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
Susan Quinn, MD

PROTOCOL TITLE
Virtual Reality-based Rehabilitation for Children with Traumatic Brain Injuries

FUNDING
National Institutes of Health

VERSION DATE
Version 5.0 3/22/23

SPECIFIC AIMS

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

The overall goal of the project is to assess the preliminary efficacy of a novel VR-based interactive cognitive training (VICT) program for cognitive rehabilitation in children with TBI.

Aim 1. Examine VICT's efficacy in improving core and daily EF skills among children with TBI.

Hypothesis 1.1: Children in the intervention group will show enhanced improvement over controls in trained VR-based EF tasks and untrained NIH Toolbox tasks from baseline to post-intervention and follow-up visits;

Hypothesis 1.2: The intervention group will show better reported daily EF than controls at the follow-up visit;

Hypothesis 1.3: Children in the intervention group will show faster improvement than controls in daily-reported EF skills between post-intervention and follow-up visits.

Aim 2. Examine VICT's efficacy in reducing attentional problems among children with TBI.

Hypothesis 2.1: Children in the intervention group will show a greater reduction in attentional problems as measured by testing on the Conners Continuous Performance Test 3rd Edition™ (Conners CPT 3™) from baseline to the post-intervention and follow-up visits than controls;

Hypothesis 2.2: Children in the intervention group will show fewer everyday attentional problems on the Behavior Assessment System for Children 3rd Ed (BASC-3) self- and parent-ratings of attention at the follow-up visit than controls;

Hypothesis 2.3: The direct effect of the VICT program in reducing attention problems will be mediated by children's EF behaviors as measured by the Behavior Rating Inventory of Executive Function, Second Edition (BRIEF2) at the follow-up visit.

Aim 3. Examine VICT's efficacy in improving HRQOL among children with TBI.

Hypothesis 3.1: The intervention group will show higher levels of reported HRQOL than controls at follow-up;

Hypothesis 3.2: The direct effect of the VICT program on HRQOL at follow-up will be mediated by children's EF skills and ratings of EF behaviors and attention at the post-intervention and follow-up visits.

BACKGROUND AND SIGNIFICANCE

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

Traumatic brain injury (TBI) is a leading cause of acquired disability in U.S. children, with an estimated 700,000 cases every year, presenting in 75% of children with trauma and accounting for 70% of deaths from childhood trauma. Childhood TBIs often result in significant impairment in cognitive functions, particularly in core executive functions (EFs) due to the vulnerability of the frontal lobes, especially after a moderate to severe TBI. Core EF is composed of three skills: inhibitory control, working memory, and cognitive flexibility. These skills are associated with impaired EF behaviors, increased attention problems, and lower health-related quality-of-life (HRQOL). However, evidence-based EF rehabilitation programs are lacking. Although a combination of diverse cognitive interventions may improve children's EF, limited affordability, accessibility, adherence, and generalizability hamper clinically adapting and implementing such interventions in the rehabilitation setting. Virtual reality (VR) offers an exciting alternative strategy for EF rehabilitation of childhood TBI due to its flexibility, accessibility, and immersive experiences in three dimensions. These properties may increase adherence to training and foster an enhanced transfer of learned EF skills to untrained tasks in everyday life. *Thus far, rigorous randomized clinical trials (RCTs) have not been conducted to establish the efficacy of VR-based EF rehabilitation for childhood TBI.*

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."

The study uses a randomized controlled trial design to investigate the efficacy of a virtual reality-based executive function training program for cognitive rehabilitation among 32 children between 6 and 17 years old (inclusive) with TBI. Participants will be recruited from Spaulding Rehabilitation Hospital (Boston, MA) and Kennedy Krieger Institute (Baltimore, MD), using the following inclusion and exclusion criteria:

Inclusion criteria:

- Diagnosed with moderate to severe TBI and 6-17 years at the time of injury;
- Moderate or severe TBI. Diagnosis is determined by multiple factors, including but not limited to: Glasgow Coma Scale score, additional clinical characteristics, and expert opinion by physician or therapists.
- Fluent in English-based communication
- Physicians note closest to time of enrollment does not include information on agitation, or if under observation for agitation, currently score <28 on the Agitated Behavior Scale indicating mild to no agitation.

