PROTOCOL TITLE:

Virtual Reality-based Rehabilitation for Children with Traumatic Brain Injuries

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	Original		
2	7_3_2018	Added new assessments, edited questions, edited study population	N
3	9_10_2018	Expanded recruitment to include other inpatient and outpatient locations and trauma registry, added Epic Patient Reminder list, changed timing of follow-up	Y
3	10_25_2018	Added fully-adjusted scores to NIH Toolbox	Y
4	11_5_2015	Added new survey (TBI-QOL)	Y
5	12_10_2015	Changed inclusion criteria related to agitated behavior. Changed wording on timing, procedures, visit structure, and recruitment for clarification purposes. Removed visit option in public locations. Added text appointment reminders, ClinCard receipts, and parking reimbursements and receipts for research only visits. Changed the blinding structure so the person doing the assessments is blinded only to the intervention group.	Y
6	4_8_2019	Added emailing flyer to recruit subjects.	

1.0 Study Summary

Study Title	Virtual Reality-based Rehabilitation for Children with Traumatic Brain Injuries
Study Design	Between-subjects Randomized Clinical Trial

Primary Objective	Refine clinically-appropriate paradigms for VR childhood TBI rehabilitation research
Secondary Objective(s)	Explore feasibility, safety and preliminary efficacy of the VICT program
Research Intervention(s)/ Investigational Agent(s)	VR-based interactive cognitive training (VICT) program
IND/IDE #	N/A
Study Population	Children 7-17 years with TBI
Sample Size	Approximately 30
Study Duration for individual participants	Up to 6 months
Study Specific Abbreviations/ Definitions	TBI-Traumatic Brain Injury VR-Virtual Reality VICT-Virtual Reality-based Cognitive Training

2.0 Objectives

2.1 Describe the purpose, specific aims, or objectives.

Our primary objective is to refine clinically-appropriate paradigms for VR childhood TBI rehabilitation research. The secondary objective is to explore feasibility, safety and preliminary efficacy of the VICT program. There are two specific aims of the study.

Aim 1. Refine clinically-appropriate paradigms for VR childhood TBI rehabilitation research.

Aim 2. Explore feasibility, safety and preliminary efficacy of the VICT program.

2.2 State the hypotheses to be tested.

Since this is a preliminary exploratory study, there are no specific hypotheses to be tested.

3.0 Background

3.1 Describe the relevant prior experience and gaps in current knowledge.

The Centers for Disease Control and Prevention (CDC) classifies childhood traumatic brain injury (TBI) as the leading cause of death and acquired disability in children, with an estimated 700,000 childhood TBI cases every year in the United States.[1-4] Defined as a disruption in the normal function of a child's brain that can be caused by a bump, blow, or jolt to the head, or a penetrating head injury, childhood TBIs often result in significant impairment in cognitive functions,[1] particularly in executive functions (EFs) due to the

vulnerability of the frontal lobes, especially in moderate to severe TBIs.[5-7] EF involves a set of core cognitive capacities for self-controlled discipline, creativity, and flexibility.[8, 9] This study will focus on training the three core EFs identified by cognitive science: inhibitory control (the ability to override a strong internal predisposition or external lure and do what is more appropriate or needed), working memory (the ability to hold and process information in mind as needed), and cognitive flexibility (the ability to adjust to changing environmental demands and think from different perspectives).[8] Deficits in core EFs have profound implications for the children's daily EF[8] and quality-of-life (QoL),[10] as reflected in increased attention problems,[11] poorer academic performance,[12] and poorer psychosocial adjustment.[13]

