PROTOCOL COVER PAGE

PROTOCOL NAME

Restoring walking with a powered exoskeleton after spinal cord injury

PROTOCOL IDENTIFYING NUMBER

Pro00036789

PROTOCOL VERSION DATE

November 5, 2019

GENERAL INFORMATION

Name and address of the sponsor of the study

University of Alberta

Name and address of the person authorized to sign the protocol and amendments

Dr Jaynie Yang
3-75 Corbett Hall
8205 114 St NW, Edmonton

Name and address of study monitor

Not required

Name, title, address and telephone number(s) of the medical expert for the trial

Name and title of the investigator(s) and sub-investigators responsible for the trial with address and phone number(s)

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Name and addresses of the clinical laboratories and/or other institutions involved in the trial

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Study Summary

Title	Restoring walking with a powered exoskeleton after complete and severe incomplete spinal cord injury
Short Title	Restoring walking with a powered exoskeleton after spinal cord injury
Protocol Number	Pro00036789
Phase	*Clinical study phase (e.g. Phase 1, 2, 3 or 4)*
Methodology	Prospective cohort study with a single, 12-week intervention.
Study Duration	Minimum of 3 years
Study Center(s)	Single centre.
Objectives	To determine: 1. the training dosage required for walking proficiency 2. the sensory and motor changes in the nervous system induced by training 3. the functionality of the device in a home like environment
Number of Subjects	12
Diagnosis and Main Inclusion Criteria	Complete or severe incomplete spinal cord injury
Study Product, Dose, Route, Regimen	ReWalk Exoskeleton
Duration of administration	1 hour /day, 4 days /week for 12 weeks
Reference therapy	None
Statistical Methodology	

Table of Contents

List of Abbreviations

(e.g.)

ICH	International Conference on Harmonisation
CRF	Case Report Form
GCP	Good Clinical Practice
HREB	Health Research Ethics Board

1 Background

1.1 Investigational Agent

ReWalk powered exoskeleton

1.2 Preclinical Data

1.3 Risk/Benefits

1) The risk of pressure sores on the legs or pelvis that are in contact with the exoskeleton is possible, because of the tight fit of the device to the body similar to braces, and rubbing of the skin as they walk.
2) The risk of falling, which occurs whenever an individual is upright, with the associated risk of bruises or fractures.
3) The risk of physical fatigue as individuals will be more active than they were previously.
4) Fainting is a possibility because of postural hypotension, especially at the beginning of training.
5) Transcranial magnetic stimulation (TMS) carries the risk of seizures. The risk is greatest with repetitive stimulation which we will not be using.

1.4 Dose Rationale

Participants will train for one hour per sessions 4 days a week.

1.5 Trial Conduct

This study will be conducted in compliance with the protocol approved by the University of Alberta Health Research Ethics Board (HREB), and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the HREB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the HREB as soon as possible.

1.6 Population

Individuals with complete or sever incomplete spinal cord injury who are unable to walk at a pace of greater than 0.4m/s

1.7 Literature

1. Yang, J.F., et al., *Repetitive mass practice or focused precise practice for retraining walking after incomplete spinal cord injury? A pilot randomized clinical trial.* Neurorehabil Neural Repair, 2014. **28**(4): p. 314-24.
2. Spungen, A.M., et al., *Exoskeletal-assisted walking for persons with motor-complete paraplegia*, in *STO-MP-HFM-228*. 2013: Neuilly-sur-Seine, France. p. 6-1 - 6-14.

