Trials

STUDY PROTOCOL

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Dosing overground robotic gait training after spinal cord injury: a randomized clinical trial protocol

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Abstract

Background Robotic exoskeletons have changed rehabilitation care available to people after spinal cord injury (SCI). Yet, the current evidence base is insufficient to identify the optimal dose and neurophysiological mechanism of robotic exoskeleton gait training (RGT) as an effective rehabilitation approach. This study will (1) examine whether the frequency of RGT after motor incomplete SCI impacts function and health outcomes, (2) analyze the neuroplastic effects of RGT dose, and (3) evaluate the safety, tolerability, and feasibility of delivering RGT.

Methods We will enroll 144 participants with motor incomplete SCI admitted to inpatient rehabilitation within 6 months of SCI. Participants will be randomized based on injury severity and level into one of 3 RGT frequency groups (high, moderate, low) or none/usual care only. Participants will complete 24 RGT sessions and be assessed at admission and discharge to inpatient rehabilitation, post-RGT intervention, 1-month post-RGT, and 9-month post-SCI. Outcomes include Walking Index for Spinal Cord Injury-II, health outcomes (gait speed, Spinal Cord Independence Measure, pain, fatigue, spasticity, general health, quality of life, physical activity), and motor evoked potential amplitudes obtained using transcranial magnetic stimulation.

Discussion Successful completion of this study will provide an evidence-based intervention, specifically tailored to meet the unique needs of people with SCI, which supports walking recovery; maximizing health, function, and ultimately participation. The intervention will further support widespread clinical implementation of exoskeleton use during acute rehabilitation.

Trial registration ClinicalTrials.gov NCT05218447. Registered on June 23, 2022.

Keywords Clinical trial, Spinal cord injury, Gait, Robotic gait training, Rehabilitation

Introduction

Background and rationale {6a}

Spinal cord injury (SCI) due to trauma is estimated to affect 250,000–368,000 Americans, with an estimated 17,810 new cases annually [1]. The ability to walk is a priority for people with SCI [2] particularly among those newly injured. Dramatic advances in robotic exoskeleton technology are rapidly being adopted into clinical rehabilitation practice to aid in walking recovery post-injury.

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More than half of expected recovery occurs in the first 2 months after SCI and subsequent improvement plateaus after 3 to 6 months [3]. This critical period for neuroplasticity suggests that functional recovery may be greater using rehabilitation approaches, such as robotic exoskeleton gait training (RGT), at a dose that maximizes neuroplastic potential.

However, the evidence is lacking regarding the dose and neurophysiological mechanism of RGT during the subacute phase of rehabilitation for people with motor incomplete SCI. Due to this lack of evidence, no clinical practice guidelines exist that delineate which gait retraining approach or dose during early phases of recovery results in the best outcomes for people with motor incomplete SCI. This study systematically builds upon previous work [4–6] and will (1) generate efficacy data concerning the dose of RGT initiated during early phases of rehabilitation in people with SCI, (2) provide mechanistic data of neuroplasticity based on RGT dose, and (3) confirm that the intervention is safe, tolerable, and feasible to administer across inpatient and outpatient rehabilitation settings. Findings will directly impact rehabilitation clinical practice and patient outcomes for people with motor incomplete SCI.

Objectives {7}

Aim 1

Using a randomized controlled trial, prospectively examine whether the dosing frequency of RGT therapy provided during the acute/subacute rehabilitation phase after motor incomplete SCI impacts functional and patient-reported outcomes.

Hypothesis 1:1 High-frequency RGT will result in significantly improved walking performance as measured by Walking in Spinal Cord Injury-II (WISCI-II) scores than moderate or low-frequency RGT therapy or no RGT at all 5 assessment periods.

Hypothesis 1.2 High-frequency RGT will result in significantly improved outcomes as measured by gait speed, Spinal Cord Independence Measure, Numeric Pain Rating Scale, Fatigue Severity Scale, Penn Spasm Frequency Scale, Patient Health Questionnaire-9, Life Satisfaction Scale-9, and physical activity) than moderate or low frequency or no RGT at each of the 5 assessment periods.

Aim 2

Investigate the difference over 9 months of the neuroplastic effect of RGT dosing as measured by single-pulse transcranial magnetic stimulation (TMS).

