PROJECT TITLE:

Short-Burst Interval Treadmill Training to Improve Community Walking Activity and Mobility in Cerebral Palsy

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1. Objectives

1.1. Purpose, specific aims, or objectives:

Ambulatory children with cerebral palsy (CP) exhibit daily walking and physical activity that is predominately low intensity with little variability (Bailey et al., 1995; Bjornson et al., 2014). These activity limitations negatively influence their ability to physically participate in day-to-day life. Therefore, these children are at greater risk for inactivity and functional decline with age. In contrast, typically developing (TD) children engage in short bursts of intense walking and physical activity interspersed with varying intervals of low intensity activity within daily life. These walking and physical activity patterns are also very different from adult patterns, which are characterized by long periods of low intensity activity. Despite these inherent differences, locomotor treadmill training (LTT) protocols designed to improve walking in children with CP simulate adult protocols, consisting of steady-state low to moderate walking activity. This type of training (i.e., body weight supported or robot-assisted) has only modest treatment effects similar to other interventions, and has multiple barriers to clinical implementation (Moreau et al., 2016; Willoughby et al., 2010). Thus, new treatment approaches are needed.

Motor learning literature suggests the need for active participation, task-specific variable training, and multiple repetitions or massed practice to learn new motor skills. LTT protocols for children with CP are inadequate in that they do not approximate the recommended daily levels of vigorous walking (task specific, massed practice) for optimal health in TD children and are not of sufficient intensity (U.S. Dept of Health, 2008). Our team's pilot work in ambulatory children with CP examined a novel protocol of task specific training in a variable massed practice format. Short bursts of vigorous intensity locomotor treadmill training (SBLTT) alternating with low/moderate intensity was specifically designed to mimic activity patterns of TD children. SBLTT was feasible, well tolerated, and resulted in significant improvements in walking capacity (i.e., 1-minute walking distance, gait speed), and walking performance (i.e., average strides/day, and strides at moderate/high stride rates).

This study is based on the premise that SBLTT, which approximates the walking intensity patterns of TD children through a novel protocol of task specific short bursts of vigorous intensity treadmill training, will improve walking capacity, performance and community mobility in children with CP, and (2) that changes in walking/mobility are mediated through improved muscle power generation during short intervals of high intensity walking. We will test the following specific aims:

- **Aim #1**. Determine the immediate and retention effects of home-based short-burst interval locomotor treadmill training (SBLTT) on walking capacity in ambulatory children with CP.

- **Aim #2**. Examine the effects of treatment on walking performance and community-based mobility.

- **Aim #3**. Examine whether the effects of home-based SBLTT on walking capacity and performance are mediated by muscle power generation.

1.2. Hypotheses to be tested:

Hypothesis #1: We hypothesize that SBLTT will be more effective than traditional LTT (TLTT) in improving walking capacity post training and during retention.

Hypothesis #2: We hypothesize that increased walking capacity of SBLTT versus TLTT will translate into increased overall strides/day, high stride rates, and time spent walking, particularly in community settings, thus enhancing community-based walking mobility.

Hypothesis #3: We hypothesize that SBLTT will significantly increase muscle power generation through intervals of high intensity walking, which in turn will lead to improved walking capacity and performance.

2. Background

2.1. Relevant prior experience and gaps in current knowledge:

Children with CP have been described as having one of the most sedentary lifestyles among those with pediatric disabilities (Longmuir & Bar-Or, 2000). Compared to TD children, youth with CP take significantly fewer steps per day and spend less time walking and engaging in activities of high intensity (Bjornson et al., 2013). Walking activity has also been shown to be predictive of restricted participation in mobility, education, and social relations for children with CP (Beckung & Hagberg, 2002). Although the literature confirms the association of walking/mobility limitations with reduced participation in daily life, direct causal relationships have not been determined (Kerr et al., 2008; Wright et al., 2008). The negative relationship of walking limitations to daily participation is reported in cohort and population based studies of youth with CP (Fauconnier et al., 2009; Lepage et al., 1998). However, the *association* of clinic-based walking with mobility in day-to-day life was reported to be mediated by daily walking activity in children with CP (Bjornson et al., 2013), and day-to-day walking is positively *associated* with reported mobility-based daily habits (Bjornson et al., 2014). Thus, the inability to achieve higher stride rates in CP appears *related* to reduced participation in mobility-based daily activities.

The SBLTT protocol proposed is in contrast to traditional LTT (TLTT) protocols that use steady-state walking speeds within each session. SBLTT is based on rehabilitation motor learning principles of task specificity (fast intense walking) (Nadeau et al., 2013), intensive massed practice (5x/week for 8 weeks with a maximum of 10 weeks to complete 40 sessions), variability of task (alternating slow/fast walking), and challenging (non-body weight support) with structured progressive training (increasing speed of fast speed bursts between sessions) (Hung, Brandao, & Gordon, 2017). Challenging and intensive motor practice have been reported to be the most effective neurorehabilitation strategies (Clearfield et al., 2009; Wolf et al., 2006).

It has been suggested that motor learning is optimized with frequent, shorter practice sessions with one session per day (Baddeley & Longman, 1978; Dail, 2004). Furthermore, variation of exercise parameters including speed and intensity has been shown to improve compliance and motivation in children (Baddeley & Longman, 1978; Baquet et al., 2010). Task variation within variable practice scheduled as serial

alternations of blocks of trials has been documented to be more effective for motor learning than either randomized or blocked practice (Landin, 1997; Schmidt et al., 2018). Therefore, SBLTT will consist of a serial blocked variable practice schedule (SBLTT alternating fast/slow walking intervals within sessions).

Therefore, we propose that gait training, whether LTT or over ground, must be performed without body weight support, including variability of task practice that is task specific and progressive in a massed practice format. Furthermore, LTT must be performed at an adequate intensity in order to engage deficient muscular resources that are essential for anti-gravity body weight support and for propulsion during the gait cycle.

2.2. Relevant preliminary data:[1]

The proposed study builds on our recent R21 SBLTT work (HD 077186), which confirmed the feasibility and safety of four weeks of 5x/week short-burst interval treadmill training (SBLTT) in ambulatory children with CP. The study included 20 sessions of a novel protocol of task specific training in a variable massed practice format. SBLTT was feasible, well tolerated, and resulted in significant improvements in walking capacity (i.e. 1-minute walking distance, gait speed), and walking performance (i.e. average strides/day, and strides at moderate/high stride rates) that were maintained at 6 weeks post.

Although the pilot data documented significant improvement as noted above, average strides per day slightly decreased from immediately post training to 6 weeks post training. Treadmill training studies in adults post stroke have documented significant improvements in walking speed and distance after 36 sessions, with the improvement diminishing after 24 sessions (Rose et al., 2017). Thus, the number of sessions proposed in this study was increased to 40 total over an 8 week period, to test the effect of an increased dosage over and above the positive results from 20 total sessions over 4 weeks from the pilot study. This design also includes a 4 week mid-assessment after 20 sessions to examine the immediate effects of the original protocol and whether gains will continue to be made between 20 and 40 sessions (4 and 8 weeks respectively) of training, as well as a longer follow-up of 24 weeks post-training to assess long term retention effects.

Analysis of high frequency (n=6; 5x/week) versus low frequency (n=6; 2x/week) found positive satisfaction reports both training frequencies of SBLTT for the pilot R21 trial. However, participants and their families preferred the high frequency (5x week) protocol over the low frequency (2x week) protocol. Of note, our home-based pilot work had a 0% drop-out rate, 100% compliance to training sessions, and no falls or reported adverse events directly related to intervention or study, thus documenting safety and feasibility. Parents reported satisfaction with high frequency home-based protocols. Families specifically noted per follow up survey that the home-based intervention made it easy for them to participate and they liked the high frequency as they felt their children were getting a 'frequent good work out'. Thus, this study will build on this prior work by further exploring the effects of this intensive, interval-based massed practice design (5x/week SBLTT).

2.3. Scientific or scholarly background:

Pediatric Activity Patterns are Different from Adult Patterns: Compared to adults, children characteristically accrue their daily physical activity in bouts of less than 5 minutes (Adamo et al., 2009). In fact, 95% of high physical activity in children occurs in bouts of less than 15 seconds and at higher heart rates (> 139 b/min) (Bailey et al., 1995; Armstrong et al., 1990) Typically, children engage in very short bursts of intense (fast) walking and physical activity interspersed with varying intervals of low and moderate intensity walking (Eissenmann et al., 2005; Bailey et al., 1995, Bjornson et al., 2010). Compared to TD children, however, children with CP do not engage in bursts of intensive (moderate/high stride rate) walking activity and spend the majority of their time in low intensity walking (Bjornson et al., 2014). This is expected as the mechanical energy cost of walking for children with diplegia is documented to be 1.5 times that of typically developing children (Van de Walle et al., 2012), with resultant lower gait speed or intensity (Duffy, Hill, & Graham, 1997). However, the energy cost of walking has been shown to decrease with increasing gait speed in CP, approaching that of TD (Marconi et al., 2012). Therefore, interventions aimed at increasing moderate to high stride rates are of paramount importance.

To date, locomotor treadmill training (LTT) protocols for children with CP have been based on adult walking activity patterns and do not approximate the high intensity short burst patterns of typically developing (TD) children or the United States Department of Health and Human Services (USDHHS) guidelines for physical activity for optimal health benefits for children (US Dept of Health & Human Services, 2008). This study will address the walking limitations of children with CP with short-burst interval training (periods of high level exertion alternating with periods of rest or lighter exertion) which was specifically designed to mimic the variable habitual walking speeds of typically developing children.

Relationships of impairments in body structure/function to daily walking activity performance, participation and community mobility limitations in CP: Decreased muscle power, strength, and rate of force development (RFD) are significant impairments that contribute to activity limitations in ambulatory children with cerebral palsy (CP) . In contrast, greater muscle endurance has been reported in CP compared to age-matched typically developing (TD) children, as demonstrated by a decreased rate of decline in normalized torque over repetitive muscle contractions (Moreau et al., 2008; Stackhouse, Binder-Macleod & Lee, 2005). Time and velocity-dependent measures of force production, such as RFD and muscle power (the ability to generate torque at higher movement speeds), respectively, have been largely ignored in CP even though many activities of daily living require force to be generated rapidly. Compared to age and gender matched TD youth, muscle power and RFD are reduced by 82% and 70%, respectively, as well as a 38-50% decrement in strength (Moreau et al., 2012; Moreau et al., 2013). Knee and leg extensor power has been significantly correlated with rising from a chair, stair climbing, balance, walking speed, and daily physical functioning (Skelton, Davies & Young, 1994; Bassey et al., 1992). Collectively, these data confirm the importance of muscle power for walking and the performance of daily functional

activities.

In addition to muscle power and strength, youth with CP exhibit impairment in walking performance (the amount and type of walking that a person actually performs in everyday life). Compared with TC children, who reach 108-146 peak strides (steps) per minute, children with CP have substantially lower peak strides/min, ranging from 29-83 (Bjornson et al., 2014; Bjornson et al., 2007). Youth with CP also ambulate with limited variability, spending the majority of their daily strides in low stride rates (< 30 strides/ min), with significantly fewer strides/day in high stride rates (> 60 strides/min) (Bjornson et al., 2014). This is in contrast to TD children who spend a similar amount of their daily strides in both low and moderate stride rates with the ability to attain significantly higher peak strides/minute activity. The inability to achieve higher stride rates in children with CP appears related to reduced mobility–based daily activities (moving around home, neighborhood, varying environments in community). To date, however, there is no documented association between walking capacity (clinic-based walking) or walking performance (daily life) with community walking mobility (where they walk).

Traditional Locomotor Treadmill Training (LTT) vs Short Burst Interval Locomotor Treadmill Training (SBLTT) in Cerebral Palsy:

Currently, no high level evidence exists in support of body-weight or robotic supported LTT in CP to enhance community walking activity performance with inconsistent evidence of a positive effect on walking speed and gross motor skills (Moreau et al., 2016; Zwicker & Mayson, 2010). These LTT protocols consist of steady-state walking speeds that are either self-selected or low to moderate in intensity.

