Low-intensity versus high-intensity home-based treadmill training and walking attainment in young children with spastic diplegic cerebral palsy

NCT #: NCT02424526

Date: 7/29/2014

Study Protocol and Statistical Analysis Plan

Study Design

This is a prospective randomized controlled study which will include 24 pre-ambulatory children with CP under 3 years of age (i.e. up to the child's third birthday), GMFCS levels I and II.

Study Sites

All assessments and interventions will be conducted at the children's homes. In order to achieve a culturally and ethnically diverse sample, children will be enrolled at three sites in two US states. Dr. Bjornson will enroll children at the Seattle, WA site, Dr. Looper will enroll children at the Tacoma, WA site and Dr. Mattern-Baxter will enroll children at the Sacramento, CA site. Seattle, WA has a relatively high-income White (non-Hispanic descent) and Asian urban population; Tacoma, WA has a relatively lower-income White, Black and Hispanic urban population; Sacramento, CA has a relatively middle-income Hispanic, Black and Asian urban and rural population.[23] Conducting the study at these 3 sites will enable us to better generalize the results to a larger population.

Participants and Characteristics

24 pre-ambulatory children with CP under 3 years of age, GMFCS levels I and II, with bilateral impairment, who show signs of walking readiness will be recruited at the 3 different study sites. Eight children will be randomly assigned to a low-intensity or a high-intensity treadmill training group at each site.

Inclusion criteria will include

- Signs of walking readiness as demonstrated by the ability to sit for 30 seconds when placed and to take 5 to 7 steps when supported at the trunk or arms. These criteria were used in previous research to assure that the children had sufficient trunk control and bipedal control for the treadmill intervention.[17] Children will be pre-ambulatory and will not engage in regular ambulation with an assistive device outside of physical therapy.
- Because young children often are not formally diagnosed with CP until 2 years of age, we will include children
    - who show bilateral symmetrical or asymmetrical impairment (i.e. diplegia and quadriplegia, but not hemiplegia)
    - who demonstrate upper motor neuron signs (i.e. spasticity and/or hyperreflexia)
    - who have been identified as high-risk for a motor disability by a physician

Exclusion criteria will be

- a history of uncontrolled seizures
- a diagnosis of a genetic disorder
- cardiac or orthopedic contraindications for standing and walking
- orthopedic surgery in the past 6 months
- use of spasticity-reducing medication or Botox injections in the past 6 months
- participation in other previous or concurrent intensive physical therapy programs

Interventions

All children will continue their regularly scheduled physical therapy during the study period. Frequency of ongoing physical therapy interventions as well as the physical therapy approach will be recorded for each child. All interventions will be conducted at the children's homes. On the first visit, the

PI will provide a portable pediatric treadmill for the family's use at no charge for the duration of the intervention period. The treadmill is designed for research and is equipped with a non-resettable minute timer and adjustable handle bars.[27] There will be a one-week training period for each child to familiarize the family with the treadmill intervention. After initial set-up of the treadmill, the PIs will conduct weekly visits to the family. The children will undergo 6 weeks of treadmill training in their homes administered by a parent or primary caregiver who has been trained to safely provide the intervention. The weekly visits will be conducted by the PIs to adjust the treadmill speed and make any needed corrections to the parents'/caregiver's technique.

Children assigned to the high-intensity group will walk on the treadmill 5 days/week, twice daily for 10-20 min for 6 weeks. Children in the low-intensity group will walk on the treadmill 2 days/week, once daily for 10-20 minutes for 6 weeks. The parents will be encouraged to take a break on two days of their choice, depending on the family's other commitments. The treadmill speed will be determined based on previous protocols developed by Dr. Mattern-Baxter.[17] The initial treadmill speed will be set at the maximum speed at which the child can maintain walking without dragging his/her feet for more than 3 seconds. The treadmill speed will be increased during the weekly investigator visits as tolerated by the child, using the same criterion. The children will wear shoes and/or their customary orthotics during the walking. The treadmill speeds will not exceed 0.6 meters/second, which is the maximal speed available on the pediatric treadmills. It is anticipated that all children will walk at a speed between 0.1 and 0.3 meters/second.