However, evidence-based EF training programs specifically designed for childhood TBI are unavailable.[14-17] As early as 2015, the CDC reported to Congress that post-TBI cognitive rehabilitation was the No. 1 unmet health care need among children with TBI and called for more innovation in this area.[2] Although a combination of computerized and non-computerized cognitive games has been shown effective in improving healthy children's EFs,[9,18] four key obstacles hamper the successful implementation of such interventions in children with TBI: affordability, accessibility, adherence, and generalizability. First, implementation of broad-spectrum EF training programs is both costly for families and resource-demanding for hospitals.[19] Second, existing EF training requires the presence of both therapists and patients at the hospital or clinic, which impedes accessibility for families living in remote areas, contributing to disparities in health outcomes. Third, existing EF training typically uses rudimentary paper-and-pencil tasks or artistically substandard flat-screen computer tasks, both of which are unappealing to children and adolescents who are increasingly accustomed to engaging video games available to them outside the medical setting.[20] This may negatively affect children's long-term rehabilitation outcomes by decreasing their willingness to participate planned training activities, especially for follow-up sessions after discharge. Fourth, partially due to the lack of variety and richness, existing EF interventions are often limited in helping children transfer learned skills to untrained life activities.[9]

3.2 Describe any relevant preliminary data.

The NCH Inpatient Rehabilitation Unit admits an average of 30 children with TBI (ICD-9 codes: 803, 850, 851, 854; no deaths, no asphyxia) annually. A five-year review of records shows that 80% (24 children/year) or more are eligible to participate in the proposed K99 study. Open-end feedback from patients and families at NCH suggested broad interest in participating in the study. Our target

sample size (N=30) is reasonable for an 18-month recruitment period. Recruitment will be monitored during the study. Additionally, we have recruited two pediatric patients with TBI from the NCH rehabilitation unit who pilot-tested the VICT program and the pre- and post-intervention measures. Both patients and their family and clinicians expressed high enthusiasm and satisfaction with the intervention.

3.3 Provide the scientific or scholarly background for, rationale for, and significance of the research based on the existing literature and how will it add to existing knowledge.

Virtual reality (VR) offers an exciting alternative EF rehabilitation strategy for three reasons. First, VR technology has the capability to offer a multitude of activities for training children with TBI in core EFs[8] within a versatile virtual environment. Such an enriched, immersive environment has already been shown effective in promoting structural and functional recovery of the human brain.[21] Furthermore, because all VR-based EF training occurs within a safely controlled, automated virtual environment, it takes minimal physical space and personnel resources to implement in a medical setting, reducing expenses for both the hospitals and the families. Second, VR-based EF training can be readily provided via Internet and mobile platforms. This allows EF training, especially those sessions scheduled after discharge, to be completed without requiring children to leave home. Last but not least, unlike traditional computer-based EF training, we expect VR-based EF training to exert two positive effects on children's rehabilitation[22]: (1) improved adherence. VR-based EF training was found especially appealing to pediatric patients in our pilot testing, possibly due to the youth population's increasing exposure to electronic games in recent years; (2) potentially better skill transfer to real life. Although research suggests mixed results of computerized training for cognitive skills in general, we expect VR training to translate trained skills into daily EF skills and overall QoL in pediatric TBI patients because (1) EFs are domain-general cognitive skills that can be gained in one setting and transferred to another;[23] (2) studies using representative national samples of children have supported EF as domain-general skills and documented positive relations between EFs and real-life outcomes,[24] and (3) Our pilot test of the VICT program on two pediatric patients with TBI at NCH showed positive changes of core EF scores after intervention (although this preliminary result should be interpreted with caution given that the changes could reflect other factors, such as natural recovery).

The overall goal of the proposed research is to evaluate the feasibility, safety, and efficacy of a VR-based interactive cognitive training (VICT) program in children 7-17 years with complicated mild to

severe TBI. The VICT program is an integrative hardware and software VR system that trains the three core EFs (inhibitory control, working memory, and cognitive flexibility)[8] within a challenging 3D-animated rescue mission. The research is significant because it will provide important feasibility and safety data regarding implementing a novel VR-based EF rehabilitation program for children with TBI. This project is also expected to provide important data regarding the intervention's efficacy on children's core EF and daily EF (primary outcome) as well as attention problems and health-related QoL (secondary outcomes). Finally, findings from this project are expected to inform future development of a comprehensive VR-based cognitive rehabilitation program to help children with TBI achieve a healthy and productive life post-injury.

