Amplify Gait to Improve Locomotor Engagement in Spinal Cord Injury (AGILE SCI) Trial

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Principal Investigator: Keith Gordon, Ph.D.

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List of Abbreviations

10MWT – 10 Meter Walk Test

ASIA – American Spinal Injury Association

AIS – American Spinal Injury Association Impairment Scale

ABC – Activities-Specific Balance Confidence scale

BBS – Berg Balance Scale

BESTest – Balance Evaluations Systems Test

BP – Blood Pressure

COM – center of mass

FGA – Functional Gait Assessment

HR – Heart Rate

IC – initial foot contact

ICIQ-UI SF – International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form

INVO – Northwestern University's Innovation and New Ventures Office

IP – Intellectual Property

ISNCSCI – International Standards for Neurological Classification of Spinal Cord Injury

iSCI – incomplete spinal cord injury

ISO – Information Security Officer

kHz – kilohertz

LEMS – Lower Extremity Motor Scores

MOS – margin of stability

NMH – Northwestern Memorial Hospital

PCT – Patent Cooperation Treaty

PHI – Protected health information

PTHMS – Department of Physical Therapy and Human Movement Sciences

PO – Privacy Officer

QoL – Quality of Life

RIC – Rehabilitation Institute of Chicago

RPE – Rate of Perceived Exertion

SBP – Systolic blood pressure

SCI – spinal cord injury

SCI/D – Spinal Cord Injury/Disorder

SD – standard deviation

SEAs – Series Elastic Actuators

SRAL – Shirley Ryan AbilityLab

TO – toe-off

VA – Veteran's Affairs

VI – LabVIEW program's subroutines are termed virtual instruments

VISN 12 – VA Great Lakes Health Care System

WISCI II – Walking Index for Spinal Cord Injury II

WHOQOL-BREF – World Health Organization Quality of Life scale

Contents

Protocol Title: Amplify Gait to Improve Locomotor Engagement in Spinal Cord Injury (AGILE SCI) Trial

1.0 Study Personnel

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- **Indicate the number of potential participating sites (both VA and non-VA) and if there is any graduated start-up plan for the sites**

The study will be conducted through the Edward Hines Jr. VA Hospital. A partial offsite waiver will be obtained to collect and analyze data at the Feinberg School of Medicine, Northwestern University.

2.0 Introduction

- **Provide scientific background and rationale for study.**
- **Include summary of gaps in current knowledge, relevant data, and how the study will add to existing knowledge.**

Regaining the ability to walk is a priority for individuals with incomplete spinal cord injury (iSCI) [1]. The development of intense locomotor training interventions [2, 3] targeting recovery rather than compensation [4] has changed the future prospects for many Veterans with iSCI who now have evidence-based resources to support their efforts to walk again that did not exist two decades ago. As successful as these interventions have been, there is broad recognition that **better methods to enhance dynamic balance are needed** [5-7].

For ambulatory individuals with iSCI, **residual balance deficits negatively impact three major areas of concern during walking: stability, speed, and endurance.** To walk, one must be able to balance [8-10], which is encompassed by the ability to control one's center of mass (COM) dynamics as the body progresses over a continuously changing base of support [11]. Following iSCI, sensory and motor deficits impair balance [12, 13], directly impacting walking function [14, 15]. Individuals with iSCI compensate for balance impairments by selecting gait patterns that passively assist in recovery from movement errors [16]. *Passive* infers that the body will "self-correct" when errors occur without requiring a sensory-motor response, making this method of balance desirable for people with iSCI. These passive mechanisms include decreasing walking speed [17] and step length [18], as well as increasing step width [18-21] and double support time [16, 22]. There are trade-offs associated with choosing gait kinematics that rely on passive mechanisms to provide dynamic balance. Increasing double-support time creates a more stable base of support but limits maximum walking speed [8, 23]. Similarly, taking wider steps creates a larger base of support but makes it more difficult to change directions [24] and significantly increases metabolic energy consumption [19]. In individuals with iSCI, 10% of the total metabolic energy required to walk is expended to maintain lateral balance [21]. These balance deficits contribute to high fall rates [25] (~75% of individuals with iSCI fall each year [25] and most falls occur during walking [26]) and the avoidance of walking in challenging environments [27]. Thus, **interventions that can effectively enhance dynamic balance should enable individuals to select faster, more metabolically efficient gait patterns, without compromising safety.**

People with iSCI exhibit a strong positive relationship between balance and both functional walking ability [14, 15, 28-30] and participation in walking activities [31]. Across ambulatory individuals with iSCI, balance is a better predictor of participation in walking activities than lower-extremity muscle strength, spasticity, balance confidence, or metabolic efficiency [31]. Ambulatory individuals with iSCI average only 2,600 steps per day [9], well below the sedentary lifestyle threshold of 5,000 steps [32]. Restricted participation in walking activities may limit social engagement and critical activities of daily living [33]. Thus, the development of interventions able to **enhance dynamic balance of ambulatory individuals with iSCI may improve participation in walking activities**. However, it is currently unknown how training interventions impact participation in walking activities. While many studies have examined the effects of exercise,

balance, and locomotor interventions on walking function in individuals with iSCI (for review see [34]), only two studies (recumbent cycling [35] and underwater walking [36]), neither of which contained a control group, have quantified changes in steps per day following an intervention. There is growing evidence in individuals post-stroke that improvement in functional walking capacity, a person's ability to execute walking in the laboratory or clinic, does not necessarily translate to increased participation in walking activities [37, 38]. If a primary goal of gait rehabilitation is to increase participation, then it is imperative that we quantify how specific interventions directly affect walking participation.

Background

Dynamic Balance during Walking

Human walking is inherently unstable [11]. During forward walking our COM naturally oscillates in the fore-aft and medio-lateral directions relative to our base of support [39]. Dynamic balance, the ability of the nervous system to anticipate and react to changes in balance during movement, is essential for creating effective and efficient goal-directed walking trajectories. In particular, the requirements of the nervous system to select strategies to successfully control medio-lateral motions are considerable in comparison to fore-aft motion, which benefits from stabilizing mechanics [40-42].

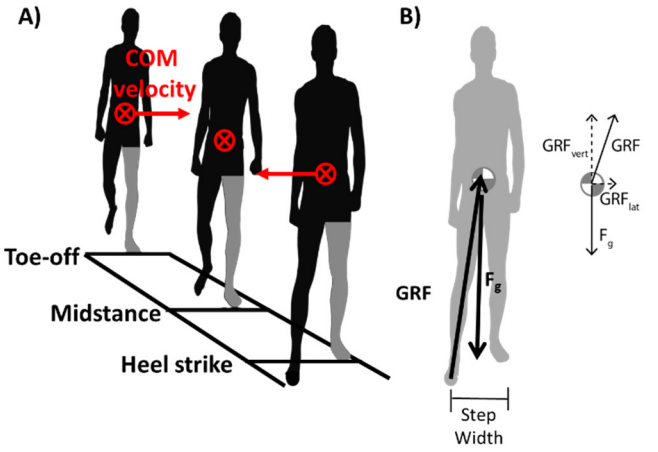


Figure 1. Control of medio-lateral motion during gait. A) During single limb support the laterally-directed COM velocity is arrested and then redirected toward the midline. B) Gravity (F_g) and the stance limb ground reaction force (GRF) create moments about the ankle joint to control medio-lateral COM velocity.

An examination of the single limb support phase of the gait cycle illustrates the challenge of controlling medio-lateral COM motion. Beginning at toe-off, the lateral velocity of the COM is relatively large and directed towards the stance limb (Figure 1A). To maintain a straight-ahead walking trajectory, this lateral velocity must be reduced to zero (ocurring around midstance), and then redirected towards the midline. Failure to arrest the lateral momentum of the COM will result in motion beyond the lateral base of support border (determined by the stance limb medio-lateral foot-placement). COM travel beyond the lateral base of support border will require a corrective step(s) to prevent a fall and restore the desired forward walking trajetory. Two moments, acting in the frontal-plane about the stance limb ankle joint, work collectively to arrest and then redirect the COM lateral velocity [43]. The larger of the two moments is created by gravity [43]. The magnitude of the gravitational moment arm will be proportional to the medio-lateral foot placement location relative to the COM (i.e. step width) (Figure 1B). The second moment about the ankle joint is create by muscle actions that modulate the magnitude, direction, and origin of the ground reaction force vector (Figure 1B).

The intact nervous system uses a combination of anticipatory and reactive control mechanisms to modulate the gravitational and ground reaction force moments. **The anticipatory component actively controls medio-lateral foot placement**. During swing phase, the nervous system modulates hip musculature to control the trajectory of the swing limb [44], which in turn will determine foot placement location for the ensuing stance phase. In non-impaired individuals, medio-lateral foot placement is highly correlated with the state of the COM dynamics during the preceeding swing phase [45, 46]. Simply stated, if the COM is falling rapidly to the right and a

larger than normal moment is required to control the body's lateral motion, then people will take a wider step to the right. The significant linear relationship between COM dynamics and lateral foot placement in non-impaired individuals suggests active involvement of the nervous system to anticipate the future requirements to control lateral COM dynamics. In comparison, the selection of consistently wide steps among individuals with iSCI [21] that are not modulated on a step-by-step basis in anticipation of COM dynamics, suggests that this population relies on passive mechanisms to maintain dynamic balance. The importance of this anticipatory component of dynamic balance for controlling lateral COM motion is highlighted by the fact that individuals post-stroke, who are classified as fallers, do not modulate their step-by-step lateral foot placement [45] in response to changes in COM dynamics during walking.

The reactive component of dynamic balance is necessary to make up for any difference between the total required moment needed to arrest and redirect the lateral COM motion and the gravitational moment created by foot placement. Specifically, the nervous system rapidly modulates muscle activity in the stance limb in response to ongoing sensory feedback [47] to create an appropriate ground reaction force vector that will supply the additonal moment about the ankle joint. Time delays associated with sensory feedback, and sensory-motor impairments create challenges for individuals with iSCI to to generate a rapid and appropirate ground reaction force in situations when the gravitational moment is insufficient to arrest the lateral COM motion. Thus, rather than try to anticipate COM dynamics and risk the possibility that the nervous system is unable to generate an appropriate ground reaction force, a more robust solution is to select passive stratiges, such as consistently wide steps, that decrease the requirements of the nervous system to generate an appropriate ground reaction force. However, the selection of passive stratagies to maintain dynamic balace will impart metabolic [19] and maneuverability penalties [24]. Thus, the **ability of the nervous sytem to both anticipate and react to ongoing COM dynamics during walking has important implications for how an individual chooses to maintain dynamic balance.**

Learning Dynamic Balance is Difficult Following ISCI

A series of compounding factors make learning dynamic balance very challenging after SCI. Research suggests that error detection is essential for the nervous system to form and update an internal model [48, 49]. The internal model is a neural representation relating a given motor command to the resulting movement [50]. An internal model allows the nervous system to predict motion, which is vital for anticipatory control of dynamic balance. For individuals with iSCI, sensory-motor impairments limit the ability of the nervous system to detect small movement errors and consequently to recalibrate their internal model so that the nervous system can correctly anticipate the natural COM oscillations during gait.

An inability to anticipate COM oscillations creates uncertainty every step. To deal with uncertainty, the nervous system adapts impedance mechanisms (specific passive mechanisms that are resistant to perturbations) to control movements [51, 52]. During walking, impedance mechanisms used to control COM motions may include body postures (e.g. wide steps [21]) and muscle co-contractions (increasing joint stiffness) [53] that are typical of "cautious gait patterns". An advantage of these impedance mechanisms is that if small movement errors or perturbations occur, the body's mechanical system can recover from these disruptions without time delays or requiring active involvement of the nervous system to accurately detect and respond. However, reliance on impedance mechanisms to maintain dynamic balance comes with metabolic penalties and can result in a relatively inflexible walking patterns that collectively may deter an individual from choosing to engage in walking activities.