Due to their young age, some of the children, particularly those in the high-intensity group, might have difficulty maintaining attention to the task during the intensive intervention. In order to keep them motivated during the treadmill walk, the treadmill will be placed in front of a TV or laptop showing an age-appropriate movie chosen by their parents. This technique has proven to be helpful in previous studies and has the added benefit of preventing the children from looking downward.[17,20] In one previous study, the average daily time walked on the treadmill was 28.2 ± 11.2 minutes for the twice daily walking periods by a similar group of children using the above described motivational techniques.[17]

Some children might be unable or unwilling to hold onto the handle bars of the treadmill. In this case, a second parent will be necessary to help the child maintain grip of the handle bars. If a second person is not available, the child's hand can be loosely strapped onto the handle bar for the duration of the walk.

Outcome Measures

Each child will be tested at pre-intervention, post-intervention, at 1-month and at 4-months following the intervention.

Valid and reliable outcome measures at the *Body Structures and Functions Level* of the International Classification of Functioning, Disability and Health (ICF) Model[28] will include the 1-minute Walk Test. Outcome measures at the *Activity Level* of the ICF model will include the Gross Motor Function Measure-66 (GMFM-66), Peabody Developmental Motor Scales-2 (PDMS-2), Functional Mobility Scale (FMS), the Timed 10-meter Walk Test and the StepWatch accelerometer. Outcome measures at the *Participation level* of the ICF Model will be the Pediatric Evaluation of Disability Inventory Mobility Scale (PEDI). Videotapes of assessments will be scored by an assessor blinded to group allocation for the GMFM and PDMS-2.

- 1-minute Walk Test: The child's walking distance will be measured in meters over 1 minute at their self-selected walking speed if the child is able to walk with an assistive device. The 1-minute Walk Test is a reliable test of walking endurance in young children with CP, when administered after a practice trial. Due to the young age and early ambulatory status of the children, the 1-minute Walk Test is more appropriate than a 6- minute Walk Test.[29]

- GMFM-66: The child's gross motor skills related to rolling, sitting, crawling, standing and walking will be assessed by observation. This measure is criterion-referenced and design to track progress over time in children with cerebral palsy. The GMFM is considered the gold standard for the assessment of children with CP and has excellent validity, reliability and sensitivity to change in young children.[3,30]
- PDMS-2: The child's gross motor skills compared to children with typical development are assessed by observation. This measure is norm-referenced and determines the amount of developmental delay in a child compared to typically developing children. The PMDS-2 is used widely and shows excellent responsiveness to change over time.[31]
- FMS: This scale is used to document the child's current mobility level and the amount required for walking at different distances. It is designed to rate a child's walking ability over household, classroom and community distances. Children are rated on a Likert scale from 1 to 6 with 1 being the lowest ranking (uses wheelchair) and 6 being the highest ranking (independent on all surfaces). The FMS has been found to reliably measure the amount of support needed for walking in children with CP.[32,33]
- Timed 10 meter walk test: The child's walking speed will be recorded over 10 meters if the child is able to walk with an assistive device. The timed 10MWT has shown to be most reliable in young children when they are encouraged to walk at a fast speed rather than a self-selected speed.[34] The children will be motivated to walk at their fastest speed when administering this test.
- PEDI: The PEDI is a valid and reliable tool that provides an assessment of a child's functional status and performance.[35] This is a parent questionnaire regarding their child's mobility needs. The Mobility Scale of the PEDI will be used, which is based on parent report and observation.

- StepWatch data will be collected for all awake daytime hours over a 7 day period at study onset before treadmill training commences and at each of the post-intervention assessments. The StepWatch accelerometer has been shown to reliably measure walking activity in children with CP.[26] To assure consistency in data collection, study investigators will participate in a 2-day training session prior to study onset. Training in use of StepWatch accelerometers and treadmills, standardization of training protocols and administration of outcome measures will assure inter-rater reliability.

Enrollment procedures

An equal number of children will be enrolled at each site for a total of 8 children per location. Of these eight children, four children will be randomly assigned to the low-intensity and four will be assigned to the high-intensity group. Randomization will be conducted via blinded drawing from administrative personnel at their respective sites.

The PI and C-PIs are all engaged in clinical practice at their facilities and have professional connections with medical and therapy facilities in their communities. At each site, advertisement for the study will be conducted via posted flyers, electronic flyers and word-of-mouth recruitment.

Dr. Mattern-Baxter will recruit children from Alta Regional Center Sacramento, the area's main provider of early intervention services, from Easter Seals Sacramento, from Shriner's Hospital Northern California, from University of California Children's Hospital, from Sutter Hospital Sacramento, and via the Sacramento Pediatric Therapy Interest Group. Dr. Mattern-Baxter successfully recruited from these sources for past studies and is known for her research in the medical and therapy community. Staff support for recruitment will come from professional connections at each recruitment site and at the University.