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4.0 Study Endpoints

4.1 Describe the primary and secondary study endpoints.

The primary study endpoint is the protocol feasibility (defined as protocol completion rate and subjective VR experience ratings) and safety (see section 4.2) of the VICT program. The second study endpoint is the preliminary efficacy of the VICT program, defined as the changes in NIH Toolbox Composite Scores before and after the intervention.

4.2 Describe any primary or secondary safety endpoints.

The primary safety endpoint is the number of adverse events. The secondary endpoint is the scores on participants' simulator sickness and exertion.

5.0 Study Intervention/Investigational Agent

5.1 Description:

The hardware of the VICT program consists of a fully-immersive High Tech Computer (HTC) VIVE™ VR viewer (OLED display with 2160×1200 resolution, 90Hz refresh rate, and 110 degrees of field of view) powered by a high-performance laptop (Dell Alienware™ 17), a pair of surround sound headphones reworked to integrate with the VR viewer, and a wireless one-hand controller for the child to interact with the virtual environment using gestures. Furthermore, to avoid the burden of the equipment's weight on a child's head, we created a special mechanical arm to suspend the VR viewer in front of a child's eyes with adjustable headphone positions. With the system securely fixed on a wheeled workstation, a child can operate the program by reclining on the bed/wheelchair in his/her own patient room. To ensure the hygiene, each child will use a new facial pad for the viewer and a pair of new earphone covers. All parts of the equipment will be sanitized with germicidal wipes after each use.

For the software, the Windows 10-based VICT program invites children to rescue an animated character named "Lubdub" from a castle. The program consists of three challenging and child-friendly tasks that correspond to the three core EFs. During the game, children need to (1) direct a group of sentinels away from the castle gates (VR Task #1, adapted from the Spatial Stroop Task to train Inhibitory

Control), (2) successfully open a series of castle gates by replicating the cryptography sequence of items surrounding each gate in forward/backward order (VR Task #2, adapted from the Visual Working Memory Task to train Working Memory), and finally (3) rescue Lubdub inside the castle by strategically matching patterns between the Lubdub and the four surrounding guards (VR Task #3, adapted from the Wisconsin Card Sorting Task to train Cognitive Flexibility). A tutorial mode preceding the training lets children learn how to interact with VR. In the training mode, children will complete each task starting at the easiest level and gradually moving to more difficult levels as easier levels are mastered. Each training session consists of 10-30 trials per task, taking about 15 minutes in total. Children will receive visual/audio feedback to learn and optimize their performance.

6.0 Procedures Involved*

The procedure involved for the study is described in detail below:

1) Baseline assessment. All approximately 30 children will complete the NIH Toolbox Cognition Battery tests, CPT 3, Virtual Reality Assessment, and the TBI-QOL Short Form prior to the randomization sequence. Both the assessor and the child will be unaware of group assignment at this point. Additionally, data regarding baseline measurement including proportion of planned baseline measures that are completed and the duration of each assessment will be documented.

2) Intervention. Following the baseline assessment, the approximately 30 children will be randomly assigned to one of the following two groups: intervention group (VICT training) or control group (a comparable VR game without cognitive training). The random allocation sequence will be generated using a SAS-based randomization program with 1:1 allocation ratio and random block sizes of 2 and 4. Both groups will first be provided a tutorial to be familiar with the VR environment. The length of time for either intervention game will be a minimum of 15 minutes of total play. If they are in the hospital, they will play approximately 15 minutes per day during their stay. If they have already been discharged from the hospital, the length of time is a minimum of 15 minutes of total play but can be more spread across their choice of days. Trained researchers who generate the randomization sequence and implement the VR will not participate in any subsequent outcome assessment. Note that although the length of training will vary across children depending on their length of stay or if they have been discharged, this arrangement has unique advantages over a fixed length of training in that: a) it provides consistency with standard therapies children are scheduled to receive, ensuring intervention to meet children's medical needs; and b) it ensures consistent timing and sufficient retention rates for future assessment.

Additionally, AEs and SAEs will be monitored in real-time throughout the intervention. Quantitative user feedback such as sickness, fatigue, and time estimates will be measured at the end of both the first and the last VR session. The

semi-structured interview from the User Feedback Survey will also be conducted at the first and last VR session on children's perceived VR experience, benefits, and challenges.