Exclusion criteria:

- Severe physical/visual/cognitive impairments secondary to TBI such as inability to follow directions, unresponsiveness, and limited motor skills that prevent proper utilization of a VR-based training and valid administration of the study measures;
- Premorbid neurological or developmental issues such as autism, developmental delay, severe language impairment or neurologic disorder before the injury that might prevent proper utilization of a VR-based game and valid administration of the study measures, and that

might confound the study findings;
- More than one post-injury seizure.
- Patients restricted from using electronic gaming devices

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.

The following study procedures will be followed in this study:

Visit 1:

Baseline Assessment:

- On first day of the study, participants will complete a standard cognitive and attention assessment using virtual reality, computer, and iPad as well as several questionnaires with a researcher. These assessments will take about 60 minutes.

Intervention Session:

- Intervention session can take place any time following the baseline assessment. Participants will be provided a tutorial to be familiar with the VR equipment, as well as a standardized interactive tutorial automatically built into the VR for completing the training tasks.
    - The VR game for the intervention group is called "Rescue the Lubdubs". In this game, children will try to rescue an animated creature called "lubdub" by defeating the guards (training inhibitory control skills), memorizing the passcode to unlock castle gates (training working memory skills), and matching partners between the lubdub's belly and its guards (training cognitive flexibility skills).
    - The VR game for the control group is a relaxing and immersive playground where children can throw projectiles (bees, beans, etc.) to different objects in the virtual environment (moving boards, water buckets, light bulbs, etc.). This game does not require the use of any of the executive functioning skills (i.e., inhibitory control, working memory, cognitive flexibility) and therefore serves as a placebo game for the control group.
- Participants will only be randomized to either intervention or control groups after completion of the baseline assessment. The randomization scheme is designed blocked randomization with random block sizes of 2 and 4 and 1:1 ratio for intervention and control treatment.
    - Randomization and the intervention session will be completed by an unblinded Research Assistant.
- Participants will then complete at least one (1) 30-minute intervention session. The child and their family can decide if they would like to play the game for a longer period of time. Breaks are permitted upon patient request at any time. AEs and serious AEs will be actively monitored throughout the intervention sessions. Anxiety in anticipation of the intervention will also be assessed before the intervention, while simulator sickness, perceived exertion, and subjective VR experience will be measured after the intervention.

Visit 2:

Post Intervention Assessment: Post-intervention assessment will be scheduled upon completion of the intervention session and should take place within 1 week after the intervention session. Research staff blinded to the participants' group assignment will administer the post-training assessment, which consists of the same set of tasks as those in

the baseline assessment, as well as VR experience questions such as motion sickness, perceived benefits and challenges, and physical exertion.

Between Visit 2 and Visit 3:

- A brief EMA-EF Survey will be sent to participants to complete daily between the post-intervention and follow-up visits, which may take about 2 minutes per day for 30 days.

Visit 3:
Follow-Up Visit

- Follow-up visits are scheduled 30 days following the post-intervention assessment (up to 12 months). Staff blinded to the participants' group assignment will administer the following measures:
    - VR and NIH Toolbox tests;
    - Conners CPT 3;
    - Children's Anxiety Meter;
    - Self-report BRIEF2, BASC-3, and PedsQL Generic Core Scales;
    - TPVT
    - Media Use Survey.
    - A parent will complete the parent-report version of BRIEF2, BASC-3, and PedsQL.

The study endpoint is the preliminary efficacy of the VICT program, defined as the changes in VR Assessment Scores, NIH Toolbox Composite Scores, and BRIEF2 Global Scores between baseline and post-intervention and between baseline and follow-up assessment.

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.

The virtual reality intervention is designed to be supplementary to standard of care at Spaulding Rehabilitation Hospital. Therefore, all participants will still receive standard of care as determined by their doctors regardless of participation of this study or random assignment to the intervention or control group.

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.

