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ORIGINAL ARTICLE

FEASIBILITY AND SAFETY OF A POWERED EXOSKELETON FOR BALANCE TRAINING FOR PEOPLE LIVING WITH MULTIPLE SCLEROSIS: A SINGLE-GROUP PRELIMINARY STUDY (RAPPER III)

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Objective: **To evaluate the feasibility, usability, safety, and potential health benefits of using an exoskeleton device for rehabilitation of people living with multiple sclerosis.**

Design: **Single-group preliminary study.**

Subjects: **Eleven adults living with multiple sclerosis, with Expanded Disability Status Scores that ranged from 6 to 7.5 (mean age (standard deviation; SD) 54.2 (11.8) years), were recruited.**

Methods: **Individual participants undertook a balance rehabilitation exercise programme using the Rex Rehab robotic exoskeleton device. Each participant undertook 4×45–60 min supervised, balance exercise sessions. Primary outcomes were: *(i)* the number of participants who completed the trial protocol safely, and *(ii)* the number and nature of adverse events reported. Secondary outcomes were: mobility; balance; spasticity; sleep; functional independence; quality of life; and device satisfaction.**

Results: **Ten out of 11 participants completed the trial protocol safely. Four adverse events were recorded (1 serious), all of which were deemed unrelated to the trial. Secondary outcomes showed allied improvements in balance, joint mobility, spasticity and quality of life. All participants found the device acceptable to use.**

Conclusion: **These results suggest that it is feasible and safe to use the Rex Rehab exoskeleton device to assist with balance rehabilitation for people living with multiple sclerosis.**

Key words: feasibility; safety; balance; multiple sclerosis; rehabilitation; robotic exoskeleton device; abdominal muscles; mobility.

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LAY ABSTRACT

Multiple sclerosis (MS) is a chronic neurological disease that can lead to symptoms, including muscle weakness and balance issues. The incidence of falls in people living with MS (PwMS) is 3 times higher than that in older people. To try to reduce this vulnerability to falls, this study aimed to evaluate the feasibility, safety, and potential health benefits of using an exoskeleton device for a balance exercise programme. Eleven PwMS undertook 4×45–60 min supervised, balance exercise sessions using the exoskeleton device. Feasibility and safety were assessed by identifying the number of participants who completed the trial safely; consideration of any issues experienced during the trial and how these were resolved. Ten participants completed the trial (1 withdrew due to their MS) and only 4 issues were reported, all of which were unrelated to the trial. Some participants also experienced improvements in balance, mobility, and quality of life.

Multiple sclerosis (MS) is a common neurological disorder characterized by an autoimmune response causing inflammation and demyelination of nerve cells within the brain and spinal cord (1). Approximately 80% of people living with MS (PwMS) experience gait and mobility impairments, while 75% experience balance disorders (2). Balance impairment may be related to a variety of factors, including muscle weakness, in-coordination, sensory disturbances, spasticity, and cerebellar symptoms (3).

While it is recognized that many PwMS have poor balance that is associated with falls (4), there is a growing body of research evidence that identifies the many benefits of exercise, including better balance (5–7). However, given that balance issues, such as increased postural sway (8), have been identified as contributory risk factors for falls, it is important to find ways that PwMS can exercise safely and effectively. Rehabilitation using assistive technology has been identified as one effective means of addressing this problem (9).

Table I. Adverse events

Number	Nature and classification of adverse event (AE) or serious adverse event (SAE)	Team support	Outcome
1	Participant informed of feeling unwell. AE	Team advised her to contact her General Practitioner (GP) and to feedback to team.	GP diagnosed that she had experienced a relapse of her relapsing remitting MS. Participant decided to withdraw from the trial.
2	On arrival for trial appointment, participant reported that she has been diagnosed with a suspected deep vein thrombosis (DVT) in right calf. AE	Team decided to await clinical diagnosis before any further exercise sessions.	Team received confirmation of exclusion of DVT diagnosis and therefore her trial session appointments were re-scheduled.
3	On arrival for trial appointment, participant reported that he had severe left-sided thoracic back pain after having fallen the previous day. AE	Neuro-physiotherapist examined his back to assess possible factors. Muscle spasm and pain were evident. Therefore, he was advised to book an emergency appointment with his GP to request examination, pain relief and a chest X-ray. Discussed with Principal Investigator by telephone. Team decided that it would not be appropriate for participant to undertake trial session due to his need to access medical care. Requested him to let us know by telephone what the outcome was from his GP appointment.	Participant informed us that he had seen his GP and had taken pain relief medication and felt well enough to re-schedule his final sessions.
4	Participant telephoned to inform team that she had an accidental fall at the weekend and had been admitted to hospital with a diagnosed fractured hip. SAE	Team awaited feedback of outcome.	Participant informed team of recovery and was re-scheduled for final data collection appointment.

