NYU School of Medicine
NYU LANGONE MEDICAL CENTER

Clinical Research Protocol

Home based adaptive arm training for children with hemiplegia

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Study Product: *Bimanual Arm Trainer (BAT, Mirrored Motion Works, NC)*

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I. Introduction

This document is a protocol for a human research study. This study is to be conducted in accordance with US government research regulations, and applicable international standards of Good Clinical Practice, and institutional research policies and procedures.

I.1 Background

Acquired brain injuries (ABI) due to hypoxia, stroke, and trauma are major causes of morbidity in children and adolescents. The response of the nervous system to acquired injury is dependent on (a) age and type of injury (b) maturity of the brain cellular mechanisms and (c) environmental factors including but not limited to child participation in rehabilitation programs. The first two of the above mentioned parameters are being actively studied in experimental animal models to further understand age- dependent neuroplasticity (Kolb and Gibb 1993; Kolb, Petrie et al. 1996; Kolb and Cioe 2003). The environmental influence on functional recovery and outcome patterns in human research subjects especially in the younger population with ABI is largely unknown due to a large number of variables and multiple barriers related to the frequency of school-based and outpatient-based rehabilitation approaches, insurance limitations, and time and transportation associated with parental/caregiver obligations. We propose to specifically study functional outcomes with home-based training in pediatric patients with residual upper limb hemiplegia in the chronic stages of recovery from ABI.

Availability of redundant motor circuits for recovery in the maturing brain

Plasticity has been described as a complex set of mechanisms underlying activity- dependent reshaping of neuronal, interneuronal and glial connections with synaptogenesis mediated by excitatory and inhibitory pathways and neuronal apoptosis (Reeves, Lyeth et al. 1995; Bittigau, Sifringer et al. 1999; Anderson, Catroppa et al. 2005). The complex responses to injury allow the brain to functionally reorganize to restore some degree of function following ABI. In fact, a superior capacity to reorganize following focal neurological lesions has been noted in the developing brain (Kennard 1936; Kennard 1938).

Electrophysiologic studies reveal that areas of the cortex adjacent to the injury show a heightened response to stimulation (Driscoll, Monfils et al. 2007), suggesting that rearrangement of interneuronal and synaptic connections in the intact adjacent cortex may lead to improved functional outcome by recruitment of these undamaged areas. However, recent technological advances in neuroimaging in early life brain injury elucidate the role of the contralesional hemisphere in reorganization following unilateral damage to the cortico-spinal tract, i.e. normally transient ipsilateral cortical projections from the contralesional hemisphere are strengthened and maintained following brain injury (Staudt 2010). These results suggest that a viable approach to re-training the affected upper limb after ABI in children may be to harness the redundant motor circuitry from the contralesional side to enhance plasticity of the available circuits in the lesioned hemisphere.

Pattern of recovery of isolated movement in upper limb joints

The enhanced capacity for recovery from pediatric brain injury is thought to stem from a neurobiological cascade of neurotransmitter release, changes in the speed of the response to injury and in the number of synaptic connections to experience (Goldman 1974; Goldman 1976; Kennard 1942). Specifically, pioneering work of surgical ablation in primary motor and premotor cortex of primates revealed two key but contradictory results: (1) the “younger” brain has fewer immediate deficits and better long term functional outcome and (2) the same animals also developed greater spasticity, uncoordinated fine finger movements and abnormalities of ambulation later on in life (Finger 1999). Interestingly, there is no direct explanation for the delay in the manifestations of ABI, but the main hypothesis is that early injury perturbs the pattern and sequence of normal maturation in some way. Exactly how the pattern of maturation is perturbed is not fully understood.

