LSU Health NEW ORLEANS

School of Allied Health Professions
Department of Physical Therapy

PROTOCOL TITLE:

Power Training Combined with Interval Treadmill Training (PT^3) to Improve Walking Activity in Cerebral Palsy

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Full Protocol: Power Training Combined with Interval Treadmill Training (PT^3) to Improve Walking Activity in Cerebral Palsy

Purpose
The primary purpose of this pilot study is to determine the effect of power training combined with locomotor treadmill training (PT^3) on the primary outcomes of walking performance and capacity in children with CP with functional walking limitations. To identify key muscular mechanisms associated with improved walking mobility, we will examine the effects of training on muscle performance and architecture.

Rationale
Walking ability significantly deteriorates in 50% of ambulatory children with cerebral palsy (CP) beginning in childhood/adolescence. Of those who stop walking, 75% will lose the ability to walk before the age of 25, severely impacting their ability to participate in daily life. Although CP is a non-progressive neurological disorder, the sequela of musculoskeletal impairments is progressive. Strength training is routinely employed in clinical practice to counteract muscle weakness but has not been shown to improve gait speed or other measures of walking capacity. One hypothesis for the lack of improvements in ambulation is the focus of resistance training programs solely on improving muscle strength. Our prior work has documented that muscle power (product of force and velocity) is reduced by 82% as opposed to a 50% decrement in muscle strength. Muscle power is required for functional activities, such as walking, climbing stairs, and transfers, where force needs to be generated quickly in order to accomplish the intended goal. To test the hypothesis that muscle power is a key limiting factor, rather than strength, we previously conducted a randomized clinical trial comparing velocity training (a type of power training) to traditional strength training (Moreau, 2013). Only the velocity training intervention significantly improved gait speed and other measures of functional walking capacity. These improvements were accompanied by increased muscle power and the architectural alterations of increased fascicle length and muscle cross-sectional area. For this proposal, we hypothesize that in order to optimize ambulatory function, it is also essential to practice the task of walking, known as task-specific training. Normal walking activity in children and adolescents consist of short intervals of high step rate activity interspersed with varying intervals of low and moderate step rates. Children with CP are not able to achieve these moderate and high step rates, presumably due to the lack of muscle power generation. Therefore, it is critical that the two approaches be combined in a package of care and that the treadmill training is interval-based in order to approximate walking patterns that are developmentally appropriate and thus, stimulate muscle power generation during walking.

Specific Aims

Aim #1. Determine the immediate and retention effects of power training combined with interval treadmill training (PT^3) on functional walking capacity in ambulatory children with CP.
We hypothesize that a combined impairment and task-specific approach, which targets muscle power deficits specifically, will have a significant effect on functional walking capacity as compared to an equivalent dosage of traditional impairment-based and task-specific approaches. In a randomized clinical trial, 48 ambulatory participants with CP (10 to 17yrs) will receive either PT^3 or an equivalent dosage of traditional strength training combined with traditional treadmill training (comparison group) for 24 sessions, 3 times per week for 8 weeks. Outcomes will be collected at baseline and immediately post-treatment. Short and long-term retention effects will be assessed at 2 and 6 months post. Self-selected gait speed will be the primary outcome with secondary outcomes of fast gait speed, the 1-Minute Walk test and Timed-up-and-Go.

Aim #2. Quantify the effects of treatment on *in vivo* muscle architecture and muscle performance.
We hypothesize that lower extremity muscle power generation is impaired and is responsible for limitations in walking activity, and that PT^3 will result in significant improvements in muscle power that will be explained partly by increases in cross-sectional area and fascicle length. Muscle architecture will be measured with ultrasound imaging, and muscle performance outcomes will be measured with isokinetic dynamometry.

Aim #3. To directly capture the effect of treatment on community-based walking activity and participation, we will use a novel combination of global position system (GPS) and accelerometry.

For this exploratory aim, we hypothesize that improved walking capacity from PT^3 will enhance community-walking activity and participation captured in real-world settings. We will use coordinate data from GPS devices synchronized with StepWatch accelerometers to directly measure strides per day, stride rates, distance, duration, and location. This novel technology will allow us to better characterize walking activity outside of the clinic/laboratory setting and has far-reaching clinical implications.

Significance and Background

Gait impairments and deterioration in ambulatory children with Cerebral Palsy (CP)

Cerebral palsy (CP) is a nonprogressive developmental disorder of movement and posture that leads to activity limitation caused by damage to the immature brain before, during, or shortly after birth (Rosenbaum, 2007). CP occurs in 3.6 per 1,000 live births or 1 in 278 children, according to the Centers for Disease Control and Prevention (CDC) and is the most common physical disability originating in childhood. The CDC reports the incidence of CP is higher than childhood cancer, hearing and vision loss, spina bifida, hemophilia, fetal alcohol syndrome, and cystic fibrosis (Yeargin-Allsopp, 2008).

Although the initial brain insult is nonprogressive, CP is a lifelong disorder due to secondary musculoskeletal problems and associated activity limitations that progress into adulthood. Gait disturbances are an activity limitation that is a hallmark characteristic of CP. The progressive deterioration of walking ability begins in early adolescence and is a serious health concern. Deterioration in walking occurs in 50% of ambulatory children with CP (Jahnsen, 2004; Opheim, 2009). Of those who stop walking, 75% report walking cessation before the age of 25 while 50% report cessation before 15 years of age (Andersson & Mattsson, 2001; Murphy, 1995). Gait speed must be adequate in order for children with CP to keep up with their peers, participate in social activities, and lessen the deterioration of walking ability. Loss of independence associated with gait deterioration can lead to lower quality of life, including decreased participation in the community. Therefore, It is imperative that interventions to improve gait speed and walking ability be implemented prior to the deterioration of walking ability. Throughout the proposal, we will use the term “ambulatory children with CP” to refer to children who are categorized in Gross Motor Function Classification System (GMFCS) levels I, II, and III (Rosenbaum, 2008). These children are able to either walk independently (level I), independently but require handrails to climb stairs (level II), or with an assistive device (level III), such as a walker or crutches.