3) Post-intervention assessment. At completion of intervention, all children will again complete the NIH toolbox Cognition Battery tests, the Conners CPT 3, the Virtual Reality Assessment, and the TBI-QOL Short Form with trained staff blinded to the intervention assignment. Data regarding post-intervention measurement including proportion of planned post-intervention measures that are completed and duration of each assessment will also be documented.

4) Follow-up assessment. All children will complete a follow-up assessment within approximately 6 months after intervention completion. Clinically, this gives the child and family a long enough time to identify cognitive and behavioral problems. Research staff blinded to group assignment will administer the NIH Toolbox tests, the Conners CPT 3, the Virtual Reality Assessment, and the TBI-QOL Short Form to children at this visit. Children will complete the child-PedsQL Generic Core Scales and their parents or legal guardians/representatives will complete the BRIEF2, CBCL-APS, and parent-PedsQL. Data regarding follow-up measurement including proportion of planned follow-up measures that are completed and duration of each assessment will be documented. Data regarding recruitment including number of children screened per month; number of children enrolled per month; proportion of eligible children who enroll, and treatment-specific retention rates will be documented throughout the study and aggregated at this stage.

7.0 Data and Specimen Banking*

7.1 *If data or specimens will be banked for future use, describe where the specimens will be stored, how long they will be stored, how the specimens will be accessed, and who will have access to the specimens.*

7.2 *List the data to be stored or associated with each specimen.*

7.3 *Describe the procedures to release data or specimens, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.*

8.0 Sharing of Results with Subjects*

8.1 Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how the results will be shared.

Individual subject results will not be shared with subjects or others. Study results in aggregated forms may be published in peer-reviewed

journals or presented at professional conferences or academic talks. The publications may be shared with subjects upon request.

9.0 Study Timelines*

9.1 Describe:

- **The duration of an individual subject's participation in the study.**
  - An individual subject's participation includes up to three assessment visits (pre-intervention visit, post-intervention visit, and follow-up visit) as well as the intervention training. The assessment visits last approximately 60 minutes per visit. The intervention training will last a minimal of 15 minutes. Since part of the purpose of the study is to explore the dose effect of the intervention, we do not set an upper limit of the intervention length, which could depend on patient's preference and patient's length of stay (if inpatient). We expect the total duration of subject's participation to last up to six months (depending on how far out the subject's follow-up appointment is scheduled upon completion of intervention).
- **The duration anticipated to enroll all study subjects.**
  - Approximately 24 months
- **The estimated date for the investigators to complete this study (complete primary analyses)**
  - August 31, 2021

10.0 Inclusion and Exclusion Criteria*

10.1 Describe how individuals will be screened for eligibility.

Using electronic medical records and working with medical colleagues located in the hospital, trained research staff will identify potential participants admitted to NCH with a complicated mild, moderate, or severe TBI. Once identified as eligible to participate, research staff will approach legal guardians and eligible children on the hospital unit to introduce the research project. Staff will ensure children are awake, alert, and able to sign the assent form (if ≥ 9 years) and demonstrate understanding of the study before being approached for consent. In addition, a trauma registry request will be performed monthly to identify TBI patients discharged within the last 3 months. These patients, if eligible, will be mailed a study invitation, followed by an introduction phone call. Additional recruitment of discharged patients will be performed at follow up appointments using study flyers. Patients may also self-refer from the public domain through postings on sites such as clinicaltrials.gov (NCT03611062) and via IRB approved recruitment emails. Discharged patients will be offered the opportunity to

return to the hospital to receive the training. Consent and assent will be obtained at an in-person meeting. All TBI patients will be tracked using a Patient Reminder List in Epic.

