PARTNERS HUMAN RESEARCH COMMITTEE
PROTOCOL SUMMARY

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR

Paolo Bonato, PhD

PROTOCOL TITLE

Robotic-assisted therapy to improve manual dexterity in children with cerebral palsy: a pilot study on clinical outcomes and muscle synergies as a possible predictor of response.

FUNDING

Thrasher Research Fund

VERSION DATE

August 3rd, 2020

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

Aim 1. Assess the effectiveness of robot-assisted training on hand function and quality of life in children with CP.

Aim 2. To study the relationship between muscle synergies and the outcomes of robot-assisted training.

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

Pediatric cerebral palsy (CP) is a group of disorders affecting movement, development and posture leading to functional limitations. CP is the most common motor disorder in children (over 2 per 1 000 live births[1]) and the leading cause of chronic childhood disability. It is attributed to non-progressive alterations occurring in the brain during fetal and newborn development[2]. Clinical features of children with CP usually include weakness, spasticity, and loss of selective motor control[3]. Often, there are deficits in the integrity of neuroanatomical structures and pathways required for precision grasping and fine motor control of the fingers[4,5]. As such, skilled finger movements and hand function do not develop normally[6-8]. This leads to severe limitations in activities of daily living (ADL)[9-11]. The severity of impairments observed in children with CP is associated with deficits in specific domains of quality of life (QoL) (*i.e.* physical well-being, and social support and peers)[9]. Also, overall participation in ADL also has a significant impact on QoL (*i.e.* physical well-being, moods and emotions, and social support and peers)[9]. Therefore, not only should therapy focus on improving motor symptoms, it should aim to improve the performance of ADL.

Based on motor learning theories, recent studies have demonstrated that **intensive, repetitive, task-oriented therapies** (IRTT) can help a paretic limb "relearn" how to perform movements that were lost after brain damage[12,13]. The same principle can be applied to children with CP that do not have to relearn given movements but rather learn how to perform them in a functionally adequate manner[14-16]. The mechanism by which functional recovery and motor learning are believed to occur is through the enhancement of neuronal plasticity[17]. A motor learning study in humans has shown that 300 to 800 repetitions per session are needed for motor learning to occur[18] yet, only an average of 32 repetitions of upper-limb movements is achieved during conventional therapy[19]. There is robust evidence that IRTT can improve motor and functional ability of the hand[20]. While there is limited evidence for the efficacy of most approaches to hand rehabilitation in CP[21], some studies have demonstrated that children with hemiplegia may benefit from intensive unimanual practice[14,15]. One approach that has demonstrated promising outcomes in hand rehabilitation in children with CP is constraint-induced movement therapy (CIMT)[22-27] since it involves restraining the non-paretic limb while providing intensive targeted practice with the paretic limb. However, the use of CIMT is fundamentally flawed when done in children[28] and, as such, must be modified; and the approach can lead to temporary deficits in QoL during the prolonged treatment period (use of a cast). Consequently, novel approaches that enable IRTT need to be implemented in children with CP. Robotic devices have become a very important area of research because of their capacity to achieve IRTT[29,30]. While the use of robotic-assisted therapy (RAT) to improve grasping and fine motor control has yet to be implemented in children with CP, RAT has been demonstrated as an effective intervention in children with CP for gait rehabilitation[31-37] and reaching movements[38,39] suggesting that using the RAT could improve hand function in this population. In the proposed study, we will assess the effectiveness of the Amadeo®. The device has been shown to improve manual dexterity in stroke survivors. The computer-controlled device maintains patients' forearm in a secure position using Velcro straps. The patients fingertips are then attached to the robotic device using mild adhesive tape (like a band aid). Patients then have to control interactive games displayed on the screen using their fingers.

In addition to assessing the efficacy of RAT, the proposed study aims to identify predictors of responsiveness to the intervention. This is of significance in order to adequately select children that will obtain the best outcome following IRTT as much variability can be observed in response to RAT. Baseline functional impairments have been shown to be important determinants of overall gross motor improvements following RAT of gait (*i.e.* more initial impairment → less improvements) suggesting that children may need to attain a certain level of motor function before being able to achieve optimal outcomes using RAT. While the current study also proposes to identify predictors of motor outcome following RAT using clinical outcome measures, we will also utilize a physiological measure (muscle synergies) that we have assessed to be a predictor of motor outcome following RAT of gait.

The scientific community widely accepts that the Central Nervous System (CNS) adopts several strategies to reduce the complexity of the control of movement[40-44]. Many authors have shown that one of these strategies consists in using a limited number of primitive signals undergoing the activation of muscles which, when combined, generate a full collection of movements[41].