Task-specific training alone for improving walking is not sufficient

Task-specificity refers to repetitive training that specifically targets the task that one is trying to rehabilitate or improve and is based on motor learning and motor control principles related to use-dependent plasticity (Schmidt & Lee, 2011; Nudo, 2003). For example, treadmill training with and without body weight support has been advocated in order to practice the task of walking while maximizing the number of steps taken per session when compared to overground walking (Dobkin, 1999). Despite the fact that task-specificity is considered to be one of the key ingredients for effective rehabilitative therapies, task-specific training alone has not been shown to be superior to other physical therapy interventions for improving walking. This finding is consistent across multiple populations, including CP, stroke, and spinal cord injury (Damiano & DeJong, 2009; Duncan, 2011; Charalambous, 2013; Mehrholz, 2012; Mehrholz, 2014). The limitation of task-specific training for individuals with CP is the reduced capability of performing repeated practice of a task due to underlying neuromuscular deficits. Furthermore, the implementation of assistive devices, such as treadmill training with body weight support or robotic training, to make it “easier” to practice walking decreases muscle activation (van Hedel, 2006), which only further exacerbate the underlying neuromuscular deficits.

Strength training is not effective in improving walking in ambulatory children with CP

Because muscle strength has been shown to be highly correlated with gait speed and walking ability and is a significant impairment in children with CP (Damiano & Abel, 1998; Ross & Engsberg, 2007), strength training is a routinely administered intervention that is considered to be a component of standard of care for children with CP. However, results of 2 systematic literature reviews (Scianni, 2009; Moreau 2016), including recent randomized controlled trials (RCTs) (Scholtes, 2012; Taylor, 2013), confirm that despite moderate increases in muscle strength, strength training is not effective in improving gait speed or other measures of walking ability in CP. A meta-analysis conducted by our research group documented a negligible effect of strength training on gait speed with an overall standardized effect size of 0.06 ($p=0.51$) (Moreau, 2016).

Power training is effective in improving walking in ambulatory children with CP

Muscle weakness has been considered one of the primary impairments contributing to activity limitations in children with CP. However, other aspects of muscle performance, such as muscle power and rate of force

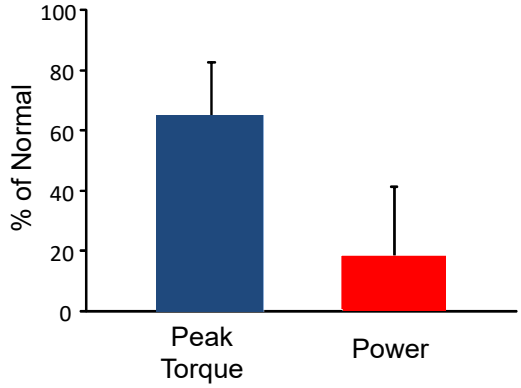

Figure 1. Knee extensor strength (peak torque)(Nm) and power (watts) in CP are 64% and 18% of age-matched TD children.

development (RFD) have received far less attention, yet are important for the performance of functional activities. Whereas strength refers to the maximum amount of force or torque that a muscle can generate, muscle power refers to the ability to generate the greatest amount of force as fast as possible and is the product of force and the velocity at which the force is produced. Strength is only concerned with maximal force or torque, whereas power involves both strength and the velocity of the movement. RFD refers to the rate at which force is developed but is distinctly different from muscle power in that it can only be calculated during maximum isometric contractions whereas power can be calculated during dynamic movements. These distinctions are important because most daily activities, such as transfers, walking, and moving from a sitting to a standing position, do not require maximal muscle strength to complete the task. Rather, these activities require force to be generated quickly in order to accomplish the intended goal. Although lower extremity muscle weakness is pervasive in CP and has been reported to be decreased by as much as 40% to 60% (Wiley & Damiano, 1998; Ross & Engsberg, 2002), we have documented that RFD and muscle power are more significantly impaired than muscle strength. We measured muscle power, RFD, and muscle strength in cohorts of ambulatory children with CP compared to an age-matched typically developing (TD) cohort. On average, peak torque, as a measure of strength, was decreased by 36% to 50%, whereas RFD and muscle power were decreased by 70% and 82%, respectively, compared to TD children (Moreau, 2012; Moreau, 2013) (Figure 1). Furthermore, lower muscle power was strongly associated with walking limitations. Our work demonstrates the importance of muscle power for walking as well as the performance of functional activities.

To examine the influence of muscle power on walking speed and functional mobility, Dr. Moreau conducted an RCT to compare the effects of high-velocity training (a type of power training) versus traditional strength training of the quadriceps on muscle architecture and performance, walking speed, and functional walking mobility (Moreau, 2013). This trial was conducted in ambulatory children with CP (GMFCS I-III), ages 10 to 18. After 8 weeks of training (24 sessions), only children undergoing high-velocity training improved their peak power production, increased their gait speed, and distance ambulated. Participants who underwent strength training (low velocity) did not improve gait speed or distance. In addition, this study was the first to document differential muscle architectural adaptations in CP between the two types of training, thus illustrating that muscles in CP are highly plastic and are capable of responding to specificity of training stimuli. Although cross sectional area (determinant of force production) increased significantly after both strength and high-velocity training, rectus femoris fascicle (fiber) length, which is the primary architectural determinant of muscle shortening velocity, significantly increased after high-velocity training but decreased after strength training ($p=.012$). This work provides direct support for the hypothesis that deficiencies in muscle power are responsible for walking limitations in CP and can be remediated to produce clinically significant improvements in walking speed and functional walking ability. Furthermore, increases in muscle power can be explained in part by muscle architectural adaptations that are specific to resistance training at higher velocities of movement. This is a central component of power training that distinguishes it from strength training. Therefore, the underlying premise for this study is that deficits in lower extremity muscle power generation are a key limiting factor for walking in children with CP. Thus, remediating muscle power deficits will lead to improved walking abilities as evidenced by our prior work. Building on this prior work, we postulate that in order to maximize ambulation potential, participants must also practice the task of walking in order to learn how to use muscle power generation during the task of walking. We hypothesize that this combined impairment-based (power training) and task-specific (treadmill training) approach (PT3) will provide the optimal stimulus to increase walking activity and participation.