Hypothesis 2.1 High-frequency RGT will lead to significantly greater change in neurophysiological measures (e.g., greater motor evoked potential (MEP) amplitudes of the corticospinal tract) than moderate, low, or no RGT.

Aim 3

Evaluate the safety, tolerability, and feasibility of delivering different dosing frequencies of RGT from inpatient to outpatient rehabilitation settings.

Hypothesis 3.1 Delivering RGT therapy at differing dosing frequencies from inpatient to outpatient rehabilitation settings will be safe, tolerable, and feasible.

Trial design {8}

This protocol will describe a single-blinded prospective, randomized trial and follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist to report relevant clinical trial details.

Methods: Participants, interventions, and outcomes

Study setting {9}

All study procedures will take place at Baylor Scott & White Institute for Rehabilitation, an inpatient and outpatient rehabilitation hospital in an urban setting in the Southwestern United States.

Eligibility criteria {10}

Patients will be screened for eligibility and qualifying patients will be approached to participate. Individuals between the ages of 16 to 85 years, within 6 months post-motor incomplete SCI, who are admitted to inpatient rehabilitation, and who meet the criteria to use an EksoNR robotic exoskeleton will be eligible. Exclusion criteria are (1) moderate to severe TBI, (2) degenerative diagnoses, (3) wound located in proximity to the exoskeleton frame, (4) severe osteoporosis/osteopenia as shown with dual-energy X-ray absorptiometry (DEXA), (5) premorbid developmental disability, significant psychological diagnosis, or other cognitive impairment.

Who will take informed consent? {26a}

Patients will be evaluated by clinicians to determine if they meet the eligibility criteria during the beginning of their inpatient stay. If a patient is not initially appropriate for intervention due to medical reasons and later determined to be appropriate during their stay, they may be approached to consent to participate. The intervention may be discontinued if there is an improvement or worsening of their condition where gait training is no longer appropriate as deemed by a clinician, or at the participant's request.

Additional consent provisions for collection and use of participant data and biological specimens {26b}
No ancillary studies were planned.

Interventions

Explanation for the choice of comparators {6b}
Existing evidence is lacking regarding which gait retraining approach or dose during early phases of recovery results in the best outcomes for people with motor incomplete SCI. This study will compare emerging technology (RGT) with traditional usual care gait training (UC) approaches across inpatient and outpatient rehabilitation settings.

Intervention description {11a}
UC gait training
UC gait training interventions will adhere to the current SCI-specific clinical practice rehabilitation guidelines which recommend that body weight–supported treadmill training (BWSTT) and conventional over-ground walking be available as options for gait training depending on resource availability, context, and local expertise [7].

Robotic gait training (RGT)
During RGT sessions, participants will wear the battery-powered wearable bionic suit, which includes motors at the hips and knees that enable individuals with lower extremity motor impairment to stand and voluntarily step over-ground with weight-bearing and alternating gait. The EksoNR robotic exoskeleton (Richmond, CA, USA) is a class II medical device (US FDA) which provides functional rehabilitation in the form of over-ground weight bearing stepping in people with SCI. The Ekso device offers a variable assist mode to allow the subject to voluntarily assist, even when the subject exerts minimal voluntary influence on the robot. In this study, the variable assist mode will be used exclusively.

Intervention composition
Each gait training session (UC and RGT) will occur during a 45-min physical therapy session. Gait training sessions will commence once patients are deemed clinically appropriate as defined by being able to tolerate standing for 15 min without orthostatic intolerance. Gait training sessions occur weekly and are completed over consecutive weeks according to their intervention assignment during inpatient and outpatient rehabilitation until the dosing schedule of gait sessions has been completed, or their intervention has been discontinued.

Fidelity of RGT delivery
To ensure the internal validity of the intervention, fidelity assessments will be utilized to determine the degree to which the RGT intervention is consistently applied across the study. The Principal Investigator and a research coordinator will provide the fidelity checks of 10% of live RGT sessions at randomly selected intervals. In the event that our intervention fidelity rate falls below 90%, our therapists will review RGT Program training modules devised by Ekso Bionics until the fidelity rate rises above our 90% threshold. Lastly, after initial project staff training, we will revisit training modules annually or as needed.