3. Yang, J.F. and K.E. Musselman, *Training to achieve over ground walking after spinal cord injury: a review of who, what, when, and how.* J Spinal Cord Med, 2012. **35**(5): p. 293-304.
4. van Hedel, H.J., M. Wirz, and V. Dietz, *Assessing walking ability in subjects with spinal cord injury: validity and reliability of 3 walking tests.* Arch Phys Med Rehabil, 2005. **86**(2): p. 190-6.
5. van Hedel, H.J., M. Wirz, and A. Curt, *Improving walking assessment in subjects with an incomplete spinal cord injury: responsiveness.* Spinal Cord, 2006. **44**(6): p. 352-6.
6. Stein, R.B., et al., *Long-term therapeutic and orthotic effects of a foot drop stimulator on walking performance in progressive and nonprogressive neurological disorders.* Neurorehabil Neural Repair, 2010. **24**(2): p. 152-67.
7. Musselman, K., et al., *Spinal cord injury functional ambulation profile: a new measure of walking ability.* Neurorehabil Neural Repair, 2011. **25**(3): p. 285-93.
8. Musselman, K.E. and J.F. Yang, *Spinal Cord Injury Functional Ambulation Profile: a preliminary look at responsiveness.* Phys Ther, 2014. **94**(2): p. 240-50.
9. Gorassini, M.A., et al., *Changes in locomotor muscle activity after treadmill training in subjects with incomplete spinal cord injury.* J Neurophysiol, 2009. **101**(2): p. 969-79.
10. Manella, K.J. and E.C. Field-Fote, *Modulatory effects of locomotor training on extensor spasticity in individuals with motor-incomplete spinal cord injury.* Restor Neurol Neurosci, 2013. **31**(5): p. 633-46.
11. Benz, E.N., et al., *A physiologically based clinical measure for spastic reflexes in spinal cord injury.* Arch Phys Med Rehabil, 2005. **86**(1): p. 52-9.
12. Melzack, R., *The McGill Pain Questionnaire: major properties and scoring methods.* Pain, 1975. **1**(3): p. 277-99.
13. Widerstrom-Noga, E., et al., *The International Spinal Cord Injury Pain Basic Data Set (version 2.0).* Spinal Cord, 2014. **52**(4): p. 282-6.
14. Ellaway, P.H., et al., *Development of quantitative and sensitive assessments of physiological and functional outcome during recovery from spinal cord injury: a clinical initiative.* Brain Res Bull, 2011. **84**(4-5): p. 343-57.
15. Thomas, S.L. and M.A. Gorassini, *Increases in corticospinal tract function by treadmill training after incomplete spinal cord injury.* J Neurophysiol, 2005. **94**(4): p. 2844-55.
16. Lam, T., et al., *A systematic review of functional ambulation outcome measures in spinal cord injury.* Spinal Cord, 2008. **46**(4): p. 246-54.
17. Musselman, K.E. and J.F. Yang, *Spinal Cord Injury Functional Ambulation Profile: A Preliminary Look at Responsiveness.* Phys Ther, 2013.

2 Trial Objectives

The objectives are to determine the walking outcomes and clinical benefits achievable with an exoskeleton and study the neuroplasticity induced by training with an exoskeleton. We hypothesize that training with the exoskeleton will allow: 1) participants with severe SCI to gain functional, independent walking, 2) improvements in trunk balance in sitting and standing for all users, 3) a reduction in spasticity as seen by clinical measures of spasticity and electrophysiological measures of reflex function. We will also measure neuroplasticity in sensory pathways from the legs to the brain with electrical perceptual threshold test, and motor pathways from the brain to the trunk, with motor evoked potentials (MEPs) in trunk muscles in response to transcranial magnetic stimulation (TMS) over the primary motor

cortex. We will further quantify pain and depression using standard questionnaires. Finally, we will determine qualitative impressions using a personal interview.

3 Trial Design

3.1 Primary Study Endpoints/Secondary Endpoints

September 30, 2018

3.2 Study Design/Type

As this will be the first Canadian trial of an exoskeleton, we are proposing a single group, interventional study.

3.3 Randomization

All participants will receive the intervention

3.4 Maintenance

None.