Treadmill training should be developmentally appropriate and reflect children's activity patterns rather than adult patterns

TD children and adolescents demonstrate physical activity patterns that are markedly different from adults. TD children engage in periods of intense bursts of physical activity (10-15 seconds) followed by less intense activity or rest, representing similar patterns to interval training (Armstrong, 1990; Bailey, 1995; Bjornson, 2007). In contrast, adults typically engage in steady-state activity of a low to moderate intensity (Tudor-Locke,

2012). Despite this, treadmill training protocols for children with CP have been developed from adult protocols, which are time or endurance-based, and therefore, are not appropriate for children and adolescents.

Gait speed and stride rate (strides/min) are common temporal-spatial parameters of walking intensity (Barreira, 2012). Dr. Bjornson reported day-to-day walking activity using stride rate monitors (Bjornson, 2010; Bjornson, 2014). Activity patterns for children with CP do not approximate the same intensity levels as those of TD children. Children with CP spend the majority of their time ambulating at low intensity levels (low stride rates < 30 strides/min) and have difficulty ramping up to medium (30-60 strides/min) and high stride rates (> 60 strides/min) (Bjornson, 2014). In addition, children with CP walked less with a significantly lower number of overall strides per day than TD youth. Therefore, we propose that treadmill training should be developmentally appropriate, reflecting the walking patterns of children rather than adults. We will address these walking limitations with "interval" treadmill training. Our interval treadmill training protocol consists of short bursts of fast walking (i.e, higher strides/min) alternating with lower to moderate intensity (i.e., lower to medium stride rates) in order to mimic age-specific walking activity that is developmentally appropriate. We also hypothesize that the inability of children with CP to ramp up to higher stride rates is due to deficits in muscle power generation. Therefore, PT3 will remediate muscle power deficits and provide the underlying muscular resources and task-specific training necessary to achieve moderate and high stride rates during walking.

Community-based as well as clinic-based outcome measures of walking activity and participation

According to the World Health Organization's International Classification of Functioning, Disability and Health (ICF), activity is defined as the execution of a task by an individual and participation refers to the involvement of an individual in a life situation. Activity and participation can be examined by capacity- and performance-based measures. Walking capacity is typically measured in the clinic and is representative of what the person is capable of doing. Walking performance, on the other hand, represents what a person actually performs in everyday life (World Health Organization, 2001). Although it is important to use valid, reliable, and standardized outcome measurements of walking capacity, such as gait speed, these outcome measures must be supplemented in order to determine overall effectiveness of an intervention, which refers to walking performance under real-world conditions. Bjornson et al. (2013) reported that daily walking performance measured with the accelerometry is positively correlated with participation in mobility-based life habits. Specifically, in persons with CP, reduced participation in daily activities appears related to the inability to achieve high stride rates. The proposed study will measure outcomes of both walking capacity in the clinical setting as well as walking performance out in community settings using accelerometry paired with global position system (GPS) monitoring. The StepWatch accelerometer precisely measures average strides per day and stride rate; however, such measures lack information on the location of walking. Linking StepWatch data with GPS allows measurement and characterization of the actual locations where walking activity occurs. This novel combination of measurement technology provides a method for assessing changes in performance and participation in real-world settings.

Preliminary Studies

Comparison of Power Training to Interval Treadmill Training

Preliminary data from our research team's current R21 (HD077186) investigating the effects of interval treadmill training in ambulatory children with CP (n = 10) showed moderate changes from pre to post-training in self-selected and fast gait speed of 0.05m/s and 0.09m/s, respectively, after 20 sessions. However, our published data from an RCT investigating high-velocity or power training in ambulatory children with CP (Section A.4) demonstrated greater changes in self-selected and fast gait speed of 0.10m/s and 0.12m/s, respectively, after 24 sessions of training ($p<0.05$) (Moreau, 2013) . These improvements met or exceeded the minimal clinically important difference (MCID) of 0.10m/s reported for gait speed in CP (Oeffinger, 2008).

Combined Power Training and Interval Treadmill Training (PT3)

We hypothesize that combining the two approaches (PT3) will provide the optimal stimulus to improve walking and will lead to significant gains in the primary outcome of gait speed. The PI's published power training program (Moreau, 2013) (i.e., high-velocity training) was conducted on an isokinetic dynamometer, which is an expensive, specialized piece of equipment that is not found in many therapy clinics. This protocol targeted the quadriceps muscle group specifically. Peak torque of the quadriceps has been shown to be highly correlated to gait speed and improved kinematics in CP (Damiano, 1995; Damiano, 2001; Moreau, 2012). To date, Moreau (2013) is the only power training study in CP to report statistically and clinically significant improvements in gait speed and muscle power and targeted the quadriceps. It is also the only RCT to directly compare power training to strength training in CP in a controlled manner that isolated the dosing ingredients that distinguish power training from strengthening, i.e. velocity of movement and load. The power training

protocol proposed in PT3 advances the prior protocol (Moreau, 2013) by 1) targeting the quadriceps primarily in addition to other muscle groups that are important for gait, including the hip extensors and ankle plantarflexors; 2) using a closed kinetic chain exercise (i.e., single and bilateral leg press), which is considered to be more functional and minimizes hamstring recruitment, while adhering to same dosing guidelines; and 3) using clinically feasible, less-costly equipment in order to provide easier translation to clinical practice.

PT3 Pilot data: PT3 was conducted in hourly sessions 3 x per week for 8 weeks (24 sessions total). (See Approach for detailed protocol.) Our pilot data for PT3 documented a mean increase of 0.16m/s and 0.17m/s in self-selected and fast gait speed, respectively, after 24 sessions of PT3, resulting in a large effect size that exceeds the MCID of 0.10m/s. Distance ambulated as measured by the 1MWT increased on average by 9.8 meters, representing a large effect size that exceeds the average MCID of 7.8 meters (Hassani, 2014). These gains exceed those from either power/velocity training or interval treadmill training alone. Our pilot data also demonstrated that muscle power collected during the performance of a bilateral leg press increased by 52% on average and was accompanied by a 9% increase in rectus femoris cross-sectional area and a 15% increase in fascicle length, as measured by ultrasound imaging. Collectively, our published data (power training) and preliminary data (interval treadmill training R21 and PT3) support our hypotheses for Aims 1 and 2 and provide evidence of the feasibility of both the testing (outcome measures) and intervention protocols.