To learn new motor patterns motor exploration is necessary [54]. When learning active mechanisms of dynamic balance (e.g. modulation of medio-lateral foot placement every step as needed to control ongoing COM oscillations) people must explore and practice this strategy. For individuals with iSCI, exploration and practice imply decreasing reliance on passive mechanisms

of dynamic balance (e.g. indiscriminately wide steps). There are two primary reasons why this is difficult. First, the risk of falling and fall-related injuries during walking is considerable for individuals with iSCI [25]. When perceived risk is great, people select risk-aware control strategies based on uncertainty of their current state [55]. For individuals with iSCI, implementation of risk-aware control strategies means choosing to *exploit existing passive strategies* for maintaining dynamic balance that will limit the risk of falling *rather than to explore new active strategies* for maintaining dynamic balance that may expose the individual to greater fall risk during the learning process. Second, reliance on passive mechanisms (e.g. slow walking [56], increased periods of double support [16]) becomes a "physiologic crutch" during balance training that limits the involvement of the nervous system in actively detecting and responding to movement errors and perturbations. Much like training wheels that impede a child's ability to learn to balance on a bicycle, heavy reliance on passive mechanism of balance deprive the nervous system of the experience (i.e. exploration) necessary to identify cause and effect relationships between motor commands and their resulting motion.

From this perspective, it becomes clear why popular forms of balance-training used with the iSCI population are inconsistent. The natural extension of the principle of task-specific training [57] when applied to improving dynamic improving balance of individuals with iSCI, is to supplement gait training with additional challenges that further increase the balance demands during walking. One method of challenging balance is to use unexpected perturbations to directly disrupt balance [5, 7]. For an individual who is highly reliant on passive mechanisms to maintain dynamic balance, the introduction of greater environmental uncertainty will only serve to reinforce reliance on these passive mechanisms used to maintain balance. We have observed this effect in our research. When individuals with iSCI are exposed to frequent and unpredictable perturbations during walking, their gait patterns become stiff and highly resistant to external perturbations [58]. While such gait patterns may be robust to perturbations, there is limited motivation for an individual to explore or practice alternative (and potentially more effective) strategies for dynamic balance. A second popular method to incorporate dynamic balance training into gait rehabilitation programs is to introduce variable balance-challenging elements (e.g. narrow pathways or obstacles) [59, 60]. Results thus far have been mixed. The experience of practicing variable tasks of progressive difficultly may be sufficient for some individuals to explore their dynamic work space and to use the feedback to form an appropriate internal model. For others, heavy reliance on passive mechanisms of stability may limit the benefits of simply engaging in variable, balance-challenging walking activities.

Movement Amplification to Improve Dynamic Balance following iSCI

An alternative model for motor learning does exist that may be particularly beneficial for retraining active control of movement patterns. Error augmentation strategies involve the performance of movements in an unstable robotic force field that exaggerates an individual's own, self-generated motions [61]. Error augmentation **may accelerate motor learning** by augmenting sensory-motor feedback [62] and allowing the impaired nervous system to identify otherwise imperceptible errors. The intensified feedback may aid an individual with sensory-motor impairments to recalibrate their internal model so that it can be used to control anticipatory components of movement. Indeed, there is evidence that error augmentation can be used successful for accelerating the adaptation of desired walk patterns [63]. A more general form of error augmentation, known a movement amplification [64], does not utilize a reference trajectory to identify errors, but instead uses a negative viscosity force field to amplify all movements (not just errors). Movement amplification is believed to aid in the acquisition of new motor patterns by **encouraging movement exploration**. Training in a movement amplification environment may allow an individual to experience a greater range of movement velocities and thus improve their ability to adapt to environmental dynamics [65]. While error augmentation and movement

amplification approaches have shown promise for retraining control of reaching movements in impaired populations [61, 64], these methods have not been applied to training dynamic balance during walking.

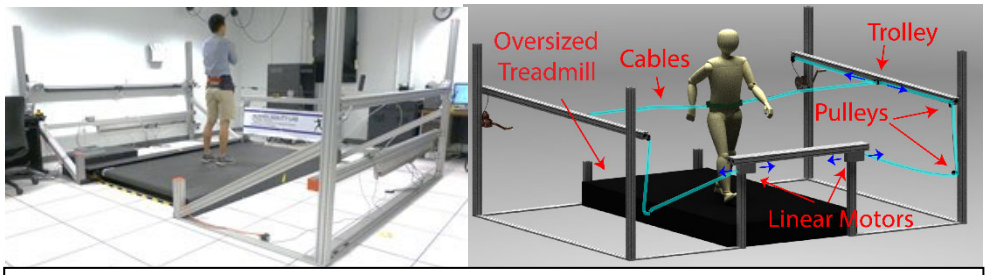


Figure 2. The Agility Trainer, a large cable robot used to apply lateral forces during gait that challenge dynamic balance.

Thus, we propose to evaluate if locomotor training performed in a movement amplification environment can enhance motor learning of dynamic balance in individuals with iSCI. Our approach to train dynamic balance has required the development of a new set of tools able to amplify COM movement during human walking. While the principle is relatively simple, apply a force to the pelvis that is proportional in magnitude and in the same direction as a user's real-time lateral velocity, the development of such a tool is non-trivial. To create the movement amplification environment, we have constructed a cable-driven robot, the Agility Trainer (Figure 2). This is a VA-owned device developed by the PI through a VA Career Development Award, [66]. Our system is designed to addresses several important considerations; create forces large enough to substantially accelerate the mass of a person, minimally restrict normal walking movements, precisely control an unstable (movement amplification) robotic system, and operates at bandwidths greater than the frequency of lateral COM movements during walking.

The Agility Trainer couples an oversized treadmill with a set of high fidelity, low inertia, back-drivable series-elastic linear actuators, capable of applying forces up to ~15% of an individual's bodyweight. A cable system routed through a series of pulleys connects each actuator to a side of a pelvic harness worn by a user. The pulleys are mounted to a trolley allowing free fore-aft motion and minimal restriction of normal COM motion during walking. Controlling movements of the two actuators in tandem allows us to quickly create velocity-based laterally-directed force fields experienced by individuals as they stand, walk, or maneuver on the treadmill. We use a combination of inner and outer feedback control loops with force and motion inputs to create a consistent movement amplification environment.

Innovation

Gait rehabilitation research following iSCI has largely focused on the effects of repetitive unobstructed walking practice performed either on a treadmill or over ground [34], and supplementation of these methods with bodyweight support [2, 3], robotic assistance [67], or functional electrical stimulation [68, 69]. For individuals with iSCI and AIS grades of C or D, these walking intensive interventions have a high probability of restoring and improving over ground walking ability [2, 3, 34]. However, residual deficits in dynamic balance remain a significant problem for individuals with iSCI [16, 25, 26]. As such, current clinical practice is to include variable forms of over ground walking activities that challenge balance [70]. Surprisingly, there has been relatively little research examining methods to directly improving walking balance after iSCI [59, 71]. We need to expand our gait rehabilitation toolbox so that clinicians have access to effective evidence-based approaches and tools that can enhance the recovery of dynamic balance for individuals with varying needs.

In our opinion, this research proposal is innovative in both its approach to addressing the recovery of balance after iSCI and in the development of new tools to deliver balance interventions. Our approach to training dynamic balance following iSCI centers on challenging the control of COM motions in a predictable (learnable) manner by amplifying an individual's own

motions. The movement amplification environment that we propose to use in this trial is similar in principle to error augmentation methods that have been shown to enhance experience-based learning of reaching movements [64], leg swing trajectories [63], and walking symmetry [72]. The consistent amplification of movements provides intensified sensory-feedback that will make it easier for the nervous to identify the relationship between a given efferent command and the resulting motion. This information is critical in the formation of a predictive internal model. As an individual improves their ability to predict their COM dynamics, reliance on passive impedance mechanisms such as an indiscriminately selecting a wide base of support, that are valuable for maintaining balance in uncertain environment, can be slowly released [73]. In addition, training dynamic balance in a movement amplification environment may speed motor learning by facilitating exploration of new movement strategies and the dynamic work space [65].

The proposed method of enhancing dynamic balance is in line with our goal to structure interventions aimed at recovery of function (active control of dynamic balance), not development of compensatory behaviors, (passive control of dynamic balance). **Training dynamic balance of individuals with iSCI by amplifying their own self-generated COM motion is a radical departure from current practice and may significantly improve our ability to train active mechanisms of stability.**

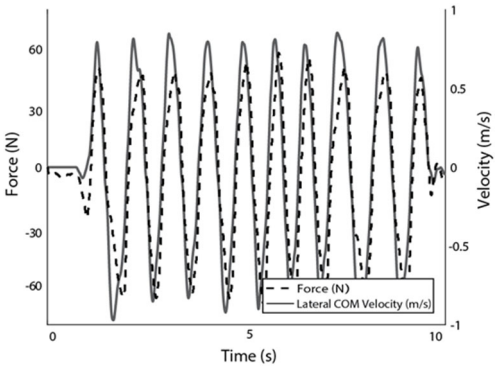


Figure 3. Movement Amplification Performance. Solid line is simulated lateral COM mass velocity (m/s) created by an external servo motor. Dashed line shows the net force (N) created in response to the oscillations. For this test the Agility Trainer was driven at a frequency of 1 Hz, with an amplitude of 10 cm. The movement amplification gain was set to 55 Nsm^{-1}, the peak gain that will be used in the proposed intervention.

Preliminary Studies

Verification of Tools Used to Create the Movement Amplification Environment

To assess the Agility Trainer's peak performance capabilities and quantify its capacity to create the movement amplification environment, we conducted a system identification test and an experimental simulation of human walking, respectively. For these tests, the Agility Trainer was connected to an external servomotor (Kollmorgen, USA) used to simulate the lateral motion of a person's COM during walking. We found the force bandwidth of our system was in the range of 4 Hz. Since human walking occurs almost entirely within this bandwidth, this performance exceeds the requirements for our purpose. As shown in Figure 3, the Agility Trainer was able to effectively create the movement amplification environment. As intended, the forces created by the Agility Trainer are qualitatively similar to movement velocity. However, there is an approximately 30 msec. lag between velocity input and force output. This lag is slightly noticeable to participants at zero-velocity when they change direction. However applied forces are small during this time period, making the effect difficult to detect. Overall, **the unique robotic tool we have developed is able to generate the desired movement amplification training environment during human walking**.

Response of Non-Impaired Individuals to the Movement Amplification Environment

Quantification of walking in the movement amplification environment was initially assessed in non-impaired participants where the effects of the environment could be isolated from neuromuscular impairment. Fifteen healthy participants walked for 10 minutes at their preferred speed in the movement amplification environment, with the gain set to 55 Nsm^{-1}, the peak gain that will be used in the proposed intervention. Participants adapted their steady-state walking patterns in response to the challenge of controlling their lateral COM motion in the movement amplification environment (Figure 4). Following 10 minutes of walking in the movement amplification environment, people adapted their gait patterns to reduce their peak lateral COM speed each stride (14% slower than baseline walking). However, this metric was 73% more variable in the movement amplification environment than during normal walking. Controlling lateral motion required energy. Metabolic cost of transport was 18% larger in the movement amplification environment than during baseline walking. Control was achieved by regulating foot placement each step. Lateral foot placement was significantly more correlated to COM dynamics ($p < 0.05$); regression R^2 was 0.82 in the movement amplification environment compared to 0.71 during baseline walking. When walking in the movement amplification environment **individuals selected gait patterns that stressed active control of lateral motion.** In addition, the increased step-to-step variability of COM speeds may facilitate exploration of movement dynamics that may be beneficial for motor learning [54]. These findings suggest that gait training in a movement amplification environment may be valuable for training impaired populations to actively control dynamic balance during walking.