Twitchell and Brunnstrom observed a sequential recovery of motor function (Twitchell 1951; Brunnstrom 1966; Brunnstrom 1970) that has stood the test of time. The Fugl-Meyer scale captures

where a patient may be in this sequence and is the most widely-used quantitative measure of motor recovery post stroke (van Wijck, Pandyan et al. 2001; Gladstone, Danells et al. 2002). The scores have also been shown to correlate with the extent of corticospinal tract damage (Zhu, Lindenberg et al. 2010). Recently, it was shown that bimanual-to-unimanual training can potentially progress recovery along this sequence, but that patients at different stages of recovery would require different training conditions – individuals with spastic paresis, who are earlier in the sequence of recovery may benefit more from bimanual-to-unimanual training with rhythmic auditory stimulation, where as those with spastic co-contraction, at a later stage in the sequence of recovery may benefit from bimanual-to-unimanual training *without* auditory stimulation (Aluru, Lu et al. 2014). This study provides benchmarks for the different stages of motor recovery and the type of training that may be beneficial to progress the individual to the next stage. We can now examine the pattern of recovery after ABI in pediatric patients with bimanual-to- unimanual training provided with a device as well as conventional non-device training at home.

I.2 Specific Aims

The specific aims of this proposal are to:

Aim 1: Introduce home-based targeted upper limb training in children with hemiplegia from ABI using a bimanual-to-unimanual training approach
We hypothesize that child-friendly home-based upper limb bimanual-to-unimanual training will lead to greater compliance and improved motor outcome on the Fugl Myer Scale compared to a conventional home training program.

Aim 2: Improve the understanding of the pattern of recovery of isolated joint movements in the pediatric population with hemiplegia following ABI.
We hypothesize that individuals receiving device-based bimanual-to-unimanual training will show improvement in active range of motion across upper limb joints compared with a conventional home training program.

This collaborative research will be performed in conjunction with the Motor Recovery Research Lab (Dr. Preeti Raghavan). The data obtained from this project will be used as preliminary data towards an NIH grant.

II. Study Design

Twenty children between the ages of 5-17 years with acquired brain injury 6 months to 2 years prior to enrollment will receive conventional home therapy (home exercise program) for 4 weeks followed by device-based home training for 4 weeks. We hope to recruit 10 children between the ages of 5-11 years and 10 children between the ages of 12-17 years. All enrolled children will complete the assessments below at baseline, after 4 weeks of conventional therapy, and after device training. The total length of study enrollment will be 8 weeks for all participants.

This is a pilot feasibility study hence sample size is small and arbitrary. Power analysis from these pilot data will be used to determine sample size in future studies. Subjects will be screened to ensure that they meet inclusion-exclusion criteria at Visit 1.

III. Subject Selection And Withdrawal

1. *Number of Subjects.*

Twenty (20) pediatric patients aged 5-17 years will be recruited. Subjects will be community dwelling individuals and will be voluntarily enrolled after obtaining the informed consent from their parent/guardian.

2. *Gender of Subjects.* There will be no gender bias for enrollment in the study

3. *Age of Subjects.* The age range of subjects is 5 -17 years

4. *Racial and Ethnic Origin.* There are no exclusions based on gender or ethnic group

5. *Inclusion Criteria*

1. Acquired Brain Injury at least 3 months prior to enrollment;
2. Unilateral hemiparesis
3. History of compliance with home exercise programs in the past.

6. *Exclusion Criteria*

1. Any social or medical problem that precludes compliance with the protocol
2. Comorbid seizure disorder or other neurological disease
3. Treatment with botulinum toxin or intrathecal baclofen in the 3 months preceding enrollment
4. Implanted neuromodulatory or electronic device or other complicating illness
5. Lack of capacity to consent

7. *Vulnerable Subjects*

The patients meeting inclusion criteria will be children. We will only enroll patients with capacity to provide informed consent. We will provide information to the subjects in terms that they can fully understand, and capacity to consent will be determined by the subject's verbal understanding of the protocol as determined by the PI. We will not exert any overt or covert coercion, and no financial incentive will be offered. The consent document that the subject will be asked to sign will be written in the language that the potential subject understands and will be approved by the IRB.

