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STUDY PROTOCOL

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A research protocol to study the critical time window for rehabilitation after incomplete spinal cord injury: early vs. late locomotor training

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Abstract

Spinal cord injury (SCI) often results in severe motor and sensory deficits, leading to significant disability. Preclinical studies and retrospective studies suggest that a critical window of enhanced neuroplasticity may exist immediately after SCI, during which therapeutic interventions could yield greater functional improvements. The impact of time interval since SCI on efficacy of rehabilitation has not been directly assessed and is the focus of this clinical trial. This study will compare the efficacy of high-intensity gait training, initiated at different time intervals post-injury, on walking performance in individuals with SCI. We hypothesize that early intervention will yield the greatest improvements in walking ability and community ambulation, compared to training initiated at 3 or 6 months after SCI, or standard of care. This randomized, multi-site clinical trial will enroll 108 participants with acute, traumatic SCI. Participants will be randomized to receive 20 h of high-intensity gait training that will be initiated either early (< 60 days post-SCI), sub-acute (3 months), chronic (6 months), or to a control group receiving standard of care. Primary outcomes include gait speed (10 m Walk Test) and walking endurance (6-Minute Walk Test). Secondary outcomes include daily step count via wearable sensors, lower extremity strength, and quality of life measures. Assessments will occur at baseline, pre/post-intervention, and at 3, 6, 9, and 12 months post-SCI. This study will provide insights into the optimal timing of rehabilitation post-SCI and could have profound effects on our approach to training individuals with SCI in the healthcare setting as well as long term recovery outcomes.

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Keywords Neuroplasticity, Spinal cord injury

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Introduction

Background and rationale

Spinal cord injury (SCI) often results in debilitating impairment and significant disability, including paralysis and sensorimotor dysfunction. Less than 1% of persons experiencing SCI achieve complete neurologic recovery by the time of hospital discharge [1]. Consequently, most individuals that sustain a SCI lose the ability to walk independently and, as a result, experience limitations in returning to community and independent living [2]. In addition, the complex and costly nature of SCI rehabilitation places a large burden on the health care system and society. There is thus a compelling need to develop more effective strategies and interventions that can maximize walking recovery for these populations.

The concept of neuroplasticity, the nervous system's capacity for structural and functional reorganization, is central to rehabilitation strategies after SCI [3]. Activity-dependent neuroplasticity through massed practice is a mainstay of post-SCI rehabilitation programs. However, despite progress in the field of rehabilitation sciences, the full potential of neuroplasticity in rehabilitation remains untapped. A significant, yet insufficiently studied, factor is the timing of post-injury intervention, which could influence therapeutic outcomes. People with SCIs are only transferred from an acute trauma center to the rehabilitation unit after their medical condition has stabilized. As a result, the time-to-admission interval and subsequent initiation of therapy is highly variable among SCI patients. While individuals with uncomplicated paraplegia may be transferred relatively quickly, admission of patients with quadriplegia to a specialized rehabilitation facility may be delayed because of comorbidities such as respiratory insufficiency or traumatic brain injury. It is possible that timing could influence a patient's response to therapy if there is a window of neuroplasticity during which training provides the greatest benefits. Moreover, this window may only be few weeks—or even less—in length.

Evidence from animal studies indicates that the timing of rehabilitative training post-SCI is crucial. Studies in rodent models of SCI demonstrate early initiation of training yields higher functional recovery compared to delayed rehabilitation. For example, one study showed that rats that began exercise therapy 1 day after SCI exhibited substantial gains in locomotor function when compared to those that began the exact same therapy 8 days later [4]. Similarly, another study in rats with SCI found significantly better improvement in stepping function when motor rehabilitative training was initiated immediately (3–4 days) following injury as opposed to three months post-injury [5]. Other studies indicate that locomotor training in animals initiated within the first few days after SCI improves motor recovery [6–8], prevents neuropathic pain [9, 10], and suppressed neuroinflammation at the lesion site [11]. Collectively, the evidence from preclinical studies suggests that there is a critical window immediately following SCI during which the nervous system exhibits heightened plasticity, responding more favorably to therapeutic interventions.