Criteria for discontinuing or modifying allocated interventions {11b}
There is no forecast for discontinuing or modifying allocated interventions for a given trial participant.

Strategies to improve adherence to interventions {11c}
Strategies to improve participant adherence to the intervention include flexible scheduling of weekly gait training sessions and assessments, and arranging transportation services for study activities occurring during after discharge from inpatient rehabilitation.

Relevant concomitant care permitted or prohibited during the trial {11d}
All study participants will receive 3 h of daily inpatient rehabilitation services. By nature, inpatient rehabilitation is transdisciplinary and includes medicine, nursing, therapy, and other health care services.

Provisions for post-trial care {30}
No provisions are provided for post-trial care.

Outcomes {12}
Aim 1
Demographic data will be collected at admission to inpatient rehabilitation and include current age and age at injury; injury severity; gender; ethnicity; education level; pre-morbid history of mental illness; residence status; income; insurance type; vocation; financial status and ASIA Impairment Scale (AIS) score. The 10MWT, WISCI-II, SCIM, NPRS, and PSFS assessments will be assessed by a licensed clinician blinded to group allocation. Patients will complete the following self-reported assessments (FSS, PHQ-9, and LISAT-9) with a blinded research coordinator.

Aim 2
Our TMS assessment protocol will closely follow the procedures recommended by The International

Table 1 Study outcome measures

Aim 1 Primary outcome: to examine the efficacy of RGT dose	
Walking Index for Spinal Cord Injury -II (WISCI-II)	*Our primary outcome*, the WISCI-II defines the physical limitation for gait secondary to impairment at the person level and indicates the ability of a person to walk after SCI [12]. Intrarater and interrater reliability are excellent at 1.0 and 0.98 respectively [13].
Aim 1 Secondary outcomes	
Gait speed* via *10-Meter Walk Test (10MWT)	Gait speed (m/s) is correlated with mobility in the community, capacity to perform activities of daily living, risk of falls, re-hospitalization, and risk of cognitive decline [14]. A change of > 0.06 m/s is considered to exceed minimally clinically important difference (MCID) [15] and test–retest reliability is excellent (ICC = 0.97) [16].
Spinal Cord Independence Measure (SCIM)	The SCIM assesses self-care management, respiration and sphincter management, and functional mobility after a SCI. With excellent interrater reliability (r = 0.90) [17], the SCIM is reported to be more sensitive to functional changes than the FIM [18].
Numerical Pain Rating Scale (NPRS)	A 0–10 Point Numerical Pain Rating Scale (NRS) is recommended as the outcome measure for pain intensity after SCI [19] during acute and subacute phases.
Fatigue Severity Scale (FSS)	The Fatigue Severity Scale (FSS) [20] measures the effects of fatigue on function. The FSS has acceptable reliability with regard to internal consistency, test–retest reliability, and validity in persons with SCI [21].
Penn Spasm Frequency Scale (PSFS)	The PSFS assesses a person's perception of spasticity frequency and severity following a SCI [22] and demonstrates excellent internal consistency (ICC = 0.90) [23].
Patient Health Questionnaire—9 (PHQ-9)	The PHQ-9 assesses the presence and intensity of depressive symptoms. For SCI, the PHQ-9 demonstrates excellent internal consistency (Cronbach's alpha = 0.87) [24].
Life Satisfaction Questionnaire (LiSAT-9)	The LISAT is a nine-item quality of life questionnaire suitable for SCI populations containing a single item assessing overall life satisfaction, along with eight additional domain-specific items [25].
Physical activity	Actigraph GT9x (Actigraph LLC, Pensacola, FL, USA) is reported to accurately measure steps in people with incomplete SCI during rehabilitation [26]. At each assessment period, the participant will also be given an Actigraph device to wear for the following 7 days.
Aim 2 Outcomes: To determine the neuroplastic effect of dosing RGT	
Transcranial magnetic stimulation (TMS)	TMS will be utilized to capture motor thresholds and MEP amplitudes from the TA, RF, and FDI muscles and be used to index corticospinal excitability. A lower motor threshold and greater MEP amplitude suggest an increased excitability. We will compute the slopes of the recruitment curves constructed for TA and RF. A flatter slope of the recruitment curve suggests a less efficient corticospinal recruitment pattern [27].
Aim 3 Outcomes: To evaluate the feasibility of delivering RGT across inpatient to outpatient rehabilitation settings	
Safety, tolerability, and feasibility	Safety, tolerability, and feasibility of RGT treatment will be measured across inpatient and outpatient practice settings. Metrics include safety (rate of adverse events), tolerability (visual analog scale of tolerability, heart rate, perceived exertion, number of steps), and feasibility (treatment completion rate).

