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Methods for a Randomized Trial of Weight-Supported Treadmill Training versus Conventional Training for Walking during Inpatient Rehabilitation after Incomplete Traumatic Spinal Cord Injury

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Abstract

The authors describe the rationale and methodology for the first prospective, multicenter, randomized clinical trial (RCT) of a task-oriented walking intervention for subjects during early rehabilitation for an acute traumatic spinal cord injury (SCI). The experimental strategy, body weight–supported treadmill training (BWSTT), allows physical therapists to systematically train patients to walk on a treadmill at increasing speeds typical of community ambulation with increasing weight bearing. The therapists provide verbal and tactile cues to facilitate the kinematic, kinetic, and temporal features of walking. Subjects were randomly assigned to a conventional therapy program for mobility versus the same intensity and duration of a combination of BWSTT and over-ground locomotor retraining. Subjects had an incomplete SCI (American Spinal Injury Association grades B, C, and D) from C-4 to T-10 (upper motoneuron group) or from T-11 to L-3 (lower motoneuron group). Within 8 weeks of a SCI, 146 subjects were entered for 12 weeks of intervention. The 2 single-blinded primary outcome measures are the level of independence for ambulation and, for those who are able to walk, the maximal speed for walking 50 feet, tested 6 and 12 months after randomization. The trial's methodology offers a model for the feasibility of translating neuroscientific experiments into a RCT to develop evidence-based rehabilitation practices.

Keywords

Motor learning; Locomotor training; Neurologic rehabilitation; Spinal cord

Ambulation is compromised in most of the more than 10,000 yearly survivors of a traumatic spinal cord injury (SCI) and for 250,000 people in the United States with chronic SCI.[1]

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Patients with complete sensorimotor loss (graded by the American Spinal Injury Association scale [ASIA] as A; see Table 1[2]) and those graded ASIA B within 1 week to 1 month of the SCI recover walking in no more than 10% to 15% of cases. Most subjects who have had enough return of motor control to regain the ability to walk will do so at greater than normal energy cost. Outcome studies of ambulation vary with the method used to classify impairment, the time of assessment after SCI, and the measures employed. Previous observational studies of the recovery of walking after SCI, such as those from the American Model Systems program,[3] have not prospectively assessed relationships between functional recovery, rate of recovery, walking speed and endurance, and quality of life in patients who were admitted for inpatient rehabilitation.

During inpatient rehabilitation soon after SCI, physical therapy ordinarily proceeds beyond supported standing only if the patient's legs are braced to lock them in extension or if the patient has the strength and balance necessary to maintain the legs in extension during weight bearing and to flex at the hips and knees when taking steps. If the arms are capable of partially supporting the person's weight during stepping in parallel bars or in a walker without inducing great energy cost, gait training proceeds.

The Spinal Cord Injury Locomotor Trial (SCILT) is designed to compare conventional inpatient and outpatient physical therapy to an intervention often called body weight–supported treadmill training (BWSTT).[4] This technique for locomotor retraining partially supports the weight of a patient by a parachute-type harness attached at the shoulders to an overhead lift. Initial weight support prevents the paraparetic legs from buckling at the knees. The lift allows vertical displacement during stepping and supports up to 50% of the subject's weight. Therapists then systematically train patients to walk on the treadmill at increasingly faster speeds and reduce the amount of weight support when feasible. The therapists aim to optimize the kinematic, kinetic, and temporal components of gait that are tied to the stance and swing phases of walking. This training aims to facilitate walking-related sensory inputs for a rhythmical, reciprocal gait pattern, without the requirements of good postural stability and full weight bearing. The training also carries over facilitative cues and an emphasis on sensory inputs relevant to stance and swing for walking over ground and in the community.

Several quasi-experimental studies in SCI suggested that BWSTT may increase the likelihood that subjects graded ASIA B, C, and D with upper motoneuron (UMN) injuries will learn to walk over ground.[5–9] Experimental neuroscientific studies suggested that improved motor output and locomotion after SCI may be inducible by mechanisms of neuroplasticity that are influenced by task-oriented sensorimotor training and paradigms for motor learning. These include 1) sprouting from primary sensory neurons and from residual descending inputs to the lumbosacral motor pools; 2) modification of spinal gray matter synaptic transmission[10,11]; 3) conduction through demyelinated but intact axons[12,13]; 4) locomotor movement patterns facilitated by lumbar spinal cord central pattern generators and related circuits for stepping[10,14–20]; 5) enhancement of activity in residual, subclinical descending pathways that must be trained to play a greater role in posture and gait[21,22]; and 6) changes in residual cortical and subcortical neuronal assemblies that represent the kinematics and forces associated with walking.[23–25]

BWSTT does not rely only on theories about central pattern generators, especially not in incomplete subjects who have some lower extremity motor control. SCILT included subjects who had lower motoneuron (LMN) injury because 20% of people with traumatic SCI have such lesions. The LMN group may not have access to the lumbosacral generators if damaged by an injury near the T-12 vertebral body. These subjects may still make use of segmental sensory inputs and reorganization within the cord above the lesion, as well as within brainstem and cortical sensorimotor networks.

SCILT, then, draws its face validity from a general hypothesis about motor skills relearning in patients with a moderate to profound loss of ascending and descending spinal pathways. By assisting patients to step so that proprioceptive and cutaneous sensory inputs to the spinal cord and brain are more typical of ordinary walking than what patients with paraparesis achieve during conventional training, and by intensive practice of such stepping on a treadmill, mechanisms of activity-dependent plasticity may increase rehabilitative gains.[1]

Progress in acute protection of spinal cord neurons and tracts and in the regeneration of axons and neuronal connections with, for example, neurotrophic factors, immune blocking substances, cell implants, and neural bridges across the level of injury offers hope for biological interventions for SCI in patients.[26] Well-defined training strategies will also be necessary to optimize the functional utility of such interventions. BWSTT may be a method to enhance the induction of activity-dependent plasticity within new, as well as residual, pathways and networks.[27–30]

TRIAL DESIGN AND METHOD

Overview

This prospective, single-blinded randomized clinical trial (RCT) included 2 arms: an experimental group that received BWSTT and over-ground gait training and a control group that received conventional standing and mobility training for the same amount of practice time. The protocol simulated current rehabilitation practices for acute traumatic SCI rehabilitation in terms of the amount of therapy related to mobility training, usual admission and discharge practices for facilities, and typical periods of inpatient and outpatient care. The investigators were concerned that the ordinary amount of mobility retraining provided during inpatient and early outpatient rehabilitation care may be less than optimal but decided that the study should proceed within common practice. Patients with incomplete SCI were stratified by severity using the ASIA impairment scale (Table 1) and by UMN or LMN injury.