Dr. Bjornson will use a directed recruitment mailing to children and their families who have received care at Seattle Children's Hospital and to community therapy providers in Western Washington State. Seattle Children's Hospital provides care to ~ 800 children with cerebral palsy each year primarily through Developmental and Rehabilitation medicine departments. Dr. Bjornson has an extensive history of recruitment for clinical trial for children with CP (i.e. Selective Dorsal Rhizotomy, Botox and Intrathecal Baclofen).

Dr. Looper will recruit from local early intervention providers (including Birth to Three Developmental Services, A Step Ahead in Pierce County, and Tacoma Learning Center), Mary Bridge Children's Hospital, the Children's Therapy Unit, and from Washington Pediatric Special Interest Group. Dr. Looper has successfully recruited subjects from these sites previously.

No problems with recruitment of study participants are anticipated due to each investigator's connections in their local medical community. If one of the sites should fall short of qualified children, more children could be covered at one of the other sites. Drop-out rates are expected to be low due to the home-based nature of the study. All of the outcome measures as well as the intervention will be conducted at the children's homes. It is possible that a young child might fall sick for any of the planned visits by the PIs, or might not fully participate in one of the visits for other reasons. In this event, the PI will reschedule a repeat visit within a few days of the original visit to collect the data.

Between the three sites, twelve children will receive high-intensity treadmill training and twelve children will receive low-intensity treadmill training. Due to the stringent inclusion and exclusion criteria, the children in the two groups are expected to show no significant between-group differences at baseline. In Dr. Mattern-Baxter's previous study on home-based treadmill training, group allocation using the same criteria led to two groups with no significant differences regarding age and developmental skills.[17]

Power Analysis

Power analysis was conducted to determine a sample size based on developmental data and based on StepWatch data.

To examine the optimal dosing for walking attainment, a projected sample size of 18 subjects (9 per group) at 95% power was calculated from Peabody Developmental Motor Scales-2 Locomotion subscale change scores from Dr. Mattern-Baxter's previous home-based treadmill training study (n=12; GMFCS levels I and II; ages 15-32 months)[17]. An additional 6 subjects will be added to strengthen the study design and allow for possible attrition, leading to a total number of 24 subjects.

To assure sufficient power to assess the effects of treadmill training on overall walking activity, a proposed sample size of 12 per group would have 80% power to detect a 3000 stride/day difference in treatment intensity as measured with the StepWatch monitor. This is based on Dr. Bjornson's cross-sectional StepWatch average stride/day data from 17 youth with CP ages 2-3 years where the mean difference between GMFCS level I and II was 3000 strides.[18]

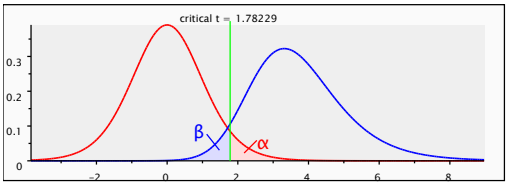


Fig. 4. Power analysis for sample size (α =0.0; Power= 0.95; Effect size=1.87; Sample size=18)

Methodology

Approval from the University Institutional Review Board was submitted on July 10, 2014 and approved on July 29, 2014 by the lead institution at California State University, Sacramento. A cooperative agreement will be put in place prior to study onset with the other institutions (please see attached). Due to the children's young age, written informed consent will be obtained from the parents. Parents will be asked to commit to a 6-week stretch uninterrupted by vacations or breaks. Study participation will be discussed and scheduled carefully with the families to allow for 6 weeks of uninterrupted intervention period. Due to the nature of the home-based administration of the intervention by parents and caregivers, high adherence to the study protocol is expected. Investigators will schedule weekly home visits and all assessments at a mutually agreed upon time that is convenient for the families.

After consenting to study participation, the parents for each child will fill out a parent questionnaire containing demographic and health information about their child. A physician form will also be signed prior to study onset to seek medical clearance for the child for the intervention. Group allocation will be determined by blinded drawing from a hat until each of the three study sites has reached a total of 4 children in each group. In the unlikely event that one site might have difficulty with subject recruitment, additional children will be enrolled at another study site.