Based on data collected during the pilot phase as well as a comprehensive assessment conducted with our clinical collaborators, we do not anticipate significant risks to the participants beyond the usual standard of care for this study. Specifically, the virtual reality equipment will be set up ergonomically to minimize the physical risks and burden of the equipment to the patients. Also, age-appropriate VR content has be designed to minimize psychological risks. Questionnaires and computerized tasks used in this study have all been used repeatedly in previous research (including the pilot study) or clinical practice without adverse effects. Because all participants will continue to receive standard therapies/care at the hospital, participation in or withdrawal from the study will not affect participants' standard care or treatment.

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.

To ensure safety of subjects, the virtual reality video-game training program used in this study was designed with developmental and clinical appropriateness in mind and has been refined based on feedback from pilot participants to protect children from further potential physical or psychological risks. Specifically, the training system consists of an individual mechanism support arm used to suspend the VR goggle in front of a participant's eyes with easy-to-adjust height/direction and stereo headphones to avoid the physical burden of a traditional VR headset on the patients' injured head. The VR system, which is securely fixed on a wheeled mobile workstation, allows a patient to operate the program either reclining on a hospital bed or in a wheelchair in his/her patient room, depending on the patient's clinical needs and personal preference. Furthermore, to ensure the hygiene of the equipment, the equipment is sanitized with germicidal wipes after each use.

Trained study staff will approach patients and their families in a sensitive and caring fashion to minimize any potential psychological uneasiness in participating in this study. The study staff will receive over the entire study period, extensive training in identifying any significant physical or mental discomfort. Breaks during both the VR training sessions and various outcome measures will be available to participants upon request. Participants who feel uncomfortable either physically or psychologically using the VR or any of the study measures will have options to withdraw from the study at any time without affecting their access to standard care. Should adverse events occur with the participants, the study staff will immediately terminate the VR game and contact attending doctors/nurses for assessment. Adverse events will be monitored in real-time and reported to the corresponding institutional IRB.

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.

A small number of participants, depending mainly on their previous experience with electronic gaming in general and VR gaming in particular, might experience symptoms related to motion sickness, such as headaches, nausea, blurred vision, and physical/mental fatigue while completing the training/tasks in the virtual environment. However, based on the data collected from the pilot study, we anticipate a minimal occurrence of these symptoms. For those who did experience such symptoms, the side effects were found (in our pilot study) to be low in strength, short-lived, and disappeared after regular breaks that we offered any time during the game per participants' preferences. Additionally, some participants might experience mental tiredness or psychological discomfort while completing questionnaires and/or other outcome measures. Such discomfort is likely to be minimal, infrequent, and short-lived. Participants have the option to refuse answering any of the questions they are not comfortable with, or completely withdrawn from any measurement instrument or the entire study should they feel so, any time during the study without affecting their standard care.

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.

Children who participate in this study may not directly benefit as the purpose of the study is to assess the preliminary efficacy of this virtual reality-based executive function training system for childhood TBI rehabilitation. However, because both the intervention group and the control group will have access to state-of-the-art virtual reality-based gaming, participants might enjoy varying levels of fun and pleasure playing with the VR games while receiving standard care at the hospital. Furthermore, standardized outcome assessments for executive functions, attention problems, and health-related quality of life might also indirectly help participants and their families gain a better understanding of their child's recovery processes. Finally, the results gained from data collected from this study might inform future refinement and development of the VR system for maximizing the potential benefits of the intervention for other children with TBI. Although the potential benefits of direct participation in this study are limited, they are reasonable in relation to the minimal risk incurred.

This study will also significantly improve our understanding of the efficacy of a novel VR-based training system designed explicitly for childhood TBI rehabilitation of executive functions. The findings from this project will not only inform future development of the VR-based intervention program but also provide the foundational expertise and empirical data necessary to develop and implement a more comprehensive multi-module VR training system that targets skills beyond executive functions, such as emotional and social skills for children with TBI. In the long term, results of this study are also likely to inform VR-based psychological rehabilitation for individuals at different developmental stages with other types of acquired brain injuries. We believe the importance of the knowledge to be gained in this study outweighs the minimal risks associated with participation in the study.

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.