Building on a preliminary study that used the current Rex Rehab exoskeleton device for people with spinal cord injury (10), this study aimed to assess the feasibility and safety of using the same exoskeleton device (11), to support a balance rehabilitation programme for PwMS.

Feasibility was assessed in the relatively broad manner adopted by other stage 1 trials (12, 13), which have addressed aspects of process, management, scientific outcome and resources.

Safety was assessed by comprehensively documenting the number and nature of adverse events and how effectively the trial team identified, managed and resolved them (Table I). Secondary objectives sought to determine whether there may be health benefits associated with undertaking a balance exercise treatment intervention supported within a Rex Rehab exoskeleton. Alongside this, we sought simple feedback comments from participants about their experiences of the trial.

METHODS

The study utilized a prospective, open-label, single-arm, non-randomized design, and was approved by the East of England-Cambridgeshire and Hertfordshire Health Research Authority Ethics panel (Research Ethics Committee (REC) reference: 16/EE/0553) Integrated Research Application System (IRAS) reference: 219334. The trial was registered with Clinical Trial Number (CTN): NCT05102682 via ClinicalTrials.gov and with the National Institute for Health and Care Research reference: NEUR 33236. Organizational registration via East Kent University Hospitals NHS Foundation Trust Research and Innovation ref: 2016/NEURO/10. (A copy of the protocol, participant consent and information sheets are provided in Appendix S1). An outline of the study components is provided in a flow chart (Fig. 1).

Setting and participants

The trial was conducted in an outpatient setting on a university campus. Participants self-referred following an advertisement placed with MS services, charities, East Kent Neuro-rehabilitation Unit, and social media platforms. All applicants were screened on the phone, with a questionnaire against the trial inclusion and exclusion criteria identified in Table II. Eleven individuals enrolled during the period April to July 2017 and provided written informed consent on trial entry.

Equipment

A Rex Rehab exoskeleton (Rex Bionics Ltd, Auckland, New Zealand) was used.

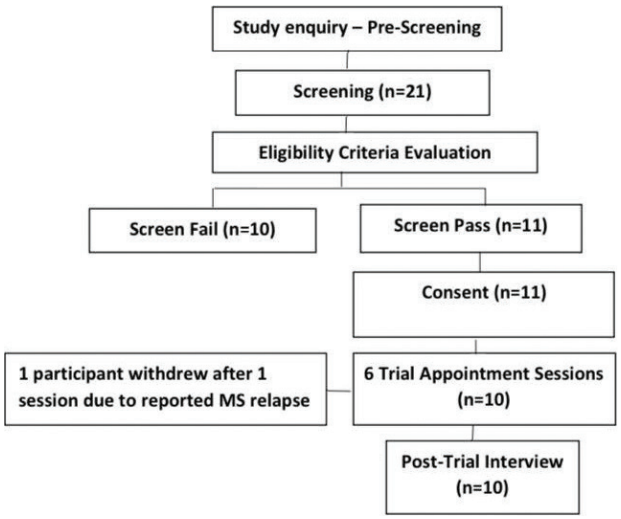

Fig. 1. Study flow chart. MS: multiple sclerosis.

Table II. Trial inclusion and exclusion criteria

Trial inclusion criteria
1. Age >18 and <90 years
2. Confirmed diagnosis of MS by a consultant neurologist as per McDonald Criteria (14)
3. Moderate to severe mobility restriction as defined by an Extended Disability Status Scale (15) score of between 6 and 7.5
4. Able to meet the anthropometric requirements of the Rex Rehab exoskeleton device (16)
5. Ability to understand the nature and purpose of the study and to give written informed consent
Trial exclusion criteria
1. History of osteoporosis or osteoporosis-related bone fractures
2. Skin integrity issues that could be adversely affected by the Rex Rehab exoskeleton device, e.g. pressure sores
3. Severe hypertonia as indicated by a score of 4 on the Modified Ashworth Scale (17)
4. A behavioural, cognitive, or communication impairment that could impair task comprehension
5. Considered medically unsuitable for rehabilitation in the opinion of the Principal Investigator Consultant Physician in Rehabilitation Medicine
6. A known allergy to materials used in the Rex Rehab exoskeleton device
7. Pregnancy
8. Concurrent participation in any other trial
9. A diagnosis of low blood pressure

Study outcomes

All outcome measurements were performed by the same neuro-physiotherapist at the beginning and end of the intervention period and training sessions were spaced at 1 week intervals, which enabled ample recovery time between sessions (18).