IV. Study Device

IV.1 Description

The device is a FDA Class I exempt medical device, and is registered with the FDA (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRL/rl.cfm?lid=461627&lpcd=PKS).The device facilitates movements of the affected hemiparetic arm by moving the unaffected arm at the shoulder and elbow joint. The device is interfaced with a video game for motivation and feedback. It also facilitates movements of the forearm and grasp and release on both the affected and unaffected sides (**Fig. 1**).

Fig.1. Bimanual Arm Trainer

Training Protocol:

The home-based training protocols both with and without the device will be consistent with the fundamental principles of neurorehabilitation as outlined by Bobath (Bobath 1978) and with motor learning principles (Shepherd and Carr 2006). The main postulates of the Bobath concept are that (1) posture and movement are not separate entities, (2) sensory input influences motor output and (3) muscle strength is a does not necessarily equal function (Vaughan-Graham, Cott et al. 2014). The principles of motor learning are repetitive task-specific practice with feedback (Bosse, Mohr et al. 2015)

Assessments: A pediatric occupational therapist will assess all subjects on the Fugl-Meyer Scale, the Assisting Hand Assessment Test, active and passive Range of Motion using video pre-and post-training, the Melbourne Assessment 2 and the PedsQL. The Melbourne Assessment 2 is a test of unilateral upper limb function and is a validated and reliable tool for evaluating upper limb movement in children with neurological conditions. The PedQL is an assessment tool that measures health related quality of live in adolescents with acute and chronic health conditions. The therapist will also teach the subjects how to use the Bimanual Arm Trainer (in the device training group) and how to perform the home exercise program (in the non-device training group).

Device-based bimanual-to-unimanual home training will be provided with the Bimanual Arm Trainer (BAT, Mirrored Motion Works, NC) shown above. The device provides bimanual-to-unimanual training of simultaneous shoulder external rotation and elbow extension, and independent training of pronation-supination and grasp and release of each hand. Range of motion and speed are recorded during training and feedback and motivation are provided through age-appropriate gaming modules. The rationale for training shoulder external rotation and elbow extension is consistent with the Bobath concept of achieving postural stability through scapular stabilization for control of more distal movements. Preliminary data with the BAT showed that training in adult stroke patients led to improvement in active range of motion in trained movements (shoulder external rotation) as well as distal untrained movements (forearm pronation and wrist extension) **(Fig. 2)**. Patients in the device group will be asked to train specific movements repeatedly with the device for *45 minutes five days a week* for 4 weeks and compliance will be monitored through training logs and remotely. We have tested a pediatric prototype of the Bimanual Arm Trainer **(Fig. 3).** Previous bimanual research has shown that training 5 days a week for 4 weeks can accelerate recovery of upper limb motor function (Stinear et al. 2014).

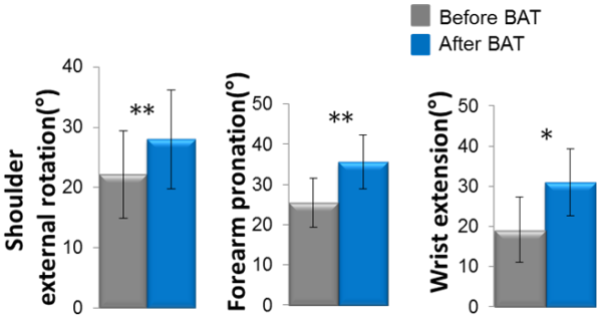

Fig. 2. Training with a previous version of the BAT for 4 weeks in adults with severe chronic hemiplegia led to improvement in active range of motion in trained (shoulder external rotation) and untrained movements (forearm pronation and wrist extension).

Fig.3. Training a child with the Bimanual Arm Trainer

Conventional non-device based home training will be provided using a home-exercise program provided by an occupational therapist and customized to the

patient's needs using the principles from Bobath and Motor Learning. Patients will also be asked to train specific movements repeatedly for *45 minutes five days a week* for 4 weeks and compliance will be monitored through training logs.

