Motivating Occupational Virtual Experiences In Therapy (MOVE-IT) Phase II

Sponsor: Barron Associates, Inc.

Funding Mechanism: NIH SBIR Grant with Subcontract to UVA

Principal Investigator: Richard Stevenson, M.D.

Version Number:5.0
08/14/2023

Statement of Compliance

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- *U.S. Code of Federal Regulations applicable to clinical studies (45 CFR 46)*
- *ICH GCP E6*
- *Completion of Human Subjects Protection Training*

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator:

Signed: _____ Date: _____

Richard Stevenson, M.D.

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List of Abbreviations

AE	Adverse Event
CFCS	Communication Functional Classification System
CFR	Code of Federal Regulations
CHAMP	Children with Hemiparesis Arm and Movement Project
CIMT	Constraint Induced Movement Therapy
CRF	Case Report Form
CSA	Combined Statistical Area
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
FWA	Federal-Wide Assurance
GCP	Good Clinical Practice
HEP	Home Exercise Program
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
JTHFT	Jebsen Taylor Hand Function Test
MOVE-IT	Motivating Occupational Virtual Experiences In Therapy
MSA	Metropolitan Statistical Area
N	Number (typically refers to subjects)
OHRP	Office for Human Research Protections
PI	Principal Investigator
QUEST	Quality of Upper Extremity Skills Test
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SUS	System Usability Scale
TAM	Technology acceptance model
UCT	Usual Care Treatment

DRAFT

List of Abbreviations - *continued*

UE	upper extremity
UVA	University of Virginia
WMFT	Wolf Motor Function Test

Protocol Summary

Title: Motivating Occupational Virtual Experiences In Therapy (MOVE-IT) Phase II

Sites: University of Virginia (Charlottesville, VA) and Duke University (Durham, NC)

Sponsor: Barron Associates, Inc. (Charlottesville, VA)

Study Design: Rater-blinded randomized controlled study

Population:

N:	48 Dyads* (24 at each of 2 sites) *Dyad=One parent/legal guardian and one minor
Ages:	4 – 14 years (inclusive)
Sex:	Any
Race:	Any
Diagnosis:	Hemiplegia resulting from cerebral palsy, stroke, or other form of brain injury

Recruitment area: Charlottesville Metropolitan Statistical Area (MSA), Raleigh-Durham-Chapel Hill Combined Statistical Area (CSA), and surrounding areas.

Subject Duration: 10-week intervention with 3 months follow up assessment.

Study Duration: Approximately 1 year

Objectives:

The primary Phase II investigational objective is to show a differential effect on the pre-to-post-intervention change in upper extremity (UE) motor function between an interventional group receiving the MOVE-IT home exercise program (HEP) and a usual care treatment (UCT) group, as assessed by the Jebsen Taylor Hand Function Test (JTHFT) and other gold-standard clinical assessments of UE function.

Blinded assessors, certified for the study instruments, will evaluate children in both groups at pre-treatment (baseline), immediate post-treatment (baseline + 10 weeks), and 3 months post-treatment. Assessments (3 total) will take place in an outpatient setting and include the following blinded instruments:

- Jebsen Taylor Hand Function Test (JTHFT) (primary outcome measure)
- Quality of Upper Extremity Skills Test (QUEST) (dissociated movements and grasp components)
- Wolf Motor Function Test (WMFT)

Additionally, parents will be asked to complete the following parental report instrument during each assessment visit:

- Pediatric Motor Activity Log (inventory of child's functional use of the UE)

For both groups, parents will be asked to maintain a weekly activity log, including activities

1 KEY ROLES

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2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Virtual worlds-based games present a unique, innovative, and timely solution for supporting high-dosage evidence-based rehabilitation that targets neuroplasticity. There exists a substantial body of work on adaptations of VR for adult rehabilitation, much of which has focused on stroke [31], [32], [33], [34]. Studies involving children have not kept pace with adult applications and pediatric applications of VR have been relegated primarily to the academic realm. Preliminary results have shown some promise, both in terms of patient engagement and efficacy, but prior research lacks well-powered RCTs and has not been translated to clinical practice [35], [36], [37], [38], [39], [40], [41].

Barron Associates, Inc. (the NIH grantee for the MOVE-IT program) previously developed the Virtual Occupational Therapy Application (VOTA), an FDA-cleared software system that enables adult stroke patients to re-learn adult activities of daily living (ADLs), such as shopping or meal preparation, by practicing the physical movements within a virtual environment that reconstructs real-world tasks [42], [43] with Kinect-based human motion capture. VOTA has been shown to improve UE function in adult stroke patients [44], [45] and is now sold commercially as SaeboVR [46].

