Clinical Trial Protocol: MS HELLEN Trial

Title

A phase 1 pre-post intervention trial with 12 week baseline control determining the merits of a lower limb robotic exoskeleton (HELLEN) in the rehabilitation of Multiple Sclerosis (MS).

Title Registration

Registry: ANZCTR : to be confirmed upon ethics approval

Protocol Version

11th July 2017

Funding

A REX Bionics Exoskeleton has been provided in-kind to the research team by the Australian Institute of Neuro-rehabilitation (AIN). This is a not for profit organisation with an agenda to improve services to neurological patients in the community. The researchers have a working relationship with the AIN to facilitate this research.

Roles and Responsibilities

The research team includes Jodie Marquez, University of Newcastle (Chief Investigator); Dr Andrew Bivard, HMRI (Chief investigator); Associate Professor Neil Spratt, University of Newcastle (Chief investigator); and Nicola Postol, University of Newcastle (PhD student, and primary therapist conducting the assessments and providing the intervention).

Associate Professor Jeanette Lechner-Scott and Amanda Lydon are involved in the recruitment of patients via the database associated with the specialised MS clinic in Newcastle, MS Base, which has grown to be to one of the largest in the country with over 700 patients.

The data will be collected, managed and analysed by the research team. Submission of scientific papers for publication will involve the whole research team and will remain the intellectual property of the University of Newcastle.

Background and Rationale

Emphasis on training in the performance of functional activities, together with attempts to improve muscle strength and coordination, continue to form the central focus of most rehabilitation programs. However, for severely affected patients, task specific training for walking is labour intensive and puts a substantial physical burden on therapists who have to facilitate movement of the limbs whilst supporting the patient to prevent falls and guarantee safety (Schuck A, Labruyre R, 2012). Several therapists are required yet despite this, systematic correction of a patient's weight shift and stride length is often not possible. In daily practice, budget constraints limit intensive hand to

hand therapy regimes and the duration of therapy sessions is therefore restricted. Essentially access to therapy in a supported standing position for those severely impaired by neurological conditions, such as MS, is largely denied (Hess, Schmidt 2003). “There has been a recent surge in research examining the effect of exercise on functionality, and a corresponding interest in the impact of exercise on quality of life (QoL). A growing body of evidence suggests that substantial QoL benefits can be gained by MS patients who engage in exercise” (Horton et al, 2010). As those severely mobility impaired patients with MS have limited access to weight-bearing therapy, there is increasing interest in the use of robotic training devices to assist therapists as they provide opportunities to increase the intensity and dosage of training and reduce the physical demands and safety of therapists and patients (Freekotte, Koopman 2014).

It is the growing evidence detailing the importance of task specific training and active standing, in tandem with advances in engineering that has led to the development of robotic technology with the capacity to facilitate gait. These are wearable lower body exoskeleton orthosis with joints and limbs corresponding to those of the human body. Several devices are currently available, but The REX Robotic Exoskeleton is unique as it does not require the use of crutches to support the upper body meaning that the user has full use of his arms/hands to allow the performance of tasks independently in standing (REX Bionics, 2016). This is an important clinical distinction as patients with MS often have weakness in their upper limbs, and cannot always use walkers/crutches to stabilise their bodies effectively. The technology offers several advantages over conventional rehabilitation strategies, especially for individuals with severe motor impairments. REX is a self-supporting robotic device, independently controlled with a joystick and control pad allowing even severely impaired patients to use it. It gives people the ability to stand, get up, turn around, exercise in a weight-bearing standing position, and sit down again on their own. As such it has substantial clinical potential and opens new perspectives for weight bearing exercise and task specific mobility training in MS patients.

The Hunter has been very fortunate that collaboration with the Australian Institute of Neuro-rehabilitation (AIN) has procured the purchase of a REX exoskeleton (HELLEN: Hunter’s Exoskeleton for Lower Limb Exercises and Neuro-rehabilitation) and motor vehicle for transport, through a donation from the Newcastle Permanent Charitable Foundation. This is the first purchase of this robotic device in Australia.

There is, to date, no published clinical research evaluating the use of the REX Bionics exoskeleton in patients with MS. The vast majority of anecdotal evidence is also in relation to the use of the REX with spinal cord injured patients. Therefore, there is a need for independent research to establish the feasibility, acceptability and efficacy of lower limb robotics as a potential rehabilitation modality in the MS population.

We anticipate that this pilot study will provide the preliminary data required about safety, feasibility and effect size estimates, which is necessary for progression to a larger randomised trial, if warranted. The results of this trial will complement those from the clinical trial currently underway by this research team investigating the merit of this robotic exoskeleton in the Acquired Brain Injured population.