The primary feasibility measurement outcomes were:

- proportion of individuals who were eligible for inclusion following screening process;
- number of participants who completed the trial;
- dropout rate: percentage of participants who dropped out of the trial;
- time taken for an individual to transfer into the Rex Rehab exoskeleton device;
- level of assistance required with the transfer;
- time taken to complete sit to stand inside the device.

The primary safety outcomes were:

- number of adverse events recorded;
- severity and nature of adverse events reported.

An adverse event (AE) is defined as an event associated with a medical device that led to death or serious injury of a patient, or may lead to such if the event recurs (19).

The secondary outcome measures were the Berg Balance Scale (BBS) (20), Modified Ashworth Scale (MAS) (17), Modified Falls Efficacy Scale (MFES) (21), Multiple Sclerosis Impact Scale (MSIS-29) (22), Health-related Quality of Life Scale EQ-5D-5L (23), Psychosocial Impact of Assistive Devices Scale (PIADS) (24), Activities-Specific Balance Confidence Scale (ABC) (25), Multiple Sclerosis Walking Scale (MSWS-12) (26), Arm Activity Measure (ArmA) (27), Epworth Sleepiness Scale (28), and the visual analogue scale for pain (VAS) (29). Passive joint range of motion (ROM) for ankles, knees and hips was measured using a standard goniometer, and standard principles for joint measurement were followed (30). For all outcome measures used, standard procedures were followed, which included the use of a standard chair (for example, as defined in the BBS scale) and standard plinth, which were adjusted as deemed suitable by the trial team. This enabled standardization of all testing measurements across all testing sessions. All participants recruited were living with chronic advanced MS and presented with a variable degree of paresis. A decision was made to make a detailed functional assessment instead of using the Medical Research Council Muscle Power Scale (31), which is an impairment-focused scale. Further information on mobility; walking aids; ataxia; relevant anti-spasticity medication and ongoing treatment is shown in Table III. Outcome measure questionnaires were presented in the same order across

Table III. Mobility, ataxia, medication and ongoing treatment

Participant number	Mobility and walking aid/s	Ataxia	Medication dose is Total per day	Ongoing treatment
001	Indoors, walks independently with stick. Outdoors uses motorized scooter	Yes	Baclofen 15 mg	None
002	Indoors, walks with 3-wheeled walking frame. Attendant pushed wheelchair for outdoors.	No	None	None
003	Walks with 1 stick	No	None	Functional electrical stimulation Right foot
004	Walks with 2 walking poles	No	Baclofen 10 mg	Functional electrical stimulation Right foot
005	Indoors, walks with 2 sticks. Attendant-pushed wheelchair for outdoors	No	Baclofen 30 mg	None
006	Indoors, walks with 1 stick or wheeled stroller frame. Attendant-pushed wheelchair for outdoors.	Yes	None	None
007	Indoors, walks with 1 stick. Attendant-pushed wheelchair foroutdoors.	No	Baclofen 90 mg Gabapentin 1,800 mg	
008	Indoors, walks with 3 wheeled tri-walker frame. Attendant-pushed wheelchair for outdoors	Yes	Copaxone	
009	Indoors, walks with wheeled frame. Powered wheelchair for outdoors.	Yes	Baclofen 30 mg	
010	Unable to walk. Transfers with Standing Aid and carer assistance at home. Transferred with use of hoist and assistance of 2 during trial. Powered wheelchair.	No	Gabapentin 1,500 mg	

all participants. A 15-min interview was conducted 10 days post-trial with participants and their caregiver if available to gain feedback on individual experiences. Interviews were audio-recorded and transcribed by the interviewer.

Intervention

The balance exercise programme was designed to focus on strengthening leg extensor and abdominal muscles, recommended as important for PwMS (32-331). The programme also included a focus on maintaining an optimal upright posture, when standing in the Rex Rehab exoskeleton device and performing dynamic balance exercises (34) (see Appendix S2 for exercise programme. Given the absence of Cochrane guidelines (35) on the optimal type, duration, intensity and frequency of exercise training sessions for PwMS, the intervention was delivered in 4 exercise sessions (with data collected before and after). This number of sessions exceeded the single session applied in the previous Spinal Cord Injury (SCI) study (10) and was constrained by the resources to hand. The time schedule between each training session was an interval of 1 week. Spasticity was measured before the training intervention, at the beginning of session 3, and at the end of the fourth session. Individual participants were offered and supported with appointment times as flexibly as possible within the available weekend diary slots of the team. As spasticity can vary throughout the day for numerous reasons, when feasible, it is recommended that therapies take place at the same period of the day.