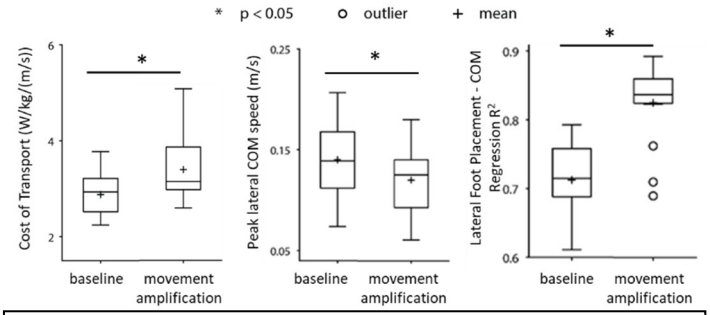


Figure 4. Non-impaired participants rapidly adapted their gait patterns to the movement amplification environment. After 10 minutes of practice, cost of transport was significantly greater in the movement amplification environment than during normal walking. Participants also adapted gait patterns that reduced their lateral COM speed per stride in the movement amplification environment. This was achieved by increasing the coupling between lateral foot placement and COM dynamics each step.

Lane Width Optimization Test: A Method to Assess Dynamic Balance during Walking

There is no current standard for assessing dynamic balance during walking in individuals with iSCI [74]. We specifically quantify dynamic balance as the capacity of an individual to control their lateral COM dynamics during forward walking. The narrow beam walking test, in which an individual attempts to walk as far as possible on a raised beam that gets progressively narrower with walking distance, [75] is a clinically-feasible method to identify the capacity of individuals with a range of abilities to control dynamic balance during walking. However, this test might not be accessible to individuals with substantial impairments because the narrowing beam restricts medio-lateral foot placement. As such, we have developed the Lane Width Optimization test to quantify the capacity to control lateral COM motion during treadmill walking without restricting foot placement.

During the Lane Width Optimization test, individuals perform two minutes of continuous treadmill walking at their preferred speed with no external assistance. A short throw projector (Hitachi, Tokyo, Japan) projects the participant's real-time medio-lateral COM position and a

target lane on the treadmill belt (Figure 5). To identify COM position, real-time 3D locations of LED-markers placed on the pelvis are collected using a 12-camera motion capture system (Qualisys, Gothenburg Sweden) and streamed to a custom LabVIEW VI (National Instruments, Austin, TX). The LabVIEW VI calculates medio-lateral COM position [76] and transforms the data into the treadmill coordinate system for display. Simultaneously, the LabVIEW VI adjusts and projects the width of a green, dynamic target walking lane (Figure 5). Participants are instructed to maintain their medio-lateral COM position within this dynamic target walking lane. The area outside of the target lane (to either the left or right) changes to red if the COM moves outside the target lane, providing an immediate visual cue that the participant has made an error and should try to return their COM to the lane immediately. The LabVIEW VI incrementally increases or decreases the lane width every 10 seconds based on performance (total time that the participant's COM is within the dynamic target lane and the number of times the COM crosses the borders of the lane during the preceding 10 second period). The narrowest lane width achieved and the associated lateral COM excursion per stride during 5 consecutive gait cycles will be the primary measures used to assess the ability to control (minimize) medio-lateral COM motions during treadmill walking.

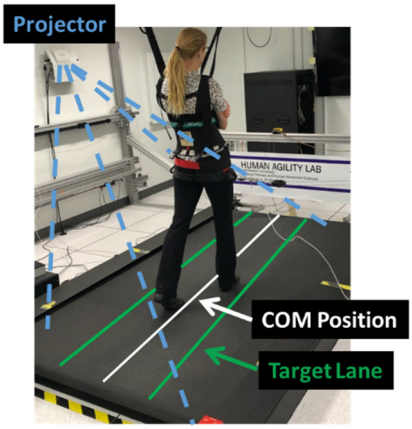


Figure 5. Lane width Optimization Test. Real-time medio-lateral COM position of the participant is projected on the treadmill. The participant is instructed to maintain the COM within a target lane. If successful, the target lane width is progressively decreased.

We have conducted the Lane Width Optimization test on 12 ambulatory individuals with chronic iSCI, who met the inclusion/exclusion criteria of the current proposed intervention, to assess feasibility and construct validity. Participants walked at their preferred treadmill speed with their arms free to move throughout the experiment. Participants were instructed to do their best to keep the line representing their COM position within the green target lane. All participants were able to perform the test and the target lane rapidly converged on a width that was challenging for everyone. There were strong and significant ($p < 0.05$) Pearson correlations between the final (narrowest) lane width achieved during the two-minute test and clinical outcome measures recorded from each participant (Pearson correlations of final lane width and the Berg Balance Scale $r = -0.67$; the 10-Meter Walk Test at maximum speed $r = -0.61$; and the Timed Up and Go $r = 0.80$). Thus, a narrower lane width corresponded with higher functional balance, walking speed, and adaptability. **The Lane Width Optimization test shows convergent validity with established clinical measures of dynamic balance and gait function.** This test will provide a quantitative method to assess control of lateral COM motion during walking.

Feasibility of Locomotor Trailing in a Movement Amplification Environment for Individuals with iSCI

We have collected pilot data demonstrating that **locomotor training performed in a movement amplification environment is safe, feasible, and likely effective for improving dynamic balance of ambulatory individuals with iSCI**. Three individuals with chronic iSCI, who met inclusion/exclusion criteria matching the proposed trial, received 16-18 treadmill training sessions in the movement amplification environment. One participant was classified as lower functioning (initial preferred gait speed < 0.5 m/s). All three participants used assistive devices (straight cane, wheelchair) during community ambulation. The goal of each 45-minute training session was to perform as much walking as possible within the movement amplification environment. We aimed to progress the movement amplification gain and treadmill walking speeds within and across sessions. As individuals' ability to walk in the movement amplification

environment improved, we introduced additional balance challenges to forward walking including lateral maneuvers, head turns, and obstacle avoidance. Training parameters were adjusted to sustain high intensity.

All participants tolerated the intervention. The lower functioning participant required regular handheld assistance that decreased with training. The other two participants rarely required handheld assistance after the initial training session. One participant inverted their ankle during training. This injury was minor, and the participant was able to continue training. During future sessions, this participant wore an ankle brace as a precautionary measure. No other injuries or other participant safety concerns occurred during training.

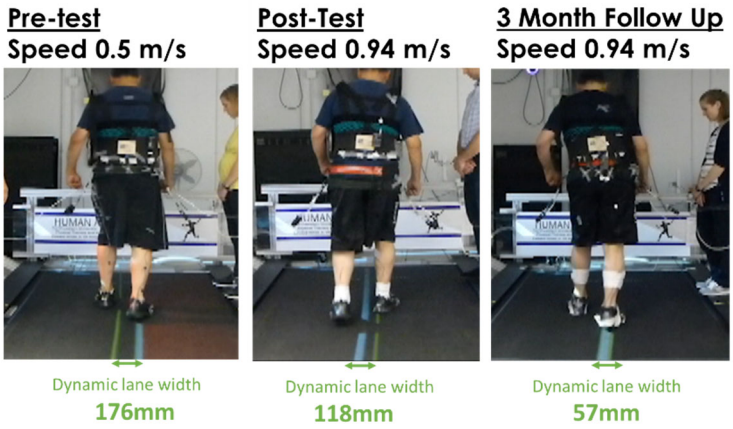


Figure 6. Lane Width Optimization Test. A participant with iSCI improved control of the lateral motion of the COM position (white line) following gait training performed in a movement amplification environment. Following training, the target lane (green lines) in which the individual could control their COM decreased substantially.

All participants learned to control walking in the movement amplification environment. Over multiple training sessions the movement amplification gait was gradually increased from 25 Nsm^{-1} (low gain) to 55 Nsm^{-1} (maximum gain) for all participants. Peak treadmill speeds during training also increased by 0.67, 0.27, and 0.63 m/s. Average peak RPE for each participant was 14.9, 18.3, and 17.4 indicating training parameters (gain, speed, and balance challenging tasks) were able to be adjusted to achieve high intensities. Average total walking time per session varied between participants: 32:04, 27:43, and 28:52 minutes. These results demonstrate that locomotor training in the movement amplification environment is safe and feasible for individuals with iSCI.

All participants demonstrated improvements in dynamic balance following the training intervention as assessed by narrowest target lane achieved on the Lane Width Optimization test and associated lateral COM excursion per stride (Figure 6). **Participants' improved dynamic balance by 31-35% compared to baseline** as measured by the Lane Width Optimization test. All three participants retained these gains at their 3-month follow up test. Clinical outcome measures supported these findings. All participants increased their fastest 10-meter walk speed (increasing by 0.1-0.22 m/s). Two participants improved their scores on the reactive postural control items from the Mini Balance Evaluation Systems Test (improvements of 2 and 4 out of 6, changing from no reaction to a single or multi-step successful response).

		Pre-Training		Post-Training	
Participant	Limb	R^2	p-value	R^2	p-value
1	Left	0.033	0.603	**0.386**	**0.000**
	Right	0.005	0.975	**0.295**	**0.001**
2	Left	**0.487**	**0.000**	**0.672**	**0.000**
	Right	**0.148**	**0.011**	**0.501**	**0.000**

Table 1: Correlation and significance between lateral foot placement and COM dynamics.

We conducted additional laboratory assessments to quantify baseline and post-training unassisted walking mechanics in two of the participants (unfortunately, these measures were not collected from our first high-functioning participant). Following training, participants selected a narrower base of support and increased their step-by-step modulation of lateral foot placement in response to COM dynamics. Specifically, participants decreased step width (12% and 13%) and increased step length (42% and 52%). In addition, lateral foot placement and lateral COM dynamics were significant and more strongly correlated after training (Table 1). These findings suggest individuals changed their strategy to control lateral motion and improved their ability to actively modulate their foot placement in response to changes in COM dynamics.

Finally, all participants self-reported improved participation in walking activities, including being able to carry food with two hands while walking in the kitchen, ability to walk alongside family members, desire to return to work, and participation in dance classes. The lowest functioning participant increased their WHOQOL-BREF raw score by 55 points, suggesting substantial improvement in quality of life. Finally, two participants self-reported substantial improvements in urogenital and/or sexual function. These results suggest that the benefits of locomotor training performed in the movement amplification environment may translate to activities of daily living.

3.0 Objectives

- **Describe the study's purpose, specific aims, or objectives.**
- **State the hypotheses to be tested.**

Dynamic balance – the ability to anticipate and react to changes in balance during movement – is essential for walking, a task with regular periods of instability resulting from periodic motion of the center of mass (COM) beyond the base of support [1]. Among ambulatory individuals with incomplete spinal cord injury (iSCI), balance deficits are common [2] and are a primary determinant of participation in walking activities (i.e. number of steps per day) [3]. This population averages only 2,600 steps per day [3], well below the 5,000 step sedentary threshold [4]. Improving dynamic balance may promote participation in walking activities. However, the capacity to enhance dynamic balance through locomotor training has been inconsistent [5, 6] and its impact on participation in walking activities is difficult to evaluate. To date, few studies have performed locomotor training interventions specifically targeting dynamic balance in iSCI populations [7, 8], and none have quantified changes in daily stepping. There is broad recognition that effective evidence-based interventions are needed to enhance dynamic balance of individuals with iSCI [7, 9, 10]. Our research finds, in response to viscous force fields that alter the requirements to control COM motion during walking, individuals with iSCI rapidly adapt their neuromechanical control strategies to maintain dynamic balance [11, 12]. This observation motives our proposal to examine a promising new approach to retrain dynamic balance by amplifying COM motion.

