Title:	**Improving the trajectory of motor development in infants and toddlers with cerebral palsy.**	
Short Title	Improving motor development in CP	
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ABBREVIATIONS AND DEFINITIONS OF TERMS

TD: Typically developing

CP: Cerebral Palsy

GMFM: Gross Motor Function Measure

BSID-III: Bayley Scales of Infant and Toddler Development, version III

PT: Physical therapy

ABSTRACT

Context: Cerebral palsy (CP) is the most common cause of physical disability in children. There is a window of opportunity to reduce the degree of lifelong disability by maximizing motor potential during the critical early years of development.

Objectives: 1) To determine the optimal treatment duration of a novel early mobility training program (dynamic supported mobility, DSM) between 6 to 24 weeks of treatment; and 2) To evaluate the clinical futility of this intervention compared to current rehabilitation practice.

Study Design: Exploratory clinical trial

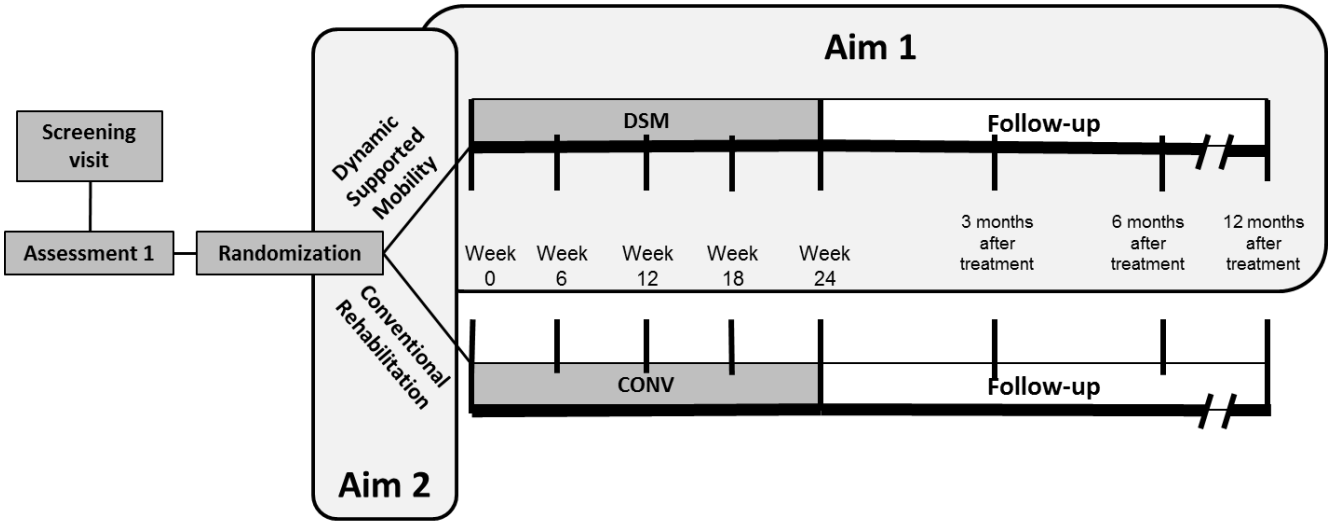
Setting/Participants: Sixty participants with, or with suspected, CP between the ages of 1-3 years will be enrolled. All testing procedures and interventions will occur in the Center for Rehabilitation at CHOP on an outpatient basis.

Study Interventions and Measures: Study participants will be randomly assigned to receive either dynamic supported mobility (DSM, experimental) treatment or intensity-matched conventional treatment. Repeated assessments of gross motor function will be performed during the treatment phase and at three follow-up points over one year after treatment to track the developmental trajectory of participants' motor function. Gross motor outcomes of DSM treatment will be compared to published percentile scores of motor function development in CP to determine if the trajectory of predicted motor development is altered, and to outcomes of intensity-matched conventional treatment.

TABLE 1: SCHEDULE OF STUDY PROCEDURES

Study Phase	Screening	Assessment 1 (0 week)	Therapy 1-18	Assessment 2 (6 week)	Therapy 19-36	Assessment 3 (12 week)	Therapy 37-54	Assessment 4 (18 week)	Therapy 55-72	Assessment 5 (24 week)	Follow up (3 mo)	Follow up (6 mo)	Follow up (12 mo)
Visit Number	1	2	3-20	21	22-39	40	41-58	59	60-77	78	79	80	81
Informed Consent/Assent	X												
Review Inclusion/Exclusion Criteria	X												
Demographics/ Medical History	X												
Bayley Scales of Infant Development	X	X								X		X	X
Randomization		X											
Gross motor function (GMFM-66)		X		X		X		X		X	X	X	X
Weight		X		X		X		X		X	X	X	X
Secondary outcomes (Postural control, physical activity, caregiver satisfaction, Child Engagement in Daily Life)		X		X		X		X		X	X	X	X
Family Empowerment Scale		X								X		X	X
Rehabilitation (either DSM or CONV)			X		X		X		X				
Possible video or photograph		X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X	X	X	X	X	X	X	X

FIGURE 1: STUDY DIAGRAM



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1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

As the most common cause of physical disability in children, CP is a disorder "…of the development of movement and posture… attributed to non-progressive disturbances that occurred in the developing fetal or infant brain."[1] Given the age at onset and the near-typical lifespan,[2] those living with cerebral palsy (CP) experience one of the highest number of disability-years among all disabling conditions. CP is the most common cause of motor disability in children[3] with a prevalence that has remained stable over recent decades at more than 3 per 1000 births or 10,000 babies per year in the United States despite advances in pre- and perinatal care.[4,5] An estimated 15 million people currently live with CP worldwide. The degree of life participation restriction in those with CP is predicted by the degree of motor disability, which varies widely from limitations in balance and coordination to full dependence on others for care.[6] This relationship between severity of motor disability and participation restriction has been reported in infancy,[7] childhood,[8,9] and adolescence and young adulthood.[10] Independent of cognitive impairment, the severity of physical disability in childhood is a predictor of later romantic relationships[11] and independent living in the early 30s.[12]

The best opportunity to maximize lifelong independence is early in motor development when the differences in motor skill between functional levels are relatively small and there is the most potential for neuroplastic change. Gross motor function plateaus by 4-7 years of age[13] after which motor ability is relatively fixed with large skill gaps between levels. In fact, the Gross Motor Function Classification System (GMFCS)[6] of motor severity remains relatively stable throughout childhood and adulthood,[14,15] regardless of treatment. *However, the early years of life are an exception* with less stability in GMFCS classifications before the age of 2 years.[16] There is also growing evidence of a critical period of neuroplasticity for motor control centers in the brain. Similar to the development of sensory systems, recent work has confirmed that plasticity in the motor system is both activity-dependent, and more robust in early as compared to later years.[17,18] Moreover, maladaptive changes that occur after central nervous injury are difficult to reverse once established.[19] These observations suggest that there is a window of opportunity for interventions applied *prior* to nearing the developmental peak to improve the trajectory of motor development and reduce lifelong physical disability.