The study addresses the following primary hypotheses:

1. Subjects classified as ASIA B or C at entry who received BWSTT recover supervised to independent walking with a reciprocal gait pattern for 150 feet (a Functional Independence Measure [FIM] locomotor score ≥ 5) significantly more often compared to those given only conventional therapy.
2. Subjects classified as ASIA D at entry who received BWSTT will walk 50 feet over ground significantly faster than conventionally treated subjects.

The secondary hypotheses are the following:

3. Subjects graded ASIA B or C on entry who walk with moderate assistance or less help at the time of outcome assessments will walk faster if they received BWSTT; more ASIA D subjects will reach a locomotor score of ≥ 5 if they received BWSTT.

4. Subjects who received BWSTT and walk with moderate assistance or less help at the time of outcome assessments have greater endurance and walk farther in 6 minutes compared to patients treated with conventional physical therapy.

5. Subjects who received BWSTT will recover a functional gait significantly sooner after the SCI compared to those who received conventional therapies alone.

6. Subjects who received BWSTT will be more independent in personal and community activities and will perceive their quality of life as being better.

7. Earlier step training permitted by BWSTT will reduce medical complications related to immobility.

8. Subjects who received BWSTT will have better sitting and standing balance as measured by the Berg Scale.

9. Subjects who received BWSTT will have less spasticity of the lower extremities, as measured by the Ashworth Scale, and fewer reflexive spasms during the time of therapy.

Inclusion and Exclusion Criteria

Subjects were rated by the ASIA at the time of randomization. Subjects graded ASIA B had to have a neurological level below C-6, so they could use their upper extremities to manage assistive devices. Subjects graded ASIA C and D could have a level below C-4 as long as they fully extended their elbows against gravity. The cervical to T-10/11-level subjects were designated as the UMN group, and the T-11 to L-3 subjects had conus/cauda equina lesions and were designated the LMN group. Subjects with a LMN lesion and absent sacral sensation were eligible and designated for the SCILT trial as ASIA B if any lumbar sensation was present, even without sacral preservation of sensation, and as ASIA C or D if motor function was present at L-3 or above. This classification for subjects with a LMN lesion differs from the usual ASIA B definition. Early after a SCI, the clinical distinction between a UMN and LMN designation may be equivocal, especially in subjects who have low thoracic sensorimotor findings. An absence of deep tendon reflexes in the lower extremities, absence of a bulbocavernous reflex, hypotonicity of the legs, and a neurogenic bladder without hyper-reflexia of the detrusor or detrusor-sphincter dyssynergia point to a LMN classification. When doubts persisted, a significantly low amplitude compound action potential of the posterior tibial or peroneal nerves from 2 to 8 weeks after the SCI was an optional test to demonstrate the presence or absence of LMN axonal involvement. Subjects misclassified as UMN or LMN at the time of randomization were reclassified by the Clinical Unit (CU) before the outcomes measures taken at 3 months, after documenting the basis for

the change with the principal investigator (PI) and the Statistical Coordinating Unit (SCU) at the University of California, Los Angeles (UCLA).

No inclusion/exclusion criteria were based on gender, childbearing potential, or racial or ethnic origin. Children and adolescents younger than age 16 were excluded because they represent a small percentage of cases of SCI, may not be mature enough to work within the training protocol, and may change in their long bone length over the course of serial assessments, which may confound the measure of walking speed. Subjects older than 70 years were excluded because they too are a small percentage of patients with uncomplicated traumatic SCI. These patients may have had cervical spondylosis that interfered with motor control prior to the acute injury. Premorbid medical problems and disabilities are also more often present, which may interfere with the training protocol and the interpretation of the functional outcome measures.

INCLUSION CRITERIA

1. Males and females between ages 16 and 70.
2. Traumatic acute SCI within 56 days of injury.
3. Incomplete lesion (ASIA B, C, or D at time of randomization) from below C-4 on at least one side of the body to no lower than L-3 on either side of the body.
4. Unable to ambulate over ground at time of randomization without at least moderate assistance (scored as a 3 or less by FIM locomotor criterion).
5. Able to offer at least 3/5 strength in the elbow extensors at time of randomization.
6. No clinically significant cognitive impairment (Mini-Mental Status Score ≥ 26 with figure drawing and sentence writing task scored as normal if subject cannot hold a pencil).
7. Signed consent form approved by the Institutional Review Board of the site.

EXCLUSION CRITERIA

1. Symptomatic fall in blood pressure or fall greater than 30 mm Hg when upright in the body weight support apparatus. If this could not be corrected in the days prior to randomization, patient was excluded.
2. Subject with a halo or other cervical brace or thoracolumbar support orthosis (TLSO) if the treating physician found BWSTT and wearing a harness to be medically contraindicated.
3. Contraindication to weight bearing on lower extremities (pelvic or leg fracture, chronic joint pain).
4. Pressure sore with any skin breakdown (beyond stage 2, using Model Systems criteria), where a harness or treadmill training or standing could, in the physician’s judgment, negatively affect healing.
5. Any debilitating disease prior to the acute SCI that caused exercise intolerance or more than minimally limited mobility-related self-care and instrumental activities

of daily living. This included exertional angina, heart failure, and clinically significant pulmonary disease (class 3 or more by American Heart Association standard); neurologic diseases such as Parkinson's, peripheral sensory or motor neuropathy, prior traumatic brain injury, and stroke; a malignancy likely to cause death within 2 years; alcoholic liver disease; and chronic alcohol or drug abuse.

6. Subject must use an antispasticity medication at the time of entry, with the exception of use limited to bedtime to prevent spasms that interfere with sleep.
7. Premorbid, ongoing major depression or psychosis; suicide attempt that caused the SCI.
8. Subject unlikely to complete the intervention or return for follow-up due to distance from home to assessment site. Subjects could be assessed at one of the other sites at 3, 6, and 12 months if necessary.
9. Participation in another rehabilitation or pharmacologic study that continued beyond the start of the trial.