PT3 and Walking Activity and Participation in Daily Life

Walking limitations in children with CP have been documented to have a negative influence on their level of participation in daily life (Fauconnier, 2009; Lepage, 1998). To date, measures of participation have been primarily obtained via child and/or parental self-report questionnaires. Responsiveness to change and the ability to show statistical significance after an intervention has been very limited due to the subjective nature of these self-reports. In fact, out of 131 studies included in a systematic literature review of interventions for children with CP, only 5% (n=7) reported outcomes for participation and only 30% for activity (Novak, 2013). In this state of the evidence paper, Novak et al. concluded that there are no proven effective interventions for addressing participation and that research and funding should be dedicated to this important area.

Participants in the pilot study for PT3 reported positive changes in participation and quality of life through the self-report questionnaires, Activities Scale for Kids performance version (ASKp) and the Patient Reported Outcomes Measurement Information System (PROMIS) Pediatric Profile (49 v1.0). For example, 2 participants reported average weekly pain scores of 6/10 and 3/10 on the PROMIS that reduced to 0/10 and 1/10, respectively, after PT3. The reduction in pain was accompanied by self-reported increases in walking activity and participation with peers and siblings in everyday life (ASKp). Similarly, at baseline, one participant ambulated with a walker at home but used a wheelchair primarily in the community and at school. After 8 weeks of PT3, he reported that he ambulated independently without an assistive device at home and 50% of the time in the community with a reduction in pain from 6/10 to 0/10, used a walker at school and for long distances, and no longer used a wheelchair. Although we were able to capture clinically meaningful changes in functional walking capacity (> MCID) with our standardized measures of self-selected and fast gait speed, 1 minute walk test (1MWT), and Timed-Up-and-Go (TUG), these measurements were obtained in the clinic and did not necessarily reflect the change in activity and participation experienced in daily life.

For Aim 3, we will implement an exploratory novel combination of GPS and walking accelerometry to measure the effects of treatment on community-based walking activity and participation captured in day-to-day life, thereby quantifying changes in community walking and mobility-based participation using objective data. Our research team has piloted this novel combination of accelerometry-based walking activity and GPS in ambulatory children with CP (GMFCS levels I, II, III) who underwent 20 sessions of interval treadmill training, which is one of the components of PT3 (R21 unpublished data). Average strides/day increased by 1441 strides/day post-training. The percentage of strides per day in medium and high stride rates increased post-training, approximating levels of TD children. These changes are reflective of walking patterns in TD children and adolescents, consisting of bursts of moderate and high step rate activity throughout the day. Figure 2 displays synchronized GPS and StepWatch data for a child with CP at GMFCS level I measured over 1 day. Synchronized GPS and StepWatch data quantified stride rates (no walking, low, medium, high stride rates) by location (soccer field, home or school). For this child, medium stride activity occurred at school and a soccer field, with no high stride rate activity documented. Thus, our preliminary data supports Aim 3 by documenting that our proposed outcomes with this novel methodology are feasible and sensitive to detecting clinically relevant information, such as the amount and location of strides and stride rate intensity levels.

Methods

Participant Characteristics

We will enroll 48 children with bilateral spastic CP (spastic diplegia) between the ages of 10-17 years and within GMFCS levels I, II or III (i.e., ambulatory). Although children in GMFCS level IV could benefit from the intervention and are considered non-community level ambulators, we chose to include only levels I-III in order to decrease the heterogeneity of clinical presentation. Only children with bilateral spasticity as their primary movement disorder will be enrolled due to their documented muscle power limitations and to control for heterogeneity. This age range was chosen because of the documented deterioration in walking ability that begins in adolescence. The PI has conducted power training in children with CP in this age range and found it to be feasible and motivating for this age group. Participants who have undergone orthopedic or neurosurgery less than 12 months prior to enrollment, injection therapies (phenol, botulinum toxin) less than 3 months prior, or are lacking greater than 25 degrees of knee extension will be excluded to remove confounding effects.

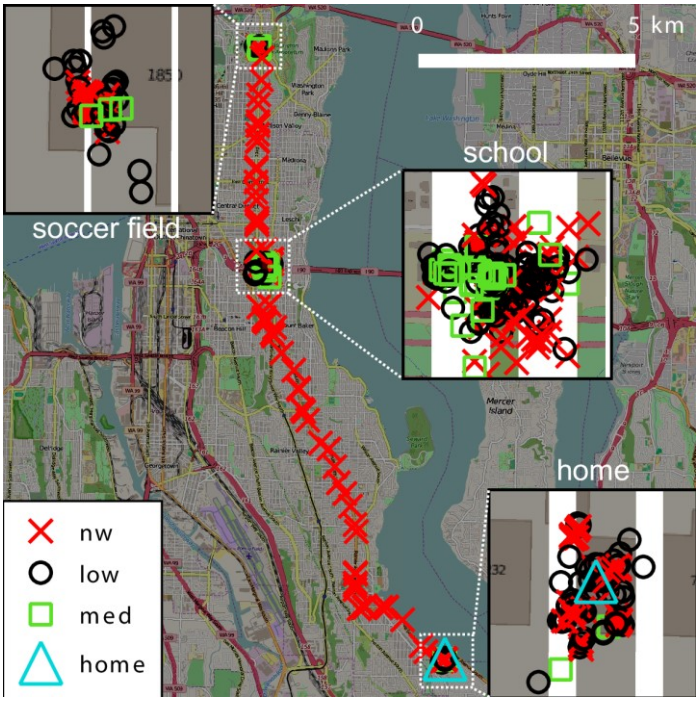

Figure 2. GPS/StepWatch synchronization map for a child with CP (GMFCS I). X = no walking (nw); O = low stride rates; □ = medium stride rates; Δ = home

Subjects: 48 ambulatory children with cerebral palsy between the ages of 10 and 17 years (24 per site - LSUHSC – New and Seattle Children's).

Settings: Intervention and testing will be performed at 2 clinical sites: LSUHSC Department of Physical Therapy research and clinical laboratory space supervised by Dr. Noelle Moreau (PI); Seattle Children's Research Institute Child Development Laboratory and Physical Therapy clinic supervised by site PI, Dr. Kristie Bjornson.