10.2 Describe the criteria that define who will be included or excluded in your final study sample.

Inclusion criteria are as follows: 1) diagnosed with TBI (ICD-9 codes 803, 850, 851, or 854) and between 7 to 17 years old (inclusive) when admitted; 2) lowest post-resuscitation Glasgow Coma Scale (GCS)=13-15 combined with trauma-related abnormalities on neuroimaging or a depressed skull fracture (complicated mild TBI, CDC/NIH definition), GCS=9-12 (moderate TBI, CDC/NIH definition), and GCS=3-8 (severe TBI, CDC/NIH definition); 3) fluent in English-based communication; and 4) Physicians note closest to time of enrollment does not include information on agitation; or if under observation for agitation, currently score $\leq$28 on the Agitated Behavior Scale (ABS), indicating mild to no agitation. To minimize the possibility of confounding by comorbidities and cognition, the following exclusion criteria are set, as consistent with existing literature: 1) severe physical/visual/cognitive comorbidities secondary to TBI that prevent proper utilization of a VR-based game and valid administration of the study measures; 2) premorbid neurological disorder or neurodevelopmental issues prior to injury that prevent proper utilization of a VR-based game and valid administration of the study measures; and 3) patients who are restricted from using electronic gaming devices.

10.3 Indicate specifically whether you will include or exclude each of the following special populations: (You may not include members of the above populations as subjects in your research unless you indicate this in your inclusion criteria.)

- **Adults unable to consent:** No
- **Individuals who are not yet adults (infants, children, teenagers):** Yes, this study will include children and adolescents 7-17 years old
- **Pregnant women:** No
- **Prisoners:** No

11.0 Vulnerable Populations*

11.1 If the research involves individuals who are vulnerable to coercion or undue influence, describe additional safeguards included to protect their rights and welfare.

Using electronic medical records and working with medical colleagues located in the hospital, trained research staff will identify potential participants admitted to NCH with a complicated mild, moderate, or severe TBI. Once identified as eligible to participate, research staff will approach legal guardians and eligible children on

the hospital unit to introduce the research project. Staff will ensure children are awake, alert, and able to sign the assent form (if ≥ 9 years) and demonstrate understanding of the study before being approached for consent.

In addition, a trauma registry request will be performed monthly to identify TBI patients discharged within the last 3 months. These patients, if eligible, will be mailed a study invitation, followed by an introduction phone call. Additional recruitment of discharged patients will be performed at follow up appointments using study flyers. Patients may also self-refer from the public domain through postings on sites such as clinicaltrials.gov (NCT03611062) and through IRB approved recruitment emails. Discharged patients will be offered the opportunity to return to the hospital to receive the training.

Consent and assent will be obtained at an in-person meeting. Children will only be approached if the subject is interested in learning more about this research after initial study introduction. The researchers will ensure that the subjects understand that participation is voluntary and will not affect any treatment he/she may receive in the current or future visits.

Link information between study data and patient identification information will be kept separately from the study data and stored on a secure server in a password protected file on a password protected computer located in the Research Institute at Nationwide Children's Hospital at NCH.

12.0 Local Number of Subjects

12.1 Indicate the total number of subjects to be accrued locally.

The study will recruit approximately 30 children with complicated mild, moderate, or severe TBI at Nationwide Children's Hospital.

13.0 Recruitment Methods

13.1 Describe when, where, and how potential subjects will be recruited.

From August 2018 to August 2020, researchers from NCH Center for Injury Research and Policy will work with colleagues throughout various departments/units across the hospital (Inpatient Rehab Unit, Neurosurgery Inpatient Unit, etc.) to identify and approach potential participants admitted to NCH. Other potential participants already discharged will be identified through trauma registry data and mailed invitation letters followed by an introduction phone call. Additional recruitment of discharged patients will be performed at follow up appointments using study flyers. Patients may also self-refer from the

public domain through postings on sites such as clinicaltrials.gov (NCT03611062) and through IRB approved recruitment emails. These participants will also be sent the study letter and receive an introduction phone call if they are interested. Once participants have been identified as appropriate for the VR intervention, the research associates will explain and consent the legal guardian and assent the patient if they are 9 or older.

Subjects will only be approached if the subject is interested in learning more about this research. The researchers will ensure that the subjects understand that participation is voluntary and will not affect any treatment he/she (or their child) may receive in the current or future visits. The legal guardian will give consent for this research, and his/her child will give assent if age >=9 years.