Our recently published systematic review and meta-analysis on the effectiveness of rehabilitation interventions to improve gait speed in children with CP documented that despite a moderate effect of gait training on improving walking speed in children with CP, gait training performed without body weight support was superior to gait training performed with body weight support and robotic training (Moreau et al., 2016). This finding is clinically significant, as access to and cost of specialized equipment limits translation to the clinical setting. This systematic review also served to elucidate limitations in the critical dosing parameters associated with current LTT protocols for children with CP, including insufficient frequency or duration of treatment, intensity, and total training volume (Moreau et al., 2016). There is wide variation in the reported LTT frequency and duration in children with CP, ranging from twice daily for 2 weeks to 2-3 times weekly for 12 weeks (Moreau et al., 2016). Furthermore, LTT has not yet been shown to translate to improvements in the duration or intensity of walking in day-to-day life in the community.

2.4. Prior approvals:

None

3. Study Endpoints[2]

3.1. Primary and secondary endpoints:

Outcome measures include:

Aim #1	**Outcome Measures**	**Definitions**
Clinic-based: • Walking Capacity (Primary)	Self-selected walking speed: 10 Meter Walk Test	Time in seconds to walk 10 meters at self-selected speed.
	Fast walking speed: 10 Meter Walk Test- fast speed	Time in seconds to walk 10 meters at fast speed.
	One Minute Walk Test	Distance walked as fast as possible in one minute.

Aim #2	**Outcome Measures**	**Definitions**
Community: • Walking Performance (Primary) • Walking Mobility • Walking mobility by location • Patient Reported- ○ Mobility ○ Gait priorities ○ Quality of gait	Walking Performance: StepWatch (SW) accelerometry (Primary outcome)	Number of daily steps, and average daily steps calculated for low, moderate and high steps rates.
	Walking mobility: StepWatch (SW) synchronized with Global Positioning System (GPS)	Locations where walking activity occurs, walking time and intensity in those locations.
	Walking mobility by locations- SW/GPS and Geographic Information System (GIS) maps	Locations of 'importance', and level and intensity of walking in these locations pre/post intervention.
	Mobility: Patient-Reported Outcomes Measurement Information System (PROMIS v1.0 Pediatric Profile)	PROMIS, developed by the NIH, measures well-being/suffering as well as ability or lack of ability to function.
	Families' perception and priorities for GAIT: Gait Outcome Assessment List (GOAL).	Gait Outcomes Assessment List (GOAL)evaluates gait priorities (child or parental report) and functional mobility of ambulatory children with CP.

Aim #3	**Outcome Measures**	**Definitions**
Muscle Power (Primary) • Knee extensors • Ankle plantar flexors	Muscle power, torque, and velocity: isotonic power and isokinetic tests on a dynamometer (Biodex System 3)	Muscle power of the knee extensors and plantar flexors will be measured via an isotonic power test and isokinetically on a dynamometer (Biodex System 3) according to published standard procedures by Dr. Moreau and colleagues (Moreau et al., 2013). Torque, position, and velocity data will be collected simultaneously.

3.2. Primary or secondary safety endpoints:

None

4. Drugs, Devices and Biologics[3]

4.1. Manufacturer and name of all drugs, devices and biologics:
N/A

4.2. Description and purpose of all drugs, devices and biologics:
N/A

4.3. Regulatory status of all drugs, devices and biologics:[4]
N/A

4.3.1. Drugs or Biologics:
☐ IND Exempt. Explain:[5] ✍Click here to enter text.
☐ IND.

4.3.2. Devices:
☐ IDE Exempt. Explain:[6] ✍Click here to enter text.
☐ Abbreviated IDE / Non-Significant Risk. Explain:[7] ✍Click here to enter text.
☐ IDE / Significant Risk.

4.4. Plans to store, handle, and administer any study drugs, devices and biologics so they will be used only on subjects and be used only by authorized investigators:
N/A

5. Procedures Involved

5.1. Study design:[8]

(Randomized-controlled, Two Arm Clinical Trial): 72 participants will be randomized to receive 40 home-based sessions (5x/week for 8 weeks with a maximum of 10 weeks to complete 40 sessions) of either (1) SBLTT, or (2) TLTT. Randomization sequences will be generated according to the study design and to balance sample per clinical characteristics, such as gender and Gross Motor Function Classification System (GMFCS) level. To avoid imbalance in group assignments across sites, we will stratify the randomization by sites to ensure intervention effects will not be confounded by sites.

5.2. Research procedures:[9]

Once informed consent and assent have been obtained, participants will be randomized according to the randomization scheme described above in section 5.1. We will enroll ambulatory children with unilateral and bilateral spastic cerebral palsy aged 6 -10 years and within GMFCS levels I, II or III (Palisano et al., 2007). Only children with spasticity as their primary movement disorder will be enrolled due to their documented strength/power limitations and to control for the heterogeneous clinical presentation found in CP. Children at GMFCS I would have to demonstrate impairment/spasticity across both the ankle and the knee (i.e., spastic catch). Movement disorder will be confirmed through screening with the Hypotonia Assessment Tool (HAT) (Jethwa et al., 2010; Knights et al., 2014). Exclusion Criteria includes orthopedic or neurosurgery within the past 9 months or (botulinum toxin/phenol) injections to the lower extremity

muscles within 3 months. There will be no changes to the participants standard of care (i.e. other therapies) during the study period.

Assessment Measurements:

At SCH, all assessment visits (i.e., walk tests, muscle strength tests) will take place in the Bjornson study lab on 5th floor of Jack R. MacDonald Building and conducted by a trained Assessor. Assessment procedures conducted by non-clinical research staff (e.g. research coordinator), trained in the role of Assessor, will be supervised in-person or via SCH Webex by Dr. Bjornson. Assessors At LSUHSC-New Orleans, all assessment visits will take place in the Department of Physical Therapy on the 7th floor at 1900 Gravier Street in New Orleans, LA. These assessment visits will occur at baseline, 4, 8 and 16 weeks post-intervention (see table below).

The table below outlines each measurement and the time period in which the measures will be obtained:

Table 1. Measures

Measure	Screening	Baseline	4 weeks	8 weeks	16 week post-intervention follow-up
Hypotonia Assessment Tool (HAT)	X				
Pre-Test Questionnaire		X			
Physical Exam					
Physical Exam		X	X	X	X
Measures of walking capacity: (Walk tests)					
10 meter walk test- self selected walking speed		X	X	X	X
10 meter walk test- fast walking speed		X	X	X	X
1 minute walk test		X	X	X	X
Measures of walking performance: (StepWatch)					
Average strides per day		X	X	X	X
Percent time walking		X	X	X	X
Peak Stride Rate		X	X	X	X
Number of Strides: low, moderate, high		X	X	X	X
Measures of walking mobility in Community (GPS)					
Walking Mobility in the Community (GPS with StepWatch)		X	X	X	X
Measures of muscle performance (BioDex)					
Knee extensor muscle power (isotonic)		X	X	X	X
Knee extensor muscle Rate of Force Development		X	X	X	X

Knee extensor muscle strength (isometric)		X	X	X	X
Measures of functional mobility (Surveys)					
PROMIS		X	X	X	X
GOAL		X	X	X	X

Physical Exam will be conducted by the principal investigator at each study visit and will include range of motion measurements for hip extension, popliteal angle, Dundee, knee extension/flexion, ankle dorsiflexion, height and weight.

Walking Capacity- Self-selected and fast walking speeds will be calculated from the 10-m Walk Test (Thompson et al., 2008). Distance walked as fast as possible in one minute will be measured by the 1-Minute Walk Test (McDowell et al., 2005). Walking capacity will be collected at baseline, after 4 weeks (20 sessions of SBLTT or TLTT), 8 weeks (40 sessions), and 16 weeks after the completion of LTT intervention (to assess retention) via blinded assessor.

Walking performance will be directly measured with the StepWatch accelerometer in each participants' daily environment (ModusHealth, 2015). Average strides per day, percent time walking each day, peak stride rate, and strides at low, moderate and high stride rates will be calculated from the raw StepWatch data.

Community walking mobility (where they walk) individualized by home versus community locations will be sampled via *a* novel combination of global position system (GPS) and StepWatch (SW) accelerometer. StepWatch accelerometry walking data will betime-matched with GPS records to allow spatial and temporal tagging of measured walking data. Data will be collected over a 7-day interval in both measurement waves, and quantified as daily, average stride count, and percent of time spent in low (1-30 strides/min), moderate (31-60 stride/min), and high (> 60 stride/min) stride rate strata (3). To characterize locations, each participant's home location will be individually defined by geocoding the home address and then digitizing a polygon to include GPS points that were in or very near home. Walking activity with GPS coordinates occurring beyond the home location was considered to have occurred within "community" locations.

Muscle performance will be captured measures of knee extensor muscle power (isotonic power test) (Moreau et al., 2013), Rapid Force Degeneration (RFD) (Moreau et al., 2012), and strength (isometric) (Moreau et al., 2012) will be tested on an isokinetic dynamometer (Biodex System 3). Torque, position, and velocity data will be collected simultaneously during the muscle performance tests as described by Moreau et al. (2013).

Functional mobility and family priorities for gait will be obtained by parent-report of the PROMIS® Pediatric Physical Activity and the Gait Outcomes Assessment List (GOAL) (National Institutes of Health, 2012; Thomason et al., 2018). Secondary single subject analysis will examine individualized community locations 'of importance' (e.g., school).

Intervention:

All SBLTT and TLTT training sessions will be conducted in the participant's home unless declined by participant. If declined, they will take place at the BDL lab located at Jack R. MacDonald Building (for SCH participants) or in the Department of Physical Therapy located on the 7th floor at 1900 Gravier Street in New Orleans, LA (LSUHSC participants). The treadmills will be transported and set up in the participant's home consistent with previous R21 protocol (HD 077186. SCH IRB #PIROSTUDY14662). All training on treadmills will be carried out in participant's homes by trained research Physical Therapists (PTs), Physical Therapy Assistants (PTAs), or Bachelor's or higher degree level trained professional with pediatric and/or work experience (i.e. athletic trainers, occupational therapists) trained to protocol fidelity (see below) competency levels ("Research Interventionists"). The study team will attempt to connect participants with a PT or PTA before exploring partnering with other types of professionals, and priority will be given to PTs or PTAs in the role of Interventionists. Additionally, we will require at least one PT or PTA on the team of Interventionists for every subject.

SBLTT: SBLTT will consist of short-bursts (30 seconds) of high speed walking alternating with 30 seconds of low/moderate speed walking. Total duration of walking per session will be up to 30 minutes of the 30 second alternating intervals (30sec high / 30sec low/moderate) with rests as needed. Both groups will receive 40 sessions delivered 5x/week for 8 weeks. Initial speeds for high speed walking will be 80-100% of each participant's over ground baseline fast walking speed, and low/moderate speed will be 80-100% of self-selected speed calculated from the 10-Meter Walk Test. This is based on Bodkin et al., which documented that self-selected treadmill speed was 80-100% of self-selected over ground speed in children with CP (Bodkin, 2006). The primary goal will be to increase fast walking speed during the high speed 30s intervals within and between sessions; secondarily, the goal will be to maximize overall session duration to 30 minutes of interval training. Tread speed for the high-speed bursts (controlled by the Research Interventionist) will be increased by .1 to .4 mph (within or between sessions) based on clinical observation (e.g. color, sweat, rate of breathing) and the Children's OMNI Scale of Perceived Exertion (Utter et al., 2002) (OMNI < 6/10), which will be collected every 5 minutes. Low speed 30s bursts will remain at the initial speed. Rest will be given if the OMNI score exceeds 8/10 or upon subject request, but training must be completed within 60 minutes. During rests the subject will stand on the treadmill or sit down. Training will resume after the rest period to reach the target duration. If subject reaches maximum walking speed, the speed will be reduced and incline will be applied to treadmill. Short-burst LTT may destabilize some participants' balance; therefore, constant physical support via walking belt at the waist by the Research Interventionist will be employed in order to catch them in the event of a trip or fall. Participants will wear a gait belt with contact guard assistance by a Research Interventionist while walking on the treadmill and will be allowed to use handrails.