The Rex Rehab exoskeleton device used is a robust powered exoskeleton that covers the waist, pelvis and lower limbs of the individual (16; Fig. 2). The user is supported securely within the device using a pelvic harness, thigh and calf cuffs, and an abdominal pad (Fig. 3). The exoskeleton device is designed for use in a clinical environment under the supervision of a Rex Rehab exoskeleton device-trained clinician and is operated by a keypad and joystick.

Individuals transferred into the Rex Rehab exoskeleton device with the appropriate level of assistance as risk assessed by the trial team. Optimal postural alignment and positioning of the individual within the device was ensured by the trial neuro-physiotherapist. Following a verbal briefing, the clinician then switched on the device and used the joystick to bring the individual up from a sitting to standing position. From the standing position, the appropriate functionality mode was selected (e.g. move forward). The device was then operated via "hands on" assistance from the trial neuro-physiotherapist, which enabled the participant to relax their arms and concentrate on their posture. The trial neuro-physiotherapist always held onto the Rex Rehab exoskeleton device to stabilize it when moving, a technique termed "spotting" taught as part of the device training (16). The Rex Rehab exoskeleton device can be operated to move in several directions: forwards, backwards and sideways, and can be directed to turn to the left or right (10, 16). Therefore, it is possible for an individual user to experience the device moving their individual body weight from one side to the other as the device moves forwards, backwards or sideways, and this can enable the user to gain awareness of weight transfer during movement, which is one component of balance and walking.

Fig. 2. Rex Rehab exoskeleton device seen from the side.

Statistical analysis

Descriptive statistics are provided for the primary outcome measures and safety data (Table I). Categorical variables were summarized by the number and percentage of responses in each category, whilst the mean and standard deviation were used to summarize continuous variables. Analyses of secondary outcome

Fig. 3. Individual user inside the Rex robotic Exoskeleton Device from the front. An upright posture, with optimal alignment of the hips, knees and ankles in standing is supported by the device. The user can rest their hands on the bars at the sides. Velcro straps secure the user's legs, and an abdominal pad across the front is used to assist and support an upright posture. The joystick and controls are visible on one side.

measures were conducted using paired *t*-tests to examine changes in scores from pre-trial to post-trial time-points. The distribution of changes in scores was assessed visually and found to be approximately normally distributed for all outcomes. Where outcomes were measured on more than 2 occasions, 2-way analysis of variance (ANOVA) was used to compare between time-points (with participant and time being the 2 factors). For the PIADS scale, measured once post-treatment, a 1-sample *t*-test was used to indicate whether the results varied significantly from zero, in relation to whether using the Rex Rehab exoskeleton device in the trial had a positive or negative impact on the rated domains. All statistical tests were performed with a 2-sided 95% significance level. The software package Stata (Version 15.1, StataCorp LLC, College Station, TX) was used for all analyses.

RESULTS

Eleven individuals were enrolled into the trial from a sample of 21 PwMS who were screened, which equates to 52%. Table IV provides participant demographic data. The most common reason for exclusion at screening was when a potential participant's calf muscle bulk exceeded 375 mm in circumference (this measurement is taken at a fixed point 80 mm below the knee), as identified in the manual (16), which was identified on 6 occasions during screening. The other reasons were low blood pressure, back pain, history of osteoporotic fractures, short tibial length and sacral lesions.

Primary outcome measures

Ten out of 11 participants (91%) completed the trial, and only 1 participant chose to withdraw due to a reported relapse of their MS. All 11 participants completed the transfer into the device with a mean time of 3 min 35 s. Five individuals managed to transfer into the exoskeleton device independently after instruction from the trial team. One required verbal support and supervision from the neuro-physiotherapist, 4 required "hands on" physical assistance from the neuro-physiotherapist, and 1 required the assistance of 2 trained team members and the use of a hoist. All participants completed the sit-to-stand task within the device with assistance from the neuro-physiotherapist.