Some studies have shown that the sensitive nature of EMG to represent an aberrant motor control in CP[45]. However, the assessment of muscle synergies during grasp has yet to be performed in this or any other population. Nonetheless, the similarity of gait synergies in CP, stroke, and

infant rhythmic-stepping indicates that there are common changes in control after brain injury that may reflect control in early development[46].

Whereas clinical measures of impairment in SMC are available[47], such measures do not provide information that is suitable to design physical therapy interventions aimed to address specific impairments and hence improve clinical outcomes of robot-assisted gait training.

If successful, the proposed approach would be expected to significantly improve clinical outcomes of manual dexterity in children with CP.

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

A sample of 10 children with CP with no major orthopedic or neurological complications that could interfere with the robot-assisted training will be recruited in the study. This sample size was calculated for an F test with an effect size of 0.4, an alpha of 0.05, a beta of 0.80, a correlation coefficient between repeated measures of 0.7, and an attrition rate of 20%. A study clinician will screen potential subjects. Screening will include a standard history and physical exam to ensure subjects meet all entry requirements after consideration of inclusion and exclusion criteria. Specifically, Dr. Nimec, the study physician, will assess all subjects' suitability for using the Amadeo.

Inclusion criteria:

- Diagnosis of CP with upper-limb impairment
- 6 to 18 years of age.
- Manual Ability Classification Scale Level II or III.
- Ability to communicate pain or discomfort.

Exclusion Criteria:

- Recent use of upper-limb robotic-assisted training within the last 3 months.
- Contraindication to robotic-assisted manual training such acute and pronounced pain symptoms despite conventional pain therapy of the upper-limb, lack of compliance, high-grade ataxia, advanced osteoporosis, and fractures of the upper-limb.
- Modified Ashworth Scale (MAS) of 4 in the upper-limb.

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

All study procedures will take place in the Motion Analysis Laboratory at Spaulding Rehabilitation Hospital, Boston, Massachusetts, USA. Spaulding Rehabilitation Hospital is an affiliated hospital of Harvard Medical School.

Assessments

Once the children are enrolled in the study, they will undergo a baseline assessment before undertaking a 6 weeks/18 sessions RAT program. Once training is completed, the children will undergo a final assessment. Finally, a follow-up assessment will be performed one month after the end of the RAT program to evaluate retention in the quality of life.

The follow up assessment will be performed 4 weeks after the end of the intervention and will consist in the cerebral palsy Quality of Life Questionnaire, which it will be provided to the subjects and they will be asked to fill it out and return to us when completed by email or mail (note: the questionnaire does not include any identifiable information).

Clinical tests

Clinical tests will be conducted by a study staff before and after the intervention. Clinical testing should last about 1 hour and will include:

• Physical examination: we will gather measures of Range of Motion (ROM) and muscular strength for the upper extremities. Passive and active movements of the shoulder (flexion, extension, abduction and adduction), elbow (flexion and extension), radioulnar joint (pronation and supination), wrist (flexion, extension, abduction, and adduction), and fingers (flexion, extension, abduction, and adduction) will be assessed with a goniometer.

• Modified Ashworth Scale (MAS)[48,49]: We will assess spasticity at the shoulder (flexion-extension); elbow (flexion-extension); radioulnar (pronation-supination), and wrist (flexion-extension).

• Quality of Upper Extremity Skills Test (QUEST): this standardized test is a validated and reliable tool to evaluate movement patterns and hand function in children with cerebral palsy. The QUEST evaluates quality of upper extremity function in four domains: dissociated movement, grasp, protective extension, and weight bearing.

• Box and block test[52]: this test assesses unilateral gross manual dexterity. Children are seated at a table, facing a rectangular box that is divided into two square compartments. The individual is instructed to move as many blocks as possible, one at a time, from one compartment to the other for a period of 60 seconds.

• The cerebral palsy Quality of Life Questionnaire[53]: this standardized test assesses 7 domains related to quality of life (social wellbeing and acceptance, feelings about functioning, participation and physical health, emotional wellbeing and self-esteem, access to service, pain and impact of disability, and family health) and was specifically developed for children between 4-12 years of age with cerebral palsy. It is designed for self- and parent proxy report.

• *Statistical analyses:* We will perform a descriptive analysis of the different outcome measures and compare results between pre and post intervention.