Progression of training: Patients with spastic paresis (Brunnstrom's stages I and II) will engage in bimanual-to-unimanual training **(Fig. 4)** with rhythmic auditory stimulation initially, those with spastic co- contraction (Brunnstrom's stages III and IV) will engage in bimanual-to-unimanual training without rhythmic auditory stimulation (Aluru, Lu et al. 2014). At each weekly review of the previous week's data, the therapist will determine the conditions of further training. Training will be progressed as per standard practice in individuals receiving standard home training by a pediatric occupational therapist.

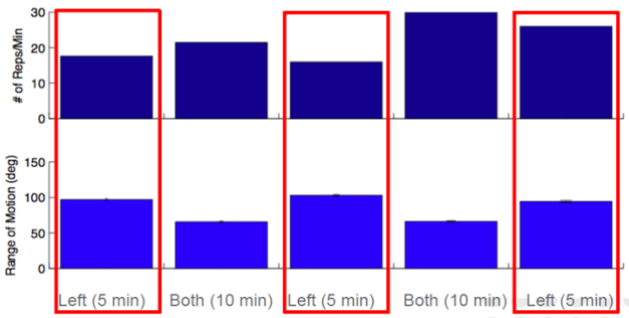

Fig. 4. Example of protocol for bimanual-to-unimanual training within a training session. The left arm (red box) was affected.

IV.2 Subject Compliance Monitoring

The study Occupational Therapist (OT) will monitor compliance with the training protocol with training logs provided to the child and parents. The OT will also review the training data and determine adherence to the treatment regimen. If subjects are consistently non-compliant and demonstrate less than 80% compliance with the training sessions (i.e., miss more than 1 training session per week), they will be dropped from the study.

V. Study Procedures

All data will be obtained solely for research purposes.

Visit 1. Subjects will provide informed consent and be screened to ensure that they meet inclusion-exclusion criteria. If they meet criteria, they will undergo further assessments using the Fugl-Meyer Scale, the Assisting Hand Assessment Test, the Melbourne Assessment 2 and the PedsQL (see attached scales). Total testing time will not exceed three hours, and the subjects will be given adequate rest breaks to ensure that they do not become fatigued. All subjects will be given a home exercise program and exercise logs to record the time spent in training at home.

Visit 2. Subjects will be assessed again 4 weeks after their home therapy program. At this visit they will also receive baseline testing and training on the device. After this visit, subjects will receive the device for training at home, which will be monitored on a weekly basis remotely by the occupational therapist to ensure compliance and to answer any questions.

Visit 3. This will be the post-device treatment assessment visit.

VI. Data Analysis & Data Monitoring

Data Analysis

Aim 1: Introduce home-based targeted upper limb training in children with hemiplegia from ABI using a bimanual-to-unimanual training approach. We will test the hypothesis that child-friendly home-based upper limb bimanual-to-unimanual training will lead to greater compliance and improved motor outcome on the Fugl-Meyer Scale, the Assisting Hand Assessment Test, active Range of Motion assessments, the Melbourne Assessment 2 and the PedsQL, compared to the conventional home training program. The groups will be compared using a two-way ANOVA.

Aim 2: Improve the understanding of the pattern of recovery of isolated joint movements in the pediatric population with hemiplegia following ABI. We will test the hypothesis that individuals receiving device-based bimanual-to-unimanual training will show improvement in active range of motion across upper limb joints compared with a conventional home training program.

The results of this study will pave the way for both understanding and meeting the needs of pediatric patients with Acquired Brain Injury in a systematic manner. Given the extent of plasticity in children there is a great need to rapidly optimize recovery so that physical, emotional and intellectual growth are as unhindered as possible. There is currently a dearth of evidence in how this can be accomplished. This study will provide pilot data for a larger study to optimize motor outcome pertaining to upper limb recovery as rapidly as possible.