Under the NIH definition of children as those under 18 years, the present study will include 'children.' Because this is a study evaluating the efficacy of a virtual reality-based executive function training program specifically designed for *childhood* TBI rehabilitation, this study will not include participants above 18 years old.

The present study will include both sexes. We expect that males will be overrepresented in the sample of children with traumatic brain injuries (TBIs) since the ratio in the pilot data collected was approximately 60% male:40% female. This overrepresentation may be due to the higher incidence of pediatric TBIs in males in the broader population. We also anticipate that mothers are more likely to complete the parent-report measures for the study based on the participation rates of fathers versus mothers in previous behavioral studies. However, the decision regarding which parent participates in the study will be left to the discretion of individual families to promote flexibility and convenience.

Recruitment to the present study will be representative of the minority distribution at Spaulding Rehabilitation Hospital and the greater Boston, MA area, and with respect to any racial influences that affect pediatric diagnoses. We expect that approximately 10% of participants to self-identify as Hispanic

or Latino, 20% as African American, 5% as Asian/Pacific Islander, and 7% as multiracial. Because traumatic brain injuries do not occur randomly in the local population, these numbers are estimated based on the relative difference in incidence rates of childhood TBI from a five-year review of records at the Spaulding Rehabilitation Hospital. These percentages reflect a slightly larger population of minorities than those reported by local sociodemographic data reported by the State of Massachusetts.

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.

The present study will only include participants who are able to communicate in English, because this prototype virtual reality video games developed for this study has instructions both in written and spoken English, but not available in other languages so far. As with any standardized psychological assessment and training instruments, availability in a different language require strict validation of psychometric properties specific to that language as well as cultures using that language. As a first step in our line of research, we plan to evaluate the efficacy of this virtual reality game in English for this study, as it is the most common language used by pediatric patients with traumatic brain injuries in the greater Boston area. And if successfully, we will incorporate other languages in future validation studies specific to the culture and population using those languages.

For guidance, refer to the following Partners policy:
Obtaining and Documenting Informed Consent of Subjects who do not Speak English
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Non-English-Speaking-Subjects.pdf

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.

The study will recruit from Spaulding Rehabilitation Hospital (SRH) and Kennedy Krieger Institute (KKI). We expect most patients will be recruited by site-PI Dr. Susan Quinn from the Pediatric Inpatient Rehabilitation Unit at SRH (Medical Director of the Unit; Site PI), and we expect KKI to enroll 8-12 subjects. Possible methods to recruit potential participants include reviewing medical records, referral by Dr. Quinn or her colleagues at SRH, self-referral by patients themselves via Clinicaltrials.gov. Flyers will also be posted within SRH facility to supplement patient recruitment. Targeted Research Announcements via Patient Gateway will also be used to increase recruitments from other MGB sites; patient information will be obtained through 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

We will provide the participating patient in the form of check with $40.00 for completing the baseline assessment, an additional $50.00 for completing the designated training (or comparable VR game for the control group) and post-intervention assessment, an additional $60 for completing the entire 30-day EMA-EF daily survey (pro-rated if completed fewer than 30 surveys), and finally an additional $80.00 for completing the follow-up assessment. In addition to the above honorarium provided to the patient, we will provide the parent with a one-time $80.00 honorarium also in the form of a check for completing the parent questionnaires at the follow-up visit.

For guidance, refer to the following Partners policies:

Recruitment of Research Subjects
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Recruitment-Of-Research-Subjects.pdf

Guidelines for Advertisements for Recruiting Subjects
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Guidelines-for-Advertisements.pdf

Remuneration for Research Subjects
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Remuneration-for-Research-Subjects.pdf

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.

The researchers will ensure that they understand study participation is voluntary and will not affect any treatment in current or future visits. Informed consent and assent will be obtained by the study PI or trained research staff per institution policy. Informed consent process will allow for all questions from participants and family are addressed satisfactorily. No study procedures will be implemented until after informed consent and assent (if applicable) are obtained.

Potentially eligible patients and family will be screened according to the inclusion and exclusion criteria. Children and legal guardians will be approached only if they are awake, alert, and interested in the study after the initial introduction. Patients may also contact the PI or research staff via contact methods provided on distributed flyers or study protocol on clinicaltrials.gov or by referral from other departments or institutions to the PI.