How best to optimize motor ability during this narrow window remains unknown. Current practice does not reflect key learning principles of typical motor development. Typical toddler movement is characterized by a high degree of motor exploration, error and movement variability, which are critical factors in the refinement of motor control. Infants and toddlers with CP often cannot create these experiences on their own, losing natural opportunities to learn more coordinated movements and establish the associated neural pathways that control skilled movement. In contrast to their typically-developing peers, young children with CP instead repeatedly practice poorly-controlled motor patterns. Our work will investigate a promising novel treatment designed to allow infants and toddlers with CP to create for themselves motor learning experiences more similar to their typically developing peers. This contribution will be significant because the treatment may have the potential to improve the trajectory of motor development and reduce lifelong physical disability in individuals with CP. The work will increase our understanding of how best to

optimize the potential of the developing brain to recover after neuromotor injury. As such, the proposed work will also inform the early treatment practices for other developmental disorders, such as early brain injury, Down Syndrome, and various neurogenetic disorders.

1.2 Name and Description of Investigational Intervention

Dynamic Supported Mobility (DSM) - The experimental therapy group will receive dynamic weight support (using the ZeroG Gait and Balance training system, Aretech LLC, Ashburn, VA) during all therapy time, and the environment will be arranged to encourage active motor exploration by the child, in order to promote the motor variability, challenge, and error experiences that characterize the typical development of upright motor skills and walking. Activities will be graded in difficulty to the child's ability and will include: moving between the floor and standing, walking, squatting to reach the floor, climbing/walking up and down steps and inclines, and other typical toddler movements, somewhat similar to a play gym for toddlers. The floor area within 3 feet below either side of the overhead track for a distance of approximately 20 feet (approximately 120 ft2 total) will be defined with colorful thin rubber interlocking mats and arranged with pediatric toys and activities, tailored to the child's interests and to encourage motor skills just beyond his/her current ability level. The dynamic support system continuously provides a constant amount of weight assistance (as determined by the therapist) by controlling the length of the cable joining the harness and track and by moving along the overhead track as the user moves about the space (i.e. cable lengthens if child moves to the floor and shortens if child climbs up steps, with no lag time). The user's movements are not restricted at all within this space. This arrangement works well to keep children within the limits of the overhead track and provide ample opportunity and space for motor play and exploration. Initial amount of weight assistance will be determined during the first therapy session by the level that allows walking and squatting to reach the floor with the least amount of assistance from the therapist. Weight assistance will be gradually reduced during the treatment phase as postural control and coordination improve. The therapist will minimally assist the child as needed to perform the movements he/she initiates.

1.3 Relevant Literature and Data

The proposed intervention has been systematically developed and pilot-tested consistent with a stage model for behavioral therapies.[20] The treatment was designed to incorporate overlapping principles of neurorehabilitation and infant motor learning in a context that promotes upright mobility skill and postural control development.

Treatment development.

Principles of neurorehabilitation. Despite increasing evidence of early critical periods for neuroplasticity,[17,18] there remains little application to individuals with CP. Treatments addressing secondary musculoskeletal impairments such as muscle and bone abnormalities that develop in response to poor motor control remain the most common treatment approaches.[21] These interventions are important to manage the course of CP, but do not address the primary impairment of poor neural control of movement.[1] The most effective rehabilitation programs include intensive, early, and challenging motor practice,[22-

[24] and these principles are supported by training-dependent plasticity in cortical structures.[25-27] *Variability* in movement patterns during rehabilitation further enhances motor outcomes[28,29] and reflects complex motor skill.[30] *Salience* is the meaningfulness of the training to the patient which promotes active engagement and facilitates neuroplasticity.[31,32] Finally, the critical role of *error* in motor learning and rehabilitation has been increasingly recognized,[33,34] with diminished long-term gains when error is eliminated from practice.[35]

Principles of infant motor learning. It is perhaps no coincidence that many neurorehabilitation principles for training motor coordination are also important components of typical infant motor learning. Motor exploration is the basis for all infant motor development[36] and in fact, practice is a more important developmental factor than age in helping infants learn to overcome their weak muscles and poor balance.[37] Typical 12- to 19-month-old children fall an average of 17 times per hour of free play,[38] and falling (*motor error*) is believed to play an important a role in learning to walk.[39] Adolph has emphasized the role of inherent *variability* in motor development,[40] and more stereotyped and predictable motor patterns (i.e. less capacity for variability and adaptability) are observed in healthy infants when free movement is restricted.[41] Finally, the degree of *salience* in a visual cue can determine whether an infant will move to it.[42] Adhering to these key principles of infant motor learning allows the training program to closely reflect the motor exploration experiences that characterize the beginning stages of walking skill, experiences that without support, infants and toddlers with CP are not able to create on their own. We call the intervention dynamic supported mobility (DSM) and additional details of its development are included in the published manuscript.[43]

Feasibility testing.

We conducted a single-subject research design pilot study to evaluate the safety, feasibility, and tolerability of the intervention, as well as the appropriateness of the primary outcome measure, in the target population.[43] Five children (aged 12-27 months, GMFCS I-III) participated in the study with repeated measures of gross motor function (GMFM-66) during 6-week baseline and treatment phases, and after a 6-week follow-up phase. No adverse events occurred. Attendance rate was 81% for Participant 3 and 100% for all others. All therapy sessions were videotaped for later activity coding to validate the motor outcomes.