Human retrospective studies corroborate the temporal significance of rehabilitative interventions suggested by rodent models, indicating a period post-SCI in which recovery potential is maximized. Most functional recovery in individuals with SCI occurs within the first 3–6 months following SCI, often reaching a plateau by 9 months [12, 13]. A retrospective study in individuals with incomplete SCI showed average functional independence score (FIM) improvement during inpatient rehabilitation is 30 FIM points compared to a 10–16 FIM point improvement from the time of rehabilitation discharge to one-year post-injury [14]. Another multi-center cohort study from the North American Clinical Trials Network registry suggests that the largest change in lower motor extremity score is observed during the first ~ 3 months after SCI (+12%), compared to 3–6 months (+4%) or 6–12 months (+6%) [15]. Chronological sequence of ASIA Impairment Scale (AIS) conversion rates throughout the first year of SCI (i.e., at 2 weeks and 1, 3, 6, and 12 months post-SCI) also suggest that the highest proportion of conversions takes place during the first 3–6 months after SCI [16].

Separate from SCI, there are examples of adult neural circuits become more adaptable during critical periods in response to environmental or epigenetic triggers. For example, in adult rats, chronic treatment with the antidepressant fluoxetine can reopen the window of plasticity in the brain, allowing the recovery of vision in cases of adult amblyopia (lazy eye) [17]. Another example involves histone acetylation, an epigenetic process that modifies chromatin structure and influences gene regulation. This process can also reopen a critical period-like plasticity in the adult visual cortex [18, 19]. And finally, in a recent clinical trial, stroke patients randomized to receive 20 extra hours of self-selected, task-specific motor therapy acutely, sub-acutely, or chronically after stroke showed highest recovery of upper extremity motor function when training was delivered sub-acutely [20].

Overall, evidence from SCI animal literature, human retrospective studies, and studies in other non-SCI conditions suggests there are optimal periods of plasticity after a neurological injury when interventions are potentially most effective. These observations underscore the likelihood of a neuroplastic window that, if properly harnessed, could influence recovery trajectories and functional outcomes in humans with SCI. The impact of time interval since SCI on efficacy of rehabilitation has not

been directly assessed and is the focus of the current clinical trial.

Objective

The objective of the proposed study is to identify a potential time window of adaptive neuroplasticity after SCI. To do this, we will compare the effectiveness of similar training protocols administered at different time intervals after an acute spinal injury. We will initiate intensive locomotor therapy as early as possible but no later than 45 days after the initial spinal trauma. We will compare this to the impact of training initiated at 3 and 6 months after injury. These interventions will be paired with multiple performance and patient-reported measures, as well as community ambulation monitoring using wearable sensors for 1-year post-injury. Understanding the recovery potential of spinal cord with respect to time could lead to a paradigm shift in SCI rehabilitation, resulting in the development of more personalized and effective therapeutic strategies that align with the natural recovery processes of the spinal cord.

Hypothesis and aims

The primary aim of this study is to establish a critical time window of plasticity following an acute, traumatic SCI by administering 20 h of additional high intensity gait training at different time intervals post-injury. We are administering additional high intensity gait training, as defined by 65–80% of max heart rate or 6–8/10 on the Modified Rate of Perceived Exertion (RPE) scale, as early as possible (at least less than 45 days from injury), 3 months post-injury, or 6 months post-injury. A control group receives the standard of care for post-SCI rehabilitation. We hypothesize that the additional high intensity gait training will improve recovery outcomes and have the greatest functional impact when initiated less than 60 days after SCI, compared to 3 months and 6 months post-injury.

The secondary aim of this study seeks to determine the relationship between functional improvement achieved over the course of 20-hour high intensity training and post-intervention walking activity up to 1 year after SCI, including community ambulation. Individuals are provided with a step tracker to monitor their daily steps for 2-week intervals at 3, 6, 9, and 12 months post-SCI. A survey administered every 2 weeks collects information about physical activity occurring outside of the study, including daily life, continued therapy, and additional skilled intervention. We hypothesize that the relative change in community ambulation, as measured by step count using ActiGraph wearables, will be the greatest for the acute intervention group compared with the subacute intervention, chronic intervention, and control groups.