Data Monitoring

The PI will be overall responsible for data monitoring.
(1) Types of Data or Events: All accumulated outcome data, enrollment numbers, reportable event data (including adverse reactions and unanticipated problems) and the overall compliance with the protocol will be monitored.
(2) Responsibilities and roles for gathering, evaluating and monitoring the data: The PI will be overall responsible for monitoring the data collected, including data related to unanticipated problems and adverse events. Data accuracy will be verified by the PI on an ongoing basis at monthly reviews of data. The PI will verify compliance with the protocol at an ongoing basis and at weekly lab meetings. Independence of judgment will be assured by using independent assessors for outcomes.
(3) Reporting adverse events and unanticipated problems to the monitoring entity: Any adverse events will be reported to and compiled by the PI on an ongoing basis. Reportable events will be reported to the IRB by the PI within 5 business days. All other SAEs will be reported annually to the IRB.
(4) Assessments: Data analysis will be performed as the data are collected to look for “unanticipated problems involving risks to participants or others” (i.e., as to whether they are unexpected, related and harmful).
(5) Criteria for action: If there are significant related and harmful adverse events at any point in time, the study will be stopped.
(6) Procedures for Communicating – dissemination of safety information: Outcome of data monitoring will be communicated to the IRB and research sponsor annually unless there are reportable adverse events or criteria for action.

VII. Data Handling and Record Keeping

Data Storage and Confidentiality: Research data will be stored in the PI’s office at Hospital for Joint Diseases. Research data will be labeled by subject codes and stored on a password protected computer and/or in a locked file cabinet. The data collection computer will be in a locked fixed location, password protected, and on a local network. Both computer and file cabinet are located in the PI’s lab at New York University’s Rusk Rehabilitation. Only the PI and her HIPAA certified delegates will have access to the data.

Data Stored for Future use: The data collected will be used as pilot data to plan future studies. New questions may come up from this study that may be addressed by reanalyzing the collected data. The data will be stored for up to 7 years. The data will be labeled, stored, and accessible to the PI and delegates as described in the section: Data Storage and Confidentiality. If patients specifically request to withdraw their data from the data stored for future use, they must do so in writing, which will be kept on file. Their data will be segregated from the rest of the data and not used for future analysis. However it will be stored for analysis of the present study and as per rules of publication, for at least 7 years post- publication.

VIII. Safety and Adverse Events

RISK/BENEFIT ASSESSMENT

Risks: The risk of injury from the BAT is minimal as it is a non-powered, non-robotic device and all movements are controlled by the patient. However training may lead to muscle soreness in the unaffected and affected arms. There is a risk of fatigue in patients with stroke who may have weakness. There is a risk of breach of confidentiality since subjects will be answering questionnaires.

Protection against Risks: Fatigue in patients with stroke will be minimized by setting the training duration to short periods tolerated by the patient initially and then increasing it gradually, to build endurance. The subjects will be told that they can take rest periods as often as needed. The speed of training will be controlled by the subject.

Potential Benefits to the Subjects: The subject's participation may provide valuable information that will help in the development of effective tele-rehabilitation. This information may help us to improve the way we treat future stroke subjects

IX. Subject Identification, Recruitment, Consent/Assent

1. Method of Subject Identification and Recruitment

Attending Physicians and Physical and Occupational therapists from the outpatient facility at New York University's Rusk Rehabilitation will refer patients with chronic stroke to the PI and study staff by giving them the PI's contact information if they meet study criteria.. Subjects who contact the PI and are found eligible for the study will be required to provide informed consent prior to participation in the study. The study protocol and informed consent forms will be approved by the IRB at NYU Medical Center. Subjects will be informed that they can discontinue the study or its procedures at any time, and that further evaluation or treatment will not be withheld. The identification and recruitment of subjects will protect the privacy of subjects and be free of undue influence.