Table 1 presents rates of motor development in each study phase, calculated using the split middle technique for single-subject study data,[44] and relative rates of motor development for the treatment (Treatment/Baseline) and follow-up phases (Follow-up/Baseline) compared to baseline. Values greater than 1.0 for relative rates of change represent increased rate of motor development, and values less than 1.0 represent decreased rate of motor development compared to the baseline rate. Participants 1-4 demonstrated rates of motor development during treatment that were 3.8 to 15.1 times greater than their respective baseline rates. All participants maintained their treatment gains, but returned to slower rates of motor development during follow-up. Participant 3 began walking alone with the dynamic support during the first therapy session. She did not start walking on her own at home, until approximately three weeks later, suggesting that the treatment allowed her to practice more advanced skills than she was able to do on her own. Participant 5 demonstrated improvement during treatment, but the rate of development was less than her baseline rate (0.3). This child made large gains during baseline when she started walking on

her own (at 16 months of age), and as a result there is no indication from these data that the intervention improved her motor ability beyond what could be predicted. She was the least affected participant (above the 50th percentile of GMFCS level I) and likely not an ideal candidate, which informed the refinement of participant selection criteria. Participant 4 was the most impaired child and demonstrated the largest relative rate of change.

Table 1. Motor development rates, representing average GMFM change per week. Relative rates of change compare treatment and follow-up phases to baseline (with 1.0 representing equal rates of change).

	Motor Development Rates			Relative Rates of Change	
ID	Baseline	Treatment	Follow-up	**Treatment/ Baseline**	Follow-up/ Baseline
1	0.05	0.55	0.04	**10.8**	0.7
2	0.16	0.61	0.08	**3.8**	0.5
3	0.30	2.05	0.20	**7.0**	0.7
4	0.05	0.77	0.24	**15.1**	4.6
5	1.56	0.46	-0.06	**0.3**	-0.04

Figure 2 presents the raw data and net change scores (treatment change minus baseline change). The net treatment change for Participant 5 was -5.7 as a result of her large improvement during baseline. Net change scores for Participants 1-4 ranged from 2.4-9.7, each exceeding the minimal clinically important difference values for treatments that have a large effect size (1.5 for GMFCS level II and 1.3 for GMFCS level III).[45] In summary, the treatment and training schedule were feasible with changes sustained at short-term follow-up, and continued systematic investigation is warranted.

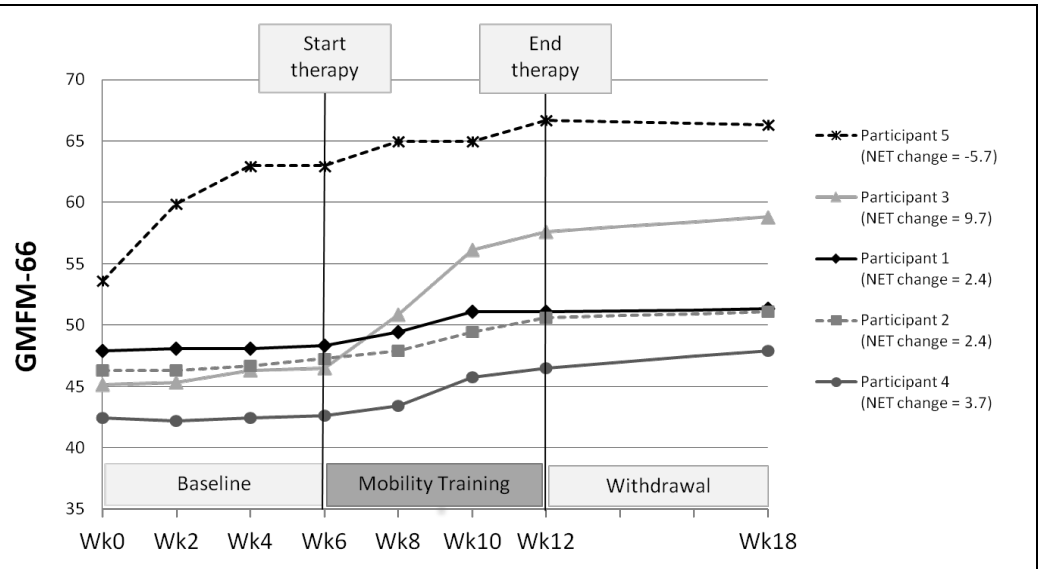

Figure 2. Motor function outcomes. Net change scores for each participant are included in the legend.

Treatments that improve a child's motor function by one GMFCS level would achieve a large and impactful change that exceeds the level of improvement realized by currently available treatments for individuals with CP.[14,15,46] Our preliminary work included just six weeks of DSM treatment. Six weeks of treatment was sufficient for one child (Participant 3) to be reclassified from a level II to I. For the other three participants who would meet the proposed selection criteria (Participants 1, 2, and 4), if improvement had continued at the observed rate, approximately 12 weeks of treatment would have been adequate for them to have improved one functional level. However, it cannot be assumed that the rate of improvement will be constant with longer treatment durations. For this reason, outcomes after 12, 18 and 24 weeks of treatment will be evaluated to establish a more complete understanding of the treatment duration-response relationship and the full potential of the treatment to alter the trajectory of motor development. These data support the feasibility of Aim 1 and provide the foundation for Hypothesis 1.1 that at least 12 weeks of DSM treatment will effectively alter the trajectory of motor development to a degree that is sustained at longer term follow-up.

For the four children who would meet the proposed selection criteria, all training videos were coded to investigate if changes were indeed related to the treatment provided. Amounts of training time spent doing activities related to each relevant GMFM subscale (C. Crawling & Kneeling, D. Standing, and E. Walking, Running & Jumping) were correlated to net changes in the respective subscale. A high degree of variance in subscale outcomes was explained by the amount of training time (r^2 = 0.80, 0.74, 0.98, 1.00, respectively). Video coding also revealed a high level of motor engagement and falls, as intended. The relationship between number of falls and total GMFM-66 change was quite strong (r=0.80), suggesting that falling and learning may have happened simultaneously. Table 2 presents video coding results (note: raw scores for activity subscales are not shown). These video coding data provide the foundation for Hypothesis 1.2 that the amounts of motor error, variability and engagement incorporated into the DSM treatment will be related to outcome.

Table 2. Video coding results, including variance explained (r^2) between training time in each GMFM activity subscale (C, D, and E) and motor change, motor engagement, and average number of falls per session.

	C. Crawling & Kneeling		D. Standing		E. Walking, Running & Jumping				
ID	NET change	Minutes/ session	NET change	Minutes/ session	NET change	Minutes/ session	r^2	Motor engagement	Falls
1	7.1	11:56	10.3	10:58	1.4	03:32	0.80	91%	11
2	2.4	09:08	17.9	12:46	0.0	03:16	0.74	87%	6
3	11.9	06:57	48.7	10:43	29.2	09:13	0.98	95%	17
4	11.9	11:23	10.3	09:42	5.6	05:01	1.00	88%	14

The proposed study involves no more than minimal risk research and no adverse events occurred in preliminary work. These circumstances support the foundation of Hypothesis 2.1 that DSM treatment will pose no more risk to participants than current rehabilitation practice.