TLTT: The TLTT group will receive the same number of sessions (40) delivered 5x/week for 8 weeks with a total duration of walking per session up to 30 minutes with rests as needed. TLTT will consist of walking at steady-state speeds. Initial treadmill

speed will be 80-100% of over ground self-selected walking speed. The overall goal will be to achieve 30 minutes of walking at a steady-state walking speed within each session. Speed will be increased on the next session by .1 to .4mph when the subject can walk for 30 minutes on the treadmill at the current speed with an OMNI score of < 6/10. Rest will be given if the OMNI exceeds 8/10 or upon subject request, but training must be completed within 60 minutes. Training will resume after rest to reach target duration. If subject reaches maximum walking speed, the speed will be reduced and incline will be applied to treadmill. Safety protocol (gait belt/contact guard assistance/handrails) will be identical to the SBLTT.

Compliance of the subjects to complete the full 30 minutes of SBLTT or TLTT will be encouraged by watching movies on tablets during training. Motivating the participants to walk at a high speed for 30 seconds will be addressed by verbal encouragement and individualizing the treadmill speeds within subjects and sessions as needed.

As confirmed feasible within our SBLTT pilot work, the SBLTT and TLTT protocols will be individualized for each participant per documented self-selected and fast walking speed at baseline, thus standardizing the dosing of training speeds relative to each participant's initial walking speed impairments. Treadmill training allows direct control of the training intensity, as the Research Interventionist manipulates the speed of the tread (walking speed). In contrast, over ground training requires the Research Interventionist to motivate the child to walk at a specific intensities.

Fidelity: Training logs of dosing/training parameters for each session will be recorded. To confirm intervention/assessment fidelity within and between the two study sites, Research Interventionists will be trained at each site by the PIs per standard operating procedures (SOP) based on study protocol. Research Interventionists must reach 100% performance and completion prior to study initiation. Study visit procedural checklists will document consistency of specific study tasks for both the intervention and assessment visits with monthly monitoring by the PIs. The PIs will observe 10% of assessment and intervention visits to monitor fidelity of intervention and assessment procedures and provide real time feedback. If performance falls <95%, the interventionist will repeat training. Dr. Bjornson will travel annually during years 1-4 to confirm fidelity of assessment and interventions with other sites.

Caregiver Satisfaction: Caregivers will be surveyed about their satisfaction with the training sessions, as well as topics such as benefits of the program, and ease or difficulty with scheduling.

Caregiver/Parent: will complete a demographic, medications, medical, surgical and therapy history survey at the consent visit. See Pre-Test Questionnaire.

5.3. Data sources that will be used to collect data about subjects:[10]

See Measures list above in sections 3.1 and 5.2.

5.4. Data to be collected, including long–term follow–up data:[11]

See Table 1 in section 5.2.

6. Data and Biospecimen Banking[12]

6.1. Complete list of the data and/or biospecimens to be included in the bank:[13]

N/A.

6.2. Location of data and/or biospecimen storage:[14]

N/A.

6.3. List of those with direct access to data and/or biospecimens in the bank:

N/A.

6.4. Length of time data and/or biospecimens will be stored in the bank:

N/A.

6.5. Procedures for protecting the confidentiality and privacy of the subjects from whom the data and/or biospecimens were collected:[15]

N/A.

6.6. How the data and/or biospecimens will be made available for future use:

N/A.

6.6.1. Who can request data and/or biospecimens from the bank:

N/A.

6.6.2. Format in which data and/or biospecimens will be provided:

N/A.

6.6.3. Process for investigators to request data and/or biospecimens:[16]

N/A.

6.6.4. Restrictions on future use:[17]

N/A.

6.6.5. Plan for providing data results from banked data/biospecimens:

N/A.

7. Sharing of Results

7.1. Plan to share results with subjects/others:[18]

Once the primary and secondary analyses are completed for all aims, the study team will develop abstracts for review to the American Academy of Cerebral Palsy and Developmental Medicine (AACPDM), American Physical Therapy Association (APTA) and American Academy of Physical Medicine and Rehabilitation annual meetings. Results will also be submitted to Clinicaltrials.gov. Unique manuscripts reporting the outcomes per each specific aim will be submitted for review for publication with the following journals: Developmental Medicine and Child Neurology, Gait and Posture,

Physical Therapy, Pediatric Physical Therapy and Archives of Physical Medicine and Rehabilitation.

Additionally, we may share individualized results with study participants and their families. As part of this, participants' families may receive a thank-you card accompanied by an optional one-page graphic summarizing the participant's StepWatch and GPS data, based on available data. This graphic could feature screenshots illustrating daily walking activity for each study timepoint (V1–V4), including the number of steps taken and a GPS map highlighting where those steps occurred. The purpose of this graphic is to visually communicate the participant's community mobility outcomes. Additionally, we may share the manuscript with participants' families once it's published. Families will be instructed to contact the study PI if they have any questions regarding the information shared.

8. Study Timelines

8.1. Duration of an individual subject's participation in the study:

24 weeks (baseline through 16 week post-intervention follow-up).

8.2. Duration anticipated to enroll all study subjects:

We anticipate enrollment to take approximately 2.5 years (see below study timeline):

Table 2. Study Timeline

Task:	Year 1				Year 2				Year 3				Year 4				Year 5			
Year/quarters	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Train Intervention/Assessment staff	X	X																		
Recruitment / Enrollment (#'s)			4	6	6	6	6	6	6	6	6	6	6	6	2					
Intervention			X	X	X	X	X	X	X	X	X	X	X	X	X					
Post treatment & follow-up assessments				X	X	X	X	X	X	X	X	X	X	X	X	X				
Data Analysis															X	X	X	X	X	X
Manuscript prep & submission																X	X	X	X	X

8.3. Estimated date for the investigators to complete this study:

June 30th, 2024.

9. Study Population[19]

9.1. Inclusion criteria for each subject population (e.g., patients, parents, providers):

We will enroll ambulatory children with unilateral and bilateral spastic cerebral palsy aged 6 -10 years and within GMFCS levels I, II or III (Palisano et al., 2007). Only children with spasticity as their primary movement disorder will be enrolled due to their documented strength/power limitations and to control for the heterogeneous clinical presentation found in CP. Children at GMFCS I would have to demonstrate impairment/spasticity across both the ankle and the knee (i.e., spastic catch). Movement disorder will be confirmed through screening with the Hypotonia Assessment Tool (HAT) (Jethwa et al., 2010; Knights et al., 2014). We will study elementary school age children as they are developmentally able to understand and participate in the

training goals while also limiting the incidence of fixed musculoskeletal contractures often found in older children with CP. Potential participants must also agree to discontinue any physical therapy sessions that they are currently receiving (unless provided by school through an Individualized Education Program) during the intervention period in order to enroll.

The parents of eligible children will also be enrolled as participants to collect assessment data and to obtain data about satisfaction.

9.2. Exclusion criteria for each subject population:

- Foster children or wards of the state.
- Children that use wheelchair or stroller mobility as their primary method of mobility (walking only at home or in therapy sessions).
- Severe visual impairment.
- Orthopedic or neurosurgery within the past 9 months or (botulinum toxin/phenol) injections to the lower extremity muscles within 3 months.
- Lower extremity fracture within the past 3 months.
- Uncontrolled seizure disorder.
- Planned surgery or changes to movement disorder medication.
- Unable to follow directions sufficiently enough to complete study visits.

9.3. Populations with special considerations, involved in the study:[20]

☒ Children/Teenagers[21]

Risk assessment specific to this vulnerable population and additional safeguards:[22]

☒ Individuals who use a language other than English[23]

- Spanish speaking families whose child speaks English will be enrolled. Study documents including recruitment materials, surveys, and instructions about devices have been translated and validated from English to Spanish. Informed consent will be obtained from the family with an in- person certified interpreter from the Research Language Core at the enrollment visit (Study Visit #1). At each visit, the study team will verify ongoing consent with the family. The in-person interpreter will be present at each study visit.
- Validation of the GOAL Spanish version will occur concurrently with administration of the survey. We will follow the requirements dictated by the author of the GOAL survey, Dr. Unni Narayanan, based at SickKids in Toronto, Ontario. 2-3 eligible Spanish-speaking participants will be enrolled in the study and the GOAL Spanish version will be administered to parent participants. SCRI Research Integration HUB will support in-person post-survey sensibility questions to assess cultural adaptation and translation validity (see sensibility questions attached).
- For intervention sessions that take place in the home setting, parent(s)/LARs will access an interpreter or bilingual study staff by phone. Prior to enrollment, the study team will provide contact information for the interpreter. They will then be asked to demonstrate proper use of the interpreter. Parent(s)/LARs that are unable to access or demonstrate proper use of the interpreter will not be enrolled in the study. During the intervention period, Interventionists will provide feedback after each home visit whether the Interpreter line was needed and/or if there were any issues. The study

team will be available remotely to troubleshoot any issues related to access or use of the interpreter line while home visits are in session.

Risks to Subjects: Subjects will include ambulatory children with unilateral and bilateral spastic cerebral palsy aged 6 -10 years and within GMFCS levels I, II or III. The risks to the subjects for the locomotor treadmill training or walking capacity/performance testing would not be greater than risk during regular physical therapy gait training sessions. Typically, ambulation on a treadmill involves a risk of tripping and falling. However, subjects will have constant contact guard support with gait belt around their trunk by the Research Interventionist. This fall prevention strategy has been effectively employed with prior trials across 240 individual SBLTT training sessions with no adverse events reported related to falls during the short-burst treadmill training. There is a mild risk of muscle cramps during treadmill training as well as temporary delayed-onset muscle soreness from power and strength testing. There's also the risk of joint pain in the knees following treadmill training. However, the investigative team has previously performed maximum strength and power testing protocols in the lower extremity in both CP and TD populations and reports of muscle soreness or joint pain have been rare and were reported mild in intensity. The questionnaires/interviews completed by the parent, demographic collection and body anthropometric measurements are solely for the research project with the level of risk considered minimal.

Protection Against Risk: The Research Interventionists administering the locomotor training will have a Bachelor's degree or higher, 1-2 years of work experience with typically developing children and persons with disabilities, and pediatric or exercise science training experience (i.e. physical/occupational therapists, physical therapy assistants, athletic/personal trainers). All Research Interventionists will be trained to competency by the principal investigator in the locomotor training protocol. Additional qualifications of athletic trainers will include experience working with clients with neuromotor disabilities—ideally cerebral palsy, power and/or treadmill training, clinical research, and at least 3 year of professional experience working with children 6-10 years old to ensure trainers are a good match for study participants. All Research Interventionists will be vetted during the hiring process by the principal investigator who will be responsible for the initial screening of background qualifications listed above. Research coordinators will be responsible for vetting related documents including CVs or resumes, licenses, insurances, and human subjects training certificates required by the Independent Investigator Agreements. Fidelity of all Interventionists will be monitored regularly per protocol.

Research therapists or non-clinical research staff performing the data outcomes assessments will also be trained to criterion by the principal investigators. All possible precautions will be taken to minimize risk of injury or distress during participation. This will include a safe environment for physical testing in the SCRI Behavior and Development Lab at Seattle Children's or in the Department of Physical Therapy at LSUHSC-NO. Research Interventionists will maintain direct contact with participants throughout training sessions on the treadmill via walking belt as well as direct the speed

changes, monitoring for fatigue and documenting any adverse events. The treadmills are unplugged and folded up in the homes when not in use by the Research Interventionists for the intervention.

In order to minimize physical risks during training, all subjects will be supported by contact guard of the Research Interventionist through a gait belt around their trunk in the Short Burst Interval Treadmill Training groups (SBLTT) and Traditional Locomotor Treadmill Training (TLTT) groups. Participants will also be allowed to use the treadmill railings as need during the training. Participants who otherwise meet the inclusion/exclusion criteria but are not tall enough to hold on to the treadmill railings will be provided with adjustable bars that can be adjusted to the participant's height. Participants will be allowed to rest and recover before they leave the intervention session to decrease any risk of falls after the training sessions. Participants will be monitored by the Research Interventionist for appropriate fatigue, muscle soreness, muscle cramps, joint pain, falls and/or unexpected physical discomfort (i.e., orthotic malalignment) during the treadmill training and walking testing. Participants will be allowed to rest as needed between training sets. Research Interventionists will address any of these issues as clinically appropriate (adjust orthotic fit, providing rest breaks, allowing the participant to drink from water bottle as needed, and/or adjusting the speed or timeline of treadmill session etc.). Our pilot study cohort had 10 adverse events, however, none were directly related to the study or the intervention. Specifically, there were no falls during training reported with 100% compliance for all training sessions.