Improving dynamic balance after iSCI is very challenging because sensory-motor impairment limits the nervous system's capacity to detect movement errors. Error detection is necessary for updating the nervous system's internal model to correctly relate motor commands to their resulting movement. On a step-by-step basis, an internal model that poorly predicts motion limits the nervous system's ability to anticipate predictable balance challenges during gait (i.e. periodic COM motion). As such, individuals with iSCI often select passively strategies (e.g. wide steps) that maintain dynamic balance with minimum requirements from the nervous system to anticipate ongoing balance demands. These passive strategies are inflexible, inefficient [13], and limit walking speed [14]. Experimental interventions that amplify self-generated movements (e.g. error augmentation) may accelerate motor learning by augmenting sensory-motor feedback [15] and thus allowing the impaired nervous system to identify otherwise imperceptible errors. Such interventions could enhance dynamic balance by recalibrating the internal model to better predict COM motion. We have developed a cable-driven robot that creates a movement amplification environment by applying a continuous viscous force field to the pelvis that is proportional in magnitude to a participant's real-time COM velocity [16]. Our purpose is to investigate if locomotor training performed in a movement amplification environment can effectively improve dynamic balance and increase participation in walking activities of individuals with iSCI.

Specific Aim 1: To evaluate if locomotor training performed in a movement amplification environment is effective for improving dynamic balance of individuals with iSCI.

Hypothesis 1: Improvements in dynamic balance during walking will be greater when locomotor training is performed in a movement amplification environment when compared to a traditional treadmill environment.

We will conduct a two-arm parallel-assignment intervention. Participants will be randomized into either a Control group receiving locomotor training [5] or an Experimental group receiving locomotor training performed in a movement amplification environment. All participants will receive 20 training sessions. We will assess changes in dynamic balance using clinical outcome measures and a quantitative laboratory test we developed to measure capacity to control COM motion during walking. Our pilot data suggests that locomotor training performed in a movement amplification environment substantially improves dynamic balance. Following locomotor training in the movement amplification environment, three individuals with iSCI improved dynamic balance as evidenced by greater than 30% improvements in COM control during walking.

Specific Aim 2: To evaluate the impact of locomotor training performed in either a movement amplification environment or in a traditional treadmill environment on participation in walking activities.

Hypothesis 2: Participation in walking activities will increase more in the Experimental Group that receives locomotor training in a movement amplification environment.

To design more effective locomotor training programs, it is essential we understand how specific interventions impact walking participation outside of the clinic. We will use activity monitors [17, 18] to quantify changes in daily stepping activity. Based on evidence identifying a strong relationship between balance and steps per day in ambulatory individuals with iSCI [3], we anticipate that training in the movement amplification environment will positively impact dynamic balance, and in turn increase participating in walking activities.

Positive outcomes from Aim 1 would support development of clinically-feasible tools to first replicate, and then evaluate, the movement amplification environment within VA clinics. Data from Aim 2 will expand our understanding of if, and how, current locomotor training interventions and targeted dynamic balance training impact participation in walking activities in the home and community settings.

- **Indicate the relevance to Veterans and the VA**

Spinal Cord Injury (SCI) affects between 259,000-1,275,000 people in the United States [77, 78], of which ~42,000 are Veterans [79]. The Department of Veterans Affairs provides the single largest network of SCI care in the nation through its 24 Spinal Cord Injury Centers. With the lifetime financial burden of SCI ranging from $682,000 to over $3 million [78], identification of methods to improve the effectiveness of SCI rehabilitation programs would directly benefit Veterans living with iSCI and improve the ability of the VA to provide Veterans with first-class health care. A major cost of SCI is impaired mobility. Limited ambulatory function can result in decreased ability to work, increased care requirements, secondary injury, depression, bone mineral density loss, diabetes, and decreased cardiovascular health. Over half of spinal cord injuries are motor incomplete [80]. Depending on the severity of the initial injury, the prognosis for the recovery of independent ambulation after iSCI is 50-95% [81]. This portion of the SCI population would directly benefit from the development of evidence-based methods to enhance dynamic balance which could improve health and reduce the physical, social, and financial costs associated with limited mobility.

4.0 Resources and Personnel

- **Include a list of personnel, their location, role in the study and their VA affiliation status**
    - Principal Investigator:
        Keith Gordon, PhD
            Hines VA and Northwestern University
            5/8 VA appointment
    - Co-Investigators:
        Jennifer Kahn, PT, DPT, NCS
            Northwestern University
            IPA
    - Collaborators:
        Christine Jelinek, MS
            Hines VA
            8/8 VA appointment
        Geoffrey Brown, MS
            Northwestern University
            IPA
        Tara Cornwell, BS
            Northwestern University
            IPA

- **Provide a brief description of each individual's role in the study. Be sure to indicate who will have access to protected health information and who will be involved in recruiting subjects; obtaining informed consent; administering survey/interview procedures; and performing data analysis.**

        Keith Gordon, PhD
            Role: Principal Investigator
                Involved in all aspects of project
        Jennifer Kahn, PT, DPT, NCS
            Role: Co-Investigator, Research Physical Therapist
                Screening, recruitment, consenting,
                Will oversee gait training interventions,
                Will contribute to data analysis, data dissemination
        Christine Jelinek, MS
            Role: Clinical coordinator
                Screening, recruitment, consenting, scheduling
                Participant Activities
        Geoffrey Brown, MS (research engineer)
            Role: Research Engineer

Responsible for maintenance and operation of all hardware

Tara Cornwell, BS (research engineer)

Role: Research Engineer

Will oversee laboratory data collections and will perform data analysis

5.0 Study Procedures

5.1 Study Design

- **Describe experimental design of the study. Include sequential and/or parallel phases of the study, including durations, and delineate which interventions are standard of care and which are research.**

Overview

Our objective is to evaluate the effects of locomotor training performed in a movement amplification environment on dynamic balance and participation in walking activities of people with chronic iSCI. We will conduct a two-arm parallel assignment intervention. Participants will be randomized into a high intensity locomotor training intervention that will be conducted in either a normal treadmill environment or in a movement amplification environment.

Specific Aim 1 will assess changes in dynamic balance following the interventions. Based on the substantial improvements observed during our case series, we hypothesize that study participants will have greater improvements in dynamic balance when the locomotor training is conducted within the movement amplification environment.

Specific Aim 2 will evaluate the impact of the two interventions on the number of daily steps individuals take in the home and community.

The knowledge gained from this study will expand our understanding of how locomotor training performed in a movement amplification environment effects dynamic balance and participation in walking activities. Positive outcomes from this randomized controlled trial would motivate translation efforts to develop clinically-feasible devices that can easily replicate the movement amplification environment for use within the VA's system of care.

Target Population

Among individuals living with SCI, 67% have motor incomplete lesions [80]. Depending on the severity of the initial injury, the prognosis for independent ambulation after iSCI is between 50 and 95% [81]. We will recruit Veterans with chronic motor incomplete SCI who are ambulatory and able to advance their limbs without assistance. We will include participants with a range of initial functional walking ability evaluated by walking speed (half of the participants preferred walking speed will be < 0.5 m/s at enrollment). Thus, the target population for this trial is the considerable proportion of individuals with iSCI who would benefit from the advancement of interventions that can improve dynamic walking balance.

Protocol Overview

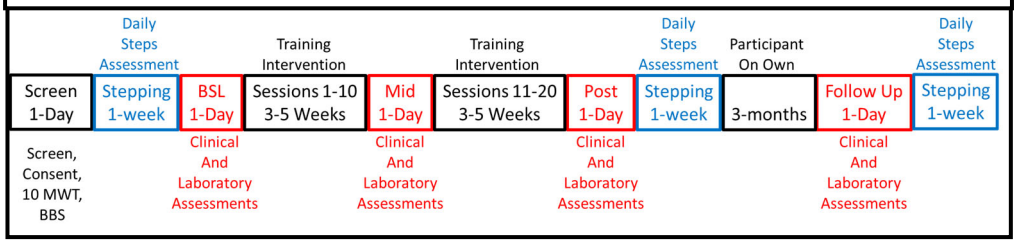
Participants will be stratified by gait speed (half of the participants will have a preferred over ground gait speed ≥ 0.5 m/s and half of participants will have a preferred over ground gait speed < 0.5 m/s) and then randomized into two locomotor intervention groups:

The **Control group** will receive high intensity locomotor training performed on a treadmill [60].

The **Experimental group** will receive high intensity locomotor training performed on a treadmill in a movement amplification environment created by the Agility Trainer.

We will conduct **clinical outcome measures** to assess changes in functional gait and balance and quality of life. We will conduct quantitative **laboratory assessments** to evaluate changes in dynamic balance and associated gait patterns. Finally, to assess if the effects of locomotor training impact participation in walking activities outside of the laboratory/clinical setting, we will measure daily **steps taken in the home and community**.

Figure 7. Timeline of the 22 to 26 week schedule for assessments and locomotor training intervention. The length of each individual study segment is indicated.



To ensure that gait and balance are stable prior to beginning the intervention, we will measure 10 m walk speed and Berg Balance Scale score during an initial **Screen**. These two measures will be repeated a week later during the Baseline (**BSL**) assessment session to ensure the participant's initial performance is stable. If measures are not stable, measures will be repeated a week later. If measures do not stabilize after three-weeks of testing, the participant will not be enrolled in the training intervention. Clinical outcome measures and laboratory assessments will be performed at four time points (**BSL**, **Mid**, **Post**, and **Follow Up**) encompassing the 20-session training intervention (Figure 7). Average number of steps taken in the home and community environment will be estimated from data recorded during 1-week periods occurring at three time points corresponding with **BSL**, **Post**, and at the 3-month **Follow Up**. (Figure 7).

Locomotor Training Interventions

We will conduct all locomotor training interventions in the Human Agility Laboratory. All training will be directed by a licensed physical therapist. Training for each intervention group will be conducted on a large commercial treadmill - belt width 1.39 m (Tuff Tread, Willis, TX) providing space to perform side steps and small lateral maneuvers [82]. For safety, participants will wear a trunk harness attached to a passive overhead safety support. Support straps will be adjusted to allow unrestricted travel across the treadmill and will not provide bodyweight support. During locomotor training, participants will wear a heart-rate monitor, to provide continuous feedback to the physical therapist on the intensity of the training, and an activity monitor, to measure number of steps during the session. For the Experimental group, the training equipment will also include the Agility Trainer to produce the movement amplification environment.

The locomotor training intervention will include 20 sessions (2 to 3 times per week). Each training session will last up to 60-minutes. The objective each session is for the participant to complete a total of 45-minutes of treadmill walking. The additional time each session will be used as needed for setup and rest breaks.

Control group: Participants randomized to the Control group will complete high intensity gait training on a treadmill. The protocol is based on evidence demonstrating that for individuals with iSCI high intensity training based on heart rate (HR) and perceived exertion (RPE) [83] resulted in significantly greater increases in treadmill and over ground walking speeds than lower intensity training interventions [60]. The goal of each session will be to achieve 40-minutes of stepping practice within a desired range for HR and RPE. We will continuously adjust training parameters to maintain a target HR between 70 and 80% of estimated age-predicted HR reserve. We will calculate HR reserve at follows:

HR reserve = (HR maximum – HR resting) + HR resting

We will estimate HR maximum [84] as: HR maximum = (208 – (0.7 x age)). If target heart rate zones cannot be achieved during training, we will use RPE as a secondary measure of intensity. We will target a rating of 15 “hard” to 17 “very hard” on the 20-point RPE rating scale during training.