13.2 Describe the source of subjects.

All inpatient and outpatient departments/units at NCH with patients with TBI, including but not limited to Inpatient Rehab Unit, Neurosurgery Inpatient Unit, Outpatient Rehab Unit, Neurosurgery Outpatient Unit. Patients may also be identified through trauma registry data. Participants may also self-refer from the public domain through postings on sites such as clinicaltrials.gov (NCT03611062) and through IRB approved recruitment emails.

13.3 Describe the methods that will be used to identify potential subjects.

Researchers from NCH Center for Injury Research and Policy will work with colleagues throughout various departments/units across the hospital (Inpatient Rehab Unit, Neurosurgery Inpatient Unit, etc.) to identify and approach potential participants admitted to NCH. Other potential participants already discharged will be identified through trauma registry data and mailed invitation letters followed by an introduction phone call. Additional recruitment of discharged patients will be performed at follow up appointments using study flyers. Patients may also self-refer from the public domain through postings on sites such as clinicaltrials.gov (NCT03611062) and through IRB approved recruitment emails.

13.4 Describe materials that will be used to recruit subjects.

Flyers and introductory letters will be used to recruit participants. (attached). Phone, SMS, and email reminders will also be sent prior to the scheduled appointments.

13.5 Describe the amount and timing of any payments to subjects.

Children will be paid $30 for completing Visit 1 (pre-intervention assessment), $40 for completing intervention/training and Visit 2 (post-intervention assessment), and $50 for completing Visit 3 (follow-up assessment). Parents will be paid $50 for completing Visit

3 (follow-up assessment). All incentives will be paid through Greenphire ClinCards.

Patients who come to the hospital solely for research purposes will also be provided a parking pass free of charge.

Patients/parents will sign receipts for both receiving the ClinCard and the parking pass (if applicable).

14.0 Withdrawal of Subjects*

The research is expected to pose minimal safety/toxicity concerns to subjects. If a subject verbally or behaviorally indicated motion sickness, VR side effects, or other discomfort, he/she will be provided with the option to withdrawn from the study upon request. Medical care will be provided at the direction of the attending physicians/nurses.

If more than 20% of subjects report SAEs due to the study procedures, the researchers will stop the study protocol, re-evaluate and revise the protocol, re-submit it for IRB approval, before resuming participant recruitment

15.0 Risks to Subjects*

We believe that there is minimal risk for being in this study.

It is possible that the subject might feel motion sickness using the virtual reality goggle. They might also experience other virtual reality side effects, which can include but are not limited to, blurry vision, eye strain, headaches, dizziness, fatigue, or nausea. The subject has the right to terminate using the virtual reality goggle any time during the study if there is any discomfort arising from using the virtual reality goggle. The risk of motion sickness will be minimized by allowing subjects to terminate use of the VR intervention at any time during the study.

Although we will take every precaution including secure data storage on password-protected computers and REDCap, there is a small chance of loss of confidentiality of study information. The risks related to patient confidentiality will be minimized by creating a separate link file for patient study ID and the MRN. The study ID will be used on the questionnaires. Patients' medical data will be reviewed and abstracted by trained researchers. All data will be stored on a secure server at NCH. The Patient ID-Participant ID link file will be stored in a separate location on the server from other study data for an additional layer of security and confidentiality.

16.0 Potential Benefits to Subjects*

There are no known direct physical, psychological or social benefits immediately for the subject, although it is possible that the subject might have fun playing the virtual reality games and he/she might experience improved cognitive rehabilitation with use of the virtual reality tools.

In general, we anticipate that this study will provide critical data to improve rehabilitation methods available for pediatric TBI patients, and potentially help future patients to further improve TBI rehabilitation.