Two methods of interpreting the preliminary data support prospective comparison of the functional outcomes of DSM treatment to conventional rehabilitation practice. First, the four participants who would meet the proposed selection criteria were receiving other rehabilitation services throughout the study and demonstrated rates of motor development during the DSM treatment phase that were 3.8 to 15.1 times their respective rates of motor development during the baseline phase (Table 1). This suggests that the DSM treatment significantly accelerated their individual rates of motor skill attainment with conventional rehabilitation services. However, motor development is not always linear,[47] so this approach is not sufficient to determine the treatment's futility compared to other treatments. Second, the same four participants all demonstrated net changes (ranging from 2.4-9.7, Figure 2) after only six weeks of treatment that exceeded the corresponding minimal clinically important difference values for treatments that have a large effect size (1.5 for GMFCS level II and 1.3 for level III).[45] However, caution should be taken as these minimal clinically important difference values were determined from a sample of children aged 4-18 years, and while unknown, it is possible that the minimal clinically important difference values would be larger earlier in development. Although promising, prospective comparison to intensity-matched current rehabilitation intervention is needed to confirm the potential advantages of DSM treatment prior to progression to a larger efficacy trial. These data support the foundation of Hypothesis 2.2 that children who receive DSM treatment will demonstrate greater gains in gross motor function than participants who receive equal amounts of CONV treatment.

Other Relevant Literature

Determining the optimal dose of pediatric rehabilitation services for children with CP and other developmental disabilities has been identified as a national priority.[48] Yet, the majority of research in the field has not explored dose-response outcomes for various interventions. The convenient, rather than scientifically-grounded, dosing of neuromotor rehabilitation historically offered during clinical trials often limits the validity and comprehensiveness of the research findings. Investigation of treatment response over a duration long enough to reach an anticipated behavioral plateau in the early stages of scientific inquiry more adequately prepares an experimental rehabilitation treatment for Phase III efficacy evaluation.[49]

Both the National Institute of Neurological Disorders and Stroke (www.ninds.nih.gov) and leaders in neurology[50] and neurorehabilitation[51] suggest that early clinical trials are the appropriate stage at which to evaluate the futility of a new treatment compared to another treatment or standard of care. These data are critical in determining if and how the science should progress in a definitive Phase III trial. Dobkin further emphasizes that while "a nonactive placebo may be the only therapy in a drug trial if no standard drug therapy exists, comparing a specific rehabilitation treatment to nothing is no longer acceptable." (2009) The intensity of treatment (minutes per week) in the proposed study will approximate the average amount of physical therapy received by young children with CP in the United States. The average amount of physical therapy is 82 (SD 60) minutes per week in the United States, and 90 (SD 60) minutes per week in the Philadelphia metropolitan area.[52] The 90 minutes per week of either treatment in the proposed study reflects this current intervention practice. However, the wide variability in the standard

amount of services means that not all children would receive this intensity outside of the research study. This variability in current practice is a common issue in identifying "standard of care" in rehabilitation trials. However, it has been determined in gold-standard trials that matching the treatment intensity of the experimental group is the most important component of the "control" group,[24,53] and our approach reflects this standard.

1.4 Compliance Statement

This study will be conducted in full accordance all applicable Children's Hospital of Philadelphia Research Policies and Procedures, all applicable Federal and state laws and regulations, and the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonisation (ICH). All episodes of noncompliance will be documented. The investigators will perform the study in accordance with this protocol, will obtain consent and assent, and will report unanticipated problems involving risks to subjects or others in accordance with The Children's Hospital of Philadelphia IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2 STUDY OBJECTIVES

2.1 Primary Objectives (or Aims)

Aim 1. To determine the optimal treatment duration of dynamic supported mobility (DSM) treatment in infants and toddlers with cerebral palsy, between 6 to 24 weeks of treatment.

> *Hypothesis 1.1.* Gross motor ability (measured by the GMFM-66) will exceed individual predicted values in infants and toddlers with cerebral palsy after 12, 18, and 24 weeks of DSM treatment, and gains will be maintained at 3, 6 and 12 month follow-up points.
>
> *Hypothesis 1.2.* Gross motor function gains will be positively related to the amount of motor error, variability and engagement experienced during DSM treatment.

Aim 2. To determine the futility of dynamic supported mobility compared to conventional rehabilitation in infants and toddlers with cerebral palsy.

> *Hypothesis 2.1.* The frequency of adverse events among participants who receive DSM treatment and those who receive conventional (CONV) treatment will not differ by greater than 10 percent.
>
> *Hypothesis 2.2.* Participants who receive DSM treatment will demonstrate significantly greater improvements in gross motor ability (measured by the GMFM-66) than participants who receive equal amounts of CONV treatment, and these differences will be maintained at each follow-up point.

2.2 Secondary Objective (or Aim)

The secondary objective is to:

- Compare physical activity at home, postural control, engagement in daily life, caregiver satisfaction and cognition in the dynamic supported mobility (DSM) therapy group to the conventional (CONV) therapy group.

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design

The proposed study is a single-blind, randomized exploratory clinical trial with repeated assessments during a 24-week treatment phase and at three follow-up points over 12 months after treatment to track the developmental trajectory of participants' motor function. Gross motor ability will be compared to published percentile scores of motor function development in CP to determine if the trajectory of predicted motor development is altered, and to outcomes of intensity-matched conventional treatment to determine if continued Phase III investigation is warranted.

3.1.1 Screening Phase

Candidate screening will be conducted by the primary research therapist using the protocol inclusion and exclusion criteria. The parent or legal guardian must provide written informed consent prior to the start of any study activities. Written assents of minors will not be obtained due to the age of the participants.

3.1.2 Study Treatment Phase (start of the study intervention)

Children will be able to continue their outside therapies, if their families' choose to do so. Whether they reduce or continue their pre-enrollment therapy schedule, families will be asked to maintain the schedule of outside physical therapy constant throughout the treatment phase. It is anticipated that most children will be receiving early intervention therapy services in the home. Other medical care will be documented but not restricted. If parents sign CHOP's standard HIPAA authorization, we will request copies of outside therapy notes to assist with documentation of co-occurring treatments. Treatment will start within one week of Assessment 1 and will be delivered by the primary or secondary research physical therapist, both of whom will be trained using the study manual to provide each type of treatment. We will follow intent to treat procedures such that no child will be withdrawn from the study for failing to adhere to the therapy schedule. A training log will be maintained for each session. One session per week will be videotaped (if separate consent is provided) for quality control to ensure that activities between the treatments remain different and are consistent with the distinguishing characteristics.