Treadmill training protocol fidelity will be monitored and documented via a case report form for every session. See CRF. As mentioned previously, subjects will be excluded if they have undergone orthopedic surgery within the past 9 months or (botulinum toxin/phenol) injections to the lower extremity muscles within the past 3 months. The inclusion/exclusion criteria have been adequate in the protection against risks in several studies conducted by the principal investigator. In order to minimize muscle soreness and to prevent muscle fatigue during the muscle strength and power testing protocols, participants will rest 2-3 minutes between sets.

The questionnaires to be completed by the parents may bring up emotional discomfort. Research staff will check in with families during the study visit for their level of comfort and assure them they do not need to answer any questions they do not want to answer. Risks to the participants' privacy are minimal and every effort will be made to maintain confidentiality with secured access and storage of data.

There is the low potential risk of intolerance or skin issues with wearing of the StepWatch/GPS devices. The principal investigator has employed StepWatch monitoring in over 700 youth with and without disabilities employing the soft knit cuff at the ankle donning strategy without any reported intolerance to wearing the device, and devices are worn over socks and orthotics (if the child wears orthotics), thus the risks of wearing the StepWatch and/or the GPS devices appears to be low.

We propose this is a low-risk study, as the intervention consists of 30 second bursts of increased intensity of gait training with a treadmill which is similar to physical therapy training the children may experience as part of their typical physical therapy treatment in the community.

Potential Benefits of the Proposed Research to the Subjects and Others:

Individual participants of this clinical trial have the potential benefit of improving their own personal walking capacity, performance, as well as community mobility from the intervention of short-burst locomotor treadmill training or traditional treadmill training. The improvements in potential strength and power gained from this intervention have also been shown to contribute to improved activity, participation, and even quality of life and far outweigh the risks. These potential benefits justify the minimal risks to the participants. Knowledge gained has the potential to inform rehabilitation strategies for others with CP and/or other neuromuscular disorders with the subsequent potential for improved walking/physical activity and mobility.

Importance of Knowledge to be Gained: The risks of the study are minimal and are not greater than those encountered during performance of routine physical or psychological examinations or tests. In addition, the information gained from this study will help clinicians determine the best methods of treadmill training for children with cerebral palsy. This study will provide information regarding the efficacy of non-invasive treatment for muscle performance deficits in CP. Other alternative treatments for muscle dysfunction in CP include highly invasive procedures, such as neurosurgery and orthopedic surgery, which are irreversible procedures.

☐ Children who are Wards of the State[24]
Risk assessment specific to this vulnerable population and additional safeguards:
N/A.

☐ Adults Unable to Consent [25]
Risk assessment specific to this vulnerable population and additional safeguards:
N/A.

☐ Neonates of Uncertain Viability or Non–Viable Neonates[26]
Risk assessment specific to this vulnerable population and additional safeguards:
N/A.

☐ Pregnant Women[27]
Additional safeguards:
N/A.

☐ Prisoners[28]
Additional safeguards:
N/A.

☐ Economically or educationally disadvantaged persons[29]
Additional safeguards:
N/A.

10. Number of Subjects

10.1. Total number of subjects to be enrolled locally:[30]

Up to 46 participants will be enrolled at the Seattle site.

10.2. Total number of subjects to be enrolled across all participating sites:[31]

A total of 72 participants are expected to be enrolled across both sites (Seattle Children's Hospital and Louisiana State University Health Sciences Center).

10.3. Number of screened subjects versus the actual number enrolled in the research:[32]

Based on experience with prior trials, we expect to screen 1000 (500 per site) participants to obtain the 72 expected enrollees.

10.4. Power analysis:

We conducted our power and sample size calculations using the results from effect size estimates extracted from published literature for TLTT and our pilot study for SBLTT, thus power calculations are based on immediately post 4 weeks (20 session) of SBLTT. For Aim 1, if we were to observe 0.144 m/s (SD=0.132) increase from baseline in the SBLTT arm and 0.072 m/s (SD=0.021) for the TLTT arm for self-selected walking speed, then 31 subjects per arm would provide 90% power to detect the difference between two study arms based on two-sample t-test. In our pilot study, we actually observed a 0.206 m/s increase with 5x/week SBLTT (n=6). In that case only 9 subjects per arm are required if we observe similar effect size with this study. However, given the small sample size, we chose the more conservative estimate. If we were to observe 7.28 meter (SD=2.82) improvement from baseline in SBLTT arm and 4.85 meters (SD=4.00) improvement from baseline for the TLTT arm for the 1-minute walk test, then 26 subjects per arm would provide 80% power to detect the difference between the two study arms based on two-sample t-test. In our pilot study, we actually observed average improvement of 13.75 meters with 5x/week SBLTT. Then only 6 subjects per arm are needed if we observe similar effect size with the present study. For Aim 2, we estimate that we will need 27 subjects per arm to detect with 80% power a difference of 550 strides/day between the two arms at 8 weeks. For Aim 3 we will examine improvement in muscle power before and after training. If we assume there is no improvement in isotonic average power with the TLTT arm and an average improvement of 7.0 watts in muscle isotonic average power (SD=9.67) in the SBLTT arm, then sample size of 31 per arm will provide 80% power to detect such a difference. Based on these calculations a sample size of 31/arm should provide 80-90% power for all three specific aims. We further increase the sample size to 36/arm (total N=72) to account for a 15% drop-out rate. Based on previous experience we believe it is a conservative estimate of drop-out rate.

11. Withdrawal of Subjects

11.1. Anticipated circumstances under which subjects will be withdrawn from the research without their consent:

A subject will be withdrawn from the study if they experience a serious adverse event, or if they become injured or undergo any procedures (such as surgery, or injection therapy) that would preclude them from completing the SBLLT or TLTT.

11.2. Procedures for orderly termination:

If a subject is withdrawn from the study, we will notify the family and the subject's data will be marked as withdrawn. Any remaining reimbursements owed to the subject will be disbursed to them within 1 month of withdrawal. The IRB will be notified of the withdrawal, along with an explanation of the reasons for withdrawal.

11.3. Procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection and withdrawal from data/biospecimen banking:

If a subject elects to withdraw from the research for any reason, we will mark the subject's data as withdrawn and disburse any remaining reimbursements owed to them. We will include the subject's withdrawal status in IRB and funding organization reports.

12. Risks to Subjects

12.1. Reasonably foreseeable risks to subjects (include each study population, each arm, and optional procedures):

As stated above in section 9.3, the risks to the subjects include:

- Possible tripping or falling during ambulation on a treadmill during training or walking capacity/performance testing.
- Temporary delayed-onset muscle soreness and/or joint pain from power and strength testing. We believe this to be a mild risk based on previous experience in other trials.
- Questionnaires completed by parents may result in emotional discomfort.
- Risk to participants' privacy
- Intolerance or skin issues associated with wearing the StepWatch/GPS device

Strategies to minimize these risks are detailed below in section 12.5.

12.2. Procedures with unforeseeable risks:

None known.

12.3. Procedures with risks to an embryo or fetus should the subject be or become pregnant:

N/A.

12.4. Risks to others who are not subjects:

N/A.

12.5. Procedures performed to lessen the probability or magnitude of risks:

Table 3. Risks and Risk Minimization

Risk	Anticipated Risk Level	Risk Minimization Strategy
Possible tripping or falling during ambulation on a treadmill during training or	Low - no greater than standard care	• Research Interventionists may have a Bachelor's degree or higher and/or pediatric and/or exercise

walking capacity/performance testing		science training experience (i.e. physical/occupational therapists physical therapy assistants, athletic/personal trainers), and will be trained to competency by the principal investigator in the study locomotor training protocol. • These individuals will have work experience with typically developing children and persons with disabilities. • We will employ safeguards such as constant contact guard support with gait belt around their trunk by the ft Interventionist • Participants will be allowed to use guardrails during training. • Participants will be allowed to rest and recover as needed and before they leave the intervention
Temporary delayed-onset muscle soreness and/or joint pain from power and strength testing	Low	Participants will rest and/or use NSAID as needed.
Questionnaires completed by parents may result in emotional discomfort	Low	Research staff will check in with families during the study visit for their level of comfort and assure them they do not need to answer any questions they do not want to answer.
Risk to patient privacy	Low	every effort will be made to maintain confidentiality with secured access and storage of data
Intolerance or skin issues associated with wearing the StepWatch/GPS device	Low	employing the soft knit cuff at the ankle and worn over socks and orthotics (if the child wears orthotics)

(i) For participants with a history of seizure or seizure-like activity, the study team will inquire with the family about the participant's typical clinical signs during a seizure

(seizure semiology) and whether their neurologist has prescribed a seizure rescue medication. This information will be collected via the Pre-Test Questionnaire. For participants who have a prescribed seizure rescue medication, the interventionist will verify that the family has the rescue medication available during the training sessions. Furthermore, active participants with a history of seizures will be asked by the interventionist if they have experienced a seizure prior to each session.

(ii) Sessions will be altered, paused, or stopped based on the participant's response regarding seizure activity. If a participant reports having a seizure since the last visit, the interventionist will assess the participant's condition and determine if it's safe to proceed with the session. Specifically, the interventionist/study team will ask: 1) when seizure happened (was there an event precipitating the seizure – [lack of sleep, fever, physical exercise, prolonged monitor use with electronic gaming, etc]; 2) duration of seizure 3) effect on gross motor function [did it affect ability to stand/walk/sit}; 4) effect interaction (i.e. response to auditory or visual cues). If there are concerns about the participant's safety or ability to continue, the session will be altered, paused or stopped accordingly.

- Altering Sessions: If a participant reports having had a seizure since their last visit, but the interventionist assesses that the participant is currently stable (i.e. seizure activity did not influence gross motor activity like walking or posture in sitting) and able to engage in the session safely, the session may be altered per discussion with PI investigator at each site (LSU/SCRI). This alteration could involve modifying the intensity, speed or duration of the planned activities to ensure the participant's well-being while still allowing them to participate to some extent.
- Pausing Sessions: If a participant reports having had a seizure since their last visit, and the interventionist observes signs or symptoms that indicate the participant may be at risk of experiencing a seizure or that their current condition poses a safety concern (i.e. seizure activity negatively influences gross motor skill such as walking or posture in sitting), sessions may be paused. A minimum 1-week seizure free period will be required before restarting sessions. Additionally, we will require written approval from the provider to resume treadmill training, especially in cases where seizures may impact motor functions (e.g., weightbearing through legs, maintaining upright posture). Any further participation or adjustment period will be subject to evaluation by the neurologist.
- Stopping Sessions: If a participant reports having had a seizure since their last visit, and the interventionist determines that continuing with the planned session would pose a significant risk to the participant's safety or well-being (i.e. seizure negatively influence motor activity such as walking or sitting posture), sessions will be stopped immediately. This decision may be made if the participant shows signs of distress, inability to safely participate in the activities (i.e decrease in active lower extremity weight-bearing while on treadmill), or if there are concerns about exacerbating their condition.
- Withdrawal from the study: In the event of a significant seizure-like episode (e.g., full-body seizure) where control of seizures cannot be confirmed through physician/neurologist management, the participant will be withdrawn from the study.

(iii) If there is a reported seizure since last training session, the Co-PI (LSU or SCRI) will review the information regarding the reported seizure before proceeding with a training session. This review will help determine if any participants need further evaluation by a neurologist or if they can safely continue in the study. Participants with a history of seizures require careful monitoring, and any changes in their seizure activity may necessitate adjustments to their participation in the study.