Federation of Clinical Neurophysiology (IFCN) committee [8] and McKay et al. [9] TMS assessments (Table 1) will take place in the research lab. During the assessment, surface electromyographic (EMG) electrodes will be placed on the following key muscles: bilateral tibialis anterior (TA), first dorsal interosseous (FDI), and rectus femoris (RF). All TMS assessments will be performed on the primary motor cortex contralateral to the less affected side because the stronger side yields more reliable measures [10]. However, EMG activity will be measured bilaterally as recommended [11]. The less affected side will be determined based on manual muscle testing.

Safety considerations Participants will be asked to complete a TMS safety screening prior to each TMS assessment. A physician co-investigator on the study will review and give approval for each participant prior to TMS assessment. People with a history of seizures, migraines, or having recently taken certain drugs/medications will be excluded from the TMS assessments.

Determination of hot-spots and motor thresholds A single pulse TMS stimulator (Duo Magcart Mp Dual, Czech Republic) and a 110-mm double cone coil (120BFVT Butterfly V-Shaped Coil 120 mm with controls) will be used to determine the hot-spot of TA, RF, and FDI. Hot-spots are defined as the location on the scalp that yields the greatest and most consistent MEP. During testing, participants will wear a Lycra swimming cap with a pre-marked 1 cm grid to guide the coil placement. Once the hot-spot is identified, resting motor thresholds (RMT) of the corresponding muscles will be determined. RMT (expressed as % of stimulator output) is defined as the minimal stimulator intensity that will yield a MEP > 50 microV in 3 out of 5 trials when the tested muscle is at rest. If RMT cannot be obtained, MEP absence will be recorded for the muscles. For each tested muscle, we will record the presence/absence of MEP.

MEP amplitudes MEP amplitudes of TA, RF, and FDI will be determined using the single pulse TMS stimulator and double cone coil. For those participants whom a RMT can be obtained, resting MEP amplitudes will be measured at the intensity of 1.2 RMT and 100% stimulator outputs as RMT is expected to change during the course of the study for the individual participant. For those without an established RMT, resting MEP will only be measured at 100% stimulator output. For each intensity, 5 suprathreshold stimulations will be applied to the hot-spot of the tested muscles.

Short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) of TA and RF of the less affected leg will be measured using paired pulse TMS. For SICI, the interpulse interval will be 2 ms while the interval will be 15 ms for ICF. For each measure of each muscle, we will collect 5 trials. The conditioned stimulus intensity will be set at 80% of RMT and the tested stimulus intensity will be 120% RMT. For individuals without an established RMT at the time of assessment, the conditioned intensity will be set at 67% of the stimulator output and the test stimulus will be set at 100% of the stimulator output.

Aim 3

Gait training session data (UC and RGT) will be captured during and after each treatment intervention. Session data will include measures of intensity [heart rate (HR) as measured by Polar® RS300X wrist-based activity monitor and patient-reported rating of perceived exertion (RPE)] and a number of steps. Reported RGT-emergent AE will include falls, skin integrity, autonomic dysreflexia, fracture, and fainting. Patients in the RGT groups will be asked to complete a brief survey weekly to report tolerability and adverse symptoms.

Participant timeline {13}

Assessments

Participants will complete a total of five assessments throughout participation in this study.