Table IV. Participant demographics and clinical characteristics

Factor	Summary
Sex, *n* (%)	
Female	8 (73)
Male	3 (27)
Age, years, mean (SD)	54.2 (11.8)
Median [IQR]	58 [48, 62]
Ethnicity, *n* (%)	
White	11 (100)
Other	0 (0)
Height, cm, mean (SD)	164 (10)
Median [IQR]	163 [155, 172]
Weight, kg, mean (SD)	64.4 (10.3)
Median [IQR]	63.5 [63, 70]
Type of multiple sclerosis (MS), *n* (%)	
Progressive	6 (55)
Relapsing remitting	5 (45)
Time since MS onset, years, mean (SD)	15.9 (7.8)
Median [IQR]	14.7 [9.8, 20.0]
EDSS score, mean (SD)	6.6 (0.3)
Median [IQR]	6.5 [6.5, 6.5]

SD: standard deviation; IQR: interquartile range; EDSS: Expanded Disability Status Scale.

Table V. Secondary outcome measure: passive joint range of movement

Outcome	N	Baseline Mean (SD)	Post-intervention Mean (SD)	Change Mean (95% CI)	t (8 degrees of freedom)	*p*-value
Hip flexion L	9	108 (12)	114 (14)	6 (–7, 19)	1.08	0.31
Hip flexion R	9	105 (8)	106 (9)	1 (–7, 9)	0.23	0.82
Hip extension L	9	6 (6)	11 (8)	6 (–1, 12)	2.06	0.07
Hip extension R	9	5 (7)	9 (9)	4 (–3, 11)	1.29	0.23
Hip abduction L	9	27 (15)	28 (20)	1 (–9, 11)	0.29	0.78
Hip abduction R	9	24 (6)	20 (10)	–4 (–9, 2)	–1.62	0.14
Hip adduction L	9	23 (7)	21 (9)	–2 (–6, 2)	–1.04	0.33
Hip adduction R	9	18 (9)	17 (6)	–2 (–4, 1)	–1.44	0.19
Knee flexion L	9	124 (11)	126 (12)	2 (–8, 12)	0.51	0.62
Knee flexion R	9	120 (14)	129 (13)	9 (3, 16)	3.51	**0.008**
Knee extension L	9	0 (0)	0 (0)	–		**–**
Knee extension R	9	0 (0)	0 (0)	–		–
Ankle dorsiflexion L	9	6 (7)	11 (12)	5 (–2, 13)	1.57	0.15
Ankle dorsiflexion R	9	7 (7)	8 (10)	1 (–3, 5)	0.54	0.60
Ankle plantarflexion L	9	32 (12)	26 (9)	–7 (–19, 5)	–1.28	0.24
Ankle plantarflexion R	9	33 (10)	26 (7)	–7 (–17, 3)	–1.70	0.13
Ankle inversion L	9	21 (7)	14 (11)	–8 (–14, –1)	–2.78	**0.02**
Ankle inversion R	9	24 (12)	15 (9)	–9 (–22, 4)	–1.56	0.16
Ankle eversion L	9	14 (8)	13 (12)	0 (–4, 3)	–0.26	0.80
Ankle eversion R	9	16 (10)	11 (9)	–4 (–11, 3)	–1.29	0.23

R: right; L: left; 95% CI: 95% confidence interval; SD: standard deviation.
The bold in these Tables identifies p values below 0.05.

Adverse events

A total of 4 AEs were recorded (Table I), 1 of which was categorized as serious, but none were directly attributable to the trial.

Secondary outcome measures

Tables V–X report statistically significant changes between baseline and post-trial measurements.

Passive joint range of motion

Mean left ankle inversion ROM decreased by 7° and mean right knee flexion increased by 9° at the end of the trial (Table V).

Balance

Four participants achieved a clinically significant improvement in balance over the course of the trial. This was determined by calculating whether a sufficient increase in points had been made by the individual relative to their initial BBS score (36) (Tables VI and VII).

Table VI. Clinically significant change in individual Berg Balance Scale scores during the trial

Baseline score categories	Clinically significant change requires an improvement by the number of points identified below for each category	No significant change (number of participants (%))	Significant change (number of participants (%))
0–24	5	2	3
25–34	7	1	1
35–44	5	2	0
45–56	4	1	0
All patients	–	6 (60%)	4 (40%)

MSIS-29

There was a positive change for all but 2 participants in how MS was perceived to impact on their daily lives during the trial (Table VII).

EQ-5D-5L

Scores increased over time by a mean of 0.17 units, with all but 3 participants reporting an improvement and none showing a decline (Table VII).

