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G-EO Gait Rehabilitation Training in Progressive Multiple Sclerosis

Study Protocol and Statistical Analysis

NCT03980145

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1.0 Rationale and Specific Aims

The logistic advantages and advanced training capabilities of the G-EO System, as well as the benefits reported in other populations, support this strategy as a potentially potent rehabilitation tool for restoring and maintaining function in progressive MS. This approach represents a paradigm shifting opportunity for improving current clinical practices for patients with progressive MS. If successful, this project will provide initial evidence for increasing patient access to the G-EO System, and this could be accomplished through "regional technology centers" using a rural health-delivery approach.

There are several novel aspects of the proposed trial: (1) the examination of a novel gait rehabilitation stimulus (G-EO System) that could alter current clinical practices; (2) the focus on patients with progressive MS who have gait impairment (i.e., those who have received minimal research attention), which was recently described as the greatest therapeutic challenge facing the MS community; and (3) a study design that accounts for standard therapy.

Specific Aims: We propose a single-blinded, randomized pilot trial of electromechanically-assisted gait training using the G-EO System in patients with progressive MS with gait disability (EDSS=4.0-7.5).

Specific Aim 1 will establish the safety and feasibility of gait training using the G-EO System.

Specific Aim 2 will determine the efficacy of gait training using the G-EO System for improving mobility, symptomatic, quality of life, and participatory outcomes.

2.0 Inclusion/Exclusion Criteria

Inclusion criteria

- 18-64 years
- Confirmed diagnosis of PPMS or SPMS (this will be confirmed by the referring physician)
- EDSS 4.0-7.5[22]
- Stable course of disease-modifying therapy over the past 6 months
- Asymptomatic (i.e., no underlying cardiovascular disease)
- Physician approval for exercise
- Willingness to visit the IU Health Neurosciences Center for testing and training

Exclusion criteria

- Pregnancy
- Current use of dalfampridine (Ampyra®)
- Conventional physical therapy or G-EO training within the past 6 months
- Height <1m or >2m
- Body weight >150 kg
- Contraindications to G-EO gait training (e.g., bone instability)

3.0 Enrollment/Randomization

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A convenience sample of 20 persons with progressive MS will be enrolled for this pilot clinical trial. Recruitment will occur through neurologists at the IU Health Neuroscience Center. Each participate will be given time to read the consent form or have it read to them and to ask questions (see Informed Consent Draft). Consent will be obtained before randomization and assessments. The consent process will take place at the Indiana Center for Advanced Neurorehabilitation (ICAN) in the Neurorehabilitation and Robotics IU Health Neuroscience Center, 355 West 16th Street, Room 1078, Indianapolis, IN 46202 (317) 963-7050.

If found eligible for the study and agree to consent to participate, subjects will be matched based on disability level (EDSS), and randomized to either conventional physical therapy (CPT) group or CPT with G-EO training using a random numbers generator and concealed allocation.

4.0 Study Procedures

Screening
Potential subjects will be referred to the study via IU Health Physicians who specialize in the treatment and management of individuals with Multiple Sclerosis. A member of the research team will screen the referral by contacting the physician and confirming they meet the necessary inclusion and exclusion criteria. Following confirmation of criteria, potential subjects will be contacted by phone to schedule an initial visit for consent and assessment of baseline data.

Assessments
The study outcomes will be collected by treatment-blinded researchers. All participants on Day 1 who consent to be in the study will complete the following mobility outcomes:

1. Spatial and temporal gait kinematics will be assessed using a PKMAS Zeno Walkway (Protokinetics). Participants will be asked to walk over a 14 foot pressure mat that will capture their gait kinematics and speed.
2. A 2-minute walk (2MWT) tests to determine walking endurance. Subjects will be asked to walk for 2 minutes along a 30m track. Subjects may stop and rest as often as needed.
3. Balance assessment using the Neurocom Balance Master. Subjects will be asked to stand on a balance platform while the load cells in the force-plate measures postural stability when challenged. All subjects will be in a safety harness to prevent falling.
4. Their level of perceived fatigue using the Modified Fatigue Impact Scale. They will complete a questionnaire.
5. Their level of depression using the Hospital Anxiety and Depression Scale. They will complete a questionnaire.
6. Their level of pain assessed by the McGill Pain Questionnaire. They will complete a questionnaire.
7. Their level of health-related quality of life assessed by the Multiple Sclerosis Impact Scale-29. They will complete a questionnaire.
8. Their perceived ability to perform Activities of Daily Living (ADL) using the Late-Life Function and Disability Inventory. They will complete a questionnaire.

Participants who complete the first 6 weeks of training will be asked to complete assessments 1 thru 3. Participants who complete all 12 weeks of training will be asked to complete all assessments one final time.

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Schedule

Following completion of day 1 assessments, all subjects will be scheduled for the intervention phase of the study. Regardless of group allocation, each participant will receive 20 total visits scheduled ideally for two times a week for 10 weeks. Following the completion of the first 10 treatments, all subjects will be asked to complete assessments #1 thru #3 above. Following completion of the additional 10 treatments (total of 20 treatment sessions), each subject will complete all assessments performed on Day 1. (See Table 1) If a subject cancels a treatment session, it will be rescheduled to ensure that all subjects complete the total of 20 treatment sessions prior to final testing. If a subject misses three consecutive treatment sessions, they will be dropped from the study due to inconsistency in treatment carryover. Cancellations and changes in patient scheduling represents a true clinical environment and represents normal clinical patient management. Therefore, the emphasis is on total number of treatments (20) and not on total number of weeks.