A portable pediatric treadmill equipped with a non-resettable minute timer and adjustable handle bars will be provided to the families at no charge for the duration of the intervention period. The treadmill handles will be adjusted to the child's correct height. There will be a one-week training period for each child to familiarize the family with the treadmill intervention. This will be achieved by demonstration by the PI, followed by correct execution by the parent. Should a parent be unable to perform the treadmill training safely, additional training will be provided. In the unlikely event that a parent should be unable to learn to perform the intervention safely, the PIs reserve the right to remove the treadmill from the home and cease the child's study participation. In this case, this subject will be reported as a drop-out and the data will be excluded.

In the improbable event of technical problems with one of the treadmills, Dr. Mattern-Baxter will substitute the treadmill with one that is currently housed and used in a community program at the University. This back-up treadmill could be shipped overnight to another site if need be.

Each child will be tested at pre-intervention, post-intervention, at 1-month and at 4-months following the intervention. The testing will be scheduled at a mutually agreed-upon and convenient time with the family at their home. The children will undergo 6 weeks of treadmill training in their homes administered by a parent or primary caregiver who has been trained to safely provide the intervention. Weekly visits will be conducted by the researchers to adjust the treadmill speed and make any needed corrections to the parents' technique. The treadmill speed will be increased each week as tolerated by the child. The speed will not exceed 0.6 meter/second. In a previous study by Dr. Mattern-Baxter using a similar sample and treadmill protocol, the average starting speed was 0.1 meters/second and increased to an average of 0.25 meter/second over the duration of 6 weeks.[17] Children assigned to the high-intensity group will walk on the treadmill 5 days/week, twice daily for 10-20 min for 6 weeks. Children in the low-intensity group will walk on the treadmill 2 days/week, once daily for 10-20 minutes for 6 weeks. The children will be motivated during the treadmill walk with a child-friendly video shown on a television, computer, or tablet. If uninterested, children will be encouraged with other motivational toys suggested by the parents. These motivational methods led to high adherence in Dr. Mattern-Baxter's previous study on a similar sample of young children with CP.[17]

There is a possibility that a child might miss a training session due to sickness or other family obligations. The parents will be encouraged to make up a missed session on a different day. In the low-intensity group, the children have 5 days/week without treadmill training that could be used as make-up days. In the high-intensity group, the children have 2 days/week without treadmill training that could be used as make-up days. If a missed day cannot be made up, the parents will be encouraged to attempt to

train for the maximal 20 minutes for each treadmill walk in order to make up some of the missed minutes during other walks. The parents will document the minutes walked and the speed of each treadmill walk on a paper flow chart that is provided to them by the PIs.

Outcome measures at the *activity level* of the International Classification of Functioning, Disability and Health (ICF) Model will include the Gross Motor Function Measure (GMFM), Peabody Developmental Motor Scales-2 (PDMS-2), Functional Mobility Scale (FMS), the Timed 10-meter Walk Test, the 1-minute Walk Test and the StepWatch accelerometer. Outcome measures at the *participation level* of the ICF Model will be the Pediatric Evaluation of Disability Inventory Caregiver Mobility Scale (PEDI). Videotapes of assessments will be scored by an assessor blinded to group allocation for the GMFM and PDMS-2. StepWatch data will be collected for all awake daytime hours over a 7 day period at study onset before treadmill training commences and at each of the post-intervention assessments. The StepWatch monitor will be secured around the child's ankle with a small knit cuff. Dr. Bjornson has successfully employed this method of monitor attachment in toddlers with and without motor limitations.[23,36] StepWatch outcomes will be average number of strides/day and the percentage of the time walking.