After enrollment and the initial assessment, participants will be randomized to receive either DSM or conventional (CONV) treatment, using a randomization scheme to ensure that motor ability does not differ at baseline. Participants will also be randomly assigned to either the primary or secondary research therapist who will each provide both

types of treatments, to minimize any differences related to individual therapist. Treatment in both groups will occur at an intensity of 3 times per week for 30 minutes.

DSM treatment. Children will receive dynamic weight support (ZeroG®, Aretech LLC, Ashburn, VA) during all DSM treatment time. The environment will be arranged to encourage active motor exploration, somewhat similar to a play gym for toddlers, to promote the motor variability, engagement, and error experiences that characterize the typical development of upright motor skills and walking. The floor area within 3 feet below either side of the overhead track for a distance of 20 feet (approximately 120 ft^2 total) will be defined with colorful thin rubber interlocking mats and arranged with pediatric toys and activities, tailored to the child's interests and to encourage motor skills just beyond his/her current ability. This arrangement worked well in pilot work to keep children within the limits of the overhead track and provide ample opportunity and space for motor play and exploration. Initial amount of weight assistance will be determined by the level that allows walking and squatting to reach the floor with the least amount of assistance from the therapist, up to a maximum of 40% of the child's weight. Greater than 40% weight support produces significant alterations in normal walking biomechanics in healthy adults (unpublished data, communication with system inventor, J. Hidler, PhD). Amount of weight assistance will be re-assessed at the start of each session, and will be gradually reduced as postural control and coordination improve to the minimum amount that allows walking and squatting to reach the floor with the least amount of assistance from the therapist. The therapist will minimally assist the child as needed to perform the movements he/she initiates.

CONV treatment. The conventional treatment group will receive traditional, therapist-directed pediatric physical therapy. Therapy will focus on early gait training strategies and encouragement of "normal" movement patterns for walking and other age-appropriate movements, with manual guidance or correction of atypical movements from the therapist. This group may use assistive devices, orthoses, and may receive static body weight support for gait training. Therapy activities will be performed in blocks of practice, with the specific activities and level of therapist assistance tailored to each child. Examples include: using a posterior rolling walker with ankle foot orthoses (braces), physically guided practice of standing from the floor through half kneeling, manual correction of side steps while cruising at a bench, and repeated sit to stand practice from a small chair. The distinguishing characteristics of each treatment are listed in Table 4.

3.1.3 Follow-up Phase

The treatment phase will end after 24 weeks of treatment. Three follow-up assessments will occur at 3, 6 and 12 months after treatment ends.

3.2 Allocation to Treatment Groups and Blinding

After the initial GMFM-66 score from Assessment 1 is obtained, participants will be randomized to either the CONV or DSM treatment, using a randomization scheme to stratify by baseline motor ability. This will ensure that the groups do not differ in motor ability at baseline. Participants will also be randomly assigned to either the primary or secondary research therapist who will each provide both types of treatments, to minimize any differences related to individual therapist. A blinded assessor will collect all outcomes

measures. Blinding of participants to treatment group is not feasible with the proposed interventions.

3.3 Study Duration, Enrollment and Number of Sites

3.3.1 Duration of Study Participation

Total study duration is 18 months, including 6 months of a treatment phase and 12 months of a follow-up phase.

3.3.2 Total Number of Study Sites/Total Number of Subjects Projected

All testing procedures and interventions will occur in the Center for Rehabilitation at CHOP. Sixty participants with CP between the ages of 1-3 years will be recruited for the study. It is expected that enrollment of 60 participants will produce 42 evaluable datasets.

3.4 Study Population

3.4.1 Inclusion Criteria

1) 12-36 months of age
2) Gross motor function below the 10th percentile for age (Bayley Scales of Infant and Toddler Development, BSID-III, corrected for gestational age, if applicable, under the age of two years).
3) Diagnosis of CP or neurological sign associated with CP (i.e. spasticity).
4) Ability to initiate pulling to stand at a surface (Score of 1 on GMFM Item 52).
5) Cognitive ability to follow one-step commands.

3.4.2 Exclusion Criteria

1) Secondary orthopedic, neuromuscular or cardiovascular condition unrelated to CP.
2) General muscle hypotonia, without other neurological signs associated with CP.
3) Independent walking ability (Score of 3 on GMFM Item 69 – Walks forward 10 steps).
4) At or above the 50th percentile of GMFCS Level I.
5) History of surgery or injury to the lower extremities in the past 6 months.

Subjects that do not meet all of the enrollment criteria may not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

4 STUDY PROCEDURES

Please refer to table 1 “Schedule of study procedures”

4.1 Screening Visit

- Informed Consent
- Physical Therapy Examination
- Medical Record Review
- BSID-III, gross motor scale
- Review of Inclusion and Exclusion criteria

4.2 Treatment Phase

4.2.1 Assessment sessions 1-5

- Randomization (Assessment 1 only)
- Weight
- Gross motor function (GMFM-66)
- Secondary outcomes (Postural control, physical activity, caregiver satisfaction, Child Engagement in Daily Life)
- BSID-III, cognitive scale (Assessments 1 and 5)
- Family Empowerment Scale (Assessments 1 and 5)
- Possible video or photograph

4.2.2 Treatment sessions 1-72

- Rehabilitation (three 30-minute sessions per week of either DSM or CONV treatment)
- Possible video or photograph

4.3 Follow-up Phase

4.3.1 Follow-up assessments (3, 6 and 12 months)

- Gross motor function (GMFM-66)
- Secondary outcomes (Postural control, physical activity, caregiver satisfaction, Child Engagement in Daily Life)
- BSID-III, cognitive scale (6 and 12 month follow-ups)
- Family Empowerment Scale (6 and 12 month follow-ups)

- Possible video or photograph

4.4 Subject Completion/Withdrawal

Subjects may withdraw from the study at any time without prejudice to their care. Intent to treat procedures will be followed such that participants will not be withdrawn from the study by the investigators for lack of adherence to the treatment schedule. Participants will not be withdrawn from the study for missing treatment sessions. The Investigator or the Sponsor (if applicable) may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded in the source documents and on the CRF.