(iv) Participants actively receiving intervention and/or assessment and with a history of seizures, will be closely monitored for potential seizure-like activity. If a zoning out episode occurs that significantly impacts walking ability (i.e, falling, inability to weight bear on the lower extremities, or other safety concern), the session will be stopped. A clinician PI or Co-PI will be alerted of any seizure-like activity occurring on the treadmill during training protocol as soon as it is observed. Given the potential risks associated with seizures during physical activity, prompt notification is essential for ensuring participant safety and appropriate response. Participants may need to be "cleared" for the next treadmill session depending on the severity and frequency of seizure-like activity observed during the previous session. Clearance for the next session will be determined by the intervention team in consultation with the participant's healthcare provider, taking into account their safety and well-being.

(v) If a participant goes from controlled to uncontrolled seizures, research activities will be paused until the seizures are brought back under control. It is essential to prioritize the participant's health and safety, and continuing research activities during a period of uncontrolled seizures could pose significant risks. Once the participant's seizures are under control again, their eligibility to resume participation will be reassessed in consultation with the healthcare provider who is managing their seizure disorder (i.e. medication dose or other treatments).

13. Potential Benefits to Subjects

13.1. Potential benefits that individual subjects may experience from taking part in the research:[33]

Individual child participants of this clinical trial have the potential benefit of improving their own personal walking capacity, performance as well as community mobility from the intervention of short-burst locomotor treadmill training or traditional treadmill training. The improvements in potential strength and power gained from this intervention have also been shown to contribute to improved activity, participation, and even quality of life and far outweigh the risks. These potential benefits justify the minimal risks to the participants.

14. Data Analysis/Management

14.1. Data analysis plan, including statistical procedures:

The primary statistical analyses will be intention-to-treat to avoid confounding by non-random participant attrition or crossover. Demographics, clinical characteristics, outcome variables will all be summarized at each time-point using descriptive statistics: frequencies and proportions for categorical variables; means and standard deviations for continuous variables, or median and interquartile range if distribution is skewed. All regression analyses will be adjusted for study site, as well as baseline characteristics clearly imbalanced between groups. Additional baseline

characteristics we consider as potential confounders include age, sex, and GMFCS level. Statistical analysis will be conducted in R, SPSS and Stata.

Analysis plan for Aim #1: Outcome measures for this aim include self-selected and fast gait speed from 10-m walk test and distance from 1-minute walk test. We will conduct cross-sectional data analysis for post-intervention (8 weeks) and at follow-up (16 weeks post-intervention) separately with primary endpoint at post 8 weeks (40 sessions) of training. Our primary analysis will be based on linear regression models, in which gait speed or 1 minute walk distance will be the dependent variables; SBLTT intervention indicator will be the predictor of interest; study site and baseline outcomes will be adjusted as covariates. With this model specification, the regression coefficient of intervention indicator captures the average difference in changes from baseline to post intervention (or follow-up) on outcomes between SBLTT and TLTT arms. The coefficient will be assessed using Wald t-test and 95% confidence intervals. In addition to cross-sectional analysis, we will examine the changes over time in outcomes through repeated measure analysis using outcomes across all four time points (baseline, 4-weeks, 8-weeks, and 16 weeks post-intervention). We will apply linear mixed effects models with a discrete time variable, intervention group indicator, and group-by-time interaction terms, plus covariates. The interaction captures the differential amount of changes from baseline at later time points between the two arms and will be the parameter of interest. The interaction coefficient will be assessed using Kenward-Roger method or bootstrap method.

Analysis plan for Aim #2: For this aim we consider the following outcomes: StepWatch outcomes (average strides per day, percent time walking each day, number of strides at moderate and high stride rates, peak stride rates), SW/GPS outcome (strides/day and intensity by walking location community vs. home), community mobility (PROMIS total score) and family gait priorities (GOAL total score). We will conduct cross-sectional data analysis for post-intervention and at follow-up separately. Similar linear regression modeling approach as outlined for Aim #1 can be applied to the cross-sectional analysis: intervention indicator will be the predictor of interested; baseline outcome and site will be covariates. Similar linear mixed effects model as described for Aim #1 can also be applied.

We will consider weekly occurrence of community walking as a count variable and apply Poisson regression model. This model would estimate whether SBLTT is associated with higher rate of community walking. The model specification is similar to other outcomes, except it is in a generalized linear model framework. Repeated measures analysis for this outcome can be conducted using generalized linear mixed effects models. Daily total strides and moderate-to-high intensity strides will be summarized according to different locations with association between various location-based walking assessed using linear regression models.

Analysis plan for Aim #3: For this aim we will estimate the amount of effects that high frequency SBLTT has on walking capacity and performance that can be explained by improvements in muscle power. We will operationalize changes from baseline in knee extensor and plantar flexor muscle power at post-intervention as

potential mediators. We will apply the extended Baron and Kenny (1986) framework with regression equations. Significance of mediated effect will be based on Sobel's test and bootstrap confidence intervals, with framework extended to include multiple mediators to assess their jointly mediated effects.

For all aims, *sub-analyses* will be carried out to examine the training (i.e., minutes trained) and clinical factors and /or biomarkers (age, gender, weight, height, baseline walking stride rates, GMFCS level, prior orthopedic or neurological surgery/Botox, etc.) that may inform positive changes in walking capacity (Aim 1), walking performance and community mobility (Aim 2), and muscle performance (Aim 3) post SBLTT and TLTT. Analyses will be *exploratory* and aim to generate hypotheses for future studies.

14.2. Quality control procedures for collected data:[34]

To ensure the accuracy of the data the following processes will be implemented:

a) The Study Coordinator will check all case report forms for completeness.
b) Data from REDCap will be manually doubled loaded directly into a database program (Microsoft Excel) for subsequent statistical analysis using SPSS, version 22.0 (SPSS, Incorporated, Chicago, IL) or SAS v 9.1.
c) Once data are entered periodic checking reports will be run to examine subject and parent response data. These reports will be run to look for any discrepancies or inaccuracies (e.g., outliers) in the data. Any discrepancies or inaccuracies will be traced back to the original data file. All data discrepancies or inaccuracies will be resolved and changed in the dataset, ensuring data integrity and cleanliness in the final dataset.

15. Confidentiality[35]

15.1. Procedures to secure the data and/or biospecimens during storage, use, and transmission:

The PIs at each site will supervise staff in storing electronic data and overseeing the integrity of study records. All participant raw data will be coded and stored separately from identifying information on a password-protected server to which only study staff has access. The data stored on the central server will be automatically coded with participant ID and no personal identifiers will be associated with these data. Study personnel will be able to access the data on the central server using a login and password in order to track compliance.

15.2. Location where the data and/or biospecimens will be stored:

As stated above, data will be maintained on a site-specific server with password protection and daily backup of data performed. At weekly intervals, data will be stored on external hardware isolated from the network to help protect against data loss from network and system malfunction.

15.3. Length of time data and/or biospecimens will be stored:

Identifable study data will be kept for 7 years, until all data has been collected and analyzed for publication. After this time, data will be de-identified and kept indefinitely.

15.4. Individuals with access to data and/or biospecimens:

The study principal investigator, biostatistician, and research coordinator will have access to the study data.

15.5. Process for the transmission of data and/or biospecimens outside Seattle Children's:

15.5.1. List of data and/or biospecimens that will be transmitted:

We do not anticipate needing to transmit study data outside Seattle Children's.

15.5.2. Individual(s) who will transmit data:

N/A.

16. Provisions to Monitor Data to Ensure the Safety of Subjects[36]

16.1. Plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe:[37]

Although the potential risks of participation to the subjects are considered to be minimal, the safety of the subjects will still be monitored regularly by the Co-PIs. Additionally, a Data Safety Monitoring Board (DSMB) will be convened for the purpose of oversight and monitoring to ensure the safety of participants and the validity and integrity of the data.

After 6 participants have been enrolled to each treatment arm, the DSMB will look at 4 week and 8 week adverse events data to monitor for any undue stress or harm from the intervention and/or by duration of the homebased training. If the adverse events are deemed greater than expected for this frequency of intervention, the study will be stopped. The pilot study cohort (n=12) had 10 adverse events, none of which were directly related to the study or the intervention. Specifically, there were no falls during training reported with 100% compliance for all training sessions.

16.2. Data reviewed to ensure safety of subjects:

All adverse events, regardless of attribution to treatment procedures, will be collected, recorded, and reviewed by the DSMB.

16.3. Safety information collection procedures:

Participants will be asked in an open-ended way about the presence of any adverse events. The likelihood that the event is related or not related to treatment will be noted. Reporting of adverse events will use a grading and attribution scale (Grading = mild, moderate severe; Attribution = Definite, Probable, Possible, Unlikely, Unrelated). Serious Adverse Events that occur to participants will be reported to the and Seattle Children's IRB immediately. Should an unanticipated adverse event or outcome be discovered, Bjornson will notify their respective IRB within 48 hours and proceed accordingly. Should there be a serious adverse event that occurs that increases the risks to the participants, the study will be stopped, an investigation will be conducted, and a findings report will be generated before the study is resumed

16.4. Frequency of cumulative data review:

Adverse events will be collected from the start of treatment through the end of study participation. As described above in 16.1, the DSMB will look at 4 week and 8 week

adverse event data as an interim safety analysis plan to determine whether the study procedures present any risk to participants.

16.5. Conditions that trigger an immediate suspension of the research:

As stated in 16.1 above, if adverse events are deemed greater than expected for this frequency of intervention, the study will be stopped. .

17. Use of Social Media

17.1. Types of social media to be used and how:

For recruitment purposes, we will place ads on Facebook and Instagram with brief information about the study and contact information for interested families. When an interested family clicks on the ad, it will direct them to the SBLT study page on seattlechildrens.org. The study team will work directly with Seattle Children's Marketing and Communications team to draft the social media advertisement/s. We will also utilize the Seattle Children's social media accounts to recruit participants, and will consult with a SCH social media specialist about this and other options for recruitment using social media platforms. Similar procedures will be followed at LSUHSC-NO.

17.2. Measures in place to protect the privacy or confidentiality of subjects:[38]

For any social media advertising or recruitment, we will first consult with a SCH social media specialist about maintaining privacy and confidentiality of potential participants. For any social media recruitment activities, we will ask families to contact the study team directly if they are interested in participating. To insure confidentiality the FACEBOOK SCH study post would when clicked on by a potential family/parent would go to a secure website where they would be instructed to contact the PI or study coordinator directly by email or phone. They will not be able to post comments to the FB SBLTT Study page. Similar procedures will be followed at LSUHSC-NO.

17.3. Types of communications that will be submitted to the IRB for review:[39]

All advertisements and/or social media text will be submitted to the IRB for review prior to deployment.

17.4. If user-generated content will be active, how it will be monitored and what actions will be taken to ensure subject safety and study integrity:

We do not anticipate user-generated content for this study.

18. Research Related Injury[40]

18.1. Available compensation in the event of research related injury:

N/A.

19. Recruitment Methods[41]

19.1. When, where, and how potential subjects will be recruited:

Subjects at SCH and LSUHSC-NO will be recruited using several strategies :

- Direct mailing and/or email to children and families who have been seen at Children's Hospital New Orleans (CHNOLA) and Seattle Children's for care

related to their CP including current participants in the Cerebral Palsy Research Network (CPRN, SCH external IRB study 00590) registry for SCH only. Initial list of patients to be screened will be done via a list generated by analytics based on ICD9/10 codes for ambulatory CP. Patients will be screened via Electronic Medical Record (EMR) review. A return letter of interest with stamped, return envelope will be included for families interested in participating.