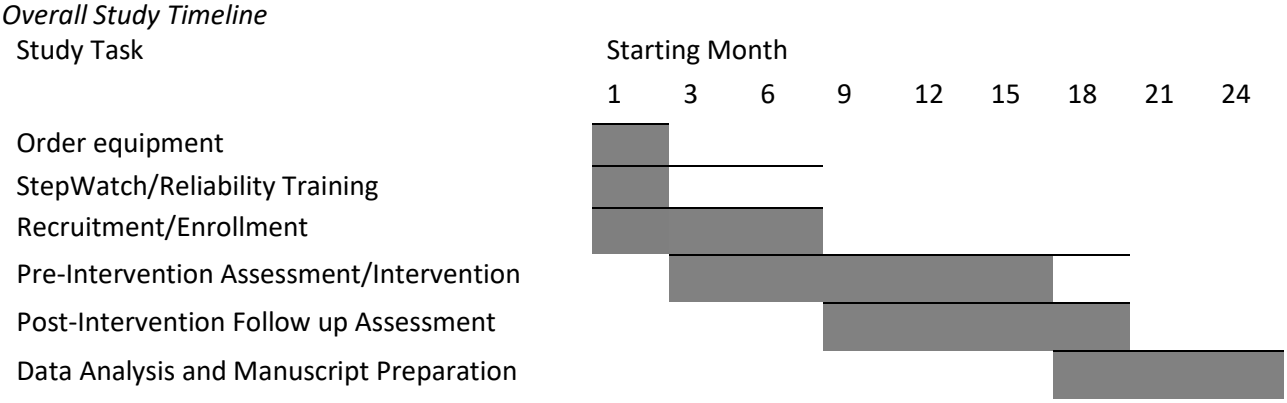
In order to address specific aim # 1 (optimal parameters for dosing home-based treadmill training by comparing high-intensity to low-intensity treadmill training)and specific aim # 2 (effects of high- versus low-intensity treadmill training on walking attainment and overall walking activity), between-group differences of all the outcome measures will be analyzed as described in the next section. Specifically, between-group differences in GMFM and PDMS-2 will examine the effects of dosage on walking attainment and skills related to standing and walking. The changes in support needed for walking will be measured by the FMS in the two groups. Differences in walking speed and walking endurance will be analyzed using the data from the Timed 10-meter Walk Test and the 1-minute Walk Test, respectively. The parent perspective on overall child mobility will be analyzed by using the PEDI. Finally, overall walking activity will be shown by between-group differences from the StepWatch data.

Data Analysis

A one-way analysis of variance (ANOVA) with repeated measures will be used for comparison of treatment groups for parametric dependent variables, i.e. PDMS-2, GMFM, Timed 10-meter Walk Test, and 1-minute Walk Test. Analysis for non-parametric data for dependent variables, i.e. PEDI and FMS, will be conducted using the Friedman test for comparison between groups. StepWatch data will be examined with the Wilcoxon sign rank test for paired data. Post hoc tests will be performed where appropriate. Alpha will be set at 0.05. In addition, data on whether children reached the minimum clinically important change will be reported for the GMFM.[37]