Spasticity

Statistically significant reductions in spasticity were detected in the left ankle plantarflexors and dorsiflexors and right ankle dorsiflexors (Table VIII).

PIADS

Participants consistently reported that taking part in the trial had made a significant positive impact on the 3 individual components of competence, adaptability and self-esteem (Table IX).

ABC/ArmA/VAS (Pain)/ESS/MSWS-12/MFES

There was no significant change between time-points for the ABC, ArmA, VAS pain, ESS scores, MSWS-12 and MFES during the trial (Tables VII and X).

The improvements observed above accorded with informal feedback from participants and, in some cases, their carers (see Appendix S3 for all feedback).

DISCUSSION

The main findings of this study are that it is feasible and safe to use this exoskeleton to support and enable

Table VII. Secondary outcome measures

Outcome Measure	N	Baseline Mean ± SD	Post-treatment Mean ± SD	Change Mean (95% CI)	t (9 degrees of freedom)	*p*-value
ABC	10	42 ± 25	43 ± 22	1 (–16, 17)	0.07	0.95
MFES	10	5.1 ± 2.7	6.6 ± 2.5	1.6 (–0.3, 3.4)	1.93	0.09
MSWS-12	10	82 ± 15	66 ± 27	–15 (–33, 2)	–1.96	0.08
MSIS-29	10	91 ± 19	65 ± 30	–26 (–42, –9)	–3.58	**0.006**
ARMA section A	10	6 ± 8	5 ± 8	–1 (–3, 1)	–1.09	0.30
ARMA section B	10	17 ± 21	13 ± 18	–4 (–12, 3)	–1.26	0.24
Berg Balance	10	25 ± 18	28 ± 16	4 (–1, 8)	1.72	0.12
EQ-5D-5L	10	0.54 ± 0.20	0.71 ± 0.06	0.17 (0.03, 0.32)	2.71	**0.02**
EQ-VAS	10	77 ± 12	85 ± 17	8 (–3, 20)	1.53	0.16

SD: standard deviation; 95% CI: 95% confidence interval; ABC: Activities- Specific Balance Confidence scale; MEFS: Modified Falls Efficacy Scale; MSWS: Multiple Sclerosis Walking Scale; MSIS: Multiple Sclerosis Impact Scale; ARMA: Arm Activity Measure; EQ-5D-5L:Health Related Quality of Life Scale; EQ-VAS: Visual Analogue Scale for Pain.

The bold in these Tables identifies p values below 0.05.

the performance of a balance exercise programme by PwMS, provided that there is a specialist team with an advanced level of clinical knowledge and expertise available to support participants. Taken together and mindful of the criteria on what constitutes a successful feasibility study (37), the outcomes showed that the intervention and assessment protocols were well-tolerated and not associated with any serious study-related adverse events.

There were only 3 minor adverse events and 1 serious adverse event, which were not directly related to the study, and which did not consume an excessive amount of unanticipated time or resources. Individuals diagnosed with relapsing remitting MS can experience a relapse at any time, and taking part in a clinical research trial would not prevent such an event. This accounts for the first AE in Table I. AEs 2 (suspected deep vein thrombosis) and 3 (back pain) were likewise un-associated with trial participation. Recording and resolving these AEs demonstrated the effectiveness of our risk assessment and safety monitoring process, given that they were quickly picked up when the participants arrived for their sessions. Direct access to the Principal Investigator within the team via telephone communication enabled swift access to expert knowledge and clinical decision-making to establish the most appropriate and safe course of action to be taken. AE 4 involved a participant who reported that they had fallen at home. It is known that the incidence of falls is 3 times higher in PwMS compared with older people (38) and this context is relevant and can account for this incident alone. It is perhaps notable that none of these AEs were connected to the use of the device or exercise programme. We suggest that this was partly due to the advanced level of clinical expertise and specialism within the trial research team, which meant for example, that individual participants were optimally positioned within the exoskeleton by the trial neurophysiotherapist and thereon kept under continuous, careful observation. An advanced level of expertise also enabled dynamic advanced risk assessment of participants, which enabled optimal safety throughout all trial exercise sessions.