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:
https://partnershealthcare.sharepoint.com/sites/phrmApply/aieipa/irb

For guidance, refer to the following Partners policy:
Informed Consent of Research Subjects:
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Informed-Consent-of-Research-Subjects.pdf

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.

Because this study involves only the use of electronic video games as the sole interventional strategy, the risk of this study is minimal. Furthermore, the site PI assures that informed consent/assent will be obtained before enrolling any child, that all participants meet eligibility criteria, and that the study is conducted according to the IRB-approved research plan. Study data will be accessible at all times for the site PI to review. The site PI will review study conduct (e.g., accrual, drop-outs, protocol deviations). The data review will also include self-reported data from participants regarding their virtual reality experiences as measured in designated instruments attached to this protocol, including physical exertion, motion sickness symptoms, and levels of fun, pleasure, motivation playing the virtual reality games. If there are more than five participants experiencing the same symptoms (such as motion sickness) as measured above, the PI will stop the study, review the study protocol, revise as necessary, and submit the modified/refined protocol for IRB approval before the study resumes.

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

The site PI will review adverse events (AEs) and serious adverse events (SAEs), as well as participants' discomfort, including fatigue and simulator sickness in real-time and in aggregate weekly. The site PI ensures all protocol deviations, AEs, and SAEs are reported to the NICHD and IRB according to the applicable regulatory requirements.

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 site-PI and research assistants will review and monitor the validity and integrity of the data collected, source documents, informed consent, and protocol implemented according to the IRB-approved protocol, on a regular basis through project meetings with all study staff. The PI will be responsible for overseeing the study protocol implementation as approved by the IRB.

For guidance, refer to the following Partners policies:

Data and Safety Monitoring Plans and Quality Assurance
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/DSMP-in-Human-Subjects-Research.pdf

Reporting Unanticipated Problems (including Adverse Events)
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Reporting-Unanticipated-Problems-including-Adverse-Events.pdf

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.

The privacy and confidentiality of study participants will be maintained by assigning each participant a unique study ID number. IRB-approved study personnel will maintain a master file that links the participants' names and their study ID numbers in a password-protected electronic

database at Spaulding Rehabilitation Hospital. All other study materials, randomization procedures, and databases will only use the study ID number for identification purposes without participants' names or any other Protected Health Information attached. All de-identified paper documents will be stored in locked cabinets in PI (Dr. Jiabin Shen)'s office/lab space at University of Massachusetts Lowell. All de-identified electronic data will be stored on a secured electronic database locally hosted by University of Massachusetts Medical School and managed by the PI Dr. Jiabin Shen and IRB-approved personnel.

Study results from the data analysis will be reported only in an aggregated format without any identifying information. The PI (Dr. Shen) and Co-I (Dr. Quinn) will ensure that all study staff observe these safeguarded measures to maintain data confidentiality and minimize any potential risks of participating in this study.

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.

Only de-identified data and source documents (e.g., original questionnaires responded by participants/parents), as well as original consenting documents will be sent to PI (Jiabin Shen)'s institution, University of Massachusetts Lowell.

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.

The above mentioned de-identified data will be stored and managed by PI (Jiabin Shen) at his lab at University of Massachusetts Lowell. His lab uses REDCap (hosted by UMass Medical School for all five UMass campus users) to manage electronic databases. UMass Lowell also uses Microsoft OneDrive Business edition for all faculty members to store research data, which will be securely protected by passwords and firewalls. De-identified paper documents/data will be stored in locked cabinets in locked lab/office space of the PI. Only PI and IRB-approved study personnel will access to these de-identified databases and documents. Participants will not be able to withdraw their data stored at UMass Lowell/REDCap because all those data will be de-identified and therefore we will be unable to trace back the data to an individual participant for deletion.

A reliance agreement will be established between Partners and UMass Lowell IRB.

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.

Spaulding Rehabilitation Hospital will not receive any data collected from outside of Spaulding. The study team at SRH will only have REDCap access to data collected at Spaulding.