Sample Size and Power

The investigators at each CU reviewed their institutional databases for the previous 2 years (Tables 2 and 3). Only 15% of their patients classified as ASIA B at the time of admission for rehabilitation were able to walk 150 feet at a supervised or better level of function at discharge. About 40% of their ASIA C and 75% of their ASIA D subjects achieved a FIM locomotor score of ≥5 (Table 2). Because of the divergence between the likelihood of scoring ≥5 between the ASIA B and C subjects compared to the ASIA D subjects, the level of independence and the walking speed, respectively, were chosen as separate primary endpoints for SCILT. The primary outcomes are to be assessed separately for each of the B, C, and D ASIA stratifications, rather than combining the B and C groups, because all have different likelihoods of achieving a score of 5 or greater on the FIM locomotor scale.

Walking speed reflects residual supraspinal input measured by lower extremity strength, as well as the energy cost of locomotion, and predicts who will evolve into a functional ambulator. Waters and colleagues[31,32] assessed a group of subjects with quadriparesis and paraparesis after SCI, most of whom ambulated with orthoses and assistive devices. The evaluation included gait velocity, oxygen cost per meter walked, and peak axial load on their canes. The ability to walk correlated with lower limb strength. Mean walking speed was 40 ± 12 m/min for 34 ambulatory subjects who used a reciprocal gait without knee-ankle-foot orthoses (KAFOs) (but with a variety of upper extremity assistive devices), 30 m/min for subjects with paraplegia who needed AFOs, and 26 m/min in subjects with low lumbar SCI who employed bilateral AFOs. Heart rates averaged 130 beats/min, suggesting a significant energy cost to walk 50 m. Normal walking speed in these comparisons was 80 m/min. Mean walking speed was 31 ± 12 m/min in 10 subjects with SCI classified as ASIA D from 6 to 24 months after injury when tested at UCLA. The over-ground speeds achieved in these studies were used for the statistical design.

For the ASIA B and C subject trial, the sample size was derived from the data obtained from the CUs (Table 3). The study hypothesis is that the probability is higher that BWSTT

compared to conventional therapy leads to a FIM score ≥5. The probability of a type 1 error was set at 0.05 significance level. The test statistic for the alternative hypothesis was based on the weighted log odds ratio with standard error estimated by the bootstrap method. We chose a power of 0.92 with alpha = 0.05 and a two-sided test for a total sample size of 50 ASIA B and 80 ASIA C subjects. To detect greater than a 20% difference in walking speed in the ASIA D subjects, a sample size of 80 subjects produced a power of 0.84. Thus, the 2 trials required up to 210 subjects (or up to 235 with 10% attrition of subjects). Recruitment was planned for 2 to 2¼ years based on the recent experience of the CUs. It was anticipated, however, that recruitment of subjects with UMN lesions would proceed ahead of subjects with LMN lesions. Based on local community demographics and Table 2, we anticipated that 35% of subjects would be underrepresented minorities and 25% women.

Entries into the RCT were stopped when the expected number of UMN subjects had been entered and the pace of entry for LMN subjects led the Safety Committee and investigators to acknowledge that SCILT would have to extend entries for a year beyond the anticipated end of the trial to enter the planned number of LMN subjects.

Facilities Contacted

The trial was initiated by the Neurologic Rehabilitation and Research Program at the University of California, Los Angeles in response to a 1998 National Institutes of Health request for clinical trial proposals. Developers of a proposal with the UCLA group included Dr Barbeau at McGill University and Drs Fugate and Basso at The Ohio State University. The PI contacted physicians at large SCI rehabilitation programs, met with interested groups at the ASIA national meeting and the annual meeting of the American Society for Neurologic Rehabilitation, and sent e-mails to investigators with relevant interests. To be considered for participation, sites had to provide data about their inpatient SCI services for the past 2 years and demonstrate their ability to enter at least 20 eligible subjects yearly (Tables 2 and 3). The investigators at each site agreed not to provide BWSTT outside of the trial to any subject who would have been eligible. Investigators at 4 of the interested sites, Magee Rehabilitation Center/Jefferson University in Philadelphia, The Ohio State University in Columbus, Rancho Los Amigos Rehabilitation Center in Los Angeles County, and Shepherd Rehabilitation Center in Atlanta, met the requirements and demonstrated institutional support. By combining the rehabilitation services at McGill University and the University of Ottawa, a fifth site qualified. The sites in Canada and at The Ohio State University had prior experience in BWSTT, which added to their value as participants. All centers had achieved national distinction as clinical research centers and as regional SCI centers of excellence for patient care. Three were long-standing members of the SCI Model Systems Program sponsored by the Department of Education—Rancho Los Amigos, Magee, and Shepherd.

Table 2 is based on the experience of the sites in 1997 on caring for subjects who met the proposed inclusion and exclusion criteria for the study. These data compared favorably with national trends for onset of SCI to time of transfer for admission to a rehabilitation facility and for mean inpatient rehabilitation length of stay, as reported for the 3444 acute SCI patients by the 1995 Uniform Data Service for Medical Rehabilitation.[33] The mean age for

traumatic SCI subjects nationally was 42 years, which again was within several years of the mean age of subjects admitted to the 5 CUs. Table 3 shows the distribution of patients at the sites who would have been eligible in 1996 and 1997 for SCILT.

The UCLA site developed the initial protocol and data collection and analysis procedures. At several meetings of the investigators, the operations manual was modified to meet concerns and new information provided by the CUs. The UCLA site chose not to participate as a site for subject recruitment and training so that it could best manage the trial at arm's length. The PI did not have access to the randomization procedure or to outcome data by assigned intervention. By remaining blinded, he was able to advise the site investigators and therapists, the SCU under Robert Elashoff, PhD, and work with an external Safety and Data Monitoring Committee.

CU Training

Reported studies using BWSTT had not described the details of their procedures. The intervention provided by rehabilitation therapists is highly experiential. Many training variables can be manipulated. The strategy, however, had to be given subjects in a reproducible fashion for SCILT to succeed. For the RCT to have internal consistency within and across CUs and provide generalizable outcomes, the investigators developed a set of defined approaches for BWSTT. The CU investigators met at UCLA with additional experts involved in developing BWSTT, including Drs Anton Wernig (Berlin) and V. Reggie Edgerton (UCLA). The literature revealed that treadmill speeds had been less than one-third of normal casual walking velocity in prior studies, and weight support was rapidly eliminated.[7] Such slow training speeds presumably did not provide typical locomotor-related sensory inputs. A consensus was reached to aim for training at treadmill speeds as close as feasible to near normal casual walking speeds, approximately 2 to 2.5 mph, and to continue some level of body weight support to help achieve these speeds. As soon as feasible, the level of weight bearing was increased in increments within and between training sessions. A complimentary over-ground walking program was also established. The Trainers Group created and revised a training manual and provided a 1-week course for all participants at UCLA.[34] At least 1 therapist from each CU was trained, followed by on-site training of at least 2 therapists and 2 therapy assistants.