Table 1 Study eligibility criteria

Inclusion Criteria	Exclusion Criteria
History of acute and traumatic SCI with AIS classification of B, C, or D between the neurological levels of C2-and T12	Orthopedic injuries, fractures, surgeries, or other conditions affecting locomotor function or weight bearing
Between 16–75 years old	A weight over 250lbs, and if so, a BMI greater than 30, or deemed clinically inappropriate due to body habitus
Weight bearing as tolerated in bilateral lower extremities and able to tolerate a harness	Moderate to severe traumatic brain injury or other neurological conditions at a severity which impairs cognition
Able to provide informed consent within 45 days of injury onset	Presence of uncontrolled orthostatic hypotension that limits active participation in intense physical rehabilitation program
Able to participate in all study related activities, including 1-year follow-up	Other medical complications such as severe heart failure or large/deep pelvic or lower abdominal wounds which may limit ability to safely don and doff a harness
For minors, consent of parents or primary caregivers/guardians and assent of the minor	Pregnancy

Methods

Study design

This clinical trial employs a randomized, multi-site, placebo-controlled, and repeated measures study design (Clinicaltrials.gov identifier NCT06176833). There are two study sites: Shirley Ryan AbilityLab (SRAlab) in Chicago, IL and Baylor Scott and White Institute for Rehabilitation (BSW) in Dallas, TX. This study received approval from Northwestern IRB (#STU00219541) and the Department of Defense Office of Human Research Oversight (Award# HT9425-23-1-0418). Recruitment and enrollment of the study began in March 2024.

Inclusion/exclusion criteria

Inclusion and exclusion criteria can be found in Table 1.

Sample size

Our total subject enrollment target is 54 participants from SRAlab and 54 participants from BSW (i.e., $n=108$ subjects) with acute (<45 days from injury), traumatic, and incomplete SCI. These numbers reflect recruitment accounting for a potential ~ 20% attrition during the study (i.e., $n=88$ subjects are needed to reach statistical power).

We used gait velocity data from a study by Lucareli et al. [21] as pilot data to calculate the required sample population. The estimated gait velocity improvement from baseline was 0.4 m/sec with the estimated standard deviation (SD) of 0.41. Based on that pilot data and the two-sample t-test comparing each intervention group with the control group, the sample sizes of 22 participants in

each of the four groups are required to achieve the nominal statistical power of 80% at $\alpha=0.05$. Assuming a 20% dropout rate, 27 participants per group with a total of 108 participants will therefore be enrolled in the beginning of the study.

With at least 22 participants completing the protocol in each group, the estimated statistical power for the outcome of distance [21] is 94% for comparing the chronic intervention group to the control group, with a group difference estimate of 10.75 and a common SD of 9.06. When data from all groups are utilized, the statistical power is expected to be higher.

Study recruitment and enrollment

SRAlab and BSW have large SCI inpatient rehabilitation facilities, which are the primary source for participant recruitment. Every year, more than 500 inpatients with SCI are admitted across the two sites' rehabilitation centers. A study recruitment team of research therapists and a medical monitor has been established at each site. The study team screens all hospital admissions based on admitting medical diagnosis codes. Our team is collaborating with the SCI inpatient therapy staff regarding potential recruitment. If an individual is eligible based on the chart review and agreeable to speaking with a researcher, a study team member describes the research study based on a standardized recruitment script. Individuals must meet all study inclusion and exclusion criteria as presented in Table 1. All eligible individuals are informed of the study procedures and risks, and provide written informed consent to be able to proceed with the screening procedures.

After consenting, study participants proceed to the next phase of a physical screening by the study therapists and a medical screen by the study physician. The screening consists of confirmation of the eligibility criteria, a vitals assessment in sitting, an upright tolerance verbal screen for history of orthostatic hypotension, a lower extremity range of motion assessment, a lower extremity spasticity assessment, a manual muscle test of ISNCSCI exam muscle groups, a trial of tolerating a donned harness for at least 2 min in sitting, a trial of all gait equipment to safely mobilize the participant prior to the first training session, and a clinical assessment of the burden of care on study personnel to meet the required intensity for gait training. If the individual is medically cleared and passes the screening, the study structure and risks are once again reviewed, and written informed consent is again provided to participate in the main portion of the trial.

Randomization

Subjects who are eligible for the study and provide informed consent are randomly assigned to one of the four intervention groups as described previously. Randomization is stratified by study site and AIS level by using adaptive covariate randomization based on the method by Pocock and Simon [22]. The Pocock-Simon covariate adaptive randomization procedure is used so that there will be an approximately equal number of participants assigned to the four groups within each study site, as well as to ensure that the groups are balanced with respect to AIS. Randomization procedure was developed by the statistical team at University of Florida. Site coordinator and intervention therapists at each site obtain the group assignment for participants at their respective sites. The outcomes therapists are blinded to all group assignments. To maintain their blinding, a sham pre- and post-intervention assessment is scheduled for participants in the control group at randomized time points.