3.5 Trial Treatment

Trial treatment will consist of instruction in the basic functions of the exoskeleton (Donning, doffing, sit to stand, standing balance and stepping). Participants will begin walking indoors on smooth floor. They will aim to practice the increase proficiency, speed and distance walked. When deemed safe, participants will walk on more challenging terrain and attempt higher level skills.

3.6 Duration

Participants will train 4 times a week for 12-14 weeks with a goal of approximately 50 sessions. Each session will aim for 1 hour of time in the device.

3.7 Discontinuation

Training will be suspended should individuals experience any adverse events such as skin breakdown. Medical attention will be sought when necessary and the participation will be discontinued if the issue cannot be resolved.
In the event of any serious adverse event which is likely to recur we will consider halting the trial.

3.8 Product Accountability

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3.9 Data Identification

None

4 Selection and Withdrawal of Subjects

4.1 Inclusion Criteria

1. Chronic (>1y after injury), non-progressive SCI
2. Body weight ,82 kg
3. Lower extremity length appropriate for ReWalk
4. Uses a manual wheelchair as primary mode of mobility
5. Able to use forearm crutches
6. Able to train 4 days/week
7. Written approval for participation from primary care physician

4.2 Exclusion Criteria

1. Comorbidities that interfere with training or measurements such as head injury
2. Bone fracture within last 2 years
3. Low bone density (femoral neck t-score <-3)
4. Hip or knee contractures >10°
5. Ankle plantarflexion contracture
6. Active pressure sores
7. Severe spasticity

4.3 Subject Withdrawal

Participants may withdraw at any time without consequence simply by informing study staff of their desire to withdraw. Data from any completed portion will be kept

4.4 Treatment of Subjects

Partcipants will engage in training as described in 3.5 four days a week for one hour per sessions

4.5 Medication

Participants will be advised to continue with their regular medication routine. They will be asked to inform the study team of any changes to their medications, in particular pain medication and medication for spasticity as these may impact the outcome measures.

4.6 Monitoring for subject compliance

All training will be supervised by a physical therapist or a certified trainer

5 Assessment of Efficacy

5.1 Efficacy Parameters

Primary Outcome Measure: The Physiological Cost Index will be estimated during the 6 minute walk test and during an identical test during wheelchair propulsion as follows:

$$\text{PCI (heartbeats/m)} = \frac{\text{(Active HR – Resting HR)}}{\text{Average locomotor speed}}$$

Heart rate (HR: beats/min) is recorded every 30 seconds with a HR monitor with Bluetooth connection to a cell phone (POLAR H7, Polar Electro Canada, Lachine, QC). Resting HR is the average HR during the last 2 min of a 5-min sitting period immediate preceding the active period, and Active HR is the last 2 min of walking or wheeling for 6 min. Walking speed is averaged over the 6 min. For the ReWalk, the device is donned before the measures in sitting. PCI will also be measured for walking without the ReWalk in participants who can do so. The caveat with using the PCI for people with SCI is that the level of injury (i.e., at or above T6) could affect the sympathetic drive, and so the comparisons should only be made within a participant. Hence, the relative effort of walking is expressed as a ratio of PCI for walking over PCI for wheelchair propulsion in the same individual.

Secondary Outcome Measures:

1. *Measures of training*
   The total step count, walking distance, average walking speed, steps per bout of walking without stopping, and duration of the session will be documented at every training session. The number of consecutive steps is counted manually for each sequence of walking, and the average number of steps/bout is used to quantify walking skill, because novice walkers often unintentionally stalled the device with inadequate toe clearance.
2. *Walking:*
   Walking speed over 10 m will be recorded during continuous walking in the ReWalk (i.e., modified 10-Meter Walk Test [10MWT]), because starting and stopping the device added unnecessary variability. The 6-Minute Walk Test (6MWT) will be performed in a 40 m hallway. The maximum walking distance without a rest, for up to 1 hour, will be measured indoors on a smooth floor at the end of training.
3. *Manual muscle strength*:
   The Upper and Lower Extremity Muscle Strength (UEMS and LEMS) were estimated with the scale from the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) (37) by a physical therapist (DL), before and after training. Upper extremity tests were only performed for those with cervical lesions.
4. *Spasticity:*
   The Spinal Cord Assessment Tool for Spasticity (SCATS) will be used to estimate clonus, flexor and extensor spasms in the lower limbs. The scores from both lower extremities are summed (total score: no spasticity=0; maximum spasticity=18). A physical therapist not involved in the training (PJM) will perform the measures weekly.
5. *Pain:*