17.0 Data Management* and Confidentiality

17.1 Describe the data analysis plan, including any statistical procedures or power analysis.

To examine the research paradigm (Aim 1), we will compute average number of children screened and enrolled per month, proportion of eligible children who enroll, treatment-specific retention rates, proportion of children who adhere to assigned condition, proportion of planned measures that are completed, and average duration of completing each measurement. To examine the feasibility and safety of the VICT program (Aim 2), the total number of AEs/SAEs, mean simulator sickness scores, and mean Borg exertion scores will be computed and compared between the intervention and control group using independent samples t-tests. Additionally, open-end feedback from children, parents, and clinicians on optimizing the VR games and best practices in protocol implementation will be synthesized and submitted to the VR development team for improvement. Finally, to explore the preliminary efficacy of the VICT program (Aim 2), difference scores from baseline to post-intervention and baseline to follow-up of the composite NIH Toolbox score, TBI-QOL, and Conners CPT 3 will be compared between the intervention group and the control group using analysis of covariance (ANCOVA) controlling for baseline scores. BRIEF2, CBCL-APS, and PedsQL (parent/child) scores at follow-up will be compared between the two groups using ANCOVA controlling for baseline scores. Cohen's d for core EFs changes will be computed as the preliminary intervention effect size. Finally, dosage effect will be evaluated within regression analyses, with dosage (0 for controls, cumulative hours of VICT training for intervention group) as the primary predictor and post-intervention NIH Toolbox scores as the outcome variable.

17.2 Describe the steps that will be taken to secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission.

All data will be independently entered into a computerized database by trained research staff and verified by the PI. All data files will be maintained in the central electronic database system, REDCap (Research Electronic Data Capture), which is securely stored at the Research Institute at NCH. Each participant will be assigned a unique Study ID number. The master file that links the participants' names to their Study IDs will be maintained only in a password

protected file in a password-protected computer at the Research Institute at Nationwide Children's Hospital. All measurement and randomization procedures will only use Study IDs to record data without participants' names attached.

17.3 Describe any procedures that will be used for quality control of collected data.

Once data are collected and entered into electronic databases by one researcher, another researcher or the PI will independently verify the records to ensure accuracy.

17.4 Describe how data or specimens will be handle study-wide:

- *What information will be included in that data or associated with the specimens?*

  The data to be collected include: Age, gender, race, injury severity scores, including Glasgow Coma Scale score and Rancho Scale level, gaming performance in the virtual program, and standard neuropsychological testing results. Demographic and medical variables listed above will be collected via patients' medical records. We will also include the amount of time spent in each rehab therapy using the Rehabilitation Provision of Services flow sheet in EPIC. Performance in games will be automatically recorded by the virtual reality computer program. Cognitive variables will be collected via standard neuropsychological tests.

  A Microsoft Excel spreadsheet will be created for use by the study recruiters in order to keep track of patients that fit the inclusion criteria and are recruited, and also of patients who meet exclusion criteria and are not recruited. The spreadsheet will include the following variables: MRN, patient name, gender, age, guardian name(s), telephone number(s), email address(es), recruited (Y/N), study ID number, study group (Intervention or Control), dates of VR therapy, times of VR therapy, and reason for exclusion (for patients that are not recruited). The rationale behind the eligibility spreadsheet is to track how many pediatric TBI patients are treated, and of those, how many are willing to participate in our study. This spreadsheet will be helpful for research project planning in order to guide our enrollment number prediction and also to reach out to families after discharge in order to schedule their follow-up research appointments. This password-protected spreadsheet will be kept in a secure file folder on password protected computers in the Research Institute at Nationwide Children's Hospital. Only researchers on the IRB will have access to the secure folder where the file is located.

- *Where and how data or specimens will be stored?*

  Data will be stored either on paper forms or electronically on password-protected computers and/or REDCap databases

- *How long the data or specimens will be stored?*

  Data will be stored up to 10 years after the completion of the study.

- *Who will have access to the data or specimens?*

  Only personnel listed on the IRB application will have access to the data.

- *Who is responsible for receipt or transmission of the data or specimens?*

  Personnel listed on the IRB application will be responsible for receipt or transmission of the data.

- *How data or specimens will be transported?*

  Currently there is no need to transport data.

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

Not Applicable as the study involves no more than minimal risk to subjects.