The MOVE-IT system, developed by Barron Associates, Inc. under NIH sponsorship, employs therapy games that combine virtual- and real-world physical elements to provide a solution suitable for both home use. MOVE-IT engages patients in repetitive practice, facilitating an evidence-based approach that integrates proven concepts in CIMT. MOVE-IT system consists of a multi-sensory smart toy (which serves as a game controller), a depth camera (e.g. Kinect), a personal computer, and a virtual world software application with mini- games designed to sustain engagement in remotely monitored home-based therapy. Software includes mini-games such as Feeding Time and Flight School (shown in Figure 1) that are designed to support mass practice of UE reaching movement involving the shoulder, elbow, and hand. For example, in Feeding Time the player uses the smart toy to capture dragon food and bring it to the hungry baby dragon. Each movement to capture the food and then bring it to the dragon requires a point-to-point UE reaching movement. Target positioning for these reaching movements (the food and the dragon) is designed to elicit a specific degree of movement, determined by participating pediatric rehabilitation doctors and OTs, and categorized by difficulty and movement type to permit tailoring of the game for the individual patient. Note that the avatar's arm in the game moves according to the sensor-derived arm joint angles, not hand position. This has the important effect of making level of difficulty for a given movement invariant to the child's arm length (a 4-year-old and 14-year-old will experience that same challenge in reaching the food and feeding the dragon). As

another example, the Flight School mini-game is designed to challenge the child's range of motion in forearm supination, an important movement in therapy for pediatric hemiplegia. The game translates the player's pronation/supination movements into left-right steering of the baby dragon's flight. The player uses these movements to steer the dragon through a series of targets to gain speed and collect rewards.

Figure 1. MOVE-IT system in use during Phase I pilot testing

The NIH-sponsored MOVE-IT Phase II program culminates in a rater-blinded randomized, controlled trial to investigate efficacy of a MOVE-IT based intervention in home use by children with hemiplegia, as measured by change in gold-standard measures of UE

function for a cohort using MOVE-IT compared to a usual care treatment (UCT) group. The University of Virginia (UVA) will serve as coordinating center and single IRB (sIRB) for a two-site MOVE-IT RCT that includes UVA and Duke University. Overall direction of the RCT will be provided by Dr. Richard Stevenson, M.D., Head, Division of Developmental Pediatrics, UVA School of Medicine and former President of the American Academy for Cerebral Palsy and Developmental Medicine. Participation of the Duke University site will be under the direction of pediatric rehabilitation specialist Dr. Robert Lark, M.D.

2.2 Scientific Rationale

Hemiplegia is a partial paralysis or weakness of one side of the body that impairs the use of the UE on the affected side and disrupts motor functions essential to self-care, play, exploratory learning, and daily activities. Causes of pediatric hemiplegia encompass any injury or illness associated with the brain, including cerebral palsy (CP), cerebral vascular accident (stroke), traumatic brain injury, brain tumor, or other illness [1]. CP impacts more than 1 in 300 children, with disproportionate prevalence in minority and economically disadvantaged populations [2]. Prevalence of CP has been reported to be 50-100% higher among black or African American children than other demographics [3]. Overall, 60% of children with CP experience some level of impairment in UE function [4], which can include reduced range of motion (e.g. in the shoulder in the frontal plane [5] and in forearm pronation/supination [6]) and the presence of significant compensatory movement (especially of the trunk). Stroke is a form of acquired brain injury caused by an occlusion or rupture of blood vessels [1]. Although more commonly associated with adults, stroke impacts individuals of all ages, including children [7].

Usual care for pediatric hemiplegia includes occupational therapy (OT) as well as adjunct therapies, such as spasticity-reducing medications. These approaches to upper-limb therapy can be considered effective to the extent they improve independence and a child's ability to meet individual goals [8].

Systematic reviews strongly support that constraint-induced movement therapy (CIMT) is one of the most effective treatments for pediatric hemiplegia [9], [10], [11], [12], [13], [14]. In CIMT, the less affected UE is constrained (i.e. typically employing a cast or mitt) while the impaired limb is engaged in intensive, repetitive, activity-based training [15], [16]. When considering alternate approaches, higher duration of training is consistently associated with better outcomes [17], [18], [8]. Meta-analysis examining 42 randomized and controlled trials involving UE interventions (n = 1454 subjects) found moderate to strong evidence supporting the superiority of intensive, task-directed training over usual care [19]. These regimes are associated with superior outcomes in spontaneous use, quality of movement, and task performance [20], [21].

Neuroplasticity provides one possible explanation for why increased dosage/intensity produces superior outcomes over usual care. Brain plasticity can be defined as the formation of new circuits and changes to internal structures that remap existing synapses to perform functions previously accomplished by injured cortical tissue [22], [23]. Although the relationship between therapy for pediatric hemiplegia and brain neuroplasticity is only beginning to be understood, emerging evidence appears to mirror findings in stroke research that frequent, longer-duration interventions improve cortical activation and neuroplasticity, and thus lead to better outcomes [24], [25]. Functional MRI results appear to show that intensive training can produce neuroplastic changes on the synaptic level in children with CP, evidenced by increased task-related brain activation in the lesioned region of the primary motor cortex [26], [27], [28].

New intensive therapy regimes strain the capacity and resources of delivery systems and challenge the creativity of individual therapists to maintain patient engagement and motivation. Total dosages for CIMT in clinical trials have involved up to 126 hours of therapist-supervised training [20]. A study comparing efficacy of 30 vs. 60 hours of CIMT for children with unilateral CP found 60 hours to be sufficient, but 30 insufficient, to achieve desired outcomes [29]. When reducing CIMT dosage to numbers more typical for usual care, outcomes fall short compared to more intensive training [29]. It thus appears that 50-60 hours are needed in clinical practice [30], but delivering such dosages strains the capacity of existing health systems and can exceed the reimbursement limits of insurers. Using delivery mechanisms typical of usual care, a 1-to-1 child-to-therapist ratio may be required to achieve adequate dosage [29]. Individual therapists also face the formidable challenge of keeping patients motivated in more frequent and longer practice sessions.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Potential risks are described below, along with mitigation measures that will be implemented by the study team.