We are aware of only 1 other feasibility and safety research trial, which examined the use of a different

Table VIII. Secondary outcome measure: Modified Ashworth Scale – Muscle spasticity

Measurement	Pre-treatment Mean (SD)	During treatment 2 Mean (SD)	During treatment 4 Mean (SD)	Post-treatment Mean (SD)	F (3, 27 degrees of freedom)	*p*-value
Hip flexors L	0.4 (0.7)	0.2 (0.4)	0.2 (0.4)	0.2 (0.4)	0.35	0.79
Hip flexors R	0.6 (1.0)	0.5 (0.5)	0.4 (0.5)	0.3 (0.7)	0.42	0.74
Hip extensors L	0.4 (0.9)	0.2 (0.6)	0.1 (0.3)	0.0 (0.0)	1.00	0.41
Hip extensors R	1.0 (1.3)	0.5 (0.9)	0.2 (0.4)	0.3 (0.7)	2.49	0.08
Hip adductors L*	0.4 (0.5)	0.6 (0.8)	0.5 (0.5)	0.3 (0.7)	0.51	0.68
Hip adductors R*	0.8 (1.0)	0.7 (0.8)	0.8 (0.9)	1.0 (1.0)	0.18	0.91
Hip abductors L	0.1 (0.3)	0.3 (0.5)	0.1 (0.3)	0.1 (0.3)	0.63	0.60
Hip abductors R	0.5 (0.7)	0.3 (0.5)	0.1 (0.3)	0.1 (0.3)	2.40	0.09
Knee flexors L+	0.0 (0.0)	0.4 (0.9)	0.2 (0.4)	0.0 (0.0)	0.89	0.53
Knee flexors R+	0.0 (0.0)	0.4 (0.9)	0.2 (0.4)	0.3 (0.5)	0.89	0.48
Knee extensors L+	0.0 (0.0)	0.6 (0.9)	0.2 (0.4)	0.0 (0.0)	1.85	0.20
Knee extensors R+	0.0 (0.0)	0.4 (0.5)	0.3 (0.8)	0.1 (0.4)	1.29	0.33
Ankle plantarflexors L	1.0 (1.2)	0.6 (0.8)	0.1 (0.3)	0.1 (0.3)	5.34	**0.005**
Ankle plantarflexors R	0.9 (0.9)	0.5 (0.8)	0.3 (0.7)	0.4 (0.7)	1.23	0.32
Ankle dorsiflexors L	0.7 (0.8)	0.3 (0.5)	0.2 (0.4)	0.1 (0.3)	3.46	**0.03**
Ankle dorsiflexors R	0.9 (0.9)	0.2 (0.4)	0.3 (0.7)	0.5 (0.5)	3.47	**0.03**

*3, 24 degrees of freedom due to missing data values.

+3, 11 degrees of freedom due to missing data values.

R: right; L: left.

The bold in these Tables identifies p values below 0.05.

Table IX. Secondary outcome measure: Psychosocial Impact Assistive Devices Scale (PIADS)

PIADS component	N	Mean (95% CI)	t (9 degrees of freedom)	*p*-value
Competence	10	0.5 (0.1, 0.9)	2.97	**0.02**
Adaptability	10	0.7 (0.3, 1.1)	3.83	**0.004**
Self-esteem	10	0.7 (0.2, 1.2)	2.97	**0.02**
Overall score	10	0.6 (0.2, 1.0)	3.37	**0.008**

powered exoskeleton for PwMS (13). This trial concluded that the exoskeleton used was feasible and safe for only 4 people out of the sample population of 13 participants. Conversely, this trial demonstrated that with an experienced trial team using the Rex Rehab exoskeleton device, it was feasible for all 10 individuals to participate and complete the trial safely. The current results accord with those of 2 other studies that examined the feasibility and safety of 2 different exoskeletons for people with SCI (10, 39), with both studies reporting safe, study protocol completion. Future studies could also compare different training regimes with or without powered exoskeleton devices. In terms of changes and improvements in participant independence and required assistance during the exercise sessions, it could also be useful to consider including a broader outcome measure to detect and record these changes over the trial period in future research.

A recent systematic review on the use of robot-assisted training for balance training for patients affected by stroke reported that robot-assisted therapy offers significant improvement in balance compared with traditional therapy (40). This endorses and supports the current study, as analysis of the secondary outcome measures revealed a clinically meaningful improvement in balance for 4 participants. This clinical change was endorsed by their subjective feedback and care-giver comments (Appendix S3). With regards to balance, relevant research has found that PwMS who are able to walk have decreased core muscle strength compared with individuals in a matched control group (41). PwMS also find it more challenging to maintain postural stability when challenged by external forces (42) and experience delays in postural adjustments (3) and fear of falls (8). Importantly, clinical research evidence demonstrates that training core abdominal muscles improves anticipatory postural adjustments and balance, and reduces the associated fear of falls (43, 44). Accordingly, the practise adopted in this study of encouraging participants to actively contract their abdominal muscles prior to and during movement may have helped their balance (see intervention details in Appendix S2). It is also notable that there were improvements during the study in the passive joint ROM at the left ankle and right knee, and a significant reduction in muscle spasticity in both left and right ankle dorsiflexor muscles and left ankle plantarflexor muscles. Such improvements could also have a positive influence on balance (9). One participant in our group of 10, was unable to stand independently and unable to walk. Future research should consider the potential inclusion of a functional sitting balance measurement scale, for example, the Function In Sitting Test (FIST) (45), for individuals who are not able to walk, which would enable more relevant data to be collected for such individuals.