Eligibility:
Inclusion criteria:
1.) Ages 10 – 17
2.) Diagnosis of primary spastic cerebral palsy
3.) Ambulatory with or without an assistive device (i.e., within Gross Motor Function Classification System Levels I – III)

Exclusion criteria:
1.) Orthopedic surgery or neurosurgery less than 12 months prior to enrollment
2.) Injection therapies to lower extremity muscles (phenol, botulinum toxin) less than 3 months prior to enrollment
3.) Lacking more than 25 degrees from full knee extension

Study Design and Randomization

This is a multi-center RCT. We will enroll 48 participants (24 per site). Participants will be randomized to receive either PT3 or the comparison intervention. We will employ a randomized block design with two blocking factors, GMFCS level and study site. This will address any clinical heterogeneity of outcome measures by functional level and study site. Outcomes assessors will be blinded to group assignment. The study biostatistician, Dr. Mercante, will generate randomization sequences in accordance with the study design.

Recruitment

Participants will be recruited from the local hospitals and physical therapy clinics. Colleagues will be sent emails and/or letters describing the purpose of the study and criteria and asking them to share the study

information and my contact information with their patients. IRB-approved letters of support from colleagues, study flyer, and a provider approach template letter will be utilized for recruitment.

Identification of potential participants may also occur through the Louisiana Children's Medical Center electronic medical record (EMR) system known as EPIC in conjunction with Children's Hospital New Orleans (CHNOLA). A request from LSUHSC personnel will be sent to CHNOLA's Director of Research Operations using the previously mentioned inclusion criteria, desired PHI (i.e. first and last name, date of birth, address, etc.), and ICD-10 codes. The CHNOLA Director of Research Operations will create an IT Ticket and send it to EPIC to have a reported generated with all requested data. After receiving PHI, LSUHSC personnel will perform a basic review of the participant's medical records to identify whether or not the participants meet basic eligibility requirements. Patients identified as a potential participant will be initially contacted by the CHNOLA Site PI (i.e. direct mail, EPIC messages, email, etc.), however all contact thereafter would be handled by the LSUHSC personnel. An approach mailing will include IRB-approved materials, including: approach letter, study flyer, return letter of interest and postage paid envelope to return letter of interest to study staff LSUHSC-NO. Approach email will include IRB-approved materials, including: approach letter, study flyer, and contact information of study staff at LSUHSC-NO.

Protocols and Timeline

Intervention Protocols:

Power Based Approach: Power training combined with interval treadmill training (PT3). Participants will receive 24, 1-hour sessions of PT3 over 8 weeks (3 x per week with minimum of 48 hours separating treatment sessions). Participants will be allowed an additional 2 weeks to make up any missed sessions for a maximum of 10 weeks to complete the 24 sessions. This protocol was based on the National Strength and Conditioning Association (NSCA) resistance training guidelines for children and adolescents for power (Faigenbaum, 2009) and on prior work. The training session will begin with a 5 minute warm-up consisting of any of the following activities, tailored to each participant: walking at self-selected speed, stationary cycling without resistance, or dynamic stretching. Training will consist of unilateral and bilateral leg presses (Total Gym GTS®, San Diego, CA), which will primarily target the quadriceps followed by the hip extensors and plantarflexors. The equipment allows for partial gravity-elimination that can be tailored to each participant depending on his/her initial level of capability. The sled can be positioned from nearly horizontal to approximately a 30 degree incline (Figure 3). Weights will be added to a weight bar to increase resistance. Target load will be 40% to 80% of 1-repetition maximum (1RM) with progression towards 80% according to the NSCA resistance training guidelines for muscle power training (Faigenbaum, 2009). Participants will undergo 1RM testing prior to the first intervention session in order to determine the initial training load. This session will occur a minimum of 48 hours prior to the first intervention session. Our pilot subjects were able to begin training with initial loads varying between 50 to 60% of 1RM. Actual loads will be determined by accounting for the angle of inclination of the sled and multiplying the load by the sine of the angle. Following the warm-up, each participant will perform 3 to 5 submaximal efforts followed by 6 sets of 5 maximum-effort repetitions at the predetermined percentage of 1RM for each leg separately. Instructions for the concentric phase of the leg press will be to "push as fast as possible" with the eccentric portion performed slow and controlled over 1-2 seconds. Performing the concentric phase of movement "explosively" or as fast as possible is a key active dosing ingredient for power training. Following the unilateral leg presses, 6 sets of 5 repetitions of bilateral leg presses will be performed at the predetermined percentage of 1RM.

Figure 3. Power training conducted on a leg press (Total Gym GTS®) in a 12yo subject with CP. The concentric portion of the leg press illustrated here is performed "explosively" or as fast as possible.

To minimize fatigue, 1-2 minutes of rest will be given between sets, and 5 minutes of rest will be provided between power training and treadmill training.

The interval treadmill training portion will include short-bursts (30 seconds) of high speed walking intervals alternating with 30 seconds of low to moderate speed walking. High speed bursts will consist of walking as fast as possible on the treadmill whereas during low to moderate speed intervals, the subject will walk at a comfortable, self-selected speed. Based on pilot data, starting tread speed for high speed walking will be 75-80% of the participant's overground fast gait speed and low speed walking bouts will begin at 75-80% of overground self-selected gait speed. Treadmill speed will be controlled by a therapist and will be modified within and between sessions based on perceived exertion as measured by clinical observation and the Children's OMNI Scale of Perceived Exertion (Robertson, 2005). Total duration of each session will be 20 to 30 minutes with rests as needed. During rests the subject will stand on the treadmill or sit down. If the subject reaches their maximum walking speed, an incline will be applied to treadmill. The overall goal will be to increase fast walking speed during the high speed intervals and to maximize duration (up to 30 minutes) within and between sessions over time. Participants will wear a gait belt with contact guard assistance at all times by the interventionist while walking on the treadmill. If needed (under discretion of the interventionist), participants will wear a harness connected to an overhead frame support for safety and will be allowed to use handrails as needed. The overhead harness will not provide any body weight support; it will only be used for safety. During pilot testing, we determined that the majority of participants preferred the gait belt over the harness. The interval treadmill training protocol is currently being tested as part of Dr. Moreau and Bjornson's R21 (HD077186) and PT3 pilot data.