Every training session will begin and end with a 2.5-minute warmup and cool down respectively. During these periods, individuals will perform straight treadmill walking. Target heart rate during these periods will be between 50 and 65% of HR reserve. The 40-minute body of the training session will be divided into four 10-minute segments. Two of the 10-minute segments will consist of **Speed-training**. The objective during Speed-training will be to achieve the highest possible speed during straight-forward treadmill walking while maintaining the target HR and RPE. The other two 10-minute segments will consist of **Balance-training**. The objective during the Balance-training segments will be to maximize repetitions of forward treadmill walking while introducing additional challenges to dynamic balance. We will utilize the following tasks to challenge dynamic balance:

1) *Lateral Stepping Maneuvers*. We will draw a chalk line down the center of the treadmill. During forward walking the physical therapist will cue the participant to move from one side of the chalk line to the other. Task difficultly will be increased by increasing the frequency of lateral maneuvers performed.
2) *Head Turns*. Participants will perform cued vertical and horizontal head turns while maintaining forward walking. Task difficulty will be progressed by increasing the magnitude and duration of the head turns.
3) *Obstacle negotiation*. Participants will be tasked with stepping over small objects during forward walking. Task difficulty will be progressed by increasing the size and frequency of obstacles.

Within the clinical decision-making framework (described below) combinations of the balance challenging tasks will be selected to; avoid repeated failures (loss of balance requiring physical assist from physical therapist to recover), achieve the appropriate heart rate and RPE, and consider the participant’s tolerance/needs. At the physical therapist’s discretion participants will be provided with hand-held assist as necessary to safely-perform the desired stepping tasks. Our goal will be to minimize any external support provided to the participants. Seated or standing rest breaks will be permitted as needed. Brief rest breaks will naturally occur during transitions between segments. We will monitor the individual and cumulative rest break time each session. We will set goals to decrease the individual and cumulative duration of rest breaks over the course of the training intervention.

The order of the individual 10-minute Speed- and Balance-training segments will be alternated within a session. We will alter which segment type (Speed- or Balance-training) is presented first from session-to-session.

Experimental group: The locomotor training protocol described for the Control group will be used for the Experimental group with one exception. The Experimental group will perform all

Speed- and Balance-training within the movement amplification environment. The objective for the Experimental group will be to progressively increase the movement amplification gain within and across sessions to increase the challenge for the participant to control their lateral COM motion. The gain of the movement amplification environment will be initially set very low (25 Nms^{-1}). When a participant can successfully ambulate in the low intensity movement amplification field without repeated failures (loss of balance requiring physical assist from physical therapist to recover), we will incrementally increase the gain of the field by (5 Nms^{-1}). We will continue to increase the gain until we reach a maximum gain of 55 Nms^{-1} dictated by the current Agility Trainer hardware and software.

Clinical Decision-Making: To ensure consistency of the intervention between participants, a simple clinical decision-making protocol will be used to guide the physical therapist's decisions about when to change intervention parameters. First the physical therapist will determine: is the participant able to accomplish the immediate walking task? Second, the physical therapist will determine: is HR and RPE in the target zone?

Is the participant able to accomplish the immediate walking task?

The immediate walking task during Speed-training is straight-forward walking. The task during Balance-training is straight-forward walking + an additional balance challenge. The physical therapist will determine that the participant is able to successfully accomplish the task if; *the participant is able to make positive reciprocal steps without limb collapse or loss of balance requiring assistance for 1-minute of walking.*

- **If successful**. First reduced or eliminate any handheld assistance. Next, if applicable, increase movement amplification gain by 5 Nms^{-1} (up to 10 Nms^{-1} above the participant's pervious highest gain within a single session or a maximum of 55 Nms^{-1}). Finally, if applicable, increase the challenge of the balance-training task. Reevaluate every minute.
- **If unsuccessful**. First, if applicable, decrease the challenge of the balance-training task. Next, if applicable, decrease the movement amplification gain by 5 Nms^{-1} (to a minimum of 25 Nms^{-1}). Finally, provide handheld assist as needed to perform the task successfully. Reevaluate every minute.

Is HR and RPE in the target zone?

Once the participant is able to successfully accomplish the walking task then the treadmill speed should be adjusted to achieve the desired HR and RPE.

- **If HR and RPE are below the target zone**. Increase treadmill speed by 0.1-0.3 mph. Reevaluated every 30 seconds.
- **If HR and RPE are above the target zone**. Decrease treadmill speed by 0.1-0.3 mph (treadmill speed should not go below the speed used during the session's warmup period). Reevaluated every 30 seconds. If HR and RPE remain above the target zone upper limit, then give a rest break.

We recognize that there is an interaction between the two decision-making trees. Specifically, increasing balance-challenges may increase the cardiovascular demands of walking, and increasing walking speed may increase the challenge to maintain dynamic balance. Based on our goal to provided targeted dynamic balance training, we will prioritize successful accomplishment of the task and stress progression of the dynamic balance demands (elimination of any handheld assist, progression of movement amplification gains, and progression of the balance-challenging tasks). We realize that for lower functioning participants prioritizing the balance challenging components of walking may result in HR and RPE below the target threshold. However, our pilot testing found that we were able to consistently adjust the movement

amplification gains, balance-challenging tasks, and walking speeds in a manner that consistently placed individuals in the target HR and RPE zone.

Documentation of Intervention

A research assistant will be present at every session to assist the physical therapist and document the following events at every training session. Specifically, we will record:

Vital signs before, during, and after training;

Total time walking within the 60-minute session;

Total number of steps (StepWatch, Modus, Washington DC);

Walking speeds;

Number of times **physical assistance** (from the physical therapist or overhead safety support) was provided to prevent fall (fall defined as inability to recover loss of balance without physical assistance);

Specific **balance-challenging tasks practiced** each session;

Movement Amplification environment gains (if applicable); and

Exertion and workload - monitored via heart rate and the 6-20 RPE scale throughout the session.

Assessment of Locomotor Training Effects

Clinical Outcome Measures

We will collect clinical outcome measures at four time points (BSL, Mid, Post, and Follow Up) surrounding the training intervention. Study personnel performing the clinical assessments will be blinded to the intervention. We will first collect demographic information and a brief medical history including:

- Demographic variables: age, gender, date of birth (BSL only)
- Date of spinal cord injury, level of injury, and cause of injury (BSL only)
- Current and past medical history (BSL only)
- Current medications
- Current ambulatory ability in the home and community including any assistive devices used during ambulation
- Self-reported number of falls in the past year (BSL only)
- Self-reported number of falls since previous assessment (Mid, Post, and Follow Up only)

Next, we will collect data using measures that span each level of the International Classification of Function, Disability, and Health (body structure and function, activity, and participation), utilizing a combination of performance based and self-report measures. First, the type of SCI will be classified using the **Lower Extremity Motor Score (LEMS)** portion of the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) [85]. The LEMS assess strength of five muscle groups representing neurological levels L2 to S1. We will also perform manual muscle tests of hip abductor strength which is important for controlling lateral motions.

We will use several clinical outcome measures to identify functional changes in gait-related balance. We will use the **Walking Index for Spinal Cord Injury II (WISCI II)**. The WISCI II evaluates the amount of physical assistance needed for gait after SCI. The WISCI II has excellent reliability and validity in the chronic iSCI population [86]. The WISCII has also been found to have a strong correlation with measures of balance [30]. The **Functional Gait Assessment (FGA)** is a ten-item test that evaluates dynamic balance and postural stability during gait [87]. Unpublished data from a study we conducted suggests the FGA is both valid and reliable

for assessing walking balance in individuals with iSCI [88]. The **10 Meter Walk Test (10MWT)** is a simple measurement of an individual's average walking speed. Research indicates there is a correlation between walking speed and balance; walking speeds below 0.48 m/s are in large part due to balance issues over long distances [89]. Gait speed will be measured at self-selected (instruction: “walk at your normal comfortable pace”), fastest-possible speed (instruction: “as fast as you safety can”). The **Activities-Specific Balance Confidence (ABC) scale** is a self-report measurement of an individual’s confidence while performing numerous postural and ambulatory activities. The ABC is a reliable and valid measure of balance confidence in individuals with iSCI who ambulate in the community [90]. The **Balance Evaluations Systems Test (BESTest)** is used to assess balance impairments across six different domains of postural control. We will specifically use the reactive balance item from the BESTest to assess changes in the capacity to react to fore-aft, and lateral perturbations [91]. The **Berg Balance Scale (BBS)** is a 14-item measure that assesses static balance [29]. The test has excellent validity and reliability data for in individuals with AIS D, however in higher functioning individuals the test suffers from a ceiling effect. As the test does not assess dynamic balance it is recommend to be used in conjunction with additional measures, such as 10MWT [92].

Finally, we will measure the intervention’s potential impact on quality of life. We will utilize an abbreviated version of **The World Health Organization Quality of Life scale** (WHOQOL-BREF) [93]. The WHOQOL-BREF is a 26-item self-report quality of life assessment focusing on areas such as physical, psychological, social and environmental health. Two of the three participants in our case series investigating the effect of locomotor training performed in a movement amplification environment reported substantial improvements in bowel/bladder and sexual function following training. This is consistent with a pervious locomotor training study [94] that also found improvements in bladder function. These improvements may be attributable to neuroplasticity or biomechanical demands related to pelvic floor and core musculature involvement in dynamic balance during locomotion. We will use the **International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ- UI SF)** a 4-item self-report of urinary incontinence to document changes in bladder function [95].

Laboratory Assessments

We will perform laboratory assessments to make quantitative measures of changes in dynamic balance during walking. Specifically, we will quantify the ability of participants to control their whole-body COM motion during treadmill walking and measure associated stepping mechanics. We will collect kinematic data as participants perform walking on an oversized treadmill (Tuff Tread, Willis, TX). We will record 3D coordinates of 40 reflective markers placed on the trunk, pelvis and lower limbs using a 12-camera motion capture system (Qualisys, Gothenburg Sweden).The participant will not be allowed to use any assistive devices (canes, walkers, handrails, or manual assistance) with the exception of any passive ankle-foot orthoses they would typically wear during community ambulation. All walking will be performed at the participant’s preferred treadmill speed (identified at the beginning of each Laboratory Assessment testing session through a staircase method of increasing and decreasing the treadmill speed until desired speed is confirmed through verbal feedback). For the Mid, Post, and Follow Up assessments, walking will be performed at both the current preferred treadmill speed (if preferred treadmill speed has changed with training) and at the preferred treadmill speed identified during BSL.

Participants will perform a series of 2-minute long walking trials performed at both their current preferred walking speed and matched to their preferred walking speeded identified during BSL. Two walking trials at each speed will be used to identify participant’s preferred walking characteristics. During these trials, participants will be instructed to walk as they feel most comfortable. No additional external support or feedback will be provided during these trials. Two additional walking trials at each speed will be used to assess the ability of the participant to control

their lateral COM motion during walking. During these walking trials, participants will perform the **Lane Width Optimization Test**. The order of all trials will be randomized. Participants will rest for at least 2 minutes between trials. Additional rest time will be provided as need.

We will post-process and analyze data from the walking trials to assess COM motion and stepping characteristics. Kinematic marker data will be processed using Visual3D (C-Motion, Germantown, MD) and a custom MATLAB (Mathworks, Natick, MA) program. Marker data will be gap-filled and low-pass filtered (Butterworth, 6 Hz cut-off frequency). Time of initial foot contact (IC) and toe-off (TO) events will be identified for each step based on fore-aft positions of the calcaneus and 2nd metatarsal markers. Medio-lateral COM position will be calculated in Visual3D as the center of the Visual3D model's pelvis. To characterize medio-lateral control of the COM during all walking trials we will identify **peak lateral COM Speed** and **lateral COM Excursion** each stride. COM velocity will be calculated as the derivative of COM position. Peak lateral COM Speed will be identified as the maximum absolute COM velocity between ipsilateral initial contact events, and lateral COM Excursion will be calculated as the difference between the maximum and minimum lateral COM positions per stride. To assess how control was instituted, we will examine **step width**, **step length**, **step time**, and **minimum lateral margin of stability** (MOS) each step using established methods [82].