(1) Soreness, pain, or increased tone post-use due to increased range and level of activity involving the upper extremity.

a. Game-integrated movements will be consistent with accepted clinical practice for occupational therapy and exercises used in previous RCTs involving intensive therapy (e.g. the CHAMP R01 program RCT, NCT01895660.);
b. Subjects will be reminded to take frequent breaks.
c. Study staff will ensure families understand that they can withdraw from the study at any time without reason or consequence.
d. At least once every two weeks, study staff will contact the participant by phone or HIPAA compliant video conferencing to collect self-reported adherence data and confirm that no change in medical status has occurred that would impact

continued participation. The staff member will inquire regarding soreness, pain, or increased tone and consult with the PI if any concerns are reported.

(2) Elevated stress or embarrassment due to frustration with the interface or inability to perform a task.

a. Initial visits with licensed pediatric therapists assesses appropriateness of MOVE-IT use for the individual patient and the home environment;

b. Physical and cognitive demands are progressive and appropriate for the participant population and consistent with existing clinical practice; and

c. At least once every two weeks, study staff will contact the participant by phone or HIPAA compliant video conferencing. If elevated stress, embarrassment, or frustration are reported, a study pediatric therapists will adjust the activity settings and follow up with the parent or guardian to ensure the issue is resolved. If the issue cannot be resolved to the satisfaction of the therapist and parent, the PI will be consulted regarding appropriateness of continued participation.

(3) Risk of accidental release of identifying and/or confidential information.

a. Potential risks of accidental release of identifying and/or confidential information will be mitigated by use of a coded identifier key for all participant data and implementation of detailed measures described in the Data Security Plan.

2.3.2 Known Potential Benefits

Potential benefits to participants in this study will include the opportunity to learn about the potential benefits of new technology and gaming for improving upper extremity function in children with hemiplegia. The knowledge gained from this study may lead to substantial benefits for both individuals (in improving motor function and functional independence) and society (by increasing access to and reducing the cost of care). Subjects assigned to the MOVE-IT HEP group may benefit from participation by improved UE motor status. Subjects assigned to the UCT group will be offered access to the MOVE-IT HEP following completion of participation as a control.

3 OBJECTIVES

The primary Phase II investigational objective is to show a differential effect on the pre-to-post-intervention change in upper extremity (UE) motor function between an interventional group receiving the MOVE-IT home exercise program (HEP) and a usual care treatment (UCT) group, as assessed by the Jebsen Taylor Hand Function Test (JTHFT) and other gold-standard clinical assessments of UE function.

Blinded assessors, certified for the study instruments, will evaluate children in both groups at pre-treatment (baseline), immediate post-treatment (baseline + 10 weeks), and 3 months post-treatment. Assessments (3 total) will take place in an outpatient setting and include the following blinded instruments:

- Jebsen Taylor Hand Function Test (JTHFT) (primary outcome measure)
- Quality of Upper Extremity Skills Test (QUEST) (dissociated movements and grasp components)
- Wolf Motor Function Test (WMFT)

Additionally, parents will be asked to complete the following parental report instrument during each assessment visit:

- Pediatric Motor Activity Log (inventory of child's functional use of the UE)

For both groups, parents will be asked to maintain a weekly activity log, including activities performed under the MOVE-IT intervention and any other therapy a child might receive.

4 STUDY DESIGN

The study is a randomized control study.

Following screening, enrolled subjects will be randomized to either the MOVE-IT home exercise program (HEP) or usual care treatment (UCT) group using a centralized and masked process developed by the study biostatistician. The HEP group is the interventional group. The UCT group is the control group. Following the control strategy previously adopted in the Children with Hemiparesis Arm and Movement Project (CHAMP) multi-site RCT (NICHD R01, trial registration number NCT01895660), children in the UCT group will be followed as they continue to receive their previously prescribed therapy services. As UCT group participants, these children will not receive any treatment services through the study. Parents will be asked to report therapy services their children receive during each assessment visit.

To ensure that an approximately equal number of subjects are randomized to the MOVE-IT HEP and UCT groups throughout the Phase II enrollment period, we will randomly assign the patients to the two study-groups in accordance with a permuted block randomization scheme. The randomization list will be generated by a UVA study biostatistician (James Patrie) using the PLAN procedure of SAS (SAS Institute Inc., Cary, NC). One subject randomization table will be generated for each site. The group assignment will be blinded to the therapists (raters) who perform the pre- and post-assessments. The group assignment will be not be blinded to the participants. The non-rater members of the IRB-approved study team will have access to the randomization list.

Demonstration of statistically significant improvement in UE motor function for participants the MOVE-IT HEP versus UCT will support the validity of MOVE-IT use as an intervention for children with hemiplegia. In home use, MOVE-IT will enable more frequent and intensive therapy with reduced travel and may extend the service range of existing rehabilitation providers to include underserved areas. In clinical practice, MOVE-IT will enable new models of delivery based on remote monitoring combined with outpatient services, increasing quality and efficiency of care. Statistical considerations for sample size determination, primary analysis, and secondary analyses are described below.