Comparison intervention (Traditional Approaches): Strength Training Combined with Treadmill Training. During pilot data collection for PT3, each combined power and treadmill training session lasted 60 minutes on average (range: 50 to 70 minutes). Therefore, the comparison group will receive an equivalent dosage of traditional treadmill training plus traditional strength training (up to 30 minutes for each component for a total of 1-hour session) delivered 3 times per week over 8 weeks. Participants will be allowed an additional 2 weeks to make up any missed sessions for a maximum of 10 weeks to complete the 24 sessions. Warm-up, equipment, and procedures for the strength training component will be identical to the power training protocols above except for the dosing ingredients that distinguish power training from strength training (load, volume, velocity), which are based on the NSCA resistance training guidelines for children and adolescents (Faigenbaum, 2009): Target load will be 60% to 85% of 1RM with progression towards 85%; volume will be 3 sets of 8-12 repetitions; both concentric and eccentric motions will be performed at slow and controlled movement speeds over 1-2 seconds. Participants will undergo 1RM testing prior to the first intervention session in order to determine the initial training load. This session will occur a minimum of 48 hours prior to the first intervention session. Traditional treadmill training will consist of steady-state walking at a constant self-selected speed for 20 to 30 minutes with rests as needed. The goal will be to increase the duration to 30 minutes. Initial treadmill speed will be 75-80% of overground self-selected walking speed and will be adjusted as needed to accommodate the participant. Speed will be increased when the subject can walk for 30 minutes on the treadmill. Similar to PT3, participants will either wear a gait belt or overhead harness without body weight support. If the subject reaches their maximum walking speed, an incline will be applied to treadmill.

Fidelity of Interventions: Intervention fidelity across sites will be addressed by in-person training of all intervention therapists by Dr. Moreau employing an intervention visit procedural checklist of visit tasks. Intervention therapists must reach 100% performance and completion prior to study initiation. Training videos and manuals will be provided for reference. Interventionists will complete checklist for every study visit with physical monitoring of intervention visits by the site PI at weeks 1, 4 and 7 for each participant with real-time feedback provided. If performance falls <95%, the interventionist will repeat training.

Testing / Assessment Protocols

Procedures: Outcomes will be assessed pre and post intervention to determine immediate effects of treatment; at 2 months post for short-term retention; and 6 months post for long-term retention (Figure 4). The goal will be to perform the baseline assessment within 1 week prior to the start of the intervention and within 1 week of completing the intervention for the post assessment but must always occur a minimum of 48 hours before or after a training session for baseline and post-assessment, respectively. However, a 2-week window will be allowed for all assessment timepoints.

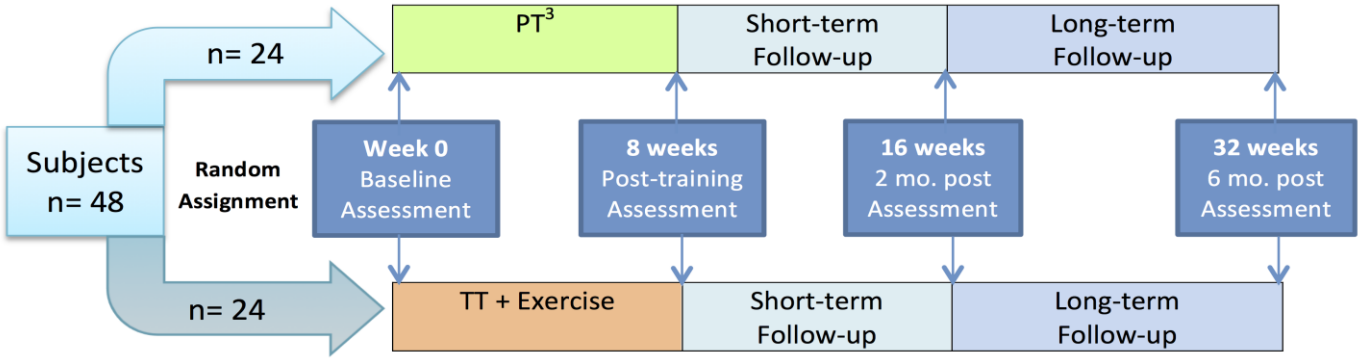

Figure 4. Experimental design for 8-week interventions and timeline for assessment. TT = treadmill training

Outcome Measures: Assessors will be blinded to group assignment.

1) Clinical Assessment: Anthropometric measurements (height, weight, leg length, lower leg length, thigh length) will be collected. Knee and ankle range-of-motion will be measured. The child will be classified according to the Gross Motor Function Classification System (GMFCS), levels I, II, or II.
2) Walking Capacity: Self-selected and fast walking speeds will be calculated from the 10-m Walk Test as the average of three trials each (33). The time that it takes to walk a distance of 10 meters is recorded. Walking capacity will also be measured with the 1-minute walk test (1MWT), in which the distance the child can walk as fast as possible in one minute is calculated (34). For the Timed up and Go (TUG) test, the child is asked to stand up from a standard chair and walk a distance of approximately 10 feet (measure as 3 meters), turn around and walk back to the chair and sit down again (46). All measures have been widely used in this population in clinical settings and shown to be reliable measures (33-34, 46). Participants will also be videotaped while walking on the treadmill from the front/back view and a side view. The walking videos will be analyzed for quality of gait using the Edinburgh Visual Gait Score.
3) Community Walking Performance Activity: The StepWatch (Song, 2006) is a pager sized, 2-dimensional accelerometer. Locational data will be collected for all participants using Qstarz BT-Q1000XT GPS data loggers (Taipei, Taiwan), which collects instantaneous latitude, longitude, altitude, speed, distance from previous point, and precision estimates at configurable intervals. Participants will wear both devices on the lateral side of the ankle inside a knit cloth cuff during all waking hours for 7 days, except during swimming, bathing, and sleeping per published protocol. Five days will be used for data analysis (4 weekdays and 1 weekend day) (Bjornson, 2010; 2011). The StepWatch will be configured to aggregate data at the same rate as the GPS data (1-minute epochs). The device data will be synchronized and joined using timestamps recorded by each device. Raw data recorded from the StepWatch will be downloaded to a computer. Average walking strides taken per day, percent time walking, and strides at low, moderate and high stride rates will be calculated from the raw StepWatch data as described in more detail by Bjornson et al. in children with cerebral palsy (3, 17). Walking activity measures from the StepWatch synchronized and coupled with the XY coordinate data from the GPS will allow quantification of the location, duration and distance of walking activity (Kang, 2013). Walking activity occurring outside a 20 meter buffer zone surrounding the geocoded home address will be classified as community-based while walking activity occurring within the 20 meter buffer will be considered to occur in the home.
4) Muscle architecture: The ultrasound imaging methods used in this study have been previously published in children with CP by Dr. Moreau (Moreau, 2009b). Briefly, images will be obtained at mid-thigh and lower leg using B-mode ultrasound imaging (GE Logiq e) with a variable frequency linear array transducer. (7-12mhz). Images will be obtained prior to any other measurements in the supine position after 20-30 minutes to allow fluid shifts to occur. Cross-sectional area will be obtained with the linear probe oriented in the axial plane. Muscle thickness, fascicle angle, fascicle length will be obtained with the probe oriented in the sagittal plane. Extended-field-of-view will be used to visualize the entire fascicle length with linear extrapolation used when needed used digitizing software (Moreau, 2013). A blinded assessor will use