- Approach mailing will include approach letter, study flyer, return letter of interest and postage paid envelope to return letter of interest to study staff at SCRI or LSUHSC-NO. Approach email will include approach letter, study flyer, and embedded email text with contact information of study staff at SCRI or LSUHSC-NO.
- If the potential subject does not reply, the study team will contact the family by phone or email up to two times. After a second phone call or email is attempted without a response, no further contact will be made.
- A report of patients in MyChart will be generated by the study coordinator via EPIC based on ICD9/10 codes for ambulatory CP at SCH only. The study team will use 'Find Patient' to screen specific patients to determine eligibility. Eligible families will be sent a MyChart message through the use of 'Send Recruitment Request' function. See attached template for approach message through MyChart. The MyChart message will include an embedded text with contact information of study staff at SCRI.
- Distribution of the study flyer to potentially eligible families at other hospitals and community providers (physicians, physical/occupational therapist, orthotists) in the Seattle and New Orleans areas (these will be used as secondary recruitment sites through physician and therapist referral). Community providers will share the flyer with families during standard clinical care visits. The flyer will contain contact information for the families to contact the study team if they are interested in participating.
- Peachjar will be utilized to reach families with children attending Greater Seattle area schools. The study team will work directly with Seattle Children's Marketing and Communications team to draft the social media advertisement/s. See attached flyer for approaching families with students in the Greater Seattle area via Peachjar.
- The study team may also share information about the study to community providers who would in turn share the information with their patients and/or potentially eligible families. Study team will contact the family by phone or email up to four times to elicit a response following a provider referral. After a fourth phone call or email is attempted without a response, no further contact will be made.
- Use of social media (see section 17).
- Postings to online special interest groups- of study flyer such as the Washington State Physical therapy association, Louisiana State Physical Therapy Association, and Pediatric special interest groups' list serve.
- Presentations to local therapy community for the proposed study population

- Spanish speaking families whose child speaks English will be enrolled. Recruitment materials, consent form, and child assent form have been translated and validated from English to Spanish.
- At SCRI, Spanish-speaking parent participants will be recruited via provider referral, approach mailing, and MyChart. At LSUHSC-NO, Spanish-speaking parent participants will be recruited via provider referrals. Community providers will share the flyer with families during standard clinical care visits and the study team will contact the family by phone or email up to two times.
- Prior to the enrollment visit, parents/LAR will be mailed or emailed an un-signed consent form to allow sufficient time for review. For recruitment purposes, a conversation will then occur via telephone with a certified interpreter to ensure understanding of the study and to briefly introduce the consent form and study details.
- Informed consent and signing of consent documents will occur in-person with a certified interpreter from the study team at the enrollment visit (Study Visit #1). This individual will be present during all assessment visits to support with interpretation.
- The study team will assess proper use of the interpreter prior to enrollment. Parent(s)/LAR that are unable to access or demonstrate proper use of the interpreter line will not be enrolled in the study.
- If the parent/LAR understands more than one language, the consent process will occur in their language for care.

19.2. Steps that will be taken to protect potential subjects' privacy interests:[42]

Patients approached through the direct mailing will have the privacy of their own home in which to read the approach letter and study flyer and to contact study staff if they have questions. At SCH, consent/assent visits will occur in private sound proof Bjornson Assessment lab at Jack R. MacDonald Building and will occur in a research laboratory at LSUHSC-NO on the 7th floor in the Department of Physical Therapy in New Orleans, LA. Alternatively, we will hold the consent/assent conference by phone when in person options are not feasible. For both sites, all PHI for approach and data collected will be stored on password protected computer research share drives with access only by study staff. Data collection forms will be coded by study ID number without PHI.

19.3. Sources of subjects:[43]

- Cerebral Palsy Research Network (CPRN, SCH external IRB study 00590) registry at Seattle Children's Hospital.
- Outpatient care clinics for cerebral palsy (physical therapy, Developmental Medicine, Rehabilitation Medicine, Orthopedics, and Neurosurgery) in Seattle and New Orleans.
- Use of social media (see section 17)

- Online special interest groups- such as the Washington State Physical therapy association, Louisiana State Physical Therapy Association, and Pediatric special interest groups' list serve.
- Local therapy community in Seattle and New Orleans

19.4. Methods that will be used to identify potential subjects:

- Initial list of patients to be screened will be done via a list generated by analytics based on ICD9/10 codes for ambulatory CP patients seen at SCH and CHNOLA. Patients will be screened via Electronic Medical Record (EMR) review.
- For participants recruited at SCH only, the study coordinator will review the list of SCH patients who are members of the Cerebral Palsy Research Network registry to identify potential participants. A study flyer will be mailed to these families along with a return letter of interest with stamped, return envelope for families interested in participating.
- For LSUHSC-NO and SCH, clinic staff at physical therapy and outpatient clinics (Developmental Medicine, Rehabilitation Medicine) will provide potentially eligible families with a study flyer and instruct them to contact the study team if they are interested in participating. These potential participants will be screened by study staff by phone once they contact staff expressing interest in the study.
- Study information (including contact information for interested families) will be posted on social media sites and in online special interest groups
- For LSUHSC-NO and SCH, presentations will be made to the local therapy community may result in interested participants. A study flyer will be provided for all interested families.

19.5. Materials that will be used to recruit subjects:[44]

- Study flyer
- Online advertisements/postings on social media sites and special interest groups

19.6. Recruitment methods not controlled by Seattle Children's:

n/a

20. Consent/Assent Process

20.1. Consent process overview:[45]

When the study team receives a notice of interest in participating from a family, a study team member will contact the family either in person (at a clinic visit), by phone, or via email to introduce the study to tell them more about the study and verify eligibility. Written parental permission will then be obtained from the parent and assent will be obtained from children ages 7 and older (as developmentally able) during the baseline visit or prior to the visit by phone. The parent participating in the study will also document their consent to participate. Study staff will discuss the nature of the study,

study procedures, importance of compliance, potential risks and benefits and duration of study. Participants will be informed that they are not obliged to participate and can withdraw at any time without impact on their care at Seattle Children's Hospital or LSUHSC-NO. There will be adequate time for questions regarding the project participation. At SCRI and LSUHSC-NO, the process of consent for Spanish-speaking parent(s)/LARs will first include a conversation about the consent form via telephone with a certified interpreter to allow the participant an opportunity to ask questions and for the researcher to measure the participant's understanding of the study prior to study enrollment. Signatures will be collected and consent will occur in-person at the Enrollment Visit (Study Visit #1) with a certified interpreter. If the parent/LAR understands more than one language, the consent process will occur in their language for care.

20.2.

Process to obtain consent documentation remotely.
Due to the Covid-19 pandemic, participating families will also have the option of submitting signed consent and assent forms via email. After reviewing the documents over the phone with a study team member, the study team member will provide instructions on how to complete the remote consent documentation process. This process includes: printing the documents at home, signing and dating the appropriate lines, scanning or taking photos of all the pages and sending the files as attachments to the study team via email.

20.3. Where the consent process will take place:

The consent process will take place at the Bjornson Assessment Lab at Jack R. MacDonald Building for SCH. For LSUHSC-NO, consent will take place in a research laboratory in the Department of Physical Therapy on the 7th floor at 1900 Gravier Street in New Orleans, LA. Alternatively, the consent process may take place by phone prior to signatures being obtained via mail or via scanned files.

20.4. Steps that will be taken to protect prospective subjects' privacy interests:[46]

Patients approached through the direct mailing will have the privacy of their own home in which to read the study flyer and to contact study staff if they have questions. Consent/Assent visits at SCH will occur in private sound proof Bjornson Assessment lab at Jack R. MacDonald Building.
Consent/Assent visits at LSUHSC-NO will occur in a research laboratory in the Department of Physical Therapy on the 7th floor at 1900 Gravier Street in New Orleans, LA. Alternatively, we will hold the consent/assent conference by phone when in person options are not feasible. All PHI will be stored on password protected computer research share drives with access only by study staff. Data collection forms will be coded by study ID number without PHI.

20.5. Waiting period available between approaching a prospective subject and obtaining consent:

We anticipate that the length of time between initial approach and obtaining consent will be between 1 day and 14 days.

20.6. Process to ensure ongoing consent:

Study participants will be engaged in study activities for approximately 24 weeks. At each visit, the study team will verify ongoing consent with the family.

20.7. If this box is checked, "SOP: Informed Consent Process for Research (HRP-090)" will be followed: ☒

20.8. If "SOP: Informed Consent Process for Research (HRP-090)" will not be followed, address the following:[47]

20.8.1. Role of the individuals listed in the application as being involved in the consent process:

N/A

20.8.2. Time that will be devoted to the consent discussion:

N/A

20.8.3. Steps that will be taken to minimize the possibility of coercion or undue influence:

N/A

20.8.4. Steps that will be taken to ensure the subject's understanding:

N/A

20.9. Non-English Speaking Subjects[48]

20.9.1. Anticipated preferred language(s) for subjects or their representatives:

English
Spanish

20.9.2. Presentation of Research Information and Documentation:

☒ Appendix A-10 of the Investigator Manual will be followed[49]

☐ Short form procedures may be used per HRP-091. If so, choose applicable box(es):

☐ Per section 5.5.1

☐ Per section 5.5.2

☒ Appendix A-10 of the Investigator Manual will not be followed. Explanation of procedures not following Appendix A-10:
For the LSU pSite, the local standard related to language certification requirements will be followed as Seattle Children's cannot provide assessment for non-SCH staff.

20.9.3. Justification if non-English speaking subjects will be excluded from the research:[50]

20.10. Subjects Who Are Not Yet Adults (Infants, Children, Teenagers)

20.10.1. Process used to determine whether an individual has not attained the legal age of consent under the applicable law of the jurisdiction in which the research will be conducted (e.g., individuals under the age of 18 years):[51]

Only children ages 6-10 years will be recruited for the study. Age will be verified through date of birth in the medical record and/or verification from the child's parent at the time of consent.

20.10.2. Parental permission will be obtained from:[52]

☐ Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

☒ One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.

☐ Neither parent.[53]

20.10.3. Process used to determine an individual's authority to consent to each child's general medical care if permission will be obtained from someone other than parents:[54]

The study coordinator will consult EPIC to verify the consenting authority of parents/guardians to ensure consent can be provided for research purposes, per HRP-013 procedures. As the non-SCH participants are not SCH patients, we will ask the person accompanying the child if he/she is a parent or legal guardian. Alternatively, or in addition to this, we could ask the physician or medical team to verify the adult is a parent or legal guardian (presumably this will be indicated in their medical record). Because participants do not receive care at LSUHSC-NO, we will ask the person accompanying the child if he/she is a parent or legal guardian and ask for proof of identity. Alternatively, or in addition to this, we could ask the physician or medical team to verify the adult is a parent or legal guardian (presumably this will be indicated in their medical record).

20.10.4. Assent will be obtained from:[55]

☒ All children. Children aged 7 and above will be asked to provide written and verbal assent to participate. For 6 year old children we will ask verbal assent with, parental consent will be obtained, however. Study staff will explain the study to the child and answer any questions

☐ Some children. Specify:.

☐ None of the children. Explain: ✍Click here to enter text.

20.10.5. Procedures for obtaining and documenting assent:

Per HRP-091, written assent for children ages 7-10 will be documented in a simple, written assent form. The child will have the opportunity to ask questions about the study, and study staff will answer them. The assent form will be written in age appropriate language and at a reading level of approximately 2nd - 3rd grade. For children under 7 years of age, written assent will not be obtained, however, the study staff will explain the study to the child and answer any questions posed by the child.

20.10.6. Plan for re-approaching children who have reached the age of majority to obtain consent:[56]

N/A- this study will only recruit children ages 6-10.

20.11. Cognitively Impaired Adults/Adults Unable to Consent[57]

20.11.1. Process used to determine whether an individual is capable of consent:

We do not anticipate enrolling cognitively impaired adults in this study.

20.11.2. Individuals from whom permission will be obtained in order of priority:[58]

N/A

20.11.3. Assent will be obtained from:

☐ All of these subjects.

☐ Some of these subjects. Specify:

☒ None of these subjects. Explain: We do not anticipate enrolling cognitively impaired adults for this study.

20.11.4. Process for obtaining and documenting assent:[59]

N/A- we do not anticipate enrolling cognitively impaired adults in this study.

20.12. Waiver or Alteration of Consent Process

20.12.1. Reasons for requesting a waiver or alteration of informed consent:[60]

N/A- we are not requesting a waiver for this study.

20.12.2. Consent Waiver/Alteration Criteria justifications:[61]

20.12.2.1. The research involves no more than minimal risk to the subjects because:

N/A.

20.12.2.2. The waiver or alteration will not adversely affect the rights or welfare of the subjects because:[62]

N/A.