Experiment protocol

The first aim of this study is to evaluate the critical time window of plasticity post-traumatic SCI. To test this, 20 h of additional high intensity locomotor training is delivered at the time points described above as compared to a standard of care group (Fig. 1). The standard of care group does not receive any additional high intensity gait

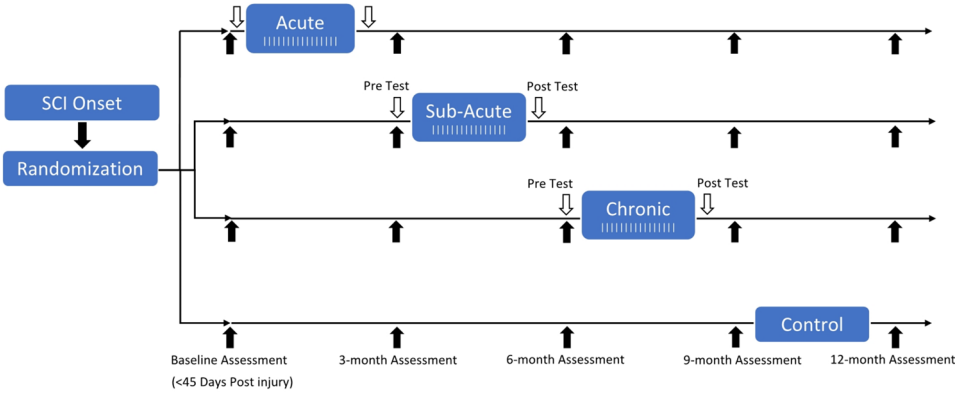

Fig. 1 Timeline of interventions and outcome assessments

training beyond the gait training that they may receive as part of their standard rehabilitation plan of care. Our intervention, body weight supported treadmill training (BWSTT), is a currently used in the standard-of-care rehabilitative therapy practice regularly at both the SRAlab and BSW.

The three training groups participate in additional body weight supported high intensity gait training as defined by heart rate intensity (65–80% of Heart Rate max) or, in the presence of autonomic dysfunction, modified RPE (6–8/10). Heart rate and oxygen saturation are continuously monitored throughout training by a portable pulse oximeter and forehead sensor secured to the individual's head with a Velcro strap. Each training session consists of at least 30 min of treadmill training at the target intensity but no more than 60 min total, allowing for self-selected rest breaks at any point during the training. The 20 training sessions occur over a 4–6 week timeperiod. A standardized method to increase or decrease gait intensity was developed to maintain consistency of training between the two sites. The intensity of treadmill training is progressively increased to manipulate the biomechanical demands of walking and challenge each individual to achieve high intensity training goals. Body weight supported treadmill training was selected as the intervention of choice, as it allows for training variability at all stages post-injury, especially acutely when an individual may not be able to walk over ground without body weight support. BWSTT is also standard practice in gait training rehabilitation.

Physical therapists at each site are assigned as either intervention or outcomes therapists. An on-site team training session was conducted in person with both research teams present to standardize the intervention to ensure participants at both sites receive similar dosage and care during the study. Outcomes administration has also been standardized for improved inter- and intrarater reliability between clinicians and sites. This training allowed for clinicians on both teams to agree to the same treadmill training setup for those requiring body weight support and limb assistance, specifically for those in the acute group and an AIS classification of B. Additional equipment that is utilized as needed to maintain the safety of the individual include an appropriately fitting harness, trial posterior leaf spring AFOs to maintain ankle integrity, adaptive grip assist cuffs for grip on handrails, and a pelvic strap to stabilize the pelvis when body weight support is provided.

The second aim of this study is to evaluate the relationship between the functional improvement in an individual's ambulation over the course of training and ambulation in the community during the first year after SCI. To establish community ambulation within daily life, participants wear a multi-sensor wearable activity monitor (Model# wGT3X-BT, ActiGraph, Pensacola, FL, USA) at the hip throughout the day for 2 weeks at various time-points during study enrollment to calculate the number of steps taken per day. The ActiGraph, along with instructions for setup, is provided by staff at each time interval assessment (3, 6, 9, and 12 months). A prepaid mailing envelope is provided for an individual to send the device back to each respective site. In addition, all participants complete an electronic questionnaire every 2 weeks to capture walking activity occurring outside of the study including daily life, outpatient therapy, or other intervention.