A certification process followed. The BWSTT team at each site completed a practice schedule with at least 4 volunteer subjects with SCI over 3 months, monitored by video each week by the Trainers Group. The video was assessed for how the therapists assisted leg, hip, and trunk control: hand placement on the legs; kinematics; and the use of varying treadmill speeds and levels of weight support. The trainees self-critiqued their efforts by checklist and described their decision making during the sessions. The therapists were encouraged to discuss training techniques among themselves via e-mail and the study website. If the Trainers Group, using a video skills check list, found that the therapists scored above 80% in their technique and problem-solving skills, a member of the Trainers Group visited the site, did some additional training over 2 days with at least 4 different subjects with SCI, and certified the physical therapists and their assistants at the site. If the therapists scored between 60% and 80%, feedback was given and practice continued, followed by a

resubmission of the videotape. If a CU did not reach the 80% level, a member of the Trainers Group visited the site. In a trial that would last 2½ years, turnover of therapists was expected. Training certification was required when a new primary therapist joined a site.

A number of commercial systems for treadmill training were available. The UCLA group worked with the Vigor Company (Stevensville, MI) to modify its body weight support system with a gas cylinder so it offered vertical displacement appropriately timed to the step cycle and helped control ground reaction forces during stance. The treadmill was raised on a platform and fitted with mobile seats so that therapists could sit with some comfort and flexibility as they manually assisted the subject's legs. Therapists had previously reported occasional hand and back injuries from their repetitive lifting and reaching activities during BWSTT.

The PI and SCU visited each site to review training accomplishments, data collection and entry mechanisms, scheduling of outcome measures, use of the study Web page, and financial issues. The coordinator at each site discussed subject identification procedures and the process of informed consent. Information from each site was shared among all CUs, especially how problems were engaged and resolved. Each site filled out data forms and carried out each entry and follow-up procedure for 3 to 4 subjects prior to the official start of the RCT.

Blinded Observer Training

Since the subject and therapists could not be blinded regarding the intervention, a single-blind design was chosen. The investigators considered a variety of ways to obtain reliable outcome data that would be assessed by someone who was unaware of the treatment assignment. Whereas videotaping a therapist carrying out the examination for outcome measures and having the tapes judged by one or more blinded observers could serve this purpose, the approach would add considerable cost and complexity to the RCT. Since the outcome measurement tools were chosen in part for their high reproducibility, the investigators decided that a trained, experienced blinded observer at each site could obtain the measures reliably. The observer was masked as to the subject's assignment by having all participants, including the subjects, agree not to mention anything about the intervention and by choosing an observer who worked away from sites of patient care.

The blinded observers were physical or occupational therapists or rehabilitation nurses qualified to perform the FIM by the Uniform Data Systems Users Group. A backup observer was also trained. If a new observer was needed over the course of SCILT, the coordinator and lead therapist at the CU trained that person. The PI visited each site and reviewed local procedures for testing subjects and transferring data directly to the SCU. The PI reviewed a videotape of the testing procedures carried out by each blinded observer on the subjects who were volunteers for the CU therapists as they practiced BWSTT under the guidance of the Trainers Group. The blinded observers were graded on their performance and practiced the standardized data-gathering techniques until rated as certified by the PI.

The blinded observers were the only persons to collect outcome data relevant to the primary and secondary hypotheses. They were notified by the coordinating physical therapist as soon

as a subject was randomized. Entry testing was performed within 24 hours of randomization or on the Monday following a Friday randomization. The observers received a calendar from the SCU that noted the date that follow-up testing was expected for all subjects at that site. The local coordinator received the same calendar and arranged a convenient schedule for the subject and blinded observer. The observer kept open 2 mornings a week to test subjects.

Screening and Recruitment

Patients admitted to SCILT sites for rehabilitation after incomplete SCI typically have to be medically stable enough to tolerate at least 3 hours of therapies a day, need more than minimal assistance for ambulation and self-care, are motivated to increase their functional independence, have adequate cognition to participate in treatments, and have adequate social supports to anticipate that they would return home on discharge. Discharge from the sites depends on when a patient becomes independent enough to be managed at home or when important functional gains have reached a short-term plateau. Within these community practice patterns, a protocol for screening, recruitment, and treatment was designed for the trial.

As close to the beginning of their formal inpatient rehabilitation program as medically feasible, all patients with a recently acquired traumatic SCI admitted to 1 of the CUs was screened by the site's physician and coordinator to determine whether they qualified to participate. A form that listed inclusion and exclusion criteria for the RCT was filled out by the physician or coordinator for every admission who had an incomplete traumatic SCI. Candidates who met initial criteria on admission were introduced to the study by the physician or coordinator. The CU personnel presented the background that led to the study and read the consent form to the eligible subject. Explanations about the RCT were written in English, French, and Spanish, along with informed consent forms and the self-completed questionnaires in the languages needed by each CU. The centers tried to make participation practical, for example, by assisting with transportation for outpatient therapy and follow-up testing. If a patient agreed to consider participating, the SCILT therapist would introduce the patient to the apparatus and give the patient the opportunity to stand upright attached to the harness if so desired. The study was not marketed beyond flyers at each site. All local publicity was limited to a simple, balanced statement about the trial that was authorized by the PI in consultation with the investigators. The SCU maintained a Web site for the public that described the trial and eligibility criteria and listed participating sites. No lectures or publications by the SCILT group were permitted to go beyond the rationale and specific aims of the RCT. The PI and site investigators decided that the RCT ought to be conducted out of the spotlight that many trials create to avoid misinterpretations by the public about the potential efficacy of BWSTT and to dissociate themselves from the marketing efforts of commercial entities that make equipment or offer their own for-profit style of therapy. Several members of the SCILT Trainers Group, however, did commercialize a training protocol late in the study.