Lab-based study

We propose to analyze the muscle synergies of subjects using a method developed by members of the Motion Analysis Laboratory and their collaborators[41,54-60]. Subjects will be asked to reach and grasp objects of different sizes and shapes. Electromyographic (EMG) activity will be collected from 16 muscles of the upper-limb (*i.e.* Teres Major, Infraspinatus, Superior trapezius, Deltoid anterior/posterior, clavicular head of Pectoralis major, Triceps brachii lateral head, Biceps brachii (long head), Brachioradialis, Extensor digitorum communis, Extensor carpi radialis longus, Flexor carpi radialis, Flexor carpi ulnaris, First dorsal interosseous, Abductor pollicis brevis, Abductor digiti minimi). This same procedure will be replicated contralaterally. Additionally, reflective markers will be placed bilaterally on the subjects' upper-limbs (i.e. C7, T10, Manubrium sterni, Xiphoid process, Acromion, Lateral epicondyle, Styloid process of the radius, Styloid process of the ulna, distal head of the first/second/third/fourth/fifth metacarpus, distal head of the first/second/third/fourth/fifth proximal and distal phalanges, and distal head of the second/third/fourth/fifth middle phalange) in order to assess movement kinematics. The entire process should last approximately 1.5 hour.

Extracting Muscle Synergies: Muscle synergies and their activation coefficients will be extracted from the EMGs using a nonnegative matrix factorization (NMF) algorithm. The NMF models the activity of the muscles as a linear combination of several muscle synergies, each activated by a time-dependent coefficient. Synergies will be extracted separately from the EMGs of each limb. A first estimate of the number of synergies of each limb will be obtained based the quality of reconstruction of the original EMG channels.

Estimating the Number of Muscle Synergies: We will decompose the EMG matrix increasing the number of synergies up to the point where the reconstructed envelopes, obtained multiplying the synergy vectors by the temporal activations, have an average R^2 similarity with the EMG envelopes above 0.8 and a minimum R^2 similarity on the individual channel above 0.6.

Quantifying Synergy Similarity: Similarity between the synergies of each limb will first be assessed using the scalar product. We will further quantify synergy similarity by estimating the dimensionality of the subspace shared between the spaces spanned by the synergies of the two limbs by computing the principal angles between sets of synergy vectors and finding the number of principal angles whose cosines are greater than a threshold.

Statistical analyses: Results of the number of synergies, and similarity between limbs will be compared descriptively.

Assessing the relationship between muscle synergies and response to therapy: he relationship between changes in the Muscle Synergies and clinical scores (QUEST and Box and Block Test) will be investigated on a case by case basis evaluating the differences between the visits.

We will ask permission to study participants to video record them during the performance of the above-described clinical tests and the lab-based study.

Training:

Training will be performed using the Amadeo®. The computer-controlled device maintains patients' forearm in a secure position using Velcro straps. The patients fingertips are then

attached to the robotic device using mild adhesive tape (like a band aid). Patients then have to control interactive games displayed on the screen using their fingers.

- Each training session will include 30 minutes of active movements that can be divided into up to 3 bouts of 10 minutes depending on patient fatigue. During the training bouts, children will be encouraged to move continuously and as actively as possible. The Amadeo® provides several interactive games to facilitate motor learning. Between bouts, children will be allowed to rest for at least 5 minutes. Adjustments in training intensity will vary according to the children's ability and endurance. Training will take place up to 4 times per week for a total of 18 sessions over up to 7 weeks. Sessions will last approximately 60 minutes (including setup, training, and rest between each bout).

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

Treatments for children with cerebral palsy to improve manual dexterity can include intensive unimanual physical therapy or constraint-induced movement therapy. The approaches focus on having patients use their impaired hand more extensively. Therapeutic options specific to providing a decrease in spasticity can include physical therapy (constraint-induced movement, strength therapy, orthoses, serial casts); oral medications (benzodiazepines, baclofen, tizanidine, dantrolene); botulinum neurotoxin injections, phenol or ethyl alcohol perineural injections, intrathecal baclofen, selective dorsal rhizotomy or musculoskeletal surgical procedures. The Amadeo® robot training is an advanced version of intensive unimanual physical therapy. It is not the current standard of care.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

Risks to participants will be minimized by following the Spaulding Rehabilitation Hospital Policy and Procedure: General Safety Precautions and Procedures for the Conduct of Human.

All laboratory equipment meets or exceeds hospital standards for electrical safety.

The robotic device that we propose to use in the study (i.e. the Amadeo® by TyroMotion) has been developed for adults and pediatric populations above 3 years of age (see device brochure). Training sessions will be always overseen by a study staff trained in the use of robotic systems for upper-limb training.

Subjects with CP are at higher than normal risk for falls and injuries from daily activities. Subjects will be under constant observation. Trained staff will be nearby to help in case of loss of balance. During training and when standing is not required, subjects will be seated on a comfortable chair.

The investigators will use hypo-allergic tapes and bandages that are unlikely to cause skin irritation.