Safety precautions

A medical monitor has been identified at each site to oversee the safety of each participant and identify any findings of concern. Adverse events are evaluated at the start of every intervention and assessment sessions. An independent Data Safety Monitoring Board will be informed of all adverse events. We expect minimal risk for the activities associated with this clinical trial.

Protection against fall risk

The primary risk is potential for falls during locomotor training or outcomes testing, as well as the possibility of bruises or abrasions from wearing harness support during training. We do not anticipate this risk will be any greater for individuals enrolled in this study compared to other individuals with spinal cord injury receiving gait therapy as part of their clinical care. A physical therapist will be present to reduce the risk of falls during the intervention and outcomes assessment.

Protection against fatigue risk

Another risk during this study is significant fatigue during the training session. Unlimited seated rest breaks will be allowed throughout the training to facilitate pacing of energy and to manage fatigue risk. The acute group is at the greatest risk for daily fatigue, as those individuals are performing the training sessions in addition to three hours of therapy. We plan to manage this fatigue by scheduling the training sessions at a mutually agreed upon time of day with the participant, and we will continue to evaluate that timing based on the individual's response.

Protection against injury risk

An individual undergoing BWSTT is at risk for the development of other injuries including pressure sores, orthopedic pain, and delayed onset muscle soreness. To reduce the risk of pressure injury development, an individual's skin is examined across the lower legs, feet, and ankles for any noted areas of non-blanchable redness by the physical therapist at the end of each session. Individuals

returning home after sessions are asked to check their skin in areas that contact the harness for early identification of pressure sore development. The acute intervention group has the nursing staff check their skin for any new areas of redness after each session. Any onset or reports of orthopedic pain will be identified, and the setup will be modified accordingly. The changes made will include modifying a therapist's hand placement and the amount of body weight support. Delayed onset muscle soreness will be addressed with increased rest breaks as needed, adequate hydration throughout session, and anti-inflammatory pain medication as prescribed by their physician available prior to sessions.

Protection of confidential information

To ensure confidentiality, study participants are assigned an alphanumeric study code when they consent to participate in the study. Participants will be identified only by their assigned study numbers. The "master list" linking personal information to the alphanumeric code will not be shared, and is kept in a secure location. All paper copies of study data will be kept in locked files in a locked office. Data entered into electronic files will be coded and kept on a password protected computer as well as on encrypted network drives. A REDCap (Research Electronic Data Capture) research database will be utilized for primary electronic data collection for the study. REDCap is a secure, web-based application for building and managing online data capture for research studies. SRAlab, BSW, University of Florida and Northwestern University are members of the REDCap consortium. Only study personnel will have access to the filing cabinets, password protected databases, and encrypted network drives. Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. These documents will also be stored securely.

Outcome measures

Primary, secondary and other outcome measures have been identified for optimal evaluation of the presence of a window of plasticity and the walking function up to 1 year post-SCI.

Primary outcome measures

The 10 m Walk Test (10MWT) and 6-Minute Walk Test (6MWT) are the primary outcomes to assess walking activity. The 10MWT (walking speed) is one of the most established outcome measures in SCI research, as it uses a continuous linear scale and because faster walking speed is a surrogate measure for overall improved lower extremity motor functional and performance [23]. The test also has excellent inter and intra rater reliability, a critical component for the frequency of assessment across two sites [24]. The 6MWT (walking endurance) is also a very established outcome measure for SCI. The American Physical Therapy Association's SCI task force recommends this measure due to its excellent psychometric properties and clinical utility at all stages post-injury [24, 25].

At various 2-week time periods throughout the study, daily step count will be tracked using ActiGraph wGT3X-BT. The hip-worn ActiGraph was chosen for its accuracy in measuring step count in people with gait impairments and its capability to differentiate wheelchair movements from steps, in contrast to commercially available wrist-worn devices [26, 27]. Tracking daily step count will allow for observation of each individual's community participation level every day for those 2 weeks. This outcome measure will allow for analysis of a person's ability to ambulate within the challenges of daily life, a significant measure.

Secondary outcome measures

International Standard for Neurological Classification of SCI exam (ISNCSCI)

INSCI, more commonly referred to as AIS, was developed by the American Spinal Injury Association (ASIA) as a universal classification tool for Spinal Cord Injury based on a standardized sensory and motor assessment. The trained admitting medical team with perform the baseline assessment, and the medical monitor will perform the full exam at the one-year follow up.