Participants in the RGT groups will complete assessments:

1. Within 5 days of initial enrollment into the study
2. Within 5 days of discharge from inpatient rehabilitation
3. Within 5 days of completing 24 RGT sessions
4. One-month (± 7 days) after completing 24 RGT sessions
5. Nine-month (± 7 days) post-SCI onset

Participants in the UC group will complete assessments:

1. Within 5 days of initial enrollment into the study
2. Within 5 days of discharge from inpatient rehabilitation
3. One-month (± 7 days) after discharge from inpatient rehabilitation
4. Two-month (± 7 days) after discharge from inpatient rehabilitation
5. Nine-month (± 7 days) post-SCI onset

Sample size {14}

Sample size determination was performed using G*Power 3.1.9 for a global F test between the 4 groups with 5 repeated measurements in each group. Estimates used in the calculations are based on our previously collected WISCI-II scores and published results on longitudinal scores [28, 29]. We estimated the correlation among repeated measures will fall between 0.5 and 0.75. Using the approximate midpoint, 0.60, we can detect a medium effect size, $f = 0.25$, with 80% power at the 5% significance level with a sample size of 124. Allowing for ~ 15% attrition due to unplanned medical events, acute care transfers, and patient withdrawals, we will enroll 36 participants per group (total $n = 144$). It is important to note that the sample size calculations are based on finding an overall statistically significant difference between groups and were not adjusted for potential subsequent pairwise comparisons.

Recruitment {15}

All study procedures will take place at Baylor Scott & White Institute for Rehabilitation, an inpatient and outpatient rehabilitation hospital in an urban setting in the Southwestern United States. Patients will be evaluated by clinicians to determine if they meet the eligibility criteria during the beginning of their inpatient stay. If a patient is not initially appropriate for intervention due to medical reasons and later determined to be appropriate during their stay, they may be approached to consent to participate.

Assignment of interventions: allocation

Sequence generation {16a}

Participants will be assigned to one of four gait training groups using 1:1:1:1 stratified blocks:

1. High-frequency RGT (4 sessions/week for 6 weeks)
2. Moderate-frequency RGT (3 sessions/week for 8 weeks)
3. Low-frequency RGT (2 sessions/week for 12 weeks)
4. Usual care (UC) gait training only, without robotic exoskeleton

Stratification will be based on specific injury characteristics (tetraplegia with AIS C, tetraplegia with AIS D, paraplegia with AIS C, and paraplegia with AIS D), and within each stratum, randomization blocks will be used to ensure equal distribution between groups.

Concealment mechanism {16b}

A centralized computerized allocation system will be implemented in RedCAP.

Implementation {16c}

The randomization schema will be developed by the study biostatistician and imported into Research Electronic Data Capture (REDCap) for the study coordinator to randomize participants using the REDCap randomization module.

Assignment of interventions: blinding

Who will be blinded {17a}

All clinical and study-specific assessments will be completed by an assessor blinded to group allocation, and biostatisticians will be blinded. Participants and therapists providing the intervention will not be blinded to group allocation nor intervention approach.

Procedure for unblinding if needed {17b}

N/A—given the setting and context of the intervention and trial, we did not plan any procedure for unblinding.

Data collection and management

Plans for assessment and collection of outcomes {18a}

All primary and secondary outcome measures captured during each of the five assessments are detailed in Table 1.

Plans to promote participant retention and complete follow-up {18b}

Strategies to promote participant retention to study activities include flexible scheduling of assessments, arranging transportation services for study activities occurring during after discharge from inpatient rehabilitation, and providing remuneration upon completion of assessments.

Data management {19}

All data will be stored on a secure server, with security meeting institutional standards for the protection of protected health information (PHI). Study data will be collected and managed using REDCap tools [30].

Confidentiality {27}

In order to assure participant confidentiality, all participants will be assigned a unique study identification number. All case report forms and databases will use the subject ID number rather than names or other private health information. Signed consent forms and non-electronic data case report forms will be maintained by the PI and stored in a secured cabinet in the Research Office Suite. All data will be stored on a secure server, with security meeting institutional standards for the protection of protected health information (PHI).

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

N/A, no biological specimens will be collected as part of this trial.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Dosing effects of RGT (Aim 1) on WISCI-II scores (Hypothesis 1) and secondary outcomes (Hypothesis 2) will be evaluated using general linear mixed effects models to assess the differences between groups and over time, as well as the time by group interaction.

To evaluate change in neurophysiological measures (Aim 2) a general linear mixed effects model will be used with single-pulse TMS as the outcome. The independent variables of interest will be changed over time,

difference between groups, and the group-by-time interaction.