To minimize fatigue, subjects will be allowed rest periods and will be monitored and observed by study staff at all times during the experiments.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

Subjects will be screened prior to and during enrollment for the presence of medical conditions that may contraindicate their participation.

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

The robotic device that we propose to use in the study (i.e. the Amadeo® by TyroMotion) has been developed for adults and pediatric populations above 3 years of age (see device brochure). Training sessions will be always overseen by a study staff trained in the use of robotic systems for upper-limb training. The risks of using the Amadeo® include muscle soreness and fatigue, but no harmful adverse events have been reported with its use. Trained study staff will stretch the hand of the participants to minimize soreness. The Amadeo® is being used in another approved protocol that is taking place within the MAL (2015-P002107).

Subjects with CP are at higher than normal risk for falls and injuries from daily activities. Some of the proposed testing procedures will assess the subject's performance of activities of daily living. In general, subjects will be at no greater risk for falls or injury than when performing tasks in the home and community setting. Subjects will be under constant observation. Trained staff will be nearby to help in case of loss of balance. During training and when standing is not required, subjects will be seated on a comfortable chair.

Subjects will be asked prior to using sensors to collect data if they recall any past occurrences of fragile skin, or sensitivity to tape or latex. The investigators will use hypo-allergic tapes and bandages that are unlikely to cause skin irritation. For individuals with fragile skin, there is a risk of skin irritation from the adhesive tape that secures the reflective markers and EMG electrodes to the skin. The risk is equivalent to wearing a Band-Aid for a few hours and peeling it off. Alcohol cleansing, shaving, and light sanding needed prior to positioning sensors might also cause mild skin irritation. It is possible that mild bruising may occur from pressure of the sensors against the skin.

Subjects may become fatigued or uncomfortable during any visit. To minimize fatigue, subjects will be allowed rest periods and will be monitored and observed by study staff at all times during the experiments.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

The potential benefits could be improved fine and gross manual control, spasticity, and quality of life in children with cerebral palsy. However, our experience with rehabilitation interventions has shown that not all subjects respond in the same way to the intervention thus, some subjects may not benefit directly from participating in the study. It is possible that gaining a better understanding of the characteristics of muscle activation patterns will eventually lead to the development of new rehabilitation protocols or a better selection of patients that will respond to the intervention. Hence, the study might benefit patients in the future.

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

No person meeting the inclusion and exclusion criteria will be excluded from participation in the study on the basis of gender, ethnicity or race.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

Non-English speaking subjects will not be excluded from the study. Interpreter services will be obtained as necessary to facilitate the informed consent process and study participation.

For guidance, refer to the following Partners policy:
Obtaining and Documenting Informed Consent of Subjects who do not Speak English
http://healthcare.partners.org/phsirb/nonengco.htm

RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

All subjects will be recruited by IRB approved study staff for this protocol. Assent will be obtained from subjects who are enrolled by proxy consent.

Recruitment strategies will include the use of the following sources:

1. Attending physicians at Spaulding Rehabilitation Hospital may refer their CP patients to the study. We will provide physicians with study information sheets and flyers.
2. Study divulgation through the orthopedic service in the Boston Children's Hospital and in Spaulding Rehabilitation Hospital.
3. Flyers posted in the outpatient specialist clinics, in pediatric and orthopedic clinics, therapy gyms and in public spaces inside and outside of the hospital.
4. Phone calls through volunteer registry.
5. Via contact with support groups and conferences.
6. Patients with CP who previously volunteered to be contacted about opportunities to participate in research studies at Spaulding Rehabilitation.
7. Contact with patients who received robotic-assisted gait training as part of the clinical program at Spaulding Rehabilitation Hospital via referrals from physical therapists.
8. Via advertisement on clinicaltrials.partners.org and researchmatch.org websites.
9. Via letter to prospective subjects co-signed by their physician and study PI.
10. Via contact to the patients listed for direct contact in the Partners Research Patient Data Registry (RPDR).

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available

Subjects will be compensated based on the procedures undertaken. The compensation amount will be as follows:

- $50 for evaluation sessions (up to 3)
- $20 for intervention sessions (up to 18)

Each subject will receive in total $510 if he/she completes the whole study. Additionally, the cost of parking will be covered if the subject is driving to Spaulding Rehabilitation Hospital.

For guidance, refer to the following Partners policies:

Recruitment of Research Subjects
http://healthcare.partners.org/phsirb/recruit.htm

Guidelines for Advertisements for Recruiting Subjects
http://healthcare.partners.org/phsirb/advert.htm

Remuneration for Research Subjects
http://healthcare.partners.org/phsirb/remun.htm

CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

Subjects who are interested and willing to participate in the study will undergo an initial phone screening to determine their eligibility. Subjects who qualify will be sent study information and will be scheduled to visit the lab and undergo a final screening in person.