Randomization

Patients who met entry criteria and consented to participate were randomized within 24 hours, or on the Monday following a Friday admission. On receipt of the initial identifying

data and inclusion/exclusion checklist by fax, the SCU randomized and stratified subjects by whether they had an UMN or LMN lesion and by whether they were rated on the ASIA as B, C, or D. Stratification by CU site was not feasible; too few subjects would have been entered into each cell. A random, permuted block design with those factors was used, along with a system to handle imbalances in assignments to each treatment arm within each site. By fax with e-mail corroboration, the SCU sent the assignment and a patient study number that was the only way to identify subjects once assigned to the CU. The receiving CU's coordinator acknowledged receipt with a return e-mail confirmation. Each CU kept a flow chart of these interactions.

Interventions

Subjects received 12 weeks of inpatient and outpatient therapy within the study. Based on the prior experience of the CUs, most subjects were expected to enter into the trial by 28 days post-SCI with a range of 10 to 35 days. The investigators anticipated that the study intervention would end, on average, by 16 weeks after onset of SCI. A minimum of 45 days and maximum of 60 days of therapy were required of subjects.

During the inpatient rehabilitation stay, each subject received at least 1½ hours of daily physical therapy 5 days a week. As an outpatient, each subject received at least 1 hour of mobility-related therapy 3 days a week in addition to other necessary treatments. Within the level of their tolerance for exercise, subjects randomized to BWSTT received 1 hour of their therapy time devoted to step training with the experimental intervention. The amount of locomotor-related physical therapy was recorded during the intervention period. The time spent in standing and stepping activities was recorded daily during the inpatient stay by the treating physical therapist and weekly by each subject during outpatient therapy up to the 12-week assessment. Physical and occupational therapy stressed typical activities outside the locomotor training time, such as self-care skills, transfers, and wheelchair mobility.

Subjects randomized to conventional therapy alone could continue at a facility closer to their home or with a home health agency if they would otherwise not be able to complete the study. This treatment was monitored by the CU physician. From the end of the intervention to the final evaluation, patients in the conventional and BWSTT groups were given a routine home locomotor therapy program that encouraged them to walk 3 times a day for at least 5 minutes in subjects with the least ability to walk. Between the end of the intervention and the 1-year follow-up, some patients continued therapy, but they were asked not to perform BWSTT.

All standing- and walking-related exercise sessions for the conventionally treated subjects were conducted by a senior physical therapist who worked on the SCI unit. The SCILT-trained physical therapist provided BWSTT and over-ground walking interventions.

BWSTT arm of the study—Each session lasted up to 60 minutes, which included warm-up and stretching. The length of bouts of stepping on the treadmill depended on the subject's endurance and capability, but 1 goal was to gradually increase to 20 minutes of continuous step training. A physician associated with the study was available to assist should medical complications arise. Heart rate and blood pressure were monitored. The intervention was not

aimed at having a conditioning effect. Earlier mobilization permitted by BWSTT could help prevent deconditioning even at submaximal exercise levels, however. Heart rates generally did not exceed 110 beats/min, and patients were not to feel more than minimally short of breath. Patients were not advanced to higher treadmill speeds or less weight support if tachycardia or dyspnea occurred. The physician and physical therapist monitored subjects for untoward effects such as hypotension, pain, and skin abrasions.

Subjects received verbal instruction as well as physical assistance as needed to practice trunk, pelvic, hip, knee, and ankle control. One trainer sat by each paretic leg and facilitated its movement by placing 1 hand above the popliteal fossa and the other above the heel. Another assistant trainer stood behind with hands on the patient's hips to facilitate trunk extension, pelvic rotation, weight shifting, and hip extension. Mirrors placed in front and along one side of the patient provided visual feedback about trunk and leg position for subjects and trainers. Optimal hip extension at the end of stance was facilitated by the patient, therapist, and passively by treadmill belt motion. Optimal foot clearance and placement, along with weight bearing that prevented knee hyperextension or give-way were emphasized, as well as a step-through pattern with symmetry of the legs in step length and stance time. Care was taken to limit excessive ground reaction forces when the leg in swing made foot contact. Since sensory information from the sole and the ankle helps signal transitions from stance to swing, AFOs were not employed during BWSTT. The ankle and foot were supported by the therapists or with a figure-of-eight wrap for foot clearance at toe off and heel strike to protect the foot.

The treadmill had no side railings. Reciprocal arm movements were encouraged. Trekking poles held parallel to the ground by assistants were used to initially aid reciprocal arm movements. Subjects were also encouraged to train over ground with reciprocal arm movements, using the poles held parallel to the floor by assistants if needed, rather than training, for example, with a walker. Bracing with AFOs and use of assistive devices were permitted during training over ground if needed for safety and to increase independence.

Training began at from 20% to 50% body weight support and at treadmill speeds of at least 1.6 mph. Treadmill speeds were varied within each session but aimed to reach belt speeds of at least 2 to 2.5 mph (68 m/min) as soon as feasible. The level of weight support was adjusted within sessions to achieve knee extension during stance and to load the stance leg as much as tolerated without causing the knee to buckle. Subjects were advanced to higher treadmill velocities and more full-limb loading until the maximum speed at which each patient exhibited his or her best step pattern at full weight bearing was achieved.

Conventional arm—The treating physical therapists at each CU were informed about the subject's participation in SCILT and instructed to offer as much mobility-related standing and walking activity as feasible, but a minimum of one-half hour per day of therapy. The therapists at the CUs employed the following general strategies. The subjects classified as ASIA B did weight bearing on a tilt table or standing frame to meet the practice time criteria of the protocol. Gait interventions targeted exercises and problem solving for balance, weight bearing, leg symmetry in swing and stance times, selective muscle strengthening, and improved motor control. Forward progression of the lower extremities was practiced at the

parallel bars and over ground, using facilitatory and inhibitory techniques to encourage reciprocal stepping and assistive and orthotic devices as needed, including walkers, Lofstrand crutches, or one or two canes when the patient needed these for safer and more independent over-ground walking.