5 STUDY POPULATION

5.1 Selection of the Study Population

Ages: 4 – 14 years (inclusive)
Sex: Any
Race: Any

Target # of subjects (at all sites) needed to complete protocol: 40.
Expected rate of screen failure/ dropouts/withdrawals from all sites: 15%.
Number of subject/dyads to be enrolled at all sites: 48.
Number of subjects who will sign a consent form under this protocol: 48 dyads.
(24 at UVA and 24 at Duke)

5.2 Inclusion/Exclusion Criteria

Criteria for inclusion

(1) Diagnosis of hemiplegia resulting from cerebral palsy, stroke, or other form of brain injury;
(2) Medically stable;
(3) Manual Abilities Classification System (MACS) rating between II and V; indicating the child experiences mild to severe difficulty in handling objects with the affected hand;
(4) Communication Functional Classification System (CFCS) rating between I and III; indicating the child usually communicates effectively with familiar communication partners, but not unfamiliar partners, in most environments;
(5) Participant has antigravity strength in the affected UE at the elbow to at least 45 degrees of active flexion;
(6) Participant has antigravity shoulder strength in the affected UE to at least 30 degrees each in active flexion, abduction/adduction, and 15 degrees in active internal/external rotation when in an upright and seated position;
(7) Participant has ability to perform a basic color-matching test and identify characters on a vision chart;

(8) Participant must be available to attend study visits;
(9) Willingness and ability to comply with scheduled visits and study procedures.

Criteria for exclusion
(1) History of uncontrolled seizures;
(2) Has received botulinum toxin injections, stem cell infusions or another form of intensive UE therapy, such as CIMT, within the prior 6 months;
(3) Unwillingness or inability to understand or follow verbal directions;
(4) Diagnosis of moderate to severe cortical-visual impairment that in the judgement of the Principal Investigator could adversely impact the subject's participation;
(5) Psychological diagnosis that in the determination of the Principal Investigator could significantly impact subject's participation or that could be aggravated by study participation;
(6) Determination that participation would result in over exertion, or significant discomfort or pain;
(7) Determination that participation would result in significant agitation or elevated stress;
(8) Visual field deficit in either eye that impairs the ability to view the computer monitor.

Restrictions on use of other drugs or treatments: None

5.3 Subject Compensation

Participants will be compensated for being in this study.

Participants will be paid a $50 stipend for each outpatient visit completed (3 total visits). Participants will not be compensated for home visits.

If a participant drops out or is otherwise disenrolled form the study, payments will be pro-rated based on number of visits completed ($50 per outpatient visit).

Participants will not receive reimbursement for actual expenses related to being in this study (e.g. travel).

6 STUDY PROCEDURES/EVALUATIONS

6.1 Study Procedures

Identical procedures will be followed at the UVA and Duke sites.

Prior to consent, candidates will be contacted by phone and the parent/guardian asked to respond to questions pertaining to eligibility (inclusion/exclusion criteria). For example:

- Does the child have a history of uncontrolled seizures?
- Has the child received botulinum toxin injections, stem cell infusions or another form of intensive arm therapy, such as CIMT, within the prior 6 months?
- Can the child move the affected arm and flex the elbow about halfway?
- Is the child's corrected vision good enough to comfortably watch a TV show for 30 minutes?

The final list of questions will be included in a telephone recruitment scripts that will be submitted for IRB approval prior to use. After pre-screening using the IRB-approved script, candidates will be scheduled for a remotely-administered consent and screening telehealth visit and for a pre-assessment visit.

- The parent/guardian will be asked to complete the following parental report instrument:
    - Pediatric Motor Activity Log (inventory of child's functional use of the UE)

<u>ALL - Outpatient Visit 1: Pre-Assessment (will last about 90 minutes)</u>

- Blinded study therapist will review consent and re-verify inclusion and exclusion criteria
- Blinded study therapist will administer clinical tests for UE function
    - Jebsen Taylor Hand Function Test (JTHFT) (primary outcome measure)
    - Quality of Upper Extremity Skills Test (QUEST) (dissociated movements and grasp components)
    - Wolf Motor Function Test (WMFT)

- If administration of the test instruments cannot be completed for any reason (e.g. subject becomes fatigued), the participants may be asked to return for an additional visit to complete the procedures. The participant will be provided the normal per-visit stipend for the additional visit.
- Subject will be assigned to either the MOVE-IT HEP or the UCT group employing the study randomization procedure and scheduled for remaining visits.

GROUP 1: MOVE-IT HEP GROUP

MOVE-IT HEP Visit 1 (will last about 90 minutes)

- A non-blinded study team member will conduct a home visit at the patient's residence.
- The team member will either drop off the system with the family OR set up the MOVE-IT system in the home and verify safety of the system setup.
- A therapist will guide the patient in practice using the MOVE-IT system either in-person at the home or via approved telehealth connection. The therapist will provide training to the parent/guardian either in-person in the home or via approved telehealth connection.

MOVE-IT HEP Home Visit 2 (will last about 60 minutes)

- A non-blinded study therapist will conduct a second home visit at the patient's residence or meet with the subject via approved telehealth connection.
- The therapist will observe the patient in practice using the MOVE-IT system and provide additional guidance and training as needed.
- If on the study therapist's recommendation, the study PI determines an additional visit is warranted to ensure a patient can safely and successfully use the system at home, an additional visit will be conducted either in the home or via an approved telehealth connection.