Table X. Secondary outcome measures: visual analogue scale (VAS) pain and Epworth Sleepiness Scale (ESS)

	N	Mean (SD)	F	*p*-value
VAS pain				
Baseline	11	1.6 (2.2)	0.85	0.52
During treatment 1	10	0.5 (0.8)	(5, 45 degrees of freedom)	
During treatment 2	11	0.7 (1.5)		
During treatment 3	10	0.5 (0.8)		
During treatment 4	9	0.7 (2.0)		
Post-treatment	10	0.9 (1.6)		
ESS				
Baseline	11	6.7 (4.1)	1.33	0.28
During treatment 2	11	7.2 (4.3)	(3, 27 degrees of freedom)	
During treatment 4	9	5.3 (4.2)		
Post-treatment	10	5.8 (4.2)		

SD: standard deviation.

For some participants, improvements translated into other benefits. For example, 1 participant was able to pick up a shoe from the ground, which he had previously been unable to do, and thus this was extremely meaningful for him. There were also allied improvements in perceived individual competence, adaptability and self-esteem recorded via PIADS for all participants, with some individuals starting new activities; for example, going to the gym and gliding, which they attributed to their positive experience of taking part in the trial. There were also statistically significant improvements in perceived health and quality of life and a reduction in the perceived impact of MS on day-to-day life, although it is noted that there were numerous secondary outcomes and due to multiple testing, changes in some outcomes may have been expected due to chance.

Study limitations

This study has several limitations. The broad study eligibility criteria meant that participants varied from being independently mobile with a walking aid to being a wheelchair user and requiring a hoist for transfers. This heterogeneity made it challenging to identify group patterns during the trial and further research would benefit from recruiting a larger sample to allow participant stratification. Beyond the primary focus of the trial, the true magnitude of secondary health benefits detected for some participants could

potentially be more accurately uncovered by increasing the number and frequency of treatment sessions, which were limited by resource availability. That said, at the end of each exercise session participants were physically and cognitively tired, reflecting the demands of the intervention, hence spacing sessions out to enable recovery is important. In future research, it would also be useful to include an initial outpatient measuring appointment, where the individual has an opportunity to try the device. This would improve screening process efficiency and might also reduce the anxiety commonly expressed by participants when they tried out the device for the first time. Given that PwMS are a vastly heterogeneous group, and that the focus of this trial was feasibility and safety, the measured improvements in secondary outcomes for participants need to be understood as simply that these are key outcome measures for use in a larger trial, which could enable a more precise and in-depth comparison with individual baselines. There was no control group to exclude potential equivalent benefit from the treatment sessions without the exoskeleton device. And, finally, to improve insight and understanding of what is meaningful and relevant to individual participants, it would be extremely valuable to include a qualitative research study in any future research study, as what matters most to the individual is not always easily captured in quantitative feasibility research studies. PwMS are a vulnerable group of individuals, who experience balance issues and are at high risk of falls, which would impact negatively on their quality of life and have implications for health and social care systems throughout the world. The clinical significance of this study is that specialist teams can safely support and enable the practice of a balance exercise programme using this exoskeleton device. We consider it important that PwMS are supported and enabled to access and use equipment that can help, and we think that future research needs to consider the availability and access to specialist teams in countries throughout the world, given that qualifications, experience and skills are highly variable.

CONCLUSION

This study demonstrates that it is feasible and safe to use the Rex Rehab exoskeleton device to assist with a balance rehabilitation exercise programme for PwMS, provided that there is a specialist team in support with an advanced level of clinical knowledge and expertise.

This study provides preliminary evidence of measurable physical and psychological health benefits for some participants after only 4 treatment sessions. These findings justify further research to gain insight into "dose" response and treatment efficacy by refining the protocol to focus on those secondary outcome measures that showed evidence of improvement. In addition, it would be valuable to explore the experiences of trial participants in more depth via qualitative methodology.

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