At the time of the scheduled test, the subject will be met by one of the study staff in the Motion Analysis Lab. Informed consent and assent will be obtained by the investigators who have completed the Partners Healthcare System's human subject protection educational requirements (i.e. HIPAA), and the CITI Program in Protection of Human Subjects, in compliance with all Federal regulations regarding such training. The parents/legal guardian will be given a copy of the IRB-approved consent form during the initial interview. Subjects will be given a copy of the IRB-approved assent form at the same time. Study staff will clearly explain to the subject and their parents/legal guardian the nature of the informed consent and assent processes, study purpose and procedures, time commitments, risks, potential benefits, treatment alternatives, rights as research participants, study staff contact information, confidentiality procedures, and arrangements for medical care provided in case of injury during the study. Subjects and their parents/guardians will be able to speak with a physician about any questions or concerns if they would like to. The subject and his/her parents/guardians will be given adequate time to consider their decision and encouraged to ask questions, both during the initial interview and throughout the study. A member of the study staff will answer any questions regarding the study at the time consent is given. Enrollment will begin when the parents/guardians thoroughly understand and signs the informed consent form, and the child thoroughly understands and signs the assent form. The subject and parents/guardians will be provided with a signed copy of the completed consent and assent form. The subject may pause or terminate his/her enrollment at any time during the study.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decision-making capacity, complete the forms for Research Involving Children as Subjects of Research and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:
http://healthcare.partners.org/phsirb/newapp.htm#Newapp

For guidance, refer to the following Partners policy:
Informed Consent of Research Subjects
http://healthcare.partners.org/phsirb/infcons.htm

DATA AND SAFETY MONITORING

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

Approval of protocol, informed consent procedures, and recruitment will be obtained from the IRB during annual reviews. Monthly data and procedural reviews by the PI in consultation with study staff will be done to identify and ameliorate any potential safety issues. Any safety concerns about the equipment or protocol will be brought to the immediate attention of Dr. Bonato. Study staff will conduct bimonthly audits to ensure compliance with regulatory standards for study documentation.

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor and the Partners' IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners' IRBs. When the investigator is also the sponsor of the IND/IDE, include the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.

NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting

Study staff will report any adverse event promptly to Dr. Bonato. Adverse events reporting will be done according to Partners Human Research policy, and appropriate changes in procedure and protocol will be implemented to prevent reoccurrence. Remedial action to prevent reoccurrence of the event will be instituted prior to resumption of the study treatment.

MONITORING AND QUALITY ASSURANCE

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example, specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in

accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

The study coordinator will be responsible for monitoring the completeness of all data and source documents. The Principal Investigator will monitor the informed consent procedures in accordance with the Informed Consent Compliance Checklist of Partners HealthCare Systems HRQIP. Prior to subject enrollment, the PI will review and approve of the consent and assent procedures that will be used by the investigator consenting individuals. The subject's data/protocol adherence will be monitored by the study coordinator at each step in the study.

For guidance, refer to the following Partners policies:

Data and Safety Monitoring Plans and Quality Assurance
http://healthcare.partners.org/phsirb/datasafe.htm

Adverse Event Reporting Guidelines
http://healthcare.partners.org/phsirb/adverse_events.htm

PRIVACY AND CONFIDENTIALITY

Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data; use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

NOTE: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

Patients will be assigned a study number, which will be used for all documentation except for a master list matching subjects names and study numbers, and forms for which subjects' names must be recorded (e.g. intake interview forms, copies of reimbursement receipts etc). The master list and interview forms will be kept in a secure location in locked offices. No non-study staff will have access to any identifiable patient study data or demographic information. All subjects' parents will be informed of their privacy rights and sign a HIPAA-compliant authorization form previously approved by the Spaulding IRB. Study staff in the Motion Analysis Laboratory will conduct quarterly audits to ensure compliance with regulatory standards for study documentation.

Videotapes and photos will be stored securely in the SRH Motion Analysis Laboratory; only investigators listed on the study application will have access to them. The videotapes will be destroyed after 7 years from the date of study closure in compliance with Partners Record Retention Policy. Patients will be given the choice to be seen or remain anonymous as well as the choice to have video/photo material used for the purpose of articles and presentations.

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS

Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent, and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

No personally identifiable data will be sent to or viewed by collaborators outside of SRH.

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

This study does not involve storing data or specimens with outside collaborators.

RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.

This study does not involve receiving data or specimens from outside collaborators.