To evaluate the safety of delivering different dosing levels of RGT from inpatient to outpatient rehabilitation settings (Aim 3), we will report the rate of RGT-emergent adverse events within each group for inpatient sessions and outpatient sessions. The number of adverse events per patient for each setting will be analyzed between groups using a generalized linear mixed effects model with a Poisson distribution and log link function. To evaluate tolerability, the visual analog scale scores will be analyzed across settings using a general linear mixed effects model. To evaluate feasibility across dose groups and settings, patients will be scored for completion of sessions in both the inpatient and outpatient settings. Analysis of feasibility will be performed with a general linear mixed effects model with a binomial distribution with a logistic link function.

All analyses will be performed overall, stratified by injury level and by AIS severity to determine if the effects of dosing vary between them. Analysis will be performed using SAS 9.4. The significance level will be set at 0.05.

Interim analyses {21b}

N/A—given the setting and context of the intervention and trial, we did not plan any interim analyses.

Methods for additional analyses {20b}

N/A—no additional analyses were planned.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Intent-to-treat analysis will be used such that a participant will remain in their randomization group for all analyses regardless of the number of treatment sessions they completed. If a patient misses one or more of their outcome assessments, their outcome data for that time period will be treated as missing. However, the chosen analysis methods will allow for data from the completed assessments for that patient will be included. Sensitivity analysis will be performed to assess the impact of missing data, by imputing a missing outcome measure using the overall average change score for the given outcome. The sensitivity analyses will be compared to the initial analysis to determine the impact of missingness on the results.

Plans to give access to the full protocol, participant-level data, and statistical code {31c}

The study investigators have full access to study datasets. The datasets used and analyzed during the study will be made available from the corresponding author on reasonable request; however, any information shared will be blinded to any identifying participant information.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The study staff (PI, Co-Investigators, research coordinators, and assistants) will be responsible for collecting and recording all clinical data. As results are collected, all Adverse Events will be identified, graded for severity, and assigned causality.

Composition of the data monitoring committee, its role and reporting structure {21a}

A 3-member external Data Safety and Monitoring Board (DSMB) will be established prior to beginning data collection. The DSMB will monitor the study and review quarterly the following: (a) participant recruitment, accrual, retention, and withdrawal information; (b) adverse events (AEs); (c) participant interview and/or performance status outcomes; (d) other safety-supporting data requested by the DSMB; and (e) summary of protocol violations and unanticipated problems.

Adverse event reporting and harms {22}

Only those adverse events directly related or caused by the study will be reported to the IRB and compiled for periodic review according to institutional policies. After assigning causality, the PI will decide the course of action for the study participant. The PI will evaluate all Adverse Events and determine whether the Adverse Event affects the risk/benefit ratio of the study and whether modifications to the protocol or informed consent form are required. Throughout this process, the PI will inform and collaborate with the research team.

Participants may experience orthostatic hypotension, skin breakdown, overheating, and autonomic dysreflexia if they have difficulty due to impaired motor and sensory function common to the SCI population. Transcranial magnetic stimulation (TMS) application might result in a minor headache or discomfort at the site of stimulation, but the incidence is rare. TMS produces clicking sounds when it is charged, which can potentially cause some temporary changes in the hearing threshold. This effect is similar to going to a musical concert and is transient (lasts 1 day). A seizure from the stimulation is the most serious side effect of TMS that occurs in less than 1 in 1000 applications of TMS sessions. Participants may experience frustration during RGT due to motor and sensory deficits common to the SCI population. All therapy staff is trained to observe and monitor for these risks and methods to limit or resolve these potential concerns.

Record of adverse events will be reported in future trial publications.

Frequency and plans for auditing trial conduct {23}

Data cleaning and auditing will occur quarterly throughout the lifecycle of the study. During quarterly data cleaning and auditing, all data collected will be subject to programmed data checks and 10% of participant paper CRFs will be checked for data entry and source document errors. Any discrepancies identified will reviewed by a data manager, principal investigator, and appropriate staff. Study personnel are expected to resolve the queries within 1 week.

Plans for communicating important protocol amendments to relevant parties {25}

All revisions and protocol amendments will be reported to the IRB as per federal regulations, the Office of Human Research Oversight (OHRO) with the USAMRDC, and the United States Department of Defense through the Spinal Cord Injury Research Program.

Dissemination plans {31a}

Trial results will be communicated to healthcare professionals and other relevant groups via publications, reporting in results databases, and presenting the data during the medical congresses and conferences.