Daily Stepping

We will assess the amount of daily stepping in the home and community during three 1-week periods. Daily stepping will be measured and recorded using a StepWatch4 (Modus, Edmonds, WA) activity monitor. The device has a battery life of 35 days and will record individual stepping data on the resolution of seconds. The device has been found to be accurate and reliable for measuring stepping activity in individuals with iSCI [96] and has been used successfully to assess daily stepping in individual with iSCI [31, 97]. During each assessment period, the microprocessor-based accelerometer will be worn around the ankle during all waking hours (except bathing) for seven continuous days. We will only analyze data on days that the StepWatch has been worn for at least 90% of waking hours. Research suggests that stable measures of walking activity in adults with iSCI can be obtained by averaging step count values from any 2-day period in a week [97]. Our primary measure of daily stepping will be the **total number of steps taken per day** averaged across the 7-day period. We will also measure changes in activity level using two secondary measures, the number of **minutes of the day with at least one step**, and **percent of a 24-hour day with no walking**.

Research Team, Organization, Management, and Communications

All members of the research team will meet as a group on a quarterly basis to review progress, discuss research-related issues, and to identify upcoming goals. Three smaller sub-groups will meet on a weekly-basis. The sub-groups will include a clinical research team who are responsible for administering and documenting the training intervention, a laboratory research team who are responsible for collection, analysis, and processing of laboratory assessments and daily stepping records, and an administrative team responsible for recruitment, IRB-related issues, purchasing, and equipment maintenance. Meeting notes will be recorded and saved in a shared online folder where they can be accessed and reviewed by the study team members.

Time Line

We will spend the first quarter of the study finalizing administrative issues, and standardizing training procedures. Once in place, we will begin recruiting and enroll participants. We will have 2-3 participants involved in the training interventions at a time. We will time study enrollments to limit disruptions during high travel/vacation periods (winter holidays). We will stagger start times in the intervention, so data collection periods and step tracking periods are spread out.

Timeline

		Year 1				Year 2				Year 3				Year 4			
	Quarter	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Tasks	IRB Approvals	X															
	Manual of Study Procedures	X															
	Training of Study Personnel	X															
	Participant Recruitment		X	X	X	X	X	X	X	X	X	X	X	X			
	Lab Assessments / Clinical Measures		X	X	X	X	X	X	X	X	X	X	X	X	X		
	Stepping Assessments		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
	Training Interventions		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
	Manuscript Preparation				X	X	X	X	X	X	X	X	X	X	X	X	X
	Grant Preparations														X	X	X

- **Description of risks to participants and of how anticipated risk will be minimized.**

Potential Risks

All participants will engage in a high intensity locomotor training intervention. The greatest risks participants will face are comparable to risks associated with other intense cardiovascular exercise and gait rehabilitation programs. Specifically, the potential risks to participation include:

- Cardiovascular difficulties and fatigue resulting from high intensity walking.
- Musculoskeletal injuries resulting from falls and/or stumbles during treadmill walking.
- Fear of falling that may be brought on by the training environment that is designed to challenge balance.
- Discomfort from the pelvic harness which fits snuggly around the waist and is used to transmit forces to the pelvis from a cable-driven robotic device.
- Emotional or psychological discomfort created by the personal nature of some of the medical history questions, clinical outcome measures, and record of daily stepping activity.

Protections Against Risk

We will continuously monitor participants for any evidence of adverse or unanticipated events during experimental testing and training sessions. In order to minimize cardiovascular risks during experimental testing and training we will monitor heart rate, blood pressure, and perceived exertion to determine if exercise should be stopped. Participants will also be allowed to stop and rest at any time. We will also monitor participants for any trips, slips, stumbles, or missteps during walking trials. Should any occur, we will stop testing to examine the participant for orthopedic injury prior to resuming testing. All participants will also be attached to a safety system consisting of a modified parachute harness attached to an overhead support that will prevent participants from falling more than several inches if they stumble when walking. All robotic equipment will have emergency shut-off switches that will be accessible to both the participant and research personnel during testing that will turn off the robotic device immediately when pushed. Hard stops and robotic controls will prevent participants from experiencing applied forces greater than a predetermined magnitude, or on certain areas (boundary's) of the treadmill belt. Research staff will continually interact with participants to monitor for any evidence of adverse or unanticipated events during testing. Before leaving the laboratory, participants will be reminded that they have the contact information for the PI and research staff (included in their copy of the informed consent form), and they will be encouraged to contact us immediately should they experience any adverse or

unanticipated events that may have been in any way related to their participation in the research study. We will also take the specific following steps to minimize risk to participants.

Cardiovascular Risks

Participants might experience cardiovascular difficulties during the high intensity treadmill training intervention. We will monitor heart rate (HR) and blood pressure (BP) along with an ensemble of information from all participants to minimize cardiovascular risk. Dependent on the location and severity of the SCI, innervation of the sympathetic nervous system may be disrupted, which can affect the HR–VO^2 relationship. Because of this, clear guidelines for prescribing and stopping exercise for individuals with SCI based on BP and HR values have not been established as they have for neurologically-intact individuals. We will monitor BP and HR and use this information in conjunction with other guidelines provided by the American College of Sports Medicine for indications to terminate exercise. Specifically, we will stop exercise if any of the following signs are observed:

- Suspicion of a myocardial infarction or acute myocardial infarction (heart attack)
- Onset of moderate-to-severe angina (chest pain)
- Drop in systolic blood pressure (SBP) below standing resting pressure or drop in SBP with increasing workload accompanied by signs or symptoms
- Signs of poor perfusion (circulation or blood flow), including pallor (pale appearance to the skin), cyanosis (bluish discoloration), or cold and clammy skin
- Severe or unusual shortness of breath
- CNS (central nervous system) symptoms (e.g., ataxia (failure of muscular coordination), vertigo (an illusion of dizzying movement), confusion)
- Serious arrhythmias (abnormal heart rhythms) (e.g. second / third degree AV block, atrial fibrillation with fast ventricular response, increasing premature ventricular contractions or sustained ventricular tachycardia)
- Participant's request to stop

After testing is complete, we will check heart rate and blood pressure of all participants to ensure that these measures have returned to baseline levels before participants leave the laboratory. We will continually interact with participants to monitor for any evidence of adverse or unanticipated events during this time.

Fatigue

Walking on the treadmill is exercise and may cause individuals to become fatigued. Participants will be given regular scheduled rest periods throughout the experiment and training. However, they may request additional rest at any point during experiments and locomotor training sessions.

Musculoskeletal Injury, Risk of Falling, and Fear of Falling

Participants might trip and fall while walking which could result in musculoskeletal injury such as an ankle sprain. To minimize this risk, participants will wear a harness that will prevent them

from falling more than several inches if they were to trip or stumble during walking. Participants will also be given time to accommodate to walking on a treadmill. The treadmill and Agility Trainer both have emergency shut-off "kill" switches to rapidly disengage the devices at any time. The emergency shut down switches will be easily accessible to both the physical therapist and the participant.

Discomfort due to Forces applied to the Pelvic Harness

We will use a padded hip belt and offer all participants additional padding as desired to minimize any discomfort. In addition, the Agility Trainer has a number of safety features that limit the magnitude of force that can be applied to participants, including mechanical stops to ensure the device does not move participants beyond their normal range of motion and emergency shut off switches that will be within research of both participants and researchers during testing. Also, we will very gradually increase the magnitude of force the device applies to participants and continually monitor participants' responses so that the magnitude of the applied forces does not exceed the individual's ability. Finally, the pelvic harness (Barry USA Inc., Delaware) is well padded and was designed to comfortably suspend circus trapeze performers.

Emotional Discomfort

Some of the questions we ask may be upsetting, or participants may feel uncomfortable answering them. If they do not wish to answer a question, they may skip it and go to the next question.

Availability of Emergency Services

All assessments and training sessions will be conducted at the Northwestern University Feinberg School of Medicine. In the event of an emergency, this facility is equipped to provide immediate care to participants. In addition, a physical therapist will be present during all experimental and training sessions. The physical therapist will continually monitor the cardiopulmonary condition of the participant and attend to any immediate health-related issues.

Potential Benefit of the Proposed Research to the Participant and Others

The overarching goal of this project is to assess the effects of a novel intervention, *locomotor training performed in a movement amplification environment*, on dynamic balance and participation in walking-related activities in individuals with iSCI. Recent scientific research [64, 65] has provided an evidence-based framework for motivating the development of tools able to create the movement amplification training environment examined in the proposed research. Locomotor training performed on a treadmill is frequently administered in clinical settings and is well-accepted because it provides a safe and straightforward method of intensely training many of the important components of walking while not requiring much space or complex equipment. However, treadmill training alone is limited because it lacks a balance-specific component. If outcomes from the proposed research are successful, the supplementation of treadmill-based locomotor training with a movement amplification environment could dramatically improve the capacity of treadmill training to enhance dynamic balance. The movement amplification

environment has the potential to transform an ordinary treadmill into a dynamic environment where people with iSCI can receive safe, challenging, and customized locomotor balance training. Overall, this proposal has the potential to dramatically enhance how gait rehabilitation is delivered and, most importantly for Veterans recovering from iSCI, the intervention may provide a means to significantly improve components of their walking effected by balance.

Several clinical gait rehabilitation breakthroughs have often been spawned from research originally developed for individuals with SCI (e.g. body weight supported treadmill training [98], robotic assisted gait training [99]). Similarly, we believe the tools and training procedures developed within the current proposal have broad applications that extend far beyond those recovering from SCI. The approach we are using has the potential to benefit a wide range of impaired populations that experience balance-related deficits (i.e. stroke, TBI, lower-limb amputee, older adults). The development of tools to enhance dynamic balance may also benefit non-impaired populations in specific professions that require excellent balance such as war fighters, search and rescue teams, and athletes. Thus, outcomes from the proposed research may provide the ground work to develop dynamic-balance related interventions for a broad range of applications.

All participants in the proposed study will receive high intensity locomotor training under the supervision of an experienced clinician. The benefits of exercise in the iSCI population can improve physical and emotional well-being [100]. In addition, there is strong evidence that locomotor training can improve walking speed, and endurance [3, 60, 101]. This intervention will also target the enhancement of dynamic balance during walking. As such, individuals enrolled in the proposed study may improve aspects of their health and functional walking ability. However, as this is an experimental study, it possible that participants may not improve their own walking ability by participating. The risks of participating are similar to that involved when participating in any physical therapy intervention aimed at improving gait.

Importance of the Knowledge to be gained

For people with SCI, balance deficits negatively impact elements of walking critical for participation in mobility-related activities. We hypothesize that for individuals with iSCI locomotor training performed in a movement amplification environment will substantially improve dynamic balance and participation in walking activates. Currently, many clinically-accepted gait rehabilitation practices including body weight supported treadmill training are likely sub-optimal for teaching locomotor balance because they lack effective balance-specific training components. Presently, there is an absence of evidence-based clinical tools to address this shortcoming. Outcomes from this project will enhance our understanding of how individuals with iSCI learn dynamic balance. This study will investigate a motor learning paradigm – amplification of an individual's own movements – that has shown promise for teaching control of upper extremity movements of individuals with neurologic injury [64, 65]. This project will extend this paradigm to train dynamic balance during walking. If successful outcomes from this study will provide a foundation for development of new technologies that can be used to apply movement amplification type environments to current gait rehabilitation practices used within the VA clinical setting.