4.4.1 Early Termination Study Visit

Subjects who withdraw from the study will have all procedures enumerated for Assessment 5 completed as the early termination visit.

4.4.2 Make-up treatment sessions

If subjects miss greater than 20% of therapy sessions, they will be given the option to make up treatment sessions at the end of the study, after Assessment 5 (at 24 weeks). If six or more make-up sessions are completed, a final post-treatment visit will be completed, which will include a repeat of all procedures enumerated for Assessment 5.

5 STUDY EVALUATIONS AND MEASUREMENTS

5.1 Screening and Monitoring Evaluations and Measurements

In addition to the measures listed below, the study database and data collection instruments will also include relevant data elements from the NINDS Common Data Elements (CDE), including elements on Demographics, Health History, Physical Exam, Treatment/Intervention Data, Protocol Experience, and Safety Data (http://www.commondataelements.ninds.nih.gov/General.aspx#tab=Data_Standards).

5.1.1 Medical Record Review

The CHOP medical record will be accessed and reviewed for potential candidates who are patients, as part of the recruitment and screening process. Non – CHOP patients will be asked to provide their relevant medical records with written HIPPA authorization from their medical facility. Screening for eligibility based on medical record review will include: date of birth and review of any significant history of orthopedic, neurologic or cardio-pulmonary conditions.

5.1.2 Physical Examination

- Physical therapy examination

- Ability to initiate pulling to stand, score of at least 1 on GMFM Item 52 (inclusion criterion).
- BSID-III, gross motor scale (inclusion criterion)

5.2 Efficacy Evaluations

5.2.1 Gross Motor Function Measure (GMFM)

The primary outcome is the GMFM-66, a Rasch-analyzed measure of gross motor function designed for children with CP.[54] Computation of the GMFM-66 score involves statistical weighting of the raw item scores for difficulty. This score will also be used with the patient's age to determine GMFCS percentile rank.[55]

5.2.2 Secondary Outcomes

Postural control. Using computerized posturography, participants will sit for 3-5 ten second trials on the force platform while center of pressure data are collected. This process will be repeated in kneeling and standing positions if the participant is able to maintain these positions. Center of pressure data will be interpreted using nonlinear measures of analysis. We will also administer the Early Clinical Assessment of Balance test, which is a test designed to measure postural control in young children with physical disabilities.

Physical activity. A wireless activity monitor will be provided to the caregiver, who will be instructed on use of the monitor at home, with a goal of recording 5 total hours of the child's free play in the following week. An envelope will be provided to return the activity monitor. Amount and magnitude of physical activity will be calculated using corresponding software.

Caregiver satisfaction. One caregiver of each participant will rate their child's performance on the caregiver's self-identified goals, and the their own (caregiver's) satisfaction with the child's performance using the Canadian Occupational Performance Measure.

Child Engagement in Daily Life. One caregiver of each participant will complete the Child Engagement in Daily Life Measure to obtain a measure of the child's participation in play in daily life.

5.2.3 Weight

The child's weight will be measured at each assessment to ensure that the percent weight support during treatment sessions is accurate.

5.2.4 Bayley Scales of Infant and Toddler Development, cognitive scale

The cognition age equivalent obtained from the BSID-III will be used as a covariate as patient cognition is known to influence response to rehabilitation.[56,57] To avoid a learning effect from repeated testing, this will be completed only every 6 months.

5.2.5 Family Empowerment Scale

One caregiver of each participant will complete the Family Empowerment Scale to obtain a measure of the caregiver's self-efficacy, also known to influence response to

rehabilitation.[58] To avoid caregivers remembering their prior responses, this will be completed only every 6 months.

5.2.6 Possible video or photograph

One treatment session will be videotaped each week to quantify participant error experience (number of falls), motor variability (time spent in one motor activity before moving to the next), and salience or motor engagement (time engaged in a dynamic motor activity) during DSM treatment, allowing evaluation of the relationship of these factors to treatment response. The videotaped sessions will also be coded for the amount of time participants spend doing activities in each of the GMFM subscales, to allow evaluation of the relationship between time spent in each activity category and outcome in each subscale. Randomly selected videos will also be used for quality checks to ensure that the two treatments remain different and consistent with the distinguishing characteristics of each group.

Occasional photographs may be taken, if separate consent is provided, for educational or scientific purposes, or as souvenirs for the children.

5.3 Safety Evaluation

Subject safety will be monitored by adverse events. Anticipated and unanticipated adverse events will be recorded to confirm that DSM treatment does not pose greater risks than current interventions.

6 STATISTICAL CONSIDERATIONS

6.1 Primary Endpoint

The primary endpoint will be the change in GMFM (Gross Motor Function Measure) from baseline to each post-treatment assessment session.

6.2 Statistical Methods

6.2.1 Baseline Data

Baseline characteristics for the total sample and by treatment group will be summarized by standard descriptive summaries (including mean, standard deviation, median, minimum, maximum and range for continuous variables and frequency counts and percentages categorical variables). We will also report the 95% confidence interval for pertinence means and proportions. Baseline characteristics in each group will be compared using two-sample tests, including t-tests, the Mann-Whitney test, and chi-square tests, as appropriate for the respective type of data.

6.2.2 Efficacy Analysis

For the analysis of Aim 1, Hypothesis 1.1 (*Gross motor ability will exceed predicted values after DSM treatment and gains will be maintained at follow-up*), GMFCS percentile ranks will be obtained after 6, 12, 18 and 24 weeks of treatment based on actual GMFM-66

scores and age, and will be compared to predicted percentile ranks based on age and initial GMFM-66 score. Mean values and 95% confidence intervals will be calculated for actual and predicted scores. Optimal treatment duration will be identified as the maximum change observed at the related time point which is maintained during the following period. If maximum change occurs after 24 weeks, this time will be considered the optimal duration. Spearman correlation will be utilized to analyze Hypothesis 1.2 (*Outcomes will be related to the amount of error, variability and engagement during treatment*), to estimate the relationship between motor improvement and the amount of motor error, variability and engagement experienced during treatment.