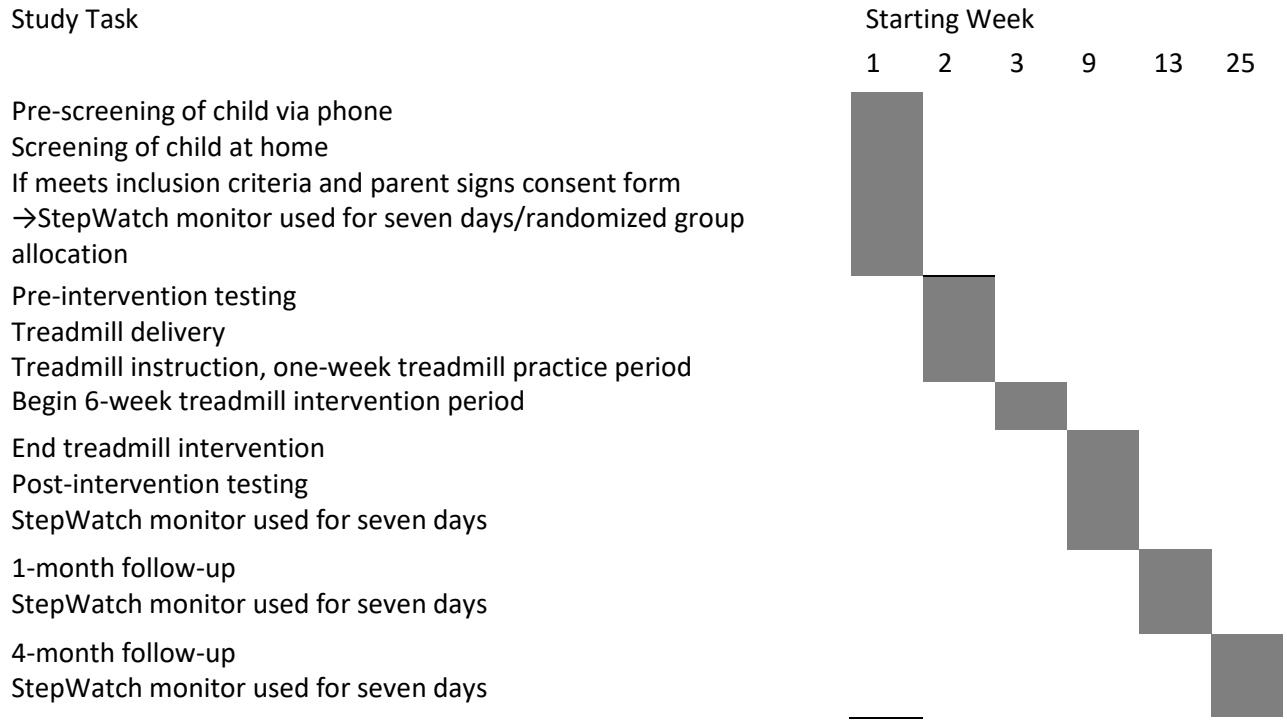
Study Timeline

Overall Study Timeline



Study recruitment will commence as soon as all study sites have signed the cooperative IRB agreement. All equipment will be ordered immediately after the receipt of the grant. Training on StepWatch use will be conducted by Dr. Bjornson at Seattle Children's Research Institute. Dr. Mattern-Baxter and Dr. Looper will participate. During the same meeting, reliability training will be conducted on other outcome measures. Recruitment and enrollment will commence immediately by distributing study information at the three sites. It is anticipated that there will be coinciding intervention and data collection for the 8 children at each site for the duration of 15 months. Two treadmills will be available at each site for the 6-week treadmill intervention periods for each child. Video review will be ongoing by the consultant, who is blinded to group allocation, as the videos become available for each child. Preliminary data analysis will be conducted in order to present initial results at conference within the grant period. Once all data is collected, there will be a second on-site meeting of the three PIs in order to assure consistent data entry and to allocate the responsibilities for study result dissemination. All three investigators will engage in manuscript preparation with Dr. Mattern-Baxter as first author. Data analysis will be performed by a statistician at the lead institution in collaboration with the PIs. Manuscript preparation will be conducted in the final two months of the 24-month study period.

Study Timeline for Each Subject



As indicated above, each child will be enrolled in the study for a total period of 26 weeks.

Human Subjects

The study protocol was submitted to the Institutional Review Board (IRB) at California State University, Sacramento, on July 10, 2014 and approved on July 29, 2014 (IRB protocol #13-14-156). In addition, the consent form, permission to be videotaped, parent questionnaire and physician form for the study were all approved by the IRB. Once the grant is received, a cooperative agreement form will be signed by the two participating universities before the study commences.

Selection of the families will be made by judgment of the PI. Factors will include parental ability to correctly perform the treadmill training and safety during treadmill training sessions. The PIs reserve the right to terminate participation in the study if parents are unable to adhere to the agreed-upon treatment regimen, or display incorrect or unsafe technique during training. Any adverse events will be reported to the IRB. Because this intervention is conventionally used in physical therapy practice, adverse events are not anticipated. A small incentive will be offered to families to encourage participation. The families have the right to terminate participation in the study without any reason or penalty.

The study will be conducted in the children's homes. The last names of the children will not be used when other persons are present in the area. The PIs will abide by Health Insurance Portability and Accountability Act (HIPAA) regulations on children's privacy. When reporting results, only ages, diagnosis, functional level and gender of children will be reported. Photographs and/or video clips of children might be used when reporting results, but only with written permission of the parents/guardians. No mention of exact geographical location will be made.

The outcome measures used in the study are all used in clinical practice and do not contain any items that might be harmful to a child. Data will be recorded in questionnaire, on standardized measure forms and in handwritten notes. Data will be obtained manually and entered into computer files. The participants and their families will be videotaped with their consent at the assessment periods and during treadmill walking and during the other assessments. Digital video files will be recorded on a video camera which is dedicated to research and will be stored on the PI's password protected computer. All forms with identifying information will be kept in a locked file cabinet. The PI will be handling all of the data entry. The information will be used for publication and presentation at conferences. All files will be kept in a locked cabinet at the university and the records will be destroyed five years after the end of the project. Video files and photos of the subject will be used during publications/presentations with the subject's written permission.

Pediatric treadmills will be used.[27] They are plugged into the wall by a switch that was installed by a licensed electrician. The treadmills will be unplugged when not in use. The treadmills were built for children with special needs. They have handle bars for the children to hold onto on the sides and front. They have a non-resettable minute-timer to keep track of the number of minutes walked during each session. They also have been built for accidental spills onto the treadmill belt and there will be no electrical shorts from moisture. The pediatric treadmill is built for the purpose of enabling children to walk and has a speed range from a very slow 0.1meter/second to 0.6 meters/second.
The StepWatch accelerometers are used to measure walking activity. They are strapped onto the child's ankle with a soft strap. In case of skin irritation from the strap, padding could be added.

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