MOVE-IT HEP Independent Practice at Home

- Participants will be asked to employ the GRASP system for UE practice at home for a total of 1 hour/day, 5 days/week over the 10-week intervention period.
- Patients will continue to perform any previously prescribed therapy.

- Once per week during this period, non-blinded study staff will employ an authorized web application on a UVA computing system to remotely monitor de-identified participant data (see Data Security Plan for details) that includes exercise adherence (duration performed), movement repetitions accomplished (exercise reps), and exercise intensity (speed).
- At least once every two weeks, non-blinded study staff will contact the participant by phone or HIPAA compliant video conferencing to collect self-reported adherence data and confirm that no change in medical status has occurred that would impact continued participation.

MOVE-IT HEP Home Visit 3 (will last about 90 minutes)

- At the end of the HEP period, a non-blinded team member will conduct a home visit at the patient's residence to recover the system hardware. Prior to recovery, a therapist will observe patients' independent use of the system either in the home or via an approved telehealth connection.
- Participants will respond to usability assessment instruments including:
    - System Usability Scale (SUS)
    - Technology acceptance model (TAM) questionnaire
    - Short response open-ended narrative questions.

  These assessments will be audio recorded using Zoom. The recordings will be stored in secure folders on O/drive at UVA and Duke Box, that only the research team has access to. The interview recording will only identify subjects with their subject ID. Transcriptions will be reviewed by a member of the research team for accuracy. Once reviewed and transcribed, all identifiable information will be removed and only the de-identified transcript will be stored and used for analysis. Another member of the research team will perform a quality check of the transcript to ensure accuracy.

GROUP 2: UCT GROUP:

- Participants in the control group will continue to receive any previously prescribed therapy services. These patients will not receive any treatment services through the study as UCT group participants.
- At least once every two weeks during the interventional period, non-blinded study staff will contact the participant by phone or HIPAA compliant video conferencing to collect self-reported adherence data and confirm that no change in medical status has occurred that would impact continued participation.

ALL - Outpatient Visit 2: Post-Assessment (will last about 90 minutes)

- Conducted at end of 10-week intervention period.
- Blinded study therapist will administer the same battery of tests used in pre-assessment.

ALL - Outpatient Visit 3: Follow-up Assessment (will last about 90 minutes)

- Conducted approximately 3 months after Post-Assessment.
- Blinded study therapist will administer the same battery of tests used in pre- and post-assessment.

To promote equipoise, parents of children in the UCT group will be provided free access to the MOVE-IT HEP following completion of the control protocol. When participation in the study is completed, all subjects will return to usual care under their individual health care provider.

A graphical summary of the MOVE-IT Phase II study is provided in Figure 2 below.