Lower extremity motor and sensory scores

This abbreviated version of the test will examine the full ISNCSCI motor exam, and sensory dermatomes of the lower extremities only. A questionnaire will be provided to include sacral dermatomes S3/S4, anal sensation, and anal motor data. This is assessed by the outcomes therapists at every outcomes appointment.

Walking index for spinal cord injury II (WISCI II)

This measure assesses the physical assistance (i.e. the number of people) and assistive devices (i.e. walking aids) a patient needs to ambulate 10 m [28]. This outcome will be measured at each outcomes assessment.

Spinal cord independence measure III (SCIM III)

The SCIM III is a SCI-specific disability assessment that describes the ability of a person with SCI to perform self-care tasks, mobility, and respiratory and sphincter management [29]. This measure allows for assessment of subjects with a broad range of clinical presentations, a key component for the individuals in this study. The level of assistance, various bladder management techniques, and frequency of bladder management are

self-reported as part of this measure. Bowel management is also monitored regarding frequency and regularity of bowel movements, assistance levels, and accidents. This is administered verbally for those unable to write or provided to be filled out by the participant at every outcomes assessment.

Additional outcome measures

Timed up and go test (TUG)

The TUG asses the time required to stand up from a standard chair, walk 3 m, turn around, walk back to the chair, and sit down. This measure better reflects the broad spectrum of activities required in daily life compared to more specific but unidimensional test that assess only gait speed or distance [24]. This assessment is done during baseline, pre- and post-intervention, and at 3, 6, 9 and 12 months post-SCI.

Gait deviation index

The Gait Deviation Index (GDI) is a dimensionless parameter represented as a single gait impairment score. It summarizes an individual's deviation from an average gait pattern using multivariate measures from three-dimensional kinematic data, resulting in a comprehensive, unambiguous, and clinically useful value [30, 31]. The precision and objectivity provided by the quantitative gait data allows for consistency and comparability between the two sites. GDI has been used in multiple studies as an outcome measure to study gait deficiency in people with SCI and other neurological conditions [32–35]. Following two ~ 15 feet walking trials at comfortable speed, for each participant, the GDI value is computed using kinematic data collected from a marker-less motion capture system. OpenCap (Stanford University, Stanford, CA) is an open source, marker-less motion capture system which utilizes two iOS devices to capture the subject's gait pattern, and HRPose, a human pose estimation algorithm, to calculate joint kinematics during a gait cycle which can be used to determine SCI-based GDI. This assessment is done during baseline, pre- and post-intervention, and at 3, 6, 9 and 12 months post-SCI.

The spinal cord injury quality of life measurement system (SCI-QOL)

An assessment questionnaire that measures physical, emotional, and social aspects of health that contribute to an individual's overall quality of life with a spinal cord injury [36]. A key highlight of this questionnaire is tracking an individual's attitudes and competence regarding self-efficacy with bowel and bladder management. Bowel accidents and bladder complications frequency are self-reported. This questionnaire is administered during baseline assessment and at 3, 6, 9 and 12 months post-SCI.

Semi-structured qualitative interview

The interview will be conducted at the conclusion of the study. This interview will be flexible and allow for open ended data, to explore a participant's experiences, and to understand their experience and point of view during the study intervention and activities.

Data analysis plan

All data will be examined and described prior to analysis as directed by our Statistical Core staff based at the University of Florida. Continuous data will be described using means, confidence intervals, medians, and ranges. Categorical data will be described using counts and percentages across different categories. Distributional assumptions underlying each proposed analytic model will be verified and, if necessary, transformations of the variables or non-parametric statistical methods will be applied as appropriate. Apparent outliers will be examined to ensure they are not data entry errors and will not be excluded from analysis if they are genuine data. Hypothesis testing and analyses for all primary and secondary study outcomes will be on the intention-to-treat sample.

A mixed linear regression model will be fit to the repeated measures with the change from baseline as the outcome. The variable of interest will be the group difference. The fixed effects in the mixed model are group (4 groups), AIS score, level of injury, and patients' demographic information (e.g., age, sex). The random effect in the mixed model is patient with the unstructured covariance matrix. Multiple testing adjustment based on the Bonferroni correction will be applied to the secondary and exploratory hypotheses.