In addition, our general understanding of how locomotor training interventions impact participation in walking-related activities of individuals with iSCI is poor [96]. This study will provide quantitative measures on how locomotor training, and locomotor training that includes a targeted dynamic balance component influence participation in walking activities. Frequently reported clinical outcome measures, such as 10-meter walk speed or 6-minute walk distance are valuable for understanding an individual's function, but these measures taken in a laboratory or clinic setting are not sufficient to gage participation. As technology to assess participation using simple wearable devices has advanced, it is important that researchers include measures of participation when evaluating locomotor training interventions. Research suggests that dynamic balance is a primary determinate of walking activity in individuals with iSCI. Currently it is unknown if engagement in training interventions targeting balance will be effective for improving participation in walking activities. Outcomes from this study will fill this void in our knowledge and provide data that will be essential for developing normative standards for changes in walking participation following locomotor training interventions.

- **Provide description of the study population (delineate all categories of subjects – patients, providers, family members, employees, etc.). Include anticipated enrollment numbers**

We aim to enroll 46 Veterans and non-Veterans with chronic motor incomplete SCI who are ambulatory. We will include participants with a range of initial functional walking abilities evaluated by walking speed (half the participants' walking speed will be < 0.5 m/s at the start of the study). All potential study participants will be screened to ensure they meet the study inclusion/exclusion criteria.

Participation in this study is open to all individuals who meet the inclusion exclusion criteria for participation. Participation will be open to people of all racial and ethical backgrounds, gender, and sexual orientation. Minorities and female participants will be actively recruited and their representation in the study is anticipated to match population demographics. Specifically, we anticipate that the ethnic and racial diversity of our participants will match the composition of the greater Chicago metropolitan area. In 2010 the United States Census Bureau reported the population of Chicago had the following ethnic and racial composition:

- Hispanic or Latino (of any race) 29%
- Not Hispanic or Latino 71%
- American Indian and Alaska Native 0.5%
- Asian 5%
- Native Hawaiian and Other Pacific Islander 0.0%
- Black or African American 33%
- White 45%

By gender, 80% of individuals with SCI are male. As such we anticipate that the male to female ratio of participants in this study will be 80% male and 20% female. This study will not include individuals under 18 years of age or vulnerable populations. Women of childbearing potential will not be excluded, although women who are pregnant will be excluded because of pregnancy-related body changes on balance.

- **Include rationale for including or excluding certain populations – in particular vulnerable populations.**

Participation in this study is open to all individuals who meet the inclusion exclusion criteria for participation.

- **As applicable, provide information on any added protections for vulnerable populations.**

This study will not recruit or enroll vulnerable populations.

5.2 Recruitment Methods

- **State how many subjects will be needed.**

We will enroll 46 participants with iSCI in the study.

- **Describe when, where, how and by whom potential subjects will be identified and recruited.**

We will enroll 46 participants with iSCI in the study. Veterans will be recruited from the Spinal Cord Injury Service at Edward Hines Jr. VA Hospital. During the last three years the Hines Spinal Cord Injury Service treated 553 unique patients with SCI. We will work with a highly experienced clinical coordinator at the Edward Hines Jr. VA Hospital to recruit participants from this facility. Ms. Jelinek has established a strong professional relationship with the clinical staff from the Spinal Cord Injury Service to identify, contact, and screen potential study participants. Ms. Jelinek has been involved with multiple SCI related studies in the past, including studies run by the PI of the proposed study. Her familiarity working with the target study population and their clinical providers will be an asset to the proposal. We anticipate that the pool of eligible participants available through the Edward Hines Jr. VA Hospital may not be sufficient to meet our full enrollment objective.

As needed, additional Veteran and non-Veteran participants will be recruited through the Shirley Ryan AbilityLab. The Shirley Ryan AbilityLab maintains the *Clinical Neuroscience Research Registry* a database of interested, potential study volunteers with SCI. The Registry is populated through referrals from associated inpatient and outpatient physical therapy clinics of the Shirley Ryan AbilityLab and through postings at clinics, support groups, and SCI organizations. The volunteer database currently has 475 volunteers with up-to-date-contact information. Of these volunteers greater than 215 individuals identify that they are able to walk in therapy, home or the community. Individuals registered in the database have consented to allowing researchers to contact them directly to discuss opportunities to participate in ongoing research projects. Dr. Kahn, a co-Investigator on this proposal, jointly oversees the maintenance and population of the volunteer database. She will ensure that the study team receives access to the database. In addition, the Shirley Ryan AbilityLab treats ~140 SCI inpatients and 225 SCI

outpatients a year. Collectively, the potential pool of study participants available between the Edward Hines Jr. VA Hospital and the Shirley Ryan AbilityLab will be more than adequate to meet the requirements for the proposed trial.

- **Describe materials that will be used to recruit subjects, e.g., advertisements. Include materials as an appendix or separate attachment.**

We will employ a multi-faceted approach to recruiting and enrolling 46 individuals with iSCI needed for this study.

First we will recruit veterans with spinal cord injury from the Spinal Cord Injury Service at Edward Hines Jr. VA Hospital. We will recruit individuals using the following means.

- Ms. Jelinek will contact clinical staff from the Spinal Cord Injury service. These individuals will be provided with a recruitment flyer attached. Clinical staff will be asked to post and/or provide the recruitment flyer to potential participants. The fly directs potential participants to contact the study PI and research staff by phone or mail.
- Recruitment flyers will be posted in the Spinal Cord Injury Service at the Edward Hines Jr. VA Hospital. Interested individuals will be directed to contact the study PI and research staff by phone or mail.

Second, additional veteran and non-veteran subjects with incomplete spinal cord injury will be recruited through the *Clinical Neuroscience Research Registry,* a database of interested, potential study volunteers with SCI, which is maintained by the Shirley Ryan AbilityLab

- Individuals registered in the database have consented to allowing researchers to contact them directly to discuss opportunities to participate in ongoing research projects. Dr. Kahn and approved study personal will call qualified individuals from the database to discuss participation in the study.
- Recruitment flyers will be posted in the lobby of the Shirley Ryan AbilityLab and on SCI outpatient floors. Interested individuals will be directed to contact the study PI and research staff by phone or mail.

Third, the PI will reach out to the Paralyzed Veterans of America local chapter and the Illinois Spinal Cord Injury Association. The PI will request to present the study in person at upcoming meetings and will ask if the study flyer can be distributed to members either through the organization's print or web-based newsletter. Interested individuals will be directed to contact the study PI and research staff by phone or mail.

Fourth, study information will be posted on http://www.clinicaltrials.gov/. Interested individuals will be directed to contact the study PI and research staff by phone or mail.

Finally, a recruitment will be posted on the PI's laboratory website. Interested individuals will be directed to contact the study PI and research staff by phone or mail.

- **Describe any payments to subjects, including the amount, timing (at the end of the study or pro-rated for partial study participation), method (e.g., cash, check, gift card), and whether subjects will experience a delay in receiving the payment.**

All participants will receive a stipend of $25 for visits including laboratory assessments and clinical outcome measures or $20 for visits that include participation in the locomotor training intervention. Participants will also receive vouchers for parking.

5.3 Informed Consent Procedures

- **Indicate if informed consent will be obtained and/or if you are requesting a waiver of informed consent or waiver of documentation of informed consent. If the research involves multiple phases, specify for which phases of the research the waiver(s) is being requested and/or the informed consent will be sought.**

Approved study team members will obtain informed written consent from all participants in the study.

- **Describe who will be obtaining informed consent, if applicable, and any circumstances that may need to be addressed (e.g. subjects with impaired decision making ability and the use of a legally authorized representative, etc.)**

Approved study team members will obtain informed written consent from all participants in the study. All participants will receive a copy of the informed consent form. Potentially eligible participants will have the study described to them verbally, either in person or over the phone before they are scheduled for any study-related testing sessions. Upon arrival at the first in-person study-related testing session, potential subjects will be provided with a detailed oral explanation of the study by an approved study-personnel. The oral explanation will use statements from the consent form and be performed in the laboratory or in another private room with only the participant and investigators present. Participants will be asked;

“Do you understand what is being asked of you in this study?”

“Do you have any questions regarding this procedure or study?”

Participants will be given the opportunity to ask questions during the consent process. Participants will have the option to have a family member present during the consent process. Individuals who are; not yet adults, cognitively impaired adults, and adults unable to provide informed consent, will not be recruited for this study.

- **If applicable, indicate how local site study personnel will be trained regarding human subjects protections requirements and how to obtain and document informed consent.**

All study personnel will complete CITI training and the Hines VA required TMS training regarding human subjects protections. Prior to administering informed consent all new study personnel will first observe a senior study personnel obtaining informed consent. New personnel will also meet with senior study personnel to review the informed consent process and associated administrative procedures.

5.4 Inclusion/Exclusion Criteria

- **Describe the criteria that determine who will be included in or excluded from the study.**

Inclusion/Exclusion Criteria

Inclusion criteria: a) age 18 to 80 years; b) medically stable with medical clearance from physician to participate; c) neurologic level of the spinal cord injury between C1-T10 with American Spinal Injury Association (ASIA) Impairment Scale (AIS) C or D; d) more than 6 months since initial injury; e) passive range of motion of the legs within functional limits and not restricting the ability to engage in locomotor training; f) able to ambulatory 10 m with no physical assistance, use of assistive devices, such as a single cane or rolling walker, and use of braces that do not cross the knee joint, such as an ankle-foot orthosis, are permitted.

Exclusion criteria: a) excessive spasticity in the lower limbs as measured by a score of > 3 on the Modified Ashworth Scale on all test muscle groups; b) inability to tolerate 30 minutes of standing; c) severe cardiovascular and pulmonary disease; d) history of recurrent fractures or known orthopedic problems in the lower extremities (i.e. heterotopic ossification); e) concomitant central or peripheral neurological injury (i.e. traumatic head injury or peripheral nerve damage in lower limbs); f) inability to provide informed consent due to cognitive impairments; g) presence of unhealed decubiti or other skin compromise; h) enrollment in concurrent physical therapy or research involving locomotor training; i) use of braces/orthotics crossing the knee joint; j) known pregnancy.

5.5 Study Evaluations

- **Describe all evaluations to be conducted (including screening; tests/questionnaires that will be administered; any procedures that subjects will be required to complete) and data collection methods. Include materials as an appendix or separate attachment.**

The following data will be recorded directly from participants.

Demographic and Medical History

After providing written informed consent, all potential participants will undergo a screening for inclusion and exclusion criteria. We will then collect demographic information and a brief medical history from participants who meet all inclusion and exclusion criteria. The information collected will include; age, gender, date of SCI, level of injury, cause of injury, current medications, current ambulatory ability in the home and community, use of any assistive devices, and self-reported falls in the past year.

Clinical Outcome Measures

Clinical Outcome measures will be performed by a clinician at four time points during the intervention. We will collect data using measures that span each level of the International Classification of Function, Disability, and Health (ICF) (body structure and function, activity, and participation), utilizing a combination of performance based and self-report measures. The measures we will use include: the Lower Extremity Motor Score (LEMS) portion of the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI), manual muscle tests of hip abductor strength, the Walking Index for Spinal Cord Injury (WISCI II), the Functional Gait Assessment (FGA), the 10 meter walk test (10MWT), the Activities-Specific Balance Confidence scale (ABC), the reactive balance test items from the Balance Evaluations Systems Test (BESTest), the Berg Balance Scale (BBS), the World Health Organization Quality of Life scale (WHOQOL-BREF) and the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ- UI SF).

Laboratory Assessments

Laboratory Assessments of dynamic balance during walking will be made at four time points during the intervention. Specifically, we will collect kinematic data as participants perform treadmill walking. To assess COM and stepping kinematics we will record 3D coordinates of 40 reflective markers placed on the trunk, pelvis and lower limbs using a 12-camera motion capture system (Qualisys, Gothenburg Sweden).