20.12.2.3. The research could not practicably be carried out without the waiver or alteration because:[63]

N/A

20.12.2.4. <u>If the research involves using identifiable private information or identifiable biospecimens</u>, the research could not practicably be carried out without using such information or biospecimens in an identifiable format because:

N/A

20.12.2.5. Whenever appropriate, the subjects will be provided with additional pertinent information after participation:

N/A

20.12.3. If the research involves a waiver of the consent process for emergency research, provide sufficient information for the IRB to make it determinations:[64]

N/A

21. Process to Document Consent in Writing

21.1. If consent will be documented in writing (check one):

- ☒ "SOP: Written Documentation of Consent (HRP-091)" will be followed.
- ☐ "SOP: Written Documentation of Consent (HRP-091)" will not be followed.

Process of documenting consent:[65]

21.2. If consent will not be documented in writing (check all boxes that apply):[66]

- ☐ A written statement/information sheet describing the research will be provided to subjects.[67]
- ☐ A written statement/information sheet describing the research will not be provided to subjects. Explain: ✍Click here to enter text.
- ☐ A consent script will be used.[68]

22. HIPAA Authorization and RCW Criteria

22.1. HIPAA Authorization (check all boxes that apply):

- ☐ The study does not involve the receipt, creation, use and/or disclosure of protected health information (PHI).[69]
- ☒ HIPAA authorization will be obtained as part of a signed consent form.
- ☒ The study will access PHI without prior authorization from subjects (including for recruitment purposes – e.g., reviewing the medical record to determine eligibility). *See 21.2 below for required HIPAA waiver/alteration criteria*.
- ☐ Subjects will review a written statement/information sheet with the appropriate HIPAA language but will not provide a written signature. See 21.2 below for required *HIPAA alteration criteria*.[70]
- ☐ Other. Explain:[71]

22.2. HIPAA Waiver/Alteration Criteria: Explain why:

22.2.1. The use or disclosure of PHI involves no more than a minimal risk to privacy of individuals, based on, at least the presence of the following elements:

22.2.1.1. An adequate plan to protect the identifiers from improper use and disclosure:

Only members of the study team will access PHI for this study. The study team will take every precaution to maintain confidentiality of participant PHI. For example, as stated in section 15, all participant raw data will be coded and stored separately from identifying information on a password-protected server to which only study staff has access. The data stored on the central server will be automatically coded with participant ID and no personal identifiers will be associated with these data.

22.2.1.2. An adequate plan to destroy identifiers at earliest opportunity consistent with conduct of research:

The research data for this study will be de-identified after the data analysis is complete.

22.2.1.3. Assurances that PHI will not be reused or disclosed to any other party or entity, except as required by law or for authorized oversight of the research:

We will not reuse nor disclose PHI to any other party or entity, except as required by law or for authorized oversight of the study.

22.2.2. The research could not practicably be conducted without the waiver or alteration of authorization:

Although we will obtain HIPAA authorization from participating parents in this study at the time of consent, we will initially determine eligibility through screening the electronic medical record for potential participants who meet eligibility criteria. Screening will occur prior to obtaining consent. We are requesting a waiver of HIPAA for the purposes of screening only.

22.2.3. The research could not practicably be conducted without access to and use of the PHI:[72]

In order to determine eligibility for the study, we will access the electronic health record as noted in 22.2.2 above. As eligibility criteria include age and diagnosis, we will be accessing PHI to verify eligibility.

23. Payments/Costs to Subjects[73]

23.1. Amount, method, and timing of payments to subjects:[74]

Participants will receive $50 after completing each of the four study assessments, for a total of $200, on a reloadable debit card. Participants will also be reimbursed for mileage travelled and parking for assessment visits. Participants will be informed of receipt requirements for reimbursements.There is no cost to the participants if devices are lost, stolen and/or damaged (i.e. StepWatch, GPS and/or treadmills).

23.2. Reimbursement provided to subjects:[75]

As stated in 23.1 above, participants will be reimbursed for mileage and parking for assessment visits. We will require documented mileage estimates, toll receipts (where applicable), and parking receipts prior to issuing reimbursements to families.

23.3. Additional costs that subjects may be responsible for because of participation in the research:[76]

As families will need to travel to Seattle Children's or LSUHSC-NO for assessment visits, they are likely to incur costs for travel, including mileage, toll charges, and parking.

24. Setting

24.1. Site(s) or location(s) where the research team will conduct the research:

- Seattle Children's Hospital - Bjornson Assessment Lab at Jack R. MacDonald Building (for baseline, 4 week, 8 week, and 16 week post-intervention assessment visits).
- LSUHSC-NO - Department of Physical Therapy, 7th floor, 1900 Gravier Street in New Orleans, LA
- Participants' home (for treadmill intervention)

24.2. Composition and involvement of any community advisory board:
N/A

24.3. For research conducted outside of the organization and its affiliates:[77]

24.3.1. Site-specific regulations or customs affecting the research:
N/A

24.3.2. Local scientific and ethical review structure:
N/A

25. Resources Available

25.1. Qualifications (e.g., training, education, experience, oversight) of investigator(s) to conduct and supervise the research:[78]

Dr. Bjornson, the Principal Investigator, is an Associate Professor of Pediatrics, Developmental Medicine and adjunct Research Assistant Professor of Rehabilitation Medicine at the University of Washington. As a pediatric physical therapist, she has over 35 years of clinical experience in settings such as the NICU, public schools, birth-to-three centers, and at Seattle Children's Hospital. Her clinical and research career has focused on interventions for spasticity and mobility limitations in children with cerebral palsy, documenting quality of life, the measurement of walking activity, and the relationship to mobility-based participation in day-to-day life of children with physical limitations. She has authored more than 40 published manuscripts and has served as a Principal Investigator or Co-Investigator on multiple grant-funded projects throughout her career.

Dr. Moreau, the co-Principal Investigator, is an Associate Professor, Department of Physical Therapy at Louisiana State University Health Sciences Center. Her area of research involves the investigation of the neuromuscular mechanisms underlying abnormal force production in children and adolescents with CP and the development of effective rehabilitation strategies to address these impairments. She has more than 20 years of experience as a physical therapist and has presented her research at more than 20 national conferences. She has been the primary author on several publications in these areas as well as an invited speaker on the use of ultrasound imaging in assessing muscle structural changes after intervention in CP. She and Dr. Bjornson have worked together on several prior projects, including the pilot project described in this application. The Louisiana State University site will be added to the study after initial IRB approval by SCH.

25.2. Other resources available to conduct the research:[79]

Feasibility:

The Neurodevelopmental Clinic/Birth Defects, Rehabilitation Medicine and Rehabilitation/Orthopedic clinics at SCH are interdisciplinary clinics that children with cerebral palsy, spina bifida, and other neurodevelopmental disorders. These clinics see approximately 350-450 ambulatory children with cerebral palsy each year. Dr. Bjornson has conducted several prior studies with this study population. Enrollment goals in prior studies, and the pilot study (with similar protocol) were met, indicating minimal issues with recruitment. The proposed enrollment numbers for this study are adequate for the available populations.

The Neurology, Orthopedic, and Interdisciplinary Cerebral Palsy clinics at Children's Hospital New Orleans will be primarily used for recruitment in addition to other local outpatient physician and therapy clinics. Dr. Moreau has conducted prior studies with this study population. The proposed enrollment numbers for this study are adequate for the available populations.

Facilities:

- The Behavior and Development Lab at SCH is a laboratory centrally located on the 4th floor at "Jack R. MacDonald Building " (2001 Eighth Ave Seattle, WA). The BDL includes a clinical space with a waiting room, four meeting and observation rooms and an additional medical examination room. These rooms will be employed for intervention and/or assessment study visits for this protocol housing the treadmills, exam tables and Biodex machine.
- The study team at SCH has offices at the downtown campus in which to conduct research activities.
- The LSUHSC-NO Department of Physical Therapy has dedicated research laboratory space for Dr. Moreau, totaling 879 square feet, and includes the following: Muscle Performance Laboratory, Human Performance Laboratory, and laboratory space dedicated to ultrasound imaging. In addition, an outpatient physical therapy clinic space of 2,097 square feet is used for combined research and clinical practice. All facilities are located on the 7th floor of the School of Allied Health building. The study team at LSUHSC-NO has offices at this location on the 7th floor.
- Data management and analysis will take place at the University of Washington Urban Form Lab. The lab is equipped with several high-end Windows PC workstations, a CenOS Linux server, and RAID storage devices. Storage and analysis of data will be accomplished using free and open source software (PostgreSQL/PostGIS for storage and analysis; R for analysis and preparation of derived analytic data sets and visualizations) as well as ArcGIS for spatial analytics and mapping. Computing resources are more than sufficient for the target of 36 subjects measured for one week over two measurement waves.

Other Resources:

- Dr Bjornson has access to StepWatch accelerometers and processing software with over 20 years of experience monitoring walking activity in

children/youth with and without physical disability. She has access to GPS devices and processing software with 5 years of experience of dual monitoring with both the StepWatch and GPS in ambulatory children with cerebral palsy Dr Bjornson will be responsible for processing of all StepWatch data and will train study staff in donning, subject education and calibration.

- Assessors will be doing baseline, V2, V3 and V4 assessments in the lab at Jack R. MacDonald Building. This includes height, weight, physical exam, biodex muscle performance testing of quadriceps strength and power, walking tests and donning/instruction in use of StepWatch pedometer and GPS which is sent home with the participant at each assessment visit.
- Interventionists will be providing the intervention of either short-burst locomotor treadmill training (SBLTT) or traditional locomotor treadmill training (TLTT) as participant is randomized. These sessions will last ~ 1 hour and will occur in the participant's home. Interventionists are trained by the PI to competency in both SBLTT and TLTT. The PI or study staff attend all first intervention visit for each interventionists and at least 10% of all home-based interventions.

26. Coordinating Center Procedures

26.1. Coordinating center institution:

SCH will serve as the coordinating center for the study. Additional sites will be added after initial approval by SCH IRB.

26.2. If Seattle Children's is the coordinating center:

26.2.1. Process to ensure communication among sites:[80]

Dr. Bjornson will communicate regularly with Dr. Moreau via email, at least bi-weekly telephone conference calls, and an annual visit to the LSU-HSCNO site. The study coordinators at each site will likewise communicate at least weekly to ensure version control of all study documents, communication of protocol changes and any adverse events, and any other issues that may arise.

26.2.2. Process to ensure all site investigators conduct the study according to the IRB approved protocol and report all non-compliance:

All study personnel with participant contact will be required to complete human subject certification prior to study initiation. To confirm intervention/assessment fidelity within and between the two study sites, Research Interventionists/Assessors will be trained at each site by the PIs per standard operating procedures (SOP) based on study protocol. Training logs of dosing/training parameters for each session will be recorded. Research Interventionists/assessors must reach 100% performance and completion prior to study initiation. Study visit procedural checklists will document consistency of specific study tasks for both the intervention and assessment visits with monthly monitoring by the PIs. The PIs will observe

10% of assessment and intervention visits to monitor fidelity of intervention and assessment procedures and provide real time feedback. If performance falls <95%, the interventionist will repeat training. Dr. Bjornson will travel annually during years 1-4 to confirm fidelity of assessment and interventions with LSU-HSCNO site. All non-compliance will be reported to the SCH IRB, which will serve as the IRB of record for the study.

26.2.3. Process to ensure all required approvals are obtained at each site:

SCH will serve as the coordinating center for the study, and will also serve as the IRB of record. After initial approval at SCH, LSU-HSCNO will be added as a site via modification. All required approvals will be completed at SCH and communicated to the study team at LSU-HSCNO.

26.2.4. Process to ensure all sites are informed of any problems and/or interim results:

The study teams at SCH and LSU-HSCNO will communicate at least biweekly by phone to ensure both sites are informed of any problems and interim results.

27. International Center for Harmonization of Good Clinical Practice (ICH-GCP)

27.1. If you have committed to conducting the described study per ICH-GCP, check this box: ☐[81]

- This is generally applicable for contracts with industry-sponsored studies or sponsor protocols. See your contract/agreement or Sponsor Documentation if you are unsure.
- Note that completing GCP training is a separate activity and does not automatically mean that you have committed to conducting the study per ICH-GCP.
- **If you check the box, upload a current curriculum vitae (CV) for the PI to the "Other Attachments" section of the "Local Site Documents" SmartForm.**

[1] Include information if this protocol is associated with other IRB-approved studies (e.g. is this application the next part/phase of a previously approved application.