external software (OsiriX 7.0.3) to calculate muscle architecture outcomes from de-identified ultrasound images from both sites (post-analysis).

5) Muscle Performance: Muscle performance measures of muscle power (11), rate of force development (RFD) (12), and strength (12, 41) will be tested on an isokinetic dynamometer (Biodex Pro System 3) for the knee extensors and ankle plantarflexors according to standard procedures previously published by Dr. Moreau in this population. An electromyographic (EMG) system (Motion Lab System) will be used to record muscle activity bilaterally from the rectus femoris, vastus lateralis, medial and lateral hamstrings, anterior tibialis, and medial gastrocnemius. Torque, position, velocity, and EMG data will be collected simultaneously during the muscle performance tests as previously described in detail by Moreau et al in order to calculate measures (42). Briefly, subjects will be in a sitting position in the dynamometer chair with the tested joint axis lined up with the axis of rotation and thigh and waist strapped to the chair to prevent extraneous movements. The knee and ankle will be allowed to flex and extend according to directions for each measure. Participants will be instructed to push as "fast and hard as possible" during testing. Muscle power and strength will also be tested on the training device described under intervention protocols (Total gym). The leg press will begin with the knee at 90 degrees of flexion and end with full extension. In order to determine velocity, a high definition video camera will record the duration of the press while displacement will be calculated with a linear position transducer. Power will be calculated as the product of force and velocity.
6) Participation: Mobility related participation in daily life will be documented by parental or child-report of selected items from the Patient-Reported Outcomes Measurement Information System (PROMIS), Gait Outcomes Assessment List (GOAL), and Activity Scale for Kids (ASK)(35-37). These questionnaires have been validated in this population (35-37). Parental report involves the parent's interpretation of their child's activities and participation.

Fidelity of Assessments (SA 1,2,3): Assessment fidelity between sites for SA1 and 3 will be addressed by in-person training of assessment therapists by Dr Moreau/Bjornson, using consistent walk test distance metrics, demonstrated StepWatch/GPS calibration/donning, and an assessment visit procedural reliability checklist of visit tasks/tests to standard of 100%. Site PIs will monitor and confirm assessment visit fidelity at every 10th study visit (10% of visits) over the study data collection period. Ultrasound imaging fidelity (SA 2) will be addressed by real-time videoconferencing of Dr Bjornson by Dr Moreau during every baseline study visit (25% of visits) and was implemented effectively with recent R21 pilot study. Fidelity of muscle performance data collection (SA 2) will be addressed between sites by in-person training by Dr Moreau at both sites and by real time PI/ per site observation every 10th visit (10% of visits) throughout the study data collection period with assessment visit procedural reliability checklist of visit tasks/tests to a standard of 100%. Training videos and manuals will be provided for reference for all of the outcome assessments. In addition to on-site training, the PI will perform site visits in Seattle every 6 months to 1 year (see timeline C.8). Dr. Moreau and Bjornson will hold monthly conference calls to discuss study progress and any protocol deviations. The entire research team will meet quarterly using closed-circuit videoconferencing.

Risks to Participants

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 wear a gait belt with contact guard assistance by the interventionist or be connected to an overhead harness which would prevent such an occurrence. Therefore, the risk of falling associated with this experiment is minimal. This fall prevention strategy has been effectively employed within the current R21 pilot protocol (R21 HD077186-01A1) with no adverse events reported related to falls during the short-burst treadmill training. Participants will also be allowed to use the treadmill railings as need during the training.

There is a mild risk of temporary delayed-onset muscle soreness from walking, power and strength training and testing, as well as joint pain, particularly in the knees. However, Dr. Moreau has previously performed maximum strength and power testing and training protocols in the lower extremity in both CP and typically developing children populations and reports of muscle soreness or joint pain have been minimal and were reported mild to moderate in intensity. Reports of joint injury are rare. In order to minimize physical risks, these protocols have been designed according to the latest resistance training guidelines for children and adolescents put forth by the National Strength and Conditioning Association (NSCA) position papers for youth

resistance training and includes scheduling rest periods between sets and 48 hours between training sessions. If muscle soreness is reported, subjects and their parents will be instructed on basic standard of care, such as stretching, icing, and use of over-the-counter nonsteroidal anti-inflammatory medications. Participants will be monitored by the intervention research physical therapist for appropriate fatigue, muscle soreness, joint pain, falls and/or unexpected physical discomfort during intervention and testing sessions.

There is minimal risk of blisters and/or chafing associated with training equipment used during the power and strength training and testing. This is no greater risk than standard of care physical therapy where a child is administered strength training. In order to minimize the risk of blisters and/or chafing, weight-lifting gloves will be provided to all subjects during training.

There are no known risks associated with ultrasound imaging.

There is minimal risk of intolerance or skin issues with wearing of the StepWatch/GPS devices.

The questionnaires/interviews completed by the parent are solely for the research project with the level of risk considered minimal to none. If the participant were to experience any emotional sadness or discomfort as a result of the questionnaires, we would refer the parent to an appropriate health care provider, such as a counselor or psychologist.

Risks to the participants' privacy are minimal and every effort will be made to maintain confidentiality with secured access and storage of data. REDCap™ will be used for data management. REDCap™ is a secure application designed for building and managing databases to allow electronic data collection from multi-site studies. Data management principles will be implemented to ensure the integrity, security, and confidentiality of all study-related data.