Outcome Measures

Measurement tools for the primary and secondary outcomes were chosen for their reliability, likely validity in relation to mobility outcomes, administrative ease, and minimal cost. Few tools, however, have been validated in trials of a physical therapy for walking after SCI. Formal gait analyses were not obtained routinely because of the cost of kinematic, kinetic, electromyographic, and temporal gait pattern data, as well as difficulty in determining the most meaningful data to statistically analyze. The Canadian CUs obtained gait studies in about 10 willing participants. In addition, scales were added on an exploratory basis to test their reliability and validity in patients with SCI. The PI discussed the content of various tools with 10 of his patients with SCI who used a wheelchair for 50% to 100% of their mobility needs. With this advice and input from the CUs, the tools chosen reflected home and community activities and quality of life that could be affected by BWSTT, such as walking compared to wheelchair use, greater independence in walking, more functional walking velocity, and improved trunk control.

DESCRIPTORS—Initial descriptors about each subject were obtained by the CU coordinator at the time the informed consent was signed. Descriptor information on entry to the study included age, sex, height and weight, residence, occupation, medications, cause of SCI, neurologic level of injury and ASIA classification on entry to the study and at the time of injury if available, time from onset of injury to entry into the study, and FIM locomotor score. The total Lower Extremity Motor Scores were collected by the SCILT physical therapist or physician at entry and by the blinded observer. This scale assigns a grade for strength (0 = *no movement*, 5 = *normal resistance*) to 5 key muscle groups of each leg, each with a different dominant root level, for a total possible score of 50. The upper extremities were also graded similarly for a total score of 50. The SCU reviewed these for consistency, especially for differences that could alter the initial ASIA group assignment. The PI reviewed and arbitrated inconsistent reports.

Using the ASIA standards of neurologic classification, the CU physician recorded the sensory and motor scores at entry, at the end of the intervention, and then at 6 and 12 months after entry. On inpatient discharge, the type of residence and total rehabilitation inpatient and, later, outpatient therapy days were recorded.

PRIMARY OUTCOMES—The tests most relevant to walking (walking speed and FIM level) were performed by the blinded observer. They were collected at entry and at 2-week intervals until the end of the intervention and then at 6 and 12 months. Measures were taken after a brief warm-up in the morning when the patient was not fatigued. AFOs and assistive devices were used if required for reciprocal stepping.

1. Subjects classified as ASIA B and C on entry were rated for level of independence for walking on a level surface for at least 50 feet if physical assistance was needed

or for 150 feet if no helper was required, using standardized criteria from the FIM 7-level locomotor subscore. For ASIA D subjects, this FIM score is a secondary outcome.

2. Subjects classified ASIA D on entry were timed performing a 50-foot walk with a reciprocal gait pattern over a flat, straight-tiled surface. The start and stop points were shown to the subject. The subject started from a standing position 2 steps behind the start line. The instruction to begin to walk was “ready and go.” As the lead foot crossed the start line, the stopwatch was started. The patient was encouraged to walk as fast as he or she felt safe. The blinded observer walked alongside the subject and provided encouragement and contact guarding as needed. Only 1 other person could assist the subject. The observer graded the level of assistance given. The walk ended when the lead foot crossed the finish line. Two trials were performed with a 5-minute rest between walks. The heart rate was measured at the start and finish, as a marker for the energy cost of locomotion. For ambulatory ASIA B and C subjects, speed is a secondary measure.

The primary outcome measures were also used as stop points for the assigned arm of therapy. The duration of conventional or BWSTT treatment was a minimum of 6 weeks in subjects who reached the endpoint of an independent level of reciprocal gait (FIM locomotor score of 6 or 7) and a normal casual walking speed of 50 feet in 15 seconds (equivalent to 100 cm/sec, 60 m/min, or 2.2 mph). These milestones indicate the potential for highly functional community ambulation, a level that relatively few patients ordinarily achieve during their rehabilitation. Training beyond 6 weeks, for up to 12 weeks, was continued for subjects in either arm who had not achieved a level of independence of 6 or 7 on the FIM locomotor subscale and who did walk 50 feet in 15 seconds or less.

SECONDARY OUTCOMES

1. Endurance was assessed by measuring the distance achieved in a continuous walk with a reciprocal gait pattern for 6 minutes. The test was performed on a flat, uncarpeted, 100-foot walkway. Thus, the walk included turns of 180 degrees. The blinded observer walked alongside the subject and provided encouragement and contact guarding as needed. Physical walking assistance was provided with the help of 1 person. The observer graded the level of assistance given. A chair was placed at the 50-foot midpoint of the walkway or an aide followed behind the subject with a wheelchair for safety purposes should the subject suddenly fatigue. Tests of walking endurance are reliable indicators and can be more sensitive to change during rehabilitation than the FIM walking subscore or speed of ambulation.[35] These data were collected at the end of the intervention (12 weeks) and at the 6- and 12-month assessments. The Berg Balance Scale assesses other potential effects of the interventions especially on chair transfers and sitting and standing balance.[36] During the 50-foot walk, the Walking Index for Spinal Cord Injury (WISCI) provided a hierarchical view of the amount of physical, bracing, and assistive device help needed by subjects to walk.[37] The WISCI has face validity, concurrent validity, and interrater reliability. For the RCT, a zero level was added, splints could be substituted for braces, and the braces were described as locked or

unlocked.[38] The blinded observer assessed these mobility measures at entry, 4 weeks, 12 weeks, 6 months, and 12 months.

2. A variation of the Rand Medical Outcomes Study SF-36 served as the primary tool used to measure any changes in quality of life. It reflects patient perceptions and preferences about physical, emotional, and social well-being. The tool has been employed in studies of patients with chronic diseases. No studies at the start of the RCT had been reported to show its validity in the population that the trial studied and, in particular, in how independence in ambulation relates to quality of life, but this measurement strategy has received considerable support.[39,40] The SF-36 was modified with some additional questions found to be useful in patients with multiple sclerosis, called the SF-54.[40] Subjects are able to fill out this form in 10 to 15 minutes. Within the physical functioning portion of the scale, 2 items were altered to better reflect the capacities of persons with SCI. The Reintegration to Normal Living (RNL)[41] and an Activities Check List (ACL) of 25 home and community activities that include hobbies, filled out by each subject, and the total FIM scores, completed by the blinded observer, also reflect aspects of quality of life, self-care, and community levels of independence. The Beck Depression Scale, completed by subjects, further assessed mood. The total FIM motor score was collected at entry, 12 weeks, and at 6 and 12 months. The SF-54, RNL, ACL, and Beck were collected at the 3, 6, and 12-month assessments, when the subjects are able to try to integrate into the community.