Table 1. Summary Clinical Trials (14-week span) Procedures with Human Subjects.

Pre-Intervention Phase		Intervention Phase	Mid Intervention Phase	Intervention Phase	Post Intervention
Day 1	Day 1 Measurement	6 weeks intervention period	Mid Treatment Assessment	6 weeks intervention period	Post Assessment
• Screening of Inclusion • Informed consent obtained • Disability match and random assignment to CPT or GEO	**Outcome Measurement** 1. Comfortable Walking Speed/Mechanics Trial 1 (14') Trial 2 (14') Trial 3 (14') 2. Walking Endurance 2 MWT 3. Balance Neurocom 4. Fatigue Modified Fatigue Impact Scale 5. Depression Hospital Anxiety and Depression Scale 6. Pain McGill Pain Questionnaire 7. Quality of Life MS Impact Scale 8. ADLs	Treatment and control group 2x a week	**Outcome Measurement** 1. Comfortable Walking Speed/Mechanics Trial 1 (14') Trial 2 (14') Trial 3 (14') 2. Walking Endurance 2 MWT 3. Balance Neurocom	Treatment and control group 2x a week	**Outcome Measurement** 1. Comfortable Walking Speed/Mechanics Trial 1 (14') Trial 2 (14') Trial 3 (14') 2. Walking Endurance 2 MWT 3. Balance Neurocom 4. Fatigue Modified Fatigue Impact Scale 5. Depression Hospital Anxiety and Depression Scale 6. Pain McGill Pain Questionnaire 7. Quality of Life MS Impact

	Late Life Function and Disability Inventory				Scale 8. ADLs Late Life Function and Disability Inventory

Intervention

The intervention will be delivered through the Neurorehabilitation and Robotics Clinic by three trained Physical Therapists with oversight from Dr. Altenburger. The clinicians involved in the delivery of the intervention will not be involved in outcome assessments. Participants in both conditions will receive conventional physical therapy (CPT) as usual care. Participants in the G-EO training condition will also receive robot-assisted gait training. This design will control for attention and social contact, total rehabilitation time, and intensity. Both conditions will be delivered at the same frequency (2x/week), intensity (40 to 60 minutes), and duration over 12-weeks. Progression will occur by increasing the session intensity weekly. Training intensity will be monitored and standardized using the Borg Rating of Perceived Exertion38 scale, and will progress from 'fairly light' (11) to 'somewhat hard' (13). This prescription is consistent and appropriate for individuals with progressive MS with mobility impairment and low fitness levels. Progression will occur by increasing the session duration by ~5min/week up to 60 minutes per session. Total training time includes both CPT and G-EO training for the G-EO condition (i.e., 30min of CPT + 30min G-EO). Training sessions will not exceed 60 minutes. We will record all training parameters. Physical therapy training sessions will involve: 3-5 minute warm-up, stretching, progressive strength training exercises, and gait and balance training. Additional strategies for home exercises, energy conservation, fall prevention, and appropriate assistive devices (i.e., orthotics) will be provided universally.

Conventional physical therapy (CPT): A CPT session will involve a 3-5 minute warm-up, stretching, progressive strength training exercises, and gait and balance training.

G-EO training: Using the G-EO System, participants will be secured with the appropriate sized harness and attached to an overhead body-weight support system, with feet secured to pressure sensitive footplates. Each session will begin with a 3-5 minute warm-up in the continuous passive mode (cadence ~40-45 steps/minute). The participant will then be transitioned into the adaptive training phase for practicing repetitive floor walking for up to 30 minutes. During this phase, the force produced by the robot is modulated to support the effort of the patient in producing a typical walking pattern.

Feasibility and Safety

Feasibility outcomes will involve process, resources, management, and scientific assessment. Process metrics will include recruitment, retention, and adherence rates assessed by the movement of participants through each stage of the study and training data. Resource metrics will include evaluation of the equipment and facilities through feedback from the therapists. Time to completion relative to proposed target dates will also be reviewed. Management metrics will include data management, documentation of patient progress, record of adverse events, and

compliance with approved protocols. Safety will be evaluated through assessment of recorded adverse events.

5.0 Statistical Considerations

Data will be analyzed using IBM SPSS Version 22.0 (IMB Corps., Armonk, NY). Descriptive statistics will characterize the sample on demographic, clinical, safety, and feasibility metrics. We will compare safety and feasibility between groups using chi-square and *t*-tests for independent samples (*Specific Aim 1*). The efficacy of the intervention on study variables (*Specific Aim 2*) will be examined using a 2 (Group) by 2 (Time), mixed factor ANOVA. A completers analysis will be conducted (i.e., ≥75% of sessions completed). Effect sizes associated with F-statistics will be expressed as eta-squared (η^2), and effect sizes based on mean differences will be expressed as Cohen's *d*.