2. Process of Consent

Assent will be obtained by the PI or HIPAA-certified delegates, in the PI's office, which is a private area, at the New York University's Rusk Rehabilitation, Hospital for Joint Diseases prior to participation in the study. The assent will be obtained jointly with the parent(s) and the minor. The assent document will be thoroughly discussed at a convenient time, free of time constraints and the subject and the parent will be given time to think about their decision. We will get the consent of the parent and the assent of the adolescent on the approved age-appropriate consent form. The subject and the

parent will be asked to provide a statement of their understanding of the procedures, risks, and a general concept of the study.

The parent (s) of the subject will be given a copy of both the consent and assent forms and be encouraged to contact the PI if they have further questions about the protocol. When the minor turns 18, we will get their consent (re-consent them). All subjects will also provide a separate consent for videotaping. The permission of only one parent will be required.

The subject (between the ages of 15-17 years old) will be asked to sign the assent form if they agree to participate in the study. The parent of the subject will be present at the time the document is signed along with the PI or her HIPAA-certified delegate

All subjects will also provide separate consent for videotaping of the clinical assessments. They will sign and date the Audio Video consent and will receive a copy of the signed consent. Videotapes of session and clinical assessments may be used for instruction and training purposes.

3. **Subject Capacity.** The subjects recruited for this study will be community-dwelling individuals with capacity to provide consent and assent. The parents will provide consent for minors (5-17) via a separate consent form.

4. **Subject /Representative Comprehension.** Capacity will be determined by a general conversation between the subject/ authorized representative and the PI to assess the subject's verbal understanding of the protocol including the nature and purpose of the study, the procedures involved, as well as the risks and benefits of participating versus not participating; appreciation of the significance of the disclosed information and the potential risks and benefits for one's own situation and condition; and the ability to engage in a reasoning process about the risks and benefits of participating versus alternatives, and; the ability to express a choice about whether or not to participate.

5. **Subject Withdrawal.** Subjects may decide not to participate in the research study at any given time without any penalty. Withdrawal can be made by informing the research study staff; including the PI; verbally or in writing. Upon withdrawal, subject's data will be removed from the study research data immediately.

6. **Debriefing Procedures.** No information will be purposely withheld from subjects.

7. **Consent Forms.** The IRB Standard Consent Forms and Assent form will be used (please see attached).

8. **Documentation of Consent.** The study and the consent form will be thoroughly discussed with each subject, section by section. Subjects will be asked to provide a statement of their understanding of the procedures, risks, and general concept of the study. The consent document, and documentation of the process, will be stored in the PI's office at the Rusk Institute of Rehabilitation Medicine, NYU Medical Center, on a password protected computer and/or in a locked filing cabinet. The computer will be in a locked, fixed location (no mobile laptop), password protected, and on a local network.

9. **Costs to the Subject.** Subjects will not incur any costs for participating in the study.

10. **Payment for Participation.** There will be no compensation for participation in this study.

X. Conflict of Interest

Conflict of Interest

Dr. Preeti Raghavan (Co-I) is the inventor of the device and she has disclosed her conflict of interest with CIMU.

XI. Investigators' qualifications and experience (CVs attached)

Renat Sukhov, MD, is the Principal Investigator at Rusk Rehabilitation. He is a specialist in pediatric rehabilitation.

Preeti Raghavan, MD is the co-Investigator and Director of the Motor Recovery Research Laboratory at Rusk Rehabilitation. She is also the inventor of the BAT device.

Pediatric Occupational Therapist (TBD) will be involved in recruitment and assessment of subjects, monitoring of compliance and administration of the training protocols. She will also be involved in the analysis and interpretation of data along with the PI and co-PI.

Zena Moore, MS is the Senior Research Coordinator on the project and will be responsible for data management and reporting under the supervision of the PI and co-PI.

XII. References

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XIII. Attachments

- Consent Form
- Audio-Video Consent
- Assent Form
- Fugl-Meyer Scale
- Assisting Hand Assessment Test
- Melbourne Assessment 2
- PedsQL