Objectives

The aim of this project is to examine the potential benefits and applicability of using HELLEN as an adjunct tool for neurorehabilitation in MS, as well as highlighting any barriers and risks to its potential use in this population. It is anticipated that this pilot data will assist in establishing priorities and directing further research in this field.

Trial Design

A phase 1 pre-post intervention trial with 12 week baseline control. This study design has the advantage of allowing all recruits in the study to receive the robotic exercise intervention. We aim to recruit 20 participants in this first stage pilot trial.

Study Setting

The trial will operate at one site only, at the University of Newcastle. A research room has been purpose built for this research in the Hunter Building with designated parking space for participants.

Eligibility Criteria

Inclusion Criteria:
1. Diagnosis of MS
2. Resident of the Hunter region over the age of 18 years
3. Severe mobility impairment whereby the participant is reliant on a mobility aid or other people for upright activities (Scores >6 on the Expanded Disability Status Scale)

Exclusion Criteria
1. Weight >100kg or <40kg; height >6'4" or <4'8" (criteria set by the REX Bionics)
2. Pregnancy
3. Unstable or severe cardiac or respiratory conditions
4. Recent fractures in lower limbs/pelvis/spine
5. Significant cognitive impairment (<19 on MoCA)
6. Any medical condition which limits the ability to exercise in an upright position

The treatment will only be delivered by REX trained Physiotherapists. Researchers, Jodie Marquez and Nicola Postol have both completed the full 3 day training course and attained competency accreditation.

Intervention

The intervention will involve 2 sessions of exercise therapy per week for 12 weeks. Each session will be up to 1 hour duration and will consist of half an hour of individualised therapy, prescribed and administered by a physiotherapist, including upright weight-bearing exercise facilitated by HELLEN as tolerated by the patient. This may be a combination of sit to stand practise, standing tolerance, weight shift, trunk control exercises, stepping practise, side stepping, squats, upper limb exercises and gait practise. These exercises will be individually tailored to meet the abilities and needs of the client. Participants will also be provided with a home exercise program

relevant to their treatment, which will be assessed and updated throughout the trial as required.

Interventions will only be progressed according to the individual participants' abilities as deemed appropriate by the administering physiotherapist. Interventions will be modified or ceased if, in communication with the participant, the researchers deem that this is necessary.

Outcomes

The timepoints for assessment of outcome measures are:

Week 0: Assessment and assignment to waiting list
Week 12: Commencement of therapy phase
Week 18: Mid- therapy assessment phase
Week 24: End of therapy phase
Week 36: Follow-up phase,12 weeks after completion of intervention

Participants will be screened for eligibility and baseline measurements will be taken before participants are assigned to a 12 week waitlist. The primary outcome of interest is functional ability as measured by the Motor Assessment Scale. Secondary outcomes include a range of impairment, mood, fitness, and quality of life measures as listed below:

All assessment forms are attached and include:

1. Medical screening form: to determine eligibility for exercise and suitability of the robotic device
2. Demographic information: Standard demographic and MS information including Kurtzke Expanded Disability Status Scale (EDSS)
3. Cognitive screen MoCA
4. Mood HADS
5. Attitude towards robotic therapy questionnaire
6. Routine physiotherapy assessments using standardised outcome tools: fatigue (FAS), function (MAS and sit to stand test), spasticity (Tardieu), quality of life (SF8), balance (functional reach), independence (Barthel Index), fitness (O2 consumption using the Cosmed K5) strength (dynamometer).
7. Those agreeing to exercise/O2 consumption testing will be assessed wearing the Cosmed K5 O2 mask. During their 3rd or 4th treatment session in HELLEN the participants will be assessed wearing the Cosmed K5 mask, during their 30 minute treatment session in HELLEN. This testing will be repeated during their final HELLEN treatment session.
8. Bioelectrical Impedance Analysis to assess changes in body composition.

Participant Timeline

Potential participants will be identified on the MS database by research nurse, Amanda Lydon. She will then make telephone contact with potential participants to inform them

of the research and gauge their interest in participating. Those interested, will be provided with an information statement detailing the study and will be contacted by Nicola Postol, in the following week by phone, to answer any questions they may have and if still interested, to arrange a convenient time for an assessment. Once they are deemed eligible, baseline measures will be collected and they will be placed on a 12 week waitlist. These measures will be repeated after the 12 week period, after 6 weeks of intervention, at the conclusion of 6 weeks of intervention and 12-weeks after the intervention period. After the wait period, twice weekly sessions will continue for 12 weeks. They will then be provided with an ongoing home exercise program. In total, participants will be enrolled in the study for 36 weeks.

Sample Size

20 participants with MS will be invited to participate in this pilot trial.

Recruitment

Potential participants will be identified by Amanda Lydon via the database maintained by the Newcastle MS clinic, MS Base.