Discussion

This trial will examine the efficacy and the dosage of RGT for improving walking and mobility in people with SCI. Although previous studies [31] have investigated the RGT effect and walking training, methodological shortcomings (e.g., design and very small sample sizes) and characteristics of interventions (e.g., duration of intervention, type of exercises) prevent drawing clear conclusions, which could help clinicians in their decision-making process. In addition, many trials did not investigate the duration of gains achieved. To address these limitations, this protocol describes a single-blinded randomized trial to be conducted with follow-up through 9 months post-SCI. High internal validity is expected, due to randomization, concealed allocation, blinding of assessors, intention-to-treat analysis [32], and adequately powered sample size.

Previous studies suggest that RGT improves several aspects of gait after training and increasing evidence indicates that the aftereffects of RGT are driven by best motor performance [33]. Better motor control, therefore, can induce lasting changes in the individual's activity and participation. Although some other effects of RGT have been identified, such as improvements in cardiorespiratory fitness, quality of life, and depression [34, 35], optimal dose of RGT to improve walking function remains unclear. This study focuses on identifying the dose of RGT that maximizes walking recovery and neuroplastic potential in individuals with SCI.

This trial has some limitations. The RGT intervention is delivered two or more times per week over several weeks, and, therefore, depends on the participants' motivation, adherence, and commitment to fully engage in the trial. Strategies to encourage participants to fully engage are integrated within the trial.

Successful completion of this trial may result in an important advance in the rehabilitation of people with incomplete motor SCI. Importantly, findings from this trial will be used to inform safe, tolerable, and feasible interventions to address walking recovery and neuroplastic potential after SCI.

Trial status

Institutional Review Board approvals were obtained in November 2021. This protocol paper reflects the study protocol version 1.8 created in December 2021. The clinical trial was registered at ClinicalTrials.gov (NCT05218447). Recruitment and enrollment were initiated in April 2022 following receipt of approval from the Office of Human Research Oversight (OHRO) with the USAMRDC. At the time of manuscript submission, the expected duration of the study, including enrollment and statistical analysis, should be 5 years. The approximate date of planned recruitment completion is September 2025.

Abbreviations

SCI	Spinal cord injury
RGT	Robotic gait training
WISCI-II	Walking in Spinal Cord Injury-II
TMS	Transcranial Magnetic Stimulation
MEP	Motor evoked potential
EksoNR	Robotic exoskeleton
DEXA	Dual-energy X-ray absorptiometry
UC	Usual care
REDCap	Research Electronic Data Capture
BWSTT	Body weight–supported treadmill training
AIS	Impairment Scale
10MWT	10-Meter Walk Test
SCIM	Spinal Cord Independence Measure
NPRS	Numeric Pain Rating Scale
PSFS	Patient Specific Functional Scale
FSS	Family Self-Sufficiency
LISAT-9	Life-Satisfaction Questionnaire-9
IFCN	International Federation of Clinical Neurophysiology
EMG	Electromyographic
TA	Tibialis anterior
FDI	First dorsal interosseous
RF	Rectus femoris
RMT	Resting motor thresholds
SICI	Short-interval intracortical inhibition
ICF	Intracortical facilitation
HR	Heart rate
RPE	Rating of perceived exertion
DSMB	Data Safety and Monitoring Board
AEs	Adverse events

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-024-08503-0.

Supplementary Material 1.

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Authors' contributions {31b}
All authors contributed to the development of the study protocol and this manuscript. All authors have read and approved the final version of the manuscript. Authorship eligibility followed ICMJE guidelines.

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Availability of data and materials {29}
The study investigators have full access to study datasets. The datasets used and analyzed during the study are available from the corresponding author on reasonable request; however, any information shared will be blinded to any identifying participant information.

Declarations

Ethics approval and consent to participate
The study obtained ethical approval from the Institutional Research Ethical Committee (021–205) of the Baylor Scott Research Institute, Dallas, TX, USA, which means all of the study procedures remain in accordance with the Declaration of Helsinki concerning Ethical Principles for Medical Research Involving Human Subjects. Informed consent will be obtained from all study participants.

Consent for publication {32}
All authors provided consent for publication.

Competing interests {28}
The authors declare that they have no competing interests.

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