: (December 19, 2019)

Goals/Milestones

FY16 Goals – Startup, kick-off and training meetings at each site; Initiate participant enrollment
☑ Q3-Participant screening and enrollment of 4 participants/site.
FY17 Goal – Continued participant screening and enrollment
☑ Q3-Participant screening, recruitment and enrollment of 8 (JJPVAMC), 4 (KF) and 6 (UMROI) participants per respective sites.
FY18 Goal – Continued enrollment
☑ Q1-Participant enrollment of 8 (JJPVAMC), 4 (KF) & 6 (UMROI)
☑ Q4-Participant enrollment of 8 (JJPVAMC), 4 (KF) & 4 (UMROI)
FY19 Goal – Completion of data collection
☑ Q2-Completion of participants
☑ Q3 to Q4 -Completion of data edits, analysis; Manuscript preparation
Comments/Challenges/Issues/Concerns - None
Budget Expenditure to Date
Projected Expenditure FY16 (Year 1): Approximate $352,335
Actual Expenditure FY16 (Year 1): Approximate $352,335