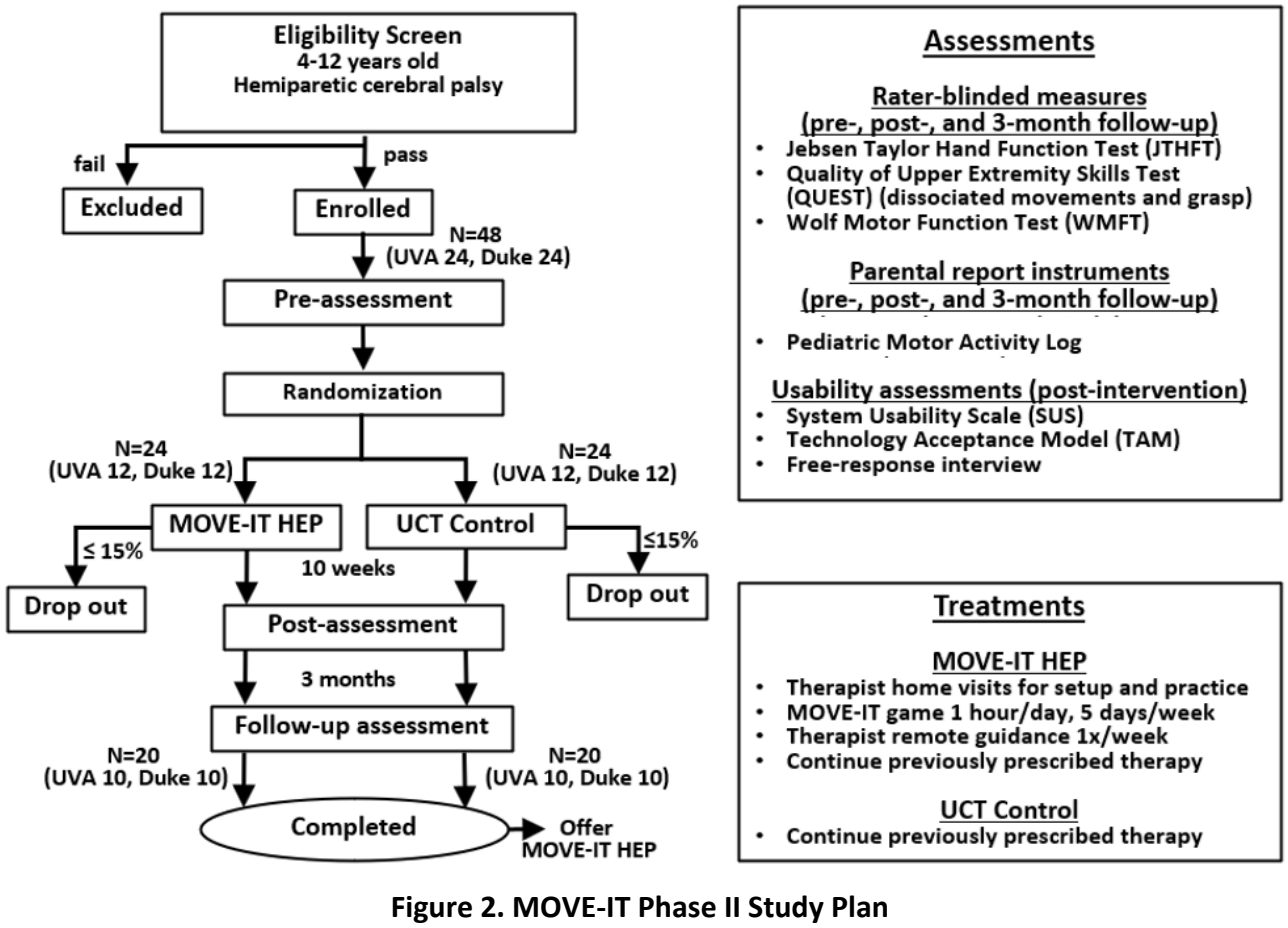

Figure 2. MOVE-IT Phase II Study Plan

6.2 Laboratory Evaluations

No laboratory evaluations will be conducted under this study.

7 STATISTICAL CONSIDERATIONS

7.1 Study Outcome Measures

7.2 Sample Size Considerations

Power analysis for the study is based on approximate effect size and variance information derived from previous RCTs involving intensive therapy for children with hemiplegia. In particular, JTHF outcomes reported by Klingels et al. provide approximate effect size and variance. For the Wilcoxon Mann-Whitney test, if 20 subjects per group (40 total) complete the protocol, we will have at least 0.80 power (α<0.05) if the true underlying probability that the MOVE-IT pre-to-post intervention change in JTHFT score is greater than the pre-to-post change for UCT is 0.75 or greater. Recruitment of 24 subjects per group will allow a conservative 15% dropout rate (e.g. compared to the CHAMP R01 program RCT, NCT01895660), which assumed 10%).

7.3 Participant Enrollment and Follow-Up

Approximately 24 subjects will be recruited at each of the two sites (48 total). Recruited children will have a diagnosis of hemiplegia resulting from cerebral palsy, stroke, or other form of brain injury; be between 4 and 14 years of age; have no history of uncontrolled seizures; and be medically stable. Children will be excluded if they received botulinum toxin injections, stem cell infusions or another form of intensive UE therapy, such as CIMT, within the prior 6 months. Children may receive other forms of treatment or intervention during and after the MOVE-IT intervention; data about such other interventions will be collected prospectively from parents.

It is expected that participant enrollment in the MOVE-IT Phase II RCT will be open for a period of approximately 10 months. Monthly enrollment is projected to average from 6-12 new subjects per month across both sites. Each subject's participation includes a 10-week interventional (or control) period and a 3-month follow-up assessment.

An approximately equal number of subjects will be recruited at the UVA Children's Hospital (n=24) and the Duke Children's Hospital (n=24) study sites, facilitated by experienced study coordinators at each site. Based on recent completion of studies of similar scope, including the CHAMP CIMT trials at UVA [12], the team anticipates being able to meet the MOVE-IT RCT goals.

7.4 Analysis Plan

Primary variable analysis involves analysis of completion times for each of the seven tasks in the JTHFT which will be summed to produce a total score. The pre-intervention scores will be subtracted from the post-intervention scores to produce a set of delta values. These delta values scores (Δ) will be analyzed via Analysis of Covariance (ANCOVA). One null hypothesis will test if the mean pre-to-post-intervention change in the total JTHFT score is equal to zero, while the second null hypothesis will test if the mean pre-to post-intervention change in the JTHFT score is the same for patients who participate in a 10-week MOVE-IT HEP and patients who under UCT over the same duration. For both null hypotheses, a $p \leq 0.05$ decision rule will be utilized as the rejection criterion. Analysis of data from the 3-month follow-up assessment will be performed in a similar manner.

Secondary variable analysis includes analysis of the pre-to-post intervention changes in the composite WMFT scores which will be analyzed in the same way as the pre-to-post intervention change in the composite JTHFT scores. The same method of analysis will be used to analyze the pre-to-post intervention changes in the QUEST scores.

The Likert scale responses to the SUS questionnaire will be summarized per question, and per question category, by frequencies and percentages. As an overall measure of system usability, a composite SUS score in the range from 0 to 100 will be derived from individual responses. By convention, a SUS score greater than or equal to 68 is indicative of an efficient, effective, and satisfying system. For the TAM questionnaire, percentages of favorable responses to the questions of each topic will be estimated via a binomial generalized estimating equation model, and a 90% confidence interval constructed. A Wald test will be used to test the null hypothesis that the odds of a favorable response are independent of the question topic.