Stepping Activity in the Home and Community

We will assess the amount of daily stepping in the home and community during three one-week periods. Daily stepping will be measured and recorded using a StepWatch4 (Modus, Edmonds, WA) activity monitor. The device has a battery life of 35 days and will record individual stepping data on the resolution of seconds. During each assessment period, the microprocessor-based accelerometer will be worn around the ankle during all waking hours (except bathing). Our primary measure of daily stepping will be the total number of steps taken per day averaged across each assessment period. Secondary measures used to quantify changes in activity level include; the number of minutes of the day with at least one step, and percent of a 24-hour day with no walking.

Performance during Individual Locomotor Training Sessions

We will collect data from participants to document the details of every locomotor training session. The data we will collect include; vital signs before, during and after training, exertion and workload - monitored via heart rate and the 6-20 point RPE scale monitored throughout the training session, and number of steps taken during the training session.

Participant perception of training effects

We will assess the perceived changes of participants following high intensity locomotor training in both training and control group to understand the effects of our training intervention. This semi-structured interview will have open ended questions and predetermined prompts used to determine the subjective impact of our training intervention on participants perceived balance confidence, walking capacity, everyday life and other changes that were noted as following participation in this intervention. This interview will be performed 3 months after training is completed. During the interview, questions will be asked by a researcher not involved in training interventions. The interview will take about 15 to 30 minutes. Interview performed will be audio recorded and transcribed by our researchers.

5.6 Data Analysis

- **Provide sample size determination and analysis (include anticipated rate of screen failures, study discontinuations, lost to follow-up etc.).**

Our primary measure to assess dynamic balance during walking is the Lane Width Optimization Test. The test challenges participants to maintain their medio-lateral COM position within a target lane during treadmill walking. If successful, the difficulty of the task becomes progressively more difficult by continuingly narrowing the width of the target lane until the participant is unable to maintain the target position. The lateral COM excursion per stride during the narrowest lane width achieved **provides a quantitative measure of dynamic balance during gait**. A reduction in the minimum lateral COM excursion following training would indicate improved dynamic balance during gait.

We performed a power analysis to determine the minimum sample size required to detect significant changes in dynamic balance using the lane width optimization test. To estimate the population variability, we used data from 13 individuals with iSCI, having similar characteristics to the target population, performing unassisted treadmill walking [102]. We found that typical lateral COM excursion per stride during preferred speed treadmill walking was 0.083 ± 0.014 m (mean ± standard deviation). To estimate effect size, we used pre- and post-intervention data from three individuals with iSCI who received 16-18 high intensity locomotor training sessions performed in the movement amplification environment. Following the intervention, these individuals improved dynamic balance (decreased their lateral COM motion excursion during walking) by 32-36%. To detect a 20% difference in improvements in dynamic balance between training groups we will need a sample size of 7 individuals per group at $\alpha = 0.05$ and a power of 80%. We plan to enroll 46 individuals. A recent locomotor training intervention using individuals with iSCI, conducted by one of our study team members at a nearby facility, lost 12% of their participants to drop out [60]. With a conservative estimate that we will lose 20% of participants to drop out, an initial enrollment of 46 individuals would yield 14 high functioning and 14 low functioning participants (stratified based on the gait speed). This number, double that estimated by the power analysis, should be sufficient to assess training effects on dynamic balance.

We plan to enroll 46 participants with iSCI in the trial. Veterans will be recruited from the Spinal Cord Injury Service at Edward Hines Jr. VA Hospital. During the last three years, the Hines Spinal

Cord Injury Service saw 553 unique patients with SCI. Our research team includes a highly experienced clinical coordinator located at the Edward Hines Jr. VA Hospital. Ms. Jelinek will work with clinicians in the Spinal Cord Injury Service to identify, contact, and screen potential study participants. As needed, additional Veteran and non-Veteran participants will be recruited through the Shirley Ryan AbilityLab. The Shirley Ryan AbilityLab maintains the *Clinical Neuroscience Research Registry* a database of interested, potential study volunteers with SCI. Of these volunteers greater than 215 individuals identify that they are able to walk in therapy, home or the community. Dr. Kahn, a co-Investigator on this proposal, jointly oversees the volunteer database and will ensure access. Collectively, the potential pool of participants available between the Edward Hines Jr. VA Hospital and the Shirley Ryan AbilityLab will be more than adequate to meet the requirements for the proposed trial.

- **Describe how, where and by whom the data will be analyzed.**

The PI, research physical therapist, research engineers, and biostatistician will work collaboratively to analyze the data. The data will be analyzed at Northwestern University.

Specific Aim 1: To test if our primary measure, changes in dynamic balance during walking, is different between the two groups following the two interventions, we will compare changes in participants' COM lateral excursion during the lane width optimization test across the four assessment periods (BSL, Mid, Post, Follow Up) and between intervention groups (Control and Experimental). To account for the correlation that arises from measuring multiple data points within each participant over time (i.e. data measured from the mid- assessment period from a specific participant will bear more resemblance to data measured from the BSL- assessment period from the same participant than a different participant) we propose to model the primary outcome using a linear mixed effects model. We will use an indicator variable for the group assignment, i.e. 1=Experimental, 0=Control, to test for the effect of intervention while controlling for potential confounders such as initial walking speed, severity and location of the SCI, spasticity, and age. The strength of the linear mixed effects models is that it can accommodate multiple data points from a single participant and can also handle missing data when data is missing at random. We will apply a similar strategy for fitting a secondary analysis to examine changes in preferred walking characteristics (average and variability of step width, step length, and minimum lateral MOS) and outcome measures (10 MWT, FGA, ABC etc.) across the four assessment periods and between intervention groups. We will transform the variables, such as log-transformation, as needed to meet the model assumption of normality.

Specific Aim 2: To test if our primary measure, changes in steps per day, are different following the two interventions, we will compare changes in participants' average steps per day across the three assessment periods (BSL, Post, Follow Up) and between intervention groups (Control and Experimental). Similar to the methods proposed above, we will model the primary outcome using a linear mixed effects model. We will use an indicator variable for the group assignment, i.e. 1=intervention, 0=control, to test for the effect of intervention while again controlling for potential confounders such as initial walking speed, severity and location of spinal cord injury, spasticity, and age.

5.7 Withdrawal of Subjects

- **Describe any anticipated circumstances under which subjects will be withdrawn from the research without their consent.**

It is unlikely that participants will be withdrawn from the study without their consent. However, there are circumstances that we would withdraw a participant.

We will withdraw a participant from the study if we identify that their participation is putting their health at risk.

We will withdraw a participant from the study if they miss scheduled study appointment visits without a valid excuse or fail to notifying study team members of their absence. We will provide participants with a warning prior to withdrawal.

We will withdraw a participant from the study if we learn that they were dishonest when answering our screening (inclusion/exclusion) questionnaire.

We will withdraw a participant from the study if they arrive for study procedures while under the influence of illegal drugs or alcohol.

- **Describe the consequences of a subject's decision to withdraw from the research and the procedures for orderly termination of participation by the subject (e.g., the subject contacting the investigator for an end-of-study visit).**

Participation in this study is voluntary. All participants have the option to choose not to participate in the study or to withdraw from the study at any time without penalty, consequences or loss of VA or other benefits.

- **Describe procedures if a subject is withdrawn or withdraws from the intervention portion of the study but agrees to continue in the follow-up phases or for safety outcome purposes.**

We will not perform follow-up testing with any participant that withdraws or is withdrawn from the study.

6.0 Reporting

- **Include procedures for reporting unanticipated problems, serious adverse events, and protocol deviations.**

Any unanticipated deaths will be reported to both the Hines IRB and the Northwestern University IRB within 24 hours of becoming aware of them. Any serious adverse events will be reported to the Hines IRB and Northwestern IRB within 48 hours of becoming aware of the event. All unanticipated adverse events or unanticipated problems involving risks to research participants or study personal will be reported to the Hines IRB and Northwestern University IRB within 48 hours. Any adverse event directly or indirectly related to the study, such as loss of confidentiality or emotional trauma, will also be reported to the Hines IRB and the Northwestern University IRB. Privacy and Data security breaches will be reported to the Hines ISO and Northwestern University ISO immediately.

- **Include information about whether the study has a Data Monitoring Committee and if so, how often it will meet.**

Dr. Gordon and Dr. Kahn will jointly be responsible for carrying out the Data Safety Monitoring Plan. The decision to have Drs. Gordon and Kahn monitor safety of the trial was based on the simplicity and limited size of the proposed project. Specifically, the following factors were considered - the proposed study is low risk, Drs. Gordon and Kahn are not blinded to the study interventions, the study involves less than 40 total participants, and experimental testing and training sessions will be conducted at a single location.

7.0 Privacy and Confidentiality

- **Describe whether the study will use or disclose subjects' Protected Health Information (PHI).**

The study will collect PHI from study participants.

- **Describe the steps that will be taken to secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, Certificates of Confidentiality, and separation of identifiers and data)**

All participants will be given a secret identification code. All experimental data collected from participants will be identified only with this identification code. Data that link the participant to the identification code will kept in a locked file cabinet.

All hard data recorded from this study will be stored in a locked file cabinet. All electronic data from this study will be coded. A complete copy of all original data will be stored in secure folders on both the Hines VA and Northwestern University servers. Only approved study-team members will be given access to data stored on the servers.

Participants' responses to questionnaires, and medical history questions and clinical testing will be recorded by hand by authorized study personnel. These forms will be identified strictly by the participant's secret identification code. This data will be entered into Microsoft Excel Spreadsheets run on an encrypted VA computer by authorized study personnel. This data too will only be identified using the participant's identification code. When not in use by authorized study personnel, all hardcopies of these forms will be locked in a secure file cabinet in the PI's office located at:

645 N Michigan Ave, Suite 1119, Chicago IL 60610.

The file cabinet will be accessible by the PI and approved study personnel. If authorized personnel leave the research team, their access to data will be terminated.

Electronic data collected from motion analysis cameras, load cells, step monitors, heart rate monitors, and other analogue devices will be de-identified. This data will be labeled with the participant's secret identification code. The data will be stored on hard drives and processed in Visual 3-D, MATLAB, and LabVIEW on secure encrypted computers located at:

645 N Michigan Ave, Suite 1147, Chicago IL 60610.

Audio recordings from the interview to understand participants' perception will also be de-identified and stored on secured computers at the above location. The electronic data will be accessible only by the PI and approved study personnel.

Data will be stored for 6 years after completion of the study. Only the PI and sub-investigators will have access to the data during this time. The study team members who collect hard copy data during the experiment will be responsible for receipt and transmission of the data from the laboratory to a locked filing cabinet. A digital copy of all original data collected for the project will be transferred to a secure Hines VA server. A VA-approved encrypted flash drive issued to an authorized member of the study team will be used to transfer data from the Northwestern server to a secure study folder on the Hines VA server. Only an authorized study team member will have access to the encrypted flash drive and study data. The authorized member of the study team will maintain possession of the flash drive at all times. Once the data are transferred, the data on the flash drive will be erased.

If unauthorized use, disclosure, transmission, removal, theft, loss or destruction of VA research-related protected health information (PHI) should occur, in accordance with VA Policy, within one hour of becoming aware of the unauthorized use, disclosure, transmission, removal, theft, loss or destruction of VA research-related PHI, a member of the research team will report the incident to the ACOS for Research, the facility ISO, and the facility PO.

- **If data and biological specimens will be banked, specify.**

Data and biological specimens will not be banked.

8.0 Communication Plan (for multi-site studies)

This is not a multi-site study.

9.0 References

Bibliography of cited literature

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