3. The initiation of even partially supported stepping by BWSTT could help prevent medical complications of early immobility. Problems include pneumonia, thrombophlebitis, pulmonary emboli, joint contractures, muscle atrophy, deconditioning, dysautonomia, pressure sores, osteoporosis, heterotopic ossification, leg and truncal spasms, and depression. Potential complications of the BWSTT intervention include an increase in spasticity, skin lesions, and joint or other limb pain. We used the Model Systems SCI Program criteria for defining medical complications such as decubitus ulcers, pneumonia versus atelectasis, deep vein thrombosis, and pulmonary emboli. The physician investigator recorded adverse reactions and complications as they happened. The PI and the Safety Committee reviewed all complications entered on the forms completed by the site's physician and physical therapist.

Medications used to treat spasms and rigidity may affect neurotransmitters in the cord and, in theory, alter spinal learning. The unnecessary use of these drugs may confound locomotor-related outcome measures. Subjects and their treating physicians were encouraged not to use anti-spasticity agents, unless the medications had a clear-cut benefit on spasms that interrupted sleep or wheelchair activities or prevented safe positioning. Their unavoidable use during therapy or at the time of outcome measures was recorded. Reliable measures of hypertonicity employed included the Ashworth Scale and the number of flexor and extensor spasms counted by each subject on the day prior to the assessment of the blinded observer. These measures of spasticity, however, do not reflect the effects of hypertonicity on mobility-related activities.

Dropouts

If a subject developed a medical complication that prevented participation in rehabilitation mobility training for more than 4 days, the length of training was extended for that lost time, for up to 2 consecutive weeks. This information was recorded and sent to the SCU. If the physician investigator at the site determined that continued BWSTT or conventional therapy was medically contraindicated for more than 2 weeks, the subject's situation was discussed with the PI and a decision made on whether the subject should continue in the study. Since the RCT planned an intention-to-treat analysis, every effort was made to keep subjects in the protocol. The SCU was informed about any discontinuance and the reasons on a standard form.

Plans for Retention and Compliance

Communication and support among sites was critical for maintaining the stamina and diligence needed to complete the RCT. The investigators encouraged the therapists, Training Group, blinded observers, and coordinators to share problems and solutions. Each CU used its commitment of institutional support to foster an understanding of randomization and of the 2 arms of the RCT for its staff. Hospital staff was trained to understand the need for the trial and to acknowledge that until the RCT was completed, no one should comment on perceptions of the efficacy of either arm. The therapists who provided conventional therapy were especially encouraged to follow the training protocol.

A public website provided information about the trial. The nonpublic website allowed CU physicians, therapists, coordinators, and blinded observers to ask questions and provide answers. The PI used the site to keep CUs aware of developments and meetings. The SCU managed the website. To add a bit of competition between sites, the website provided monthly summaries of the number of subjects within the UMN and LMN subgroups at each site, a monthly summary of number of subjects entered compared to the number expected by that date, and the number who completed their 6- and 12-month assessments. The SCU also reviewed this information with each CU to keep the trial on schedule for recruitments and assessments. The SCU provided each coordinator and blinded observer with a calendar of the anticipated date of follow-up assessment shortly after a subject had been randomized. The follow-up reminder was reinforced by e-mail, at least 2 weeks in advance. In addition, questions or answers that were not of general interest were relayed by e-mail, and important developments, such as adverse reactions, were made known to all by e-mail. Two hundred and fifty e-mail messages to and from the PI were exchanged over the first 3 years of the RCT.

Each site shared ways to retain its subjects. The coordinator visited subjects during the inpatient stay and called every 2 weeks of outpatient care and monthly before the 6- and 12-month assessments. Every effort was made to accommodate a subject's personal schedule for follow-up visits. Subjects who needed help to defray travel expenses to complete their last 4 weeks or final 12 visits to a CU for outpatient therapy received $20 per visit for transportation. Subjects were paid $50 to return for each of 3 outcomes assessments. This payment covered travel expenses and helped ensure compliance with these critical assessments.

Data Entry and Management

An operations manual produced at UCLA provided detailed information and flow charts for all procedures related to the conduct of the trial. The manual included the methods for BWSTT and problem-solving algorithms for its application.

The physical therapist or coordinator at each CU sent completed forms to the SCU's data entry clerk as soon as the scannable forms were completed. The information was not part of a patient's inpatient or outpatient hospital record. The independent blinded observer's measures were sent directly to UCLA. The coordinator at each of the CUs maintained a folder with the name and address of each subject, along with all baseline data collected by the physician and coordinator.

The SCU maintained a database containing the patient identification number and treatment assignment that will be merged with other study variables at the end of the trial. A separate database was created and data were entered and saved using Microsoft Access. These files and the separate patient logs will be converted into SAS format for statistical analyses. The database software includes programs to check whether entered data fall into plausible ranges and whether data are complete. Data entries were checked by the SCU for accuracy by repeating the entry procedure and looking for discrepancies. The primary data manager contacted a coordinator or blinded observer at a CU if data on the forms appeared inconsistent, for example, if the impairment group assignment is inconsistent with the motor examination on the ASIA or if the FIM locomotor score is inconsistent with the time to do the 50-foot walk.

Unblinding Procedures

The external Safety and Data Monitoring Committee, appointed by the PI and the NIH program director, served as an independent oversight body. To optimize its interactions, the committee was drawn from academic sites in Los Angeles County but not from UCLA. The committee monitored the progress of patient accrual, data management, patient safety, and scheduled and requested interim analyses of data. The Safety Committee was blinded as to the therapy assignment of subjects but had the option of becoming unblinded if adverse reactions threatened the safety of subjects.

Data Analyses

The statistical design included an interim analysis when one-half of the planned number of subjects had a 6-month assessment for the primary outcomes. At that stage, the Safety Committee determined if the study appeared to demonstrate efficacy or lack of efficacy for one arm compared to the other within the ASIA B, C, or D groups and overall. They assessed the potential futility of continuing to enter subjects if the conditional power was too small to expect that additional accrual would result in significant effects (that is, rejection of the null hypothesis).