Therapy session adherence and activity will be assessed by way of a binomial generalized estimating equation model, in which therapy adherence and activity measures (collected via parental logs) will be compared between the patients who participate in a 10-week MOVE-IT HEP and patients under UCT over the same duration.

All biostatistical design and analysis will be conducted by Mr. James Patrie, a Pstat accredited Senior Biostatistician within the Department of Public Health Sciences of the University of Virginia School of Medicine.

Data from the UVA and Duke sites will be combined during analysis. Randomization will be done at each site. Variation between the two sites is expected to be minimal. The effect of the treatment to be tested is expected to be the same among the two sites, which

will use identical protocols.

8 SUBJECT CONFIDENTIALITY

Subject confidentiality is held strictly in trust by the participating investigators, their staff, the sponsor, and their agents. The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the sponsor. The clinical study site will permit access to appropriate documents and records that may require inspection by the sponsor or its authorized representatives including de-identified study data.

Only IRB-registered protocol staff will have access to the actual identities of the participants, which will remain anonymous to all non-IRB authorized persons.

The sources of human research data will include the following.

1. Demographic information, including age, sex, race, and ethnicity.
2. Results of screening instruments.
3. Rater-blinded assessment instruments including: JTHFT, QUEST, and WMFT.
4. Parental report instrument Pediatric Motor Activity Log.
5. MOVE-IT game-derived measures including achieved therapy duration, and functional movement repetitions.
6. Weekly activity logs
7. SUS and TAM usability questionnaires
8. Transcribed usability data including think-aloud expressions during system use; captured in digital video, screen captures, and therapist notes.

Potential risks of accidental release of identifying and/or confidential information will be mitigated by use of a de-identified coded key for all subject data. The cipher that relates participants to the key will exist in hard (paper) copy only and be stored in a locked cabinet in a controlled-access room at the study sites. All data sheets will be properly controlled and shredded prior to disposal.

De-identified data covering primary and secondary measures will be analyzed by the study biostatistician. The de-identified data and the results of biostatistical analysis will be provided to the sponsor via encrypted means. Results will be reported by the sponsor to the NIH via annual and final progress reports, and incorporated into one or more manuscripts to be submitted for publication in

medical journals and/or conference proceedings accessible via PubMed Central. The MOVE-IT RCT will be registered with ClinicalTrials.gov and results information will be submitted according to ClinicalTrials.gov timelines.

9 INFORMED CONSENT

The informed consent process includes parental or legal guardian permission and child verbal assent. All permission and assent forms will be approved by the IRB. Initial prescreening will be conducted by telephone to determine if a candidate meets basic enrollment criteria including age, diagnosis, and general health status. The parent or guardian of individuals passing phone prescreening will be provided a read-ahead copy of the permission and assent forms. The forms will include a summary of the study protocols, details on inclusion and exclusion criteria, and details on exercise components. Candidates will subsequently be scheduled for an initial consent and screening visit.

During the administration of the permission and assent process, trained study staff will provide the parent or guardian and child an informational overview, verbally guide them through the permission form, provide a summary for each section and ask for verbal confirmation of understanding of each section. The parent will then be given an opportunity to read the entire form, or have the form read to them if they are unable or prefer not to read it themselves. The study therapist will then verify understanding by asking the following question: “If you were to explain what is happening in this study to a family member or friend, what would you say to them?” If the parent or guardian is unable to demonstrate understanding, the study therapist will re-review the permission form and repeat the question. Individuals will be informed of the ability to withdraw from the study at any time and for any reason with no negative consequence.

If the parent or guardian demonstrates understanding of the protocol, he/she will be given the opportunity to sign the permission form. The child will then be given the opportunity to provide assent. The child will be provided with a summary of the study and give the opportunity to demonstrate his or her understanding and willingness to participate. If permission and assent are provided, the parent or guardian will be provided a copy of the signed forms. The original will be filed in the secure study file.

<u>Consent Visit (in-person or remotely administered, will last about 45 minutes)</u>

- The child and a parent/guardian will take part in remotely-administered telehealth visit with a study coordinator or a study therapist by phone or HIPAA compliant video conferencing (e.g. Zoom Health) OR take part in-person.
- Participants will be asked pre-screening questions to verify inclusion and exclusion criteria.
- Participants at the University of Virginia will complete informed consent and assent using DocuSign or alternative institutionally-approved method.

- Participants at Duke University will complete informed consent and assent using a wet signature if the consenting meetings takes place in-person, such as in clinic. If the consenting process takes place via HIPAA compliant video conferencing or phone, study staff will direct the parent/guardian to sign the consent in the appropriate spaces. Study staff will then provide a mailing address for the participant to send the completed consent form. Duke study staff will document the reason remote consent was obtained (i.e. in-person consent not possible due to distance from Duke University).

10 DATA AND SAFETY MONITORING PLAN-IRB-HSR TO SERVE AS SIRB OF RECORD

This study has been deemed minimal risk. Because this study poses minimal risk to the subject, **adverse events will only be collected or recorded if a causal relationship to the study intervention is suspected.** If any adverse event is considered serious and unexpected, the event must be reported to the IRB-HSR within 7 days from the time the study team receives knowledge of the event.