Data Collection Methods

Data will be collected by Nicola Postol in the Physiotherapy Robotics Laboratory (HE14) at the University of Newcastle. Outcome measures will be collected at the beginning of the waitlist phase, the commencement of the trial phase, 6 weeks into the intervention phase, at the end of the intervention (12 weeks), and at the 12 week follow up appointment. The outcome measures have been attached. They have been chosen to reflect a variety of expected benefits of the intervention, and the range of impairments experienced by people with MS.

As the intervention is at no cost to the participants, and offers a type of treatment not currently available to MS patients, there is inherent motivation for the participants to maintain their continued participation in the trial, until the completion of the follow up. For any participants who are lost to follow-up, their last measurements will be imputed into the data and analysed according to intention to treat principles.

Data Management

All data collected from individuals will be maintained in a de-identified form. The data records will be coded using alphanumeric coding to differentiate individual subjects for purposes of analysis. The key for the code will be stored separately on a password protected personal computer. This coding process will be final and subjects will not be re-identified unless they wish to be removed from the study in which case their data will be re-identified, removed from analysis, and destroyed.

Paper copies of clinical measures will contain identifying information about each participant − these will be kept in a separate locked filing cabinet, within the chief investigator's office. Identifying information (names, addresses and contact details)

will not be kept on any database or computer file from the creation of these data files. The data will be coded using an alphanumerical system and the code sheet will be kept in a password protected file on the researcher's computer. Databases will be kept on secured networks (accessible only via password to the researchers named on this application) and hard drive back−up copies will be kept in the same locked filing cabinet as the paper data.
Video files will be downloaded onto the researcher's password protected computer, and deleted from the camera.

All data and findings will be kept for 5 years, consistent with criteria for scientific fraud issues. After that time, all data will be disposed of by shredding or electronic deletion.

In the event that principle investigator Jodie Marquez ceases to be engaged with the University of Newcastle, Dr Andrew Bivard will assume responsibility for the study data.

Statistics

The data collection phase of the trial is expected to take a year. Descriptive statistics, including means and standard deviations (SD), will be calculated for demographic and outcome data. Change scores for each outcome from baseline will be tested using independent t tests for continuous variables and $\chi 2$ tests for categorical variables. Differences from enrolment, baseline, post intervention and 12-week follow up will be evaluated for statistical significance. All analyses will be conducted on an intention-to-treat basis, with missing follow-up data conservatively imputed using the last observation carried forward method. All statistical analysis will be conducted by a qualified statistician.

Descriptive statistics, including means and standard deviations, will be calculated for demographic data. A linear mixed model will be used to detect a significant difference between outcome scores during each time period. The value of the baseline score at the start of the trial and after intervention will be used as a covariate, and analysis conducted to correct for differences in baseline scores and to ensure there is no effect of order. All analyses will be conducted on an intention to treat basis, with missing follow-up data conservatively imputed using the last observation carried forward method.

Data Monitoring

This is a pilot study. No formal interim analysis or DMC is required.

This study will be internally monitored. Chief investigators Spratt, Marquez and Bivard will be responsible for ensuring treatment application, data collection, analysis and statistical evaluation are all conducted within accepted scientific practices. Patients will be monitored carefully during the administration of the treatment and adverse events will be documented and submitted to the HREC for evaluation.

Harms

Adverse events will be immediately reported to the ethics committee.

Research Ethics Approval

Application for ethics approval has been given by the Hunter New England Human Research Ethics Committee (17/08/16/4.02).

Protocol Amendments

Protocol amendments affecting future participants will be communicated via a revised participant information form. The research protocol, where necessary, will be revised and disseminated to all relevant parties.

Informed Consent

This will be obtained via the attached form, and completed upon initial contact with Nicola Postol – the researcher/physiotherapist responsible for providing the intervention.

Confidentiality

This will be maintained in accordance with routine therapist-patient requirements, and all data will be stored as previously outlined.

Declaration of Interests

All investigators work in the field of neurological therapy/medicine and/or research. Their interests outside of this clinical trial are aligned with the research. There are no conflicts of interest to declare.

Access to Data

All investigators (Neil Spratt, Jodie Marquez, Andrew Bivard, and Nicola Postol) will be able to access the data for analysis, which will lead to the publication of manuscripts for submission to scientific journals.

Ancillary and post-trial care

Those who participate in the trial will be provided with an updated home exercise program on completion of the trial, and advice about local therapy services that may be relevant for ongoing rehabilitation or health care. If interested, the participants will be informed of future research activity by this research team.

Dissemination Policy

All participants will be provided with a summary of the findings from this research and will be offered the option of receiving a copy of any publications relating to this research.

There will be no professional writers employed. The scientific papers and conference presentations relating to the study will be generated by the research team.