In our secondary aim, we will determine the relationship between functional improvement and average daily step count for up to 1-year post-injury. Such data is often known as the unequal spacing of measurements, in which each patient may have different numbers of days with recorded daily step count [37]. We will use the longitudinal model for unbalanced repeated measures computed by a generalized estimating equation (GEE) with robust standard error estimates [38]. This statistical model was applied in a similar clinical trial [20]. This model will be utilized to determine if timing of the intensive training and the optimal activity levels affect functional improvement after adjusting for the following covariates: AIS score, level of injury, and patients' demographic information.

Data safety monitoring board

We have set up a Data Safety and Monitoring Board (DSMB) comprising physicians and statisticians. This board ensures oversight of the study's overall conduct, including safety, ethics, patient recruitment and

retention, and the adequacy of the study design to meet specific aims. They offer feedback to the study team on potential protocol amendments. The DSMB also reviews serious adverse events (SAEs) and adverse events (AEs), and is notified of any interim concerns. The DSMB operates independently from the study sponsor and has no conflicts of interest.

Discussion

This is the first large-scale, multi-site, randomized clinical trial that aims to identify a potential time window of neuroplasticity following acute traumatic spinal cord injury. This trial addresses a critical gap in our understanding of how the timing of rehabilitation interventions can influence long-term recovery outcomes. Currently, the time interval since injury is not considered a critical component in an individual's therapy plan of care in rehabilitation programs due to limited scientific evidence. However, the response to therapy could be highly time-dependent, with a window of neuroplasticity during which training provides greater benefits than at other times.

Identifying a period of heightened plasticity could help optimization of our rehabilitation protocols and reinforce early mobilization. The existing standardized inpatient rehabilitation model, typically involving 3 h of training per day, 5 days a week, may need adjustments for individuals with SCI if increased training during this critical period is shown to improve long-term functional outcomes. Understanding the impact of training timing could enhance long-term outcomes for individuals with SCI and prioritize increased efficiency of care within the broader healthcare system.

Participants will be followed for up to one-year post-injury to assess the long-term effects of training administered at different times. This extended follow-up will provide a detailed understanding of the long-term impacts of training during the critical window. A key outcome metric in this study will be an individual's daily step count, monitored using an activity tracker. This outcome will deliver insight into an individual's ability to integrate ambulation into their daily lives, a critical component of translational rehabilitation research.

We believe that neuroplasticity is most prominent during the early period following SCI and that the early intervention group will show the most significant improvements in functional outcomes. Specifically, we anticipate that participants who receive high-intensity locomotor training during this early window will demonstrate greater improvements in function and overall mobility at one year post injury compared to the other training groups and control group. This study's findings could lead to practical adjustments in current rehabilitation practices, making them more effective and personalized. Ultimately, our goal is to enhance the quality of life for individuals with SCI by optimizing the timing of rehabilitation interventions based on neuroplasticity.

Abbreviations

SCI	Spinal Cord Injury
FIM	Functional Independence Measure
AIS	ASIA Impairment Scale
ASIA	American Spinal Injury Association
RPE	Rate of Perceived Exertion
IRB	Institutional Review Board
BWSTT	Body Weight Supported Treadmill Training
AFO	Ankle Foot Orthosis
ISNCSCI	International Standard for Neurological Classification of SCI
WISCI II	Walking Index for Spinal Cord Injury II
SCIM III	Spinal Cord Independence Measure III
TUG	Timed Up and Go Test
GDI	Gait Deviation Index
SCI	QOL-Spinal Cord Injury Quality of Life Measurement System
GEE	Generalized Estimating Equation
DSMB	Data Safety Monitoring Board
SAE	Serious Adverse Events
AE	Adverse Events
6MWT	6-Minute Walk Test
10MWT	10 m Walk Test
BMI	Body Mass Index

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Author contributions

All authors reviewed the manuscript and approved the final version for submission. Conceptualized and designed the study: AK, GS, CS, WZR, MSS. Prepared the initial draft of the manuscript: MH, RCC, AB, AO. Approved final version of the manuscript: AK, GS, CS, WZR, MSS.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study received approval from Northwestern University's IRB (#STU00219541, also the IRB of record for BSW) and the Department of Defense Office of Human Research Oversight (Award# HT9425-23-1-0418). The study is in accordance with the Declaration of Helsinki. Potential participants read and sign the study's informed consent form prior to enrollment. We plan to provide updates on important protocol modifications to the funding agency, public (clinicaltrials.gov), and study participants, as applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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