The initial protocol emphasized the development of valid statistical models to carry out data analyses. SCILT is essentially 2 clinical trials: ASIA B and C combined and ASIA D since

the primary endpoint is different for each ASIA stratification—walking independence score (FIM walking scale) and walking speed. The statistical design for the first trial is as follows:

Asia	Lesion	BWSTT	Conventional
B	UMN		
B	LMN		
C	UMN		
C	LMN		

This design has 2 stratification factors and 1 treatment factor with repeated measurements at baseline and biweekly for the first 12 weeks, then at 6 and 12 months. The primary endpoint for trial 1 is the FIM walking score at month 6. The primary analyses consist of an ANCOVA model for the FIM walking score at month 6 as follows:

$$Y_{ijkl6} = \mu_i + {}_{-j} + {}_{-k} + \delta_l + (\delta\_)_{jl} + (\delta\_)_{kl} + \gamma * Y_{ijkl0} + \theta * X_{ijkl} + {}_{-ijkl}$$

$_i = 1, 2, \ldots n_{jkl}$ – *individual*

$_j = 1, 2$ – *ASIA B versus C*

$_k = 1, 2$ – *UMN versus LMN*

$_l = 1, 2$ – *BWSTT + conventional versus conventional*

Y_{ijkl0} = *FIM walking score at baseline (covariate)*

X_{ijkl} = *duration from onset of SCI to study entry (covariate)*

$_{-ijkl}$ = *error term for the individual observation*

The resulting ANCOVA will enable us to study possible treatment by stratification interaction, main effects, and initial covariates. To carry out this analysis, detailed diagnostics for model adequacy, goodness of fit, outlier observations, and so forth will be carried out. A similar model will be developed for the second clinical trial for patients classified as ASIA D.

Analyses for the secondary endpoints will use the appropriate models. Correlation among the secondary and primary variables will be obtained for each clinical trial. For example, over the course of the RCT, we will examine relationships between the primary outcomes of locomotor independence and walking speed with walking endurance, the maximum heart rate after walking 50 feet, level of injury, changes in ASIA classification, the Lower Extremity Motor Scores, and the WISCI. We will look for aspects of quality of life that are reflected in locomotor capacity. This will be considered in several ways, including a bivariate ANCOVA. The full database includes measurements of endpoints made over time. A repeated measures ANCOVA using alternative nonparametric time trend curve estimation methods will be carried out making use of generalized estimating equation methodology.

DISCUSSION

Multicenter RCTs of physical therapies have been an uncommon undertaking for those who practice neurologic rehabilitation. This problem derives from confounding issues. Few neurophysiologically sound hypotheses have worked their way into the clinical arena. Few styles of physical therapy are carried out in a reproducible fashion across rehabilitation centers. Pharmacologic interventions, especially for chronic symptoms or signs such as spasticity, outdistance studies of physical therapies, in part because dose-response curves are determined by preliminary drug studies, the intervention is precise, and outcome measures are kept simple, perhaps too simple to reveal much clinical impact.[42] Outcome measures pose their own limitations. Many tools that examine disability, impairment, participation, and quality of life have floor and ceiling limitations or are too broad for discerning the benefit of an intervention for a well-defined problem.[1]

The SCILT investigators believe they have standardized a conventional and an experimental physical intervention as best as reasonably possible across sites and therapists. Differences in outcomes between sites, of course, would degrade this confidence. Parametric and nonparametric outcome measures used in the RCT ought to provide clinically meaningful changes if, indeed, BWSTT is efficacious at an early stage after SCI at the intensity and duration applied. The results will also be relevant to people with chronic or complete SCI who, in the future, may receive biological interventions that will have to be combined with locomotor training to enhance gains for walking.[28]

Recent trials of well-defined interventions for neurologic rehabilitation, such as this RCT and the upper-extremity practice intervention for narrowly defined patients with stroke called EXCITE, open the door for planning other multicenter trials, regardless of the efficacy of either of these pioneering efforts. These trials demonstrate that prospective, randomized multicenter trials with masked outcomes can be organized to test a physical intervention in a representative population and can be managed to completion.

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Table 1

American Spinal Injury Association (ASIA) Impairment Scale[a]

A—Complete: no sensory or motor function below the lesion, including sacral segments S-4 and S-5.
B—Incomplete: sensory but not motor function is preserved below the neurological level and includes S-4 and S-5.
C—Incomplete: motor function is preserved below the level and more than half of key muscles below the level are graded <3/5 (British Medical Council Scale).
D—Incomplete: motor function is preserved below the level, and at least half of key muscles below the neurological level have a muscle grade ≥3/5.
E—Normal: sensory and motor tests are normal.

[a] Standard neurological classification of spinal cord injury

Table 2

Site Data for Patients with Acute Traumatic Spinal Cord Injury (SCI) in 1997

Clinical Unit	Mean Onset of SCI to Rehab Admit (days)	Mean Inpatient Rehab Stay (days)	Ethnicity (%): White, Hispanic, African American. Asian. Native American	Total SCI Patients per Year / SCILT Eligible Subjects per Year
National Uniform Data System, 1995	28	38 ± 31	N/A	N/A
Magee/Jefferson	26	27	59, 6, 34, 0.5, 0	178 / 26
IRM/McGill-ORH	28	38	93, 0, 3, 1, 3	126 / 23
Ohio State	15	29	85, 1, 13, 1, 0	98 / 20
Rancho Los Amigos	13	33	22, 47, 25, 5, 0.5	78 / 20
Shepherd	20	42	55, 1, 29, 2, 0.5	140 / 32

SCILT, Spinal Cord Injury Locomotor Trial

Table 3

Rehabilitation Admission ASIA Score and Level versus Discharge FIM Walking Score for All CUs in 1996 and 1997 (SCILT-eligible subjects)

	ASIA B		ASIA C		ASIA D	
Level	**<5**	**≥5**	**<5**	**≥5**	**<5**	**≥5**
C5			11	7	5	17
C6			1	1	4	9
C7	5			2	1	1
C8	2				1	2
T1	1					1
T2						
T3	2		1			
T4	2		2		1	
T5	2		1	1		
T6		1	1			
T7	2		2		1	2
T8	5	1		1		1
T9				1		1
T10	2		2	1	1	1
T11	3		1			1
T12	7	4	6	3		3
L1	5	2	15	11		4
L2	1		1	2		2
L3	3		4	2	1	4
Totals for ASIA level	50		90		64	
Totals for FIM groups	42–8		48–32		15–49	
UMN group	26–2		22–14		14–36	
LMN group	16–6		26–18		1–13	

ASIA, American Spinal Injury Association scale; FIM, Functional Independence Measure; CU, Clinical Unit; SCILT, Spinal Cord Injury Locomotor Trial