Daily rating of pain immediately before and after a training session will be determined with a numerical rating scale between zero (no pain) and 10 (worst pain imaginable). Neuropathic pain over a week will be estimated with the McGill Pain Questionnaire Pain Rating Index, completed prior to a training session once a week. Range of scores for the Pain Rating Index is 0 for no pain, to 78 for maximum pain.

6. *Balance:*
   Sitting balance will be measured on a force platform (Model OR6-7-1000, AMTI, Watertown, MA), with feet unsupported and hands crossed over the chest. For the limits of stability, visual feedback of the instantaneous centre of pressure with 8 equally spaced targets in a circle is displayed on a computer monitor, about 2 m in front of the participant. Participants lean as far as possible towards each target in random order. For postural sway, participants sit on the force plate as above with eyes closed, and the trajectory of the centre of pressure is measured for a maximum of 30 sec of sitting (42, 43) or until balance is lost. The tests will be repeated several times on different days before training to account for learning, then repeated at the midpoint, end, and 2 months post training.
7. *Strength of sensory pathways:*
   Skin sensation will be measured by surface electrical stimulation (Digitimer DS7A, Hertfordshire, England) of the C3-S2 sensory key points (44) defined by ISNCSCI (37), using disposable electrodes. Single pulses at a stimulus frequency of 2-3 Hz, pulse width 0.5 ms, are applied from below threshold to a maximum of 10 mA, twice. Sensory threshold is the lowest current at which a tapping sensation was reported out of the 2 trials.
8. *Strength of descending motor pathways:*
   Single-pulse transcranial magnetic stimulation (TMS) (Magstim 200, Whitland, UK) will be delivered through a double-cone coil placed at the vertex with current flowing in an anterior to posterior direction, to induce motor evoked potentials (MEPs) in the back extensor muscles bilaterally. Bipolar surface EMG electrodes (Kendall H59P, Mansfield, MA) record the responses at 8 vertebral levels spanning the injury (Cariga et al 2002). Responses will be recorded with the muscles at rest, and stimulus intensity at 60% (n=1), 70% (n=1) or 80% (n=9) of maximum stimulator output (MSO) depending on the participant's tolerance. Responses will also be recorded with background muscle contraction, elicited by a variety of maneuvers such as chair push-ups, arm raises, resisted back extension, and slight forward lean. The stimulus intensity for these trials will be set to a level that produces a consistent response at rest.

5.2 Method and Timing

Measurements for all outcomes will be done at least twice at entry into the study, once at the midpoint of training, once at the end of training and once 2 months after the end of training. In addition, the pain rating scale will be administered at the beginning and end of each training sessions, the McGill pain questionnaire and the SCATS measure will be performed weekly during training.

6 Assessment of Safety

6.1 Safety Parameters

Participants will be screened by a study team member to ensure that they do not have any contraindications to using the device. In addition, participants will be asked to have their primary care physician sign a letter indicating that they have no health concerns that would make it unsafe for them to use the exoskeleton.
A licensed physical therapist will supervise the training session and all training will be conducted by trainers certified by ReWalk to provide this training. A second person will assist the trainer at all sessions.

6.2 Method and Timing

Inspection of skin for potential issues will be done prior to donning and following doffing of the device at each training session. Participants will be instructed to inspect their skin at home and to report any abrasions or open areas to the trainer.