To address Aim 2, Hypothesis 2.2 (*Participants who receive DSM treatment will demonstrate greater improvements than participants who receive CONV treatment, and the differences will be maintained at follow-up*) will be analyzed by comparing GMFM-66 outcomes between participants receiving DSM treatment and those receiving CONV treatment. Baseline characteristics in each group will be compared using two-sample tests, including t-tests, the Mann-Whitney test, and chi-square tests, as appropriate for the respective type of data. We will then use a univariate approach for comparing the two treatments using analyses of variance and covariance (ANCOVA). Measurements at 6, 12, 18 and 24 weeks, as well as at both follow-up points after treatment will be individually compared between the two treatment conditions using baseline score, cognition and caregiver self-efficacy as covariates. We will also use a multivariate approach using linear mixed effects model[59] or the Generalized Estimating Equation (GEE).[60] The advantage of using the mixed effects model or the GEE approach is that they will not drop subjects from the analysis due to not having measurement at any of the post-treatment time points. Also, such analyses will allow us to examine the between subjects effects which represent a factor with two levels (treatment conditions) and within subjects effects which represent time effects (pre and post measurements) and a time by condition interaction. The random effect model will be implemented utilizing SAS Proc Mixed and the GEE will be implemented by SAS Proc Genmod. (SAS/STAT User's Guide, 2004, Version 9. Cary, NC: SAS Institute, Inc). Cognition and caregiver self-efficacy will be included as covariates in these analyses. Two-sided p values of less than 0.05 will be considered statistically significant. Similar procedures will be used for the analysis of secondary outcomes, with appropriate tests for parametric (postural control, physical activity) and non-parametric measures (caregiver satisfaction, Child Engagement in Daily Life).

6.2.3 Safety Analysis

To address Hypothesis 2.1 (*Adverse events will not differ by greater than 10% between treatments*), type and frequencies of adverse events will be presented descriptively by treatment. A magnitude of difference of less than 10% will be considered as similar between treatments.

6.3 Sample Size and Power

This is a proof of concept futility study and to keep the number of participants to the minimum necessary, sample size estimation was not driven to achieve a specific effect size or statistical power, but rather to derive estimates and confidence intervals. A minimum of 15 subjects receiving a novel treatment has been recommended for early studies of dose-response and futility in neurorehabilitation.[51] We also calculated predicted change and 95%

confidence intervals for both treatments. Predicted change after DSM treatment was determined from the data of the four pilot children who would meet the proposed selection criteria. A mean GMFM-66 increase of 5.3 was observed after six weeks of treatment. Assuming such change will be doubled after 12 or more weeks of treatment, a 10.6 increase from baseline is predicted as a minimum change after DSM treatment. Predicted change after CONV treatment was determined from maximum change in published GMFM-66 scores over six months in a 24 month old child classified as GMFCS level II.[55] A 1.8 increase from baseline is predicted after CONV treatment. We estimated that with a sample size of 17 participants receiving each treatment, a 2-sided 95% confidence interval for the difference in GMFM-66 will extend +/- 6 from the observed difference assuming that the common standard deviation (SD) is 9 (nQuery Advisor 6.0), which was larger than observed in the pilot data for a conservative estimate. An additional 8 children (4 in each group) will be enrolled to account for an anticipated attrition rate of 20%. Based on random assignment, 21 participants will receive DSM treatment, and another 21 will receive CONV treatment.

7 SAFETY MANAGEMENT

7.1 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study.

7.2 Adverse Event Reporting

Since the study procedures are not greater than minimal risk, SAEs are not expected. If any unanticipated problems related to the research involving risks to subjects or others happen during the course of this study (including SAEs) they will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

8 STUDY ADMINISTRATION

8.1 Treatment Assignment Methods

8.1.1 Randomization

After the initial GMFM-66 score from Assessment 1 is obtained, participants will be randomized to either the CONV or DSM treatment, using a randomization scheme to stratify by baseline motor ability. This will ensure that the groups do not differ in motor ability at baseline. Participants will also be randomly assigned to either the primary or secondary research therapist who will each provide both types of treatments, to minimize any differences related to individual therapist. A blinded assessor will collect all outcomes measures. Blinding of participants to treatment group is not feasible with the proposed interventions.

8.1.2 Blinding

A blinded assessor will collect all outcomes measures. Blinding of participants to treatment group is not feasible with the proposed interventions.

8.2 Data Collection and Management

Hard copies of case report forms and source data will be stored in a locked cabinet in a locked office. Electronic source data will be stored on a network share drive with access controlled by the PI. All data will be entered and stored in a project-specific REDCap (Research Electronic Data Capture) database. The database will be password-protected and daily backups will be stored. It will incorporate range checks and between-variables consistency checks to ensure quality control.

The electronic postural control data will be shared with researchers (Nicholas Stergiou, PhD and his team) at University of Nebraska Omaha, who are experts in nonlinear analysis of biomechanical data and will assist our team in interpreting these data. A portion of the treatment videos will be shared with motor development experts (Karen Adolph, PhD and her team) at New York University (NYU) who will assist our team in coding the videos for structure of walking behavior using their established methods of detailed infant movement analysis. The data files will stored in a secure, password protected electronic location, and will be regularly backed up.

8.3 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy and that the Investigator and other site personnel will not use such data and records for any purpose other than conducting the study. Participants will be assigned a unique identifier that contains no protected health information. Access to all data will be controlled by the PI. No identifiable data will be used for future study without first obtaining IRB approval. The investigator will obtain a data use agreement between the provider (the PI) of the data and any recipient researchers (including others at CHOP) before sharing either limited or identifiable datasets.

8.4 Regulatory and Ethical Considerations

8.4.1 Data and Safety Monitoring Plan

The incidence of adverse events is expected to be low in this single-site minimal risk research. The PI will be responsible for monitoring the data and safety of all participants. All study procedures will receive IRB approval prior to recruitment or enrollment of participants. In addition to the data management procedures outlined above, the PI will hold biweekly study team meetings to evaluate the safety and progress of all research procedures. Standard procedures for all data collection methods will be reviewed at the start and periodically throughout the study. Data checks for errors will be performed prior to analysis. Training log review and random video checks will be conducted regularly to ensure that the rehabilitation programs are delivered as intended. The PI will be actively involved in reviewing the progress of each study participant and will bring to the attention of the IRB adverse events and unexpected problems. Unexpected safety concerns will also be communicated with the NINDS Program Official in accordance with study regulations.

Additionally, if we experience adverse events in more than 15% of total participants, we will appoint a Study Monitoring Committee to review the safety events that occurred and monitor safety for the remaining duration of the study.