[2] In clinical trials, an endpoint is an event or outcome that can be measured objectively to determine whether the intervention being studied is beneficial. Some examples of endpoints are survival, improvements in quality of life, relief of symptoms, and disappearance of the tumor.

[3] Include information on a drug or biologic in this section if: (1) the study specifies the use of an approved drug or biologic; (2) the study uses an unapproved drug or biologic; (3) the study uses a food or dietary supplement to diagnose, cure, treat, or mitigate a disease or condition; or (4) data regarding subjects will be submitted to or held for inspection by the Food and Drug Administration (FDA). Only include information on a device in this section if: (1) the study evaluates the safety or effectiveness of a device; (2) the study uses a humanitarian use device (HUD) for research purposes; or (3) data regarding subjects will be submitted to or held for inspection by the FDA. Please note that mobile medical applications may meet the definition of a device – see FDA Guidance.

[4] See the Investigator Manual HRP-103 for sponsor requirements for FDA-regulated research.

[5] Explain what IND exemption category applies to the drug and why. Note that a drug is not exempt from an IND unless all criteria for one category are met. See "HRP-306: Drugs" for more information.

[6] Explain what IDE exemption category applies to the device and why. Note that a device is not exempt from an IDE unless all criteria for one category are met. See "HRP-307: Devices" for more information.

[7] Explain why the device is NOT a significant risk device. A significant risk device means an investigational device that: (a) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; (b) is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; (c) is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or (d) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

[8] Be sure to indicate if controls will be included and include information about why control arms are ethically acceptable.

[9] Describe all of the research procedures being performed. Be sure to make it clear which procedures apply to each subject population. When applicable, describe how research procedures differ from standard of care and/or affect standard of care. Describe any audio/video recording that will be involved.

[10] Attach all surveys, scripts, and data collection forms to the "Supporting Documents" page.

[11] Include information about the frequency of data collection.

[12] See HRP-001 - SOP – Definitions for definition of banking. Type N/A if N/A. If the data is subject to NIH Genomic Data Sharing Policies (e.g. you will submit data to dbGaP, NDAR, FITBIR), indicate here.

[13] If applicable, include a list of identifiers that will be banked.

[14] Be general (e.g., researchers' lab, clinic, etc.)

[15] Generally, data and/or biospecimens should be released in a coded, non – identifiable manner.

[16] Include a description of the process used to verify and document that any required approvals have been obtained prior to release of data/biospecimens from the bank.

[17] You can allow for use for broad purposes

[18] This includes putting results and/or data in the subject medical records.

[19] If your population will differ from the representative population where the study will take place (e.g., race, ethnic group, or gender), provide a rationale for the differences.

[20] If you check a box below, be sure to include the additional safeguards associated with the population.

[21] Refer to HRP-416 CHECKLIST: Children.

[22] If the study is minimal risk, explain why. Must also include, as applicable: (1) why direct benefits are anticipated, (2) why risks are justified by anticipated benefit and/or the relationship between risk and prospective benefit compared to available alternatives, (3) why risk represents only minor increase over minimal risk, (4) how study procedures are reasonably commensurate with those inherent to the child's actual or expected conditions, (5) whether the interventions/procedures are likely to yield generalizable knowledge about the participant's condition and why it is of "vital importance" to understanding or amelioration of the participant's underlying disorder or condition, and (6) an explanation of what alternative methods/approaches were considered to make the above assessments (as applicable).

[23] This includes subjects and their parent(s)/LAR.

[24] This population may be wards of the state or any other agency, institution, or entity. Refer to HRP-416 CHECKLIST: Children, Section 6, for additional guidance on required considerations for this population.

[25] This refers to both cognitive impairments and adults who are incapacitated for any other reason. As applicable, refer to HRP-417 CHECKLIST: Cognitively Impaired Adults.

[26] Refer to HRP-413 CHECKLIST: Neonates and HRP-414 CHECKLIST: Neonates of Uncertain Viability.

[27] Refer to HRP-412 CHECKLIST: Pregnant Women.

[28] Refer to HRP-415 CHECKLIST: Prisoners

[29] Indicate how you will ensure that there is no coercion or undue influence

[30] A subject is considered "enrolled" when they consent to be in the study.

[31] Only applicable for multisite studies.

[32] i.e., numbers of subjects excluding screen failures.

[33] Payment for participation is not considered a benefit.

[34] For example, data will be double entered, data will be reviewed by another study team member to ensure accuracy, etc.

[35] If your study is multisite and there are differences in how confidentiality will be maintained by the coordination center and our local site, this should be explained in this section (e.g. local site will have samples that are linked to a person's name, but the coordination center will only receive coded samples without any links). Confidentiality regarding use of Social Media will be explained in a protocol section below.

[36] Applicable for studies that present more than minimal risk.

[37] Include information about who (describe in terms of role or group) will review the data.

[38] This should be specific to the social media you are using for the research.

[39] All communications that are directed towards subjects and specific to a particular study will require prior IRB review and approval. All non-IRB reviewable communications can be described in general terms by category – news stories, relevant publications – and representative examples of each can be provided.

[40] Applicable if the research involves more than minimal risk to subjects. If minimal risk, this section is N/A.

[41] If this is a multicenter study and subjects will be recruited by methods not under the control of the local site (e.g., call centers, national advertisements) those methods should also be described here.

[42] "Privacy interest" refers to a person's desire to place limits on whom they interact or whom they provide personal information.

[43] For example: medical records, CIS, clinical databases, other study records. If the study will access PHI for recruitment purposes without prior authorization from subjects, please address this in the HIPAA Authorization section below.

[44] Attach copies of these documents to the Recruitment Materials section of the study SmartForm. For printed advertisements, attach the final copy. For online advertisements, attach the final screen shots (including any images). When advertisements are taped for broadcast, send the final audio/video tape to IRB@seattlechildrens.org. You may attach the wording of the advertisement to the SmartForm prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.

[45]Include how you will ensure that subjects and/or their parent/legally authorized representative have sufficient opportunity to discuss and consider whether or not to participate in the research. .

[46] "Privacy interest" refers to a person's desire to place limits on whom they interact or whom they provide personal information.

[47] This section describes the way(s) in which the processes for this study will not follow Seattle Children's SOP.

[48] See HRP-090, HRP-091, and Investigator Manual HRP-103 for more information.

[49] Note the Short Form Consent may only be used when certain conditions are met. See HRP-091 for requirements for Short Form consent form use.

[50] Seattle Children's IRB prohibits the exclusion of non-English speaking populations from research unless there is sufficient justification for the exclusion. See Investigator Manual HRP-103 for more information.

[51] For research conducted in the state, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "children." The age of majority in Washington is 18; however, sometimes younger children have ability to consent for certain types of care (e.g. sexual reproduction/health; mental health; drug/alcohol treatment). For research conducted outside of the state, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of "children" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)." If the sites in other states in the study are conducting their own IRB review, you do not need to worry about this--type N/A. If you are conducting research and are actively recruiting participants outside of Washington who are NOT coming to SCH to give consent and who will be covered under SCH IRB approval, this section should be addressed in your protocol.

[52] For minimal risk studies and greater than minimal risk studies that offer a prospect of benefit, the IRB generally requires one parent to provide permission for the child to participate.

[53] If parental permission will not be obtained, please address this in the Waiver or Alteration of Consent Process below.

[54] See HRP-013 for more information.

[55] The IRB generally follows the following guidelines for written assent: children 7-12 should provide written assent on the "simple" assent form (HRP-502G); children 13-17 should provide written assent by co-signing the parental permission form (HRP-502A). The IRB will consider other assent scenarios (e.g. verbal assent for some or all children; not requiring assent for some or all children; or waiving assent): please provide details about the plan for your study. See HRP-090 and HRP-416 for more information on waiving assent and when assent is not necessary.

[56] See Appendix A-13 of the Investigator Manual HRP-103 for requirements for re-consent at age 18. If you think you meet the conditions for a waiver at 18, please address this in the Waiver or Alteration of Consent Process below.

[57] See "HRP-417 Cognitively Impaired Adults" for further information.

[58] For example: durable power of attorney for health care, court appointed guardian for health care decisions, spouse, and adult child. If you are following HRP-013 in order to make this determination, simply state that in this section. For research conducted in the state, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "legally authorized representative." For research conducted outside of the state, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this research. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of "legally authorized representative" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)." If the sites in other states in the study are conducting their own IRB review, you do not need

to worry about this--type N/A. If you are conducting research and are actively recruiting participants outside of Washington who are NOT coming to Washington to give consent and who will be covered under SCH IRB approval, this section should be addressed in your protocol.

[59] The IRB may allow the person obtaining assent to document assent on the consent document.

[60] For example: consent/parental permission will not be obtained, required information will not be disclosed, the research involves deception, waiver for participants who turn 18, waiver for information collected about a non-present parent, or other waivers as necessary.

[61] The IRB needs to make all the waiver findings and key to this determination is that the IRB understand why it is not practicable to do the research without a waiver of consent. You need to provide a rationale in order for the IRB to consider whether the waiver criteria are met. See "HRP-410: Waiver or Alteration of the Consent Process" for further information.

[62] Possible reasons might include: a) you are not collecting information that could put subjects or their families at harm, e.g., affect eligibility for insurance, employability, stigmatization; b) you are not collecting information that would alter or affect the subject's care; c) any publication or presentation of research results would be done in a manner that would never reveal an individual's identity either directly or indirectly.

[63] Possible reasons could be: a) inability to locate families because of the lengthy time period over which the records/samples were created; b) many of the subjects whose records, data, or biospecimens will be used may have died and contacting the families about the research could cause harm and anguish to families; c) all eligible patients must be included in the study for the results to be meaningful.

[64] See "HRP 419: Waiver of Consent for Emergency Research" for further information.

[65] This section describes the ways in which the procedures will not be following Seattle Children's SOP.

[66] See "HRP-411: Waiver or Written Documentation of Informed Consent" for further information.

[67] An information sheet template can be found in the Click IRB Library and should be attached to the consent form of the study SmartForm. For internet research, the information sheet can be translated to an on-line format, if desired.

[68] The IRB sometimes requires a script if you are having the consent conversation over the phone rather than in person. Templates for a consent script are available on the IRB website on the Participant Recruitment page and should be attached to the study SmartForm.

[69] PHI is health information that is also identifiable because it includes one or more of the 18 HIPAA identifiers. See Investigator Manual HRP-103 for the list of HIPAA identifiers.

[70] If your study involves using or creating PHI and your only contact with participants is online, you can request an alteration of HIPAA authorization to remove the signature requirement. As an alternative to a waiver of documentation of consent and an alteration of HIPAA authorization, you must demonstrate that the electronic consent signatures are compliant with applicable state/international law (in Washington, see RCW 19.34.300).

[71] For example: altering HIPAA elements for international research.

[72] Possible reason could be: the nature of the research is specific to individuals' health and requires access to individuals' health records.

[73] See "HRP-316: Payments" for further information.

[74] Methods of payment include check, ClinCard, gift cards, etc. Provide details on who will be the recipient of the payment (parent or child).

[75] Reimbursement is used when the subject is paid back for travel expenses such as transportation, food, childcare, or lodging. Reimbursement is generally distributed to person who incurred cost (usually parent) and requires receipts to be submitted.

[76] This could include things like fuel/transportation costs, parking, and/or childcare.

[77] Type N/A if this section does not apply.

[78] Provide enough information to convince the IRB that the principal and/or co-investigator(s) are appropriately qualified to conduct and supervise the proposed research. When applicable, describe their prior clinical experience with the test article or study-related procedures, or describe their knowledge of the local study sites, culture, and society.

[79] For example, as appropriate: (1) Justify the feasibility of recruiting the required number of suitable subjects within the agreed recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit? (2) Describe the time that you will devote to conducting and completing the research. (3) Describe the facilities in which the research will be conducted. (4) Describe the availability of medical or psychological resources that subjects might need as a result of an anticipated consequences of the human research. (5) Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.

[80] Including communication between sites of current study document versions and modifications.

[81] If you check the box, you are required to conduct your study according to the principles outlined at https://www.ich.org/products/guidelines/efficacy/efficacy-single/article/integrated-addendum-good-clinical-practice.html.