6.3 Adverse Event Reporting

Any adverse event will be reported to the HREB. In the event of a serious adverse event, the event will be reported in writing to the HREB, using the approved Local Serious Adverse Event Report form.

6.4 Definitions

Unanticipated events are any events during the training or testing that require medical attention.
Serious events are any events associated with the study activities that led to the need to seek immediate medical attention at a hospital emergency and requires in-patient hospitalization.
Related events are events that occurred during training or testing that were not originally present.

6.5 Adverse Event Follow-up

Serious events will be followed-up by a physician. The event will be reviewed by the study team, the Ethics Review Board and the Department of Quality Management in Clinical Research to determine if further action is necessary.

7 Statistical Plan

7.1 Statistical Methods

The weekly measures from SCATS and the Pain Rating Index from the McGill Pain Questionnaire will be described using Group-Based Trajectory Modeling (GBTM), as the measures are repeated over many time points (i.e., time series), and GBTM is ideal for describing such measures to explore possible clusters of individuals who follow a similar trajectory of change over time; it is not an inferential statistic. The GBTM is an unsupervised, statistical modeling method to approximate the trajectory of changes in discrete data over time, assuming that the population distribution of trajectories arises from a finite, unknown number of groups of individuals who follow distinct longitudinal trajectories. The approach allows us to determine, in a naturally heterogeneous population, whether there are subgroups that follow different trajectories over time. It has been used successfully in tracking the time-course of participation in people after stroke. The Akaike information criteria will be used to estimate the relative quality of GBTM models in clustering the presumed trajectories, i.e., the relative amount of information lost by a GBTM model compared to other. Other outcomes will be analyzed by t-test (or non-parametric versions) for continuous variables and chi-square test (or Fisher's exact test) for categorical variables.

7.2 Subject Population(s) for Analysis

We will endeavor to recruit up to 45 participants. Since this device has only just become available there is no data to indicate the possible variation in response. The numbers have been chosen based on our prior experience with training patients with SCI to walk, and on the literature regarding walking training in this population.

7.3 Significance

Insert the level of significance to be used.

7.4 Termination Criteria

Any serious adverse event directly related to our intervention will be evaluated and discussed with both the Ethics Committee and the Department of Quality Management in Clinical Research to determine if the trial should be discontinued.

7.5 Accountability Procedure

Missing or spurious data will be dealt with under the guidance of the statistician.

7.6 Deviation Reporting

If the statistician recommends deviation from the original statistical plan, these changes will be reported in the final report.

8 Direct Access to Source Data/Documentation

The investigators will permit trial-related audits, reviews and regulatory inspections, providing direct access to the source data and documentation.

9 Quality Control and Quality Assurance

Insert how you will ensure that this study is conducted – and that data are generated, documented (recorded), and reported - in compliance with this protocol, with GCP, and any other applicable regulatory requirements.

We are working with the Department of Quality Management in Clinical Research, U of Alberta, using their many templates for Case Report Forms and other data logging forms. Staff will be trained to comply with the protocol and with GCP standards.

10 Ethical Considerations

This study will be conducted according to Canadian and international standards of Good Clinical Practice for all studies. Applicable government regulations and University of Alberta research policies and procedures will also be followed.

This protocol and any amendments will be submitted to the University of Alberta HREB for formal approval to conduct the study. The decision of the HREB concerning the conduct of the study will be made in writing to the investigator.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the HREB. The formal consent of a subject, using the HREB-approved consent form, will be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

11 Data Handling and Record Keeping

All information collected will be kept confidential, except when professional codes of ethics or the law require disclosure. All data collected will be identified by a participant code. Unique identifiers are only in hardcopy files, and will be stored in filing cabinets in a locked room. Only the investigators, their graduate students and study team will have access to the data.

12 Finance and Insurance

These will be addressed in a separate agreement with the institutions.

13 Publication Plan

These will be addressed in a separate agreement with the institutions.

14 Supplements