8.4.2 Risk Assessment

All treatment and assessment activities in the proposed research present no more than minimal risk to study participants. Children will have one-on-one supervision at all times during the assessment and treatment procedures by a licensed pediatric physical therapist. Risks include those involved with any pediatric physical therapy session or toddler play session, including bumps and bruises from falling or crashing into toys, and the unlikely possibility of muscle strain or soreness from overuse. The environment will be prepared such that only items safe for toddlers and young children will be in the treatment and assessment areas.

DSM treatment, which encourages falling, will occur over a floor of thin rubber mats to minimize the impact of falls. The weight support harness for DSM therapy is custom-made for the target age range, includes special provisions for small bodies and sensitive skin, such as narrow straps and use of neoprene, and will also prevent the impact of falls. The harness may prevent or reduce the impact of falling. Parents will be advised to dress the children in slim-fitting garments that have sleeves and their axilla areas will be checked periodically to assure that there is no skin redness from the harness. If children experience any discomfort with the harness, it will be repositioned until it is comfortable.

Additionally, protected health information will be collected as part of study records, and breaches of this information outside of the study team resulting in loss of confidentially is an unlikely but potential risk. We will follow CHOP policies to ensure compliance with HIPAA and IRB regulations for safeguarding participant information to protect against loss of confidentiality. Electronic data will be stored in secure, HIPAA-compliant, password-protected systems. Hard copies of data collection instruments and training logs will be stored in a locked cabinet in the PI's locked office. Participants will be assigned a unique identifier that contains no protected health information. Access to the identifiers of the coded data will be controlled by the PI and only study team members will have access to the electronic and paper data. All members of the study team will undergo Human Subjects Research training.

All adverse events will be reported in accordance with IRB and NIH requirements. All risks and alternative treatment options will be explicitly stated in consent documents.

8.4.3 Potential Benefits of Trial Participation

It is unknown whether the functional mobility of the participants will improve as a result of study participation, but evidence suggests that greater physical activity leads to improved motor performance. The results of the pilot study and outcomes of conventional early intervention rehabilitation also suggest that at least modest gains can be expected from participation in either rehabilitation treatment. The knowledge gained will inform early rehabilitation practice for other children with CP and other neurodevelopmental conditions, may lead to the development of other interventions, and the risk to participants is minimal.

8.4.4 Risk-Benefit Assessment

If the study hypotheses are supported, there will be implications for the rehabilitation of individuals with CP and other neurodevelopmental conditions, and the results will likely lead to the development of other interventions, including those that can by conducted in the home and smaller clinical settings. This knowledge is important because CP is the most common cause of physical disability in children, affecting over 10,000 babies each year in the United States, and few interventions exist for meaningful functional improvement. The 15 million individuals who live with CP worldwide experience this physical disability for their entire lifespan. There is no more than minimal risk to study participants, with the potential to learn important information about how to optimize motor development potential in young children with neurological injury. Therefore, the risk to potential benefit ratio for the proposed study is very small, and the potential importance is high.

8.5 Recruitment Strategy

Our goal is to enroll 16 and 20 participants in Years 1 and 2, respectively. The primary avenue for recruitment will be through the Neonatal Follow-up clinic at CHOP, directed by Dr. Bernbaum. Eligible patients seen in CHOP's CP clinic and those with CP who are receiving services at the Center for Rehabilitation will also be invited to participate. Potential candidates who are not CHOP patients will be reached through the internet (www.clinicaltrials.gov and the CHOP Research Institute website http://www.research.chop.edu/research/clinical_research/) and mailings to local clinicians, including therapists, developmental pediatricians, and pediatric neurologists. All recruitment materials will receive prior ethics approval.

We will also be working with the Recruitment Enhancement Core, including posting messages in the "This Week at CHOP" email to employees. Additionally, we will also work with the National Rehabilitation Information Center (NARIC) to send out notifications regarding our study. For both the "This Week at CHOP" and NARIC postings, we will use the approved blurb below in Section 7.01 (5.0) that is currently used on CHOP's public website.

We will also work with PeRC to distribute mailings to potential participants. PeRC will provide the study team with a list of names and contact information for mailings. Potential participants will be asked to call or email a member of the study team for additional information. Interested participants will be contacted via phone or email for a information about the study.

We will also work with Research Communications to create a short video about our study. This video will be distributed to rehabilitation therapists and early intervention agencies at CHOP and in the community outside of CHOP. This video can be shared with colleagues and/or caregivers of potential participants.

8.6 Informed Consent/Assent and HIPAA Authorization

A parent or legal representative of each potential participant will receive a verbal and written explanation of the purposes, procedures and risks of the study. If they are interested, the child will be scheduled for an initial physical therapy examination with the primary

research physical therapist. The therapist will conduct an examination to determine if the child meets the selection criteria. If eligible, the family will have the option to consider participation and later inform the therapist if they choose to participate, or they will be able to sign the informed consent documents at that time. Informed consent will be obtained by the research physical therapist, the trained study coordinator, or an investigator, and will be documented in the electronic database. The family will have the opportunity to ask questions throughout the entire process. The parent or legal representative must provide written informed consent prior to the start of any study activities. Written assents of minors will not be obtained due to the age of the participants.

8.7 Payment to Subjects/Families

8.7.1 Reimbursement for travel, parking and meals

To encourage attendance at scheduled appointments, caregivers of participants will receive $5 per session to reduce their transportation cost burden (which is $3 parking for patients and $2 fuel, or public transportation for the participant and a caregiver at $3.10 round trip per person within the city). This will be applicable to all visits, including both treatment and assessment sessions. Payment will be made through the ClinCard participant incentive program supported by the Research Institute.

8.7.2 Payments to parent for time and inconvenience (i.e. compensation)

Caregivers of participants will additionally receive $25 for completion of each of the 8 assessments, including all applicable measures. Payment will be made through the ClinCard participant incentive program supported by the Research Institute.

8.7.3 Payments to subject for time, effort and inconvenience (i.e. compensation)

In accordance with CHOP patient incentive guidelines, no monetary payment will be made to participants as they will be between 1-3 years of age.

8.7.4 Gifts

Participants will receive small tokens of appreciation for participation throughout the study, such as stickers, stuffed animal or other small toys.

9 PUBLICATION

Outcomes will be disseminated to various stakeholders, including pediatric and neurologic clinicians, rehabilitation researchers and parents. Examples of peer-reviewed scientific publications include *Developmental Medicine & Child Neurology*, *Neurorehabilitation and Neural Repair*, *Physical Therapy*, and *Gait & Posture*.

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