10.1 Definitions

10.1.1 How will you define adverse events (AE)?

Do not change this answer

An adverse event will be considered any undesirable sign, symptom or medical condition considered **related to the intervention**. Medical condition/diseases present before starting the intervention will be considered adverse events only if they worsen after starting the study and that worsening is considered to be related to the study intervention. An adverse event is also any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable private information under the research.

10.1.2 How will you define an unanticipated problem?

Do not change this answer

An unanticipated problem is any issue that involves increased risk(s)
to participants or others. This means issues or problems that cause the subject or others to be placed at greater risk than previously identified, even if the subject or others do not incur actual harm. For example if a subject's

confidentiality is compromised resulting in serious negative social, legal or economic ramifications, an unanticipated problem would need to be reported. (e.g. serious loss of social status, loss of job, interpersonal conflict.)

10.1.3 What are the definitions of a protocol deviation and/or noncompliance?

Do not change this answer

A protocol deviation is defined as any change, deviation, or departure from the study design or procedures of research project that is NOT approved by the IRB-HSR prior to its initiation or implementation. Protocol deviations may be major or minor.

Noncompliance can be a protocol deviation OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulations**.** Noncompliance may be minor or sporadic, or it may be serious or continuing.

Additional Information: see the IRB-HSR website at
Protocol Deviations, Non-compliance and Protocol Exceptions

10.2 What risks are expected due to the intervention in this protocol?

Expected Risks related to study participation	**Pick One**
There is a small risk that breaches of privacy and/or confidentiality might occur. The risk of violation of subject privacy and confidentiality is minimal due to the requirements of the privacy plan in this protocol.	Occurs rarely
There is a minor risk that soreness, pain, or increased tone may occur post-use due to increased range and level of activity involving the upper extremity. The risk is minor as game-integrated movements are consistent with accepted	Occurs rarely

clinical practice and exercises used in previous RCTs involving similar therapy (e.g. the CHAMP R01 RCT, [12]).	
There is a minor risk of elevated stress or embarrassment due to frustration with the interface or inability to perform a task. The risk is minor as cognitive demands are progressive and appropriate for the participant population and consistent with existing clinical practice. Study pediatric therapists will tailor the activities to the capabilities of the patient.	Occurs rarely

10.3 When will recording and reporting of unanticipated problems/adverse events begin?

__x___After subject begins study intervention

10.4 When will the recording/reporting of unanticipated problems/adverse events end?

___x__Subject completes participation in the protocol

10.5 What is your plan for safety monitoring?

Do not change this answer

Safety monitoring and aggregate review of adverse events, unanticipated problems, protocol violations and any data breach will be performed by the PI and IRB-HSR through continuation review at least annually.

10.6 What is your plan for reporting an Unanticipated Problem, Protocol Deviations or Data Breach?

10.6.1 Reporting Requirements for UVA Site

Type of Event	To whom will it be reported:	Time Frame for Reporting	How reported?
Unanticipated Problems that are not adverse events or protocol deviations This might include a Data Breach.	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Unanticipated Problem report form. Unanticipated Problem Report Form
Protocol Deviations/Noncompliance (*The IRB-HSR only requires that MAJOR deviations be reported, unless otherwise required by your sponsor, if applicable.)*	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Protocol Deviation, Noncompliance and Protocol Exception Reporting Form Protocol Deviation Protocol Exception Reporting Form

Data Breach* of Protected Health Information	The UVa Corporate Compliance and Privacy Office ITC: if breach involves electronic data Police if breach includes items that are stolen: Stolen on UVA Grounds OR Stolen off UVa Grounds- contact police department of jurisdiction of last known location of PHI	As soon as possible and no later than 24 hours from the time the incident is identified. As soon as possible and no later than 24 hours from the time the incident is identified. IMMEDIATELY.	UVa Corporate Compliance and Privacy Office- Phone 924-9741 **ITC:** Information Security Incident Reporting procedure, https://security.virginia.edu/report-information-security-incident Police: phone- (434) 924-7166

*A data breach is defined in the HITECH Act (43 USC 17932) as an unauthorized acquisition, access, or use of protected health information (PHI) that compromises the security or privacy of such information.

Additional Information may be found on the IRB-HSR Website: Data Breach

10.6.2 Reporting Requirements for the non-UVA site(s)

Type of Event	To whom will it be reported:	Time Frame for Reporting	How reported?
Unanticipated Problems that are not adverse events or protocol deviations This might include a Data Breach.	UVA study team/ Data Coordinating Center UVA lead site or DCC will report to the IRB-HSR per table above	Within 7 calendar days from the time the study team received knowledge of the event.	**Written documentation.** **May use the** Relying Site Unanticipated Problem Reporting Form
Protocol Deviations/Noncompliance *The IRB-HSR only requires that MAJOR deviations be reported, unless otherwise required by your sponsor, if applicable.* **OR** **Protocol Exceptions** *See definition- only allowed if there is a commercial sponsor or a DSMB that has granted the protocol exception.*	UVA study team/ Data Coordinating Center UVA lead site or DCC will report to the IRB-HSR per table above	Within 7 calendar days from the time the study team received knowledge of the event.	**Written documentation.** **May use the** Relying Site Protocol Deviation/Exception Reporting Form

Data Breach	Per local relying institution requirements The UVA IRB-HSR only needs to be notified of any data breach that meets the criteria of a UP	Per local relying institution requirements	Per local relying institution requirements.

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