Benefits
Individual participants of this clinical trial have the potential benefit of improving their own personal walking capacity, walking performance, as well as community participation from the intervention. The muscle architectural adaptations and resulting improvements in muscle power gained from this intervention have also been shown to contribute to improved activity, participation, and even quality of life.

Data Safety Monitoring
The PI and site PI will assume primary responsibility for assessing the eligibility of subjects to participate in the study and monitoring the safety of participants in the study. 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 PIs. Specifically, Drs Moreau and Bjornson will conduct quarterly safety monitoring meetings to review information related to the safety of study participants and summarize any adverse events.

Adverse events will be collected from the start of treatment through the end of study participation. All adverse events regardless of attribution to treatment procedures will be collected and recorded. 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 LSUHSC and Seattle Children's IRB immediately. Should an unanticipated adverse event or outcome be discovered, Dr Moreau or 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. This study is a clinical trial with a relatively small number of participants in a vulnerable population (children with cerebral palsy). The experimental intervention and the comparison intervention propose low risk to the participants. Dr. Mercante will also monitor the data for any inconsistencies or outliers.

Data Safety Monitoring Board (DSMB): For this trial, we propose a 3-member DSMB. Dr. Edward Trapido has agreed to serve as the chair of the DSMB, in order to provide an unbiased assessment. This study is a clinical trial with a relatively small number of participants in a vulnerable population (children with cerebral palsy).

However, this study involves minimal risk (defined in 45 Code of Federal Regulations (CFR) Subpart A, Sec. 46.102), as the experimental intervention consists of power training combined with interval treadmill training, and the comparison intervention consists of treadmill training and strengthening. Resistance training and treadmill training are both components of standard physical therapy care. The combination of the two training modalities, including distinct differences in dosing parameters (intensity, volume, velocity) between the experimental and comparison interventions, is being tested. Both interventions have been tested separately and combined by the PI without any adverse events reported. Although this study meets the criteria for exemption, additional supplemental monitoring through an Independent Data Monitoring Committee (IDMC) will be implemented if requested by the funding agency.

The DSMB will be charged with oversight and monitoring to ensure the safety of participants and the validity and integrity of the data. The committee will meet quarterly to review data and any reported adverse events. Any adverse events will be reported to the Seattle Children's and LSUHSC-NO IRB. At any time, the committee will have final authority to conclude the study without any further enrollment.

Power Calculations: The sample size calculations for Specific Aim 1 focus on assessing differences in changes from baseline to 8 weeks in mean outcome between the PT3 and control groups. Estimates of variability and clinically relevant effect sizes for Specific Aims 1 & 2 were obtained from preliminary data for the treatment effect estimates and from Moreau et al. (2013) for the comparison group effect estimates. Assuming a statistical model for a replicated randomized complete block experiment with fixed treatment factor (PT3 vs comparison) and a 0.050 two-sided significance level, the null (primary) hypothesis of no difference in mean change from baseline to 8 weeks in self-selected gait speed between groups will have 90% power to detect a difference of 0.12 m/s given a common standard deviation of 0.167 m/s with a sample size of n=24 per group. A sample size of 24 in each group will also have 79% power to detect a difference of 0.137 m/s in fast gait speed, assuming a common standard deviation of 0.127 m/s. Specific Aim 2: A sample size of 24 in each group will have 99% power to detect a difference in mean peak power of 0.819 watts/kg with a common standard deviation of 0.485 watts/kg with a 0.050 two-sided significance level. A sample size of 24 in each group will have 90% power to detect a difference in mean fascicle length of 1.55 cm given a common standard deviation of 1.61 cm. Specific Aim 3: Average number of strides per day (over a 5 day period) were obtained from Bjornson et al. (2014) with the differences observed between GMFCS levels II and II used to approximate the expected differences between treatment groups. Assuming a common standard deviation of 1,580 average strides/day, a sample size of 24 will have 90% power to detect a difference in average strides/day between treatment groups as small as 1,510 strides/day. In the event that we experience dropout, the primary analysis of each aim will still have > 80% power to accommodate as high as a 25% dropout rate (n=19 per group).

Data Analysis Plan: The primary analysis will compare differences in changes from baseline to 8 weeks post in mean response between the treatment and comparison group using a general linear model with blocking factors for intervention site and GMFCS levels as fixed factors. By employing a randomized block design, we can statistically account for any clinical heterogeneity of outcomes by study site and GMFCS levels should this occur. To gain insight into both short and long-term retention of treatment effects, response profiles over the 4 time points will be compared using a linear mixed effects model with sites and GMFCS level as blocking factors, treatment group and time as fixed effects factors, and subjects as a random factor. These models will be used for analysis of the primary and secondary response variables of Specific Aims 1 and 2. The outcomes of Specific Aim 3 will use similar analysis models but will include an additional factor to allow comparison between home and community walking activity as a separate analysis. To assess the potential impact of gender on study outcomes, gender will be included in each of the models as a fixed effect. If significant gender effects are observed, we will report both adjusted and unadjusted estimates of treatment effects to more fully reveal the role of gender. Type I error rate will be set at 0.05. The primary dataset for analysis is the intent-to-treat dataset consisting of all patients randomized to intervention. The Statistical Analysis System (SAS®), V9.4 will be used for statistical analysis using GLM and MIXED procedures.

Data Management and Fidelity: REDCap™ will be used for data management. REDCap™ is a secure application designed for building and managing databases to allow electronic data collection from multi-site studies and allows instantaneous access to data. Dr. Mercante will provide oversight to extensive quality control checks incorporated into the data entry system, such as real-time validation rules (with automated data type and range checks) at the time of data entry, and tracking of critical study events, such as assessment and

intervention visits requiring physical oversight as described previously. Data management principles will be implemented to ensure the integrity, security, and confidentiality of all study-related data.

Project Timeline

Task:	Year 1				Year 2				Year 3				Year 4				Year 5			
Train Intervention/Assessment staff	X	X																		
Seattle site visit by PI	X	X		X			X			X				X						
Recruitment / Enrollment (#'s)			4	4	4	4	4	2	4	4	4	2	4	4	4					
Intervention			X	X	X	X	X	X	X	X	X	X	X	X	X					
Post & follow-up assessments				X	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

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