19.0 Provisions to Protect the Privacy Interests of Subjects

Password-protected spreadsheet and other electronic databases will be kept in a secure file folder on password protected computers in the Research Institute at Nationwide Children's Hospital. Only researchers on the IRB will have access to the secure folder where the file is located.

Eligible subject information will be entered on a hospital approved password protected computer password protected data registry in a locked research office. Enrolled subjects will be assigned a study ID number which will be how all study documents are labeled. The PI and limited trained research staff will be responsible for maintaining all components of the research record containing participants' identifying information.

We will use several strategies to protect the privacy of participants:

1. Research staff will be trained in the importance of protecting participants' privacy.
2. Each participant will be identified by a unique ID number rather than by name or medical record number. Participants' names will not appear on materials

used during data analysis. The master list of participants' names and corresponding numbers will be kept only in electronic format in a password protected file in a secure folder on password protected computers.

3. All electronic data files will be stored in secure folder on a password-protected computer in a locked research office. Only members of the research team will have access to the files.
4. All hard copies of the data will be kept in a locked file cabinet in a locked office. No hard copies will be kept of the master list of participants' names and corresponding numbers. Only study staff will have access to these documents.
5. Publications of reports will not identify participants in the study or contain information leading to the identification of participants.

We have no plans to contact subjects after their study participation or to share their PHI with other investigators.

20.0 Compensation for Research-Related Injury

Not Applicable as the study involves no more than minimal risk to subjects.

21.0 Economic Burden to Subjects

21.1 Describe any costs that subjects may be responsible for because of participation in the research.

There are no costs that subjects may be responsible for because of participation in the study.

22.0 Consent Process

Researchers from Research Institute at Nationwide Children's Hospital will obtain informed consent from subjects for this research.

Researchers from NCH Center for Injury Research and Policy will work with colleagues throughout various departments/units across the hospital (Inpatient Rehab Unit, Neurosurgery Inpatient Unit, etc.) to identify and approach potential participants admitted to NCH. Other potential participants already discharged will be identified through trauma registry data and mailed invitation letters followed by an introduction phone call. Additional recruitment of discharged patients will be performed at follow up appointments using study flyers. Patients may also self-refer from the public domain through postings on sites such as clinicaltrials.gov (NCT03611062) and through IRB approved recruitment emails. These participants will also be sent the study letter and receive an introduction phone call if they are interested. Once participants have been identified as appropriate for the VR intervention, the research associates will explain and consent the legal guardian and assent the patient if they are 9 or older.

Subjects will only be approached if the subject is interested in learning more about this research. The research associates will ensure that the subjects

understand that participation is voluntary and will not affect any treatment he/she (or their child) may receive in the current or future visits.

When legal guardians are not available to consent, persons who are authorized to consent/sign for medical care as listed on EPIC will provide consent (in addition to the patient's assent if older than 9 years old).

23.0 Process to Document Consent in Writing

Not applicable as this study presents no more than minimal risk of harm to subjects and involves no procedures for which written documentation of consent is normally required outside of the research context.

24.0 Setting

24.1 Describe the sites or locations where your research team will conduct the research.

- *Identify where your research team will identify and recruit potential subjects.*

  Subjects will be identified and recruited throughout various departments/units across the hospital (Inpatient Rehab Unit, Neurosurgery Inpatient Unit, etc.). Other potential participants already discharged will be identified through trauma registry data and mailed invitation letters followed by an introduction phone call. Additional recruitment of discharged patients will be performed at follow up appointments using study flyers. Patients may also self-refer from the public domain through postings on sites such as clinicaltrials.gov (NCT03611062) and through IRB approved recruitment emails. These participants will also be sent the study letter and receive an introduction phone call if they are interested.

- *Identify where research procedures will be performed.*

  All research procedures will be performed at Nationwide Children's Hospital.

- *Describe the composition and involvement of any community advisory board.*

  N/A

25.0 Resources Available

25.1 *Describe the resources available to conduct the research: For example, as appropriate:*

- *Justify the feasibility of recruiting the required number of suitable subjects within the agreed recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?*
- *Describe the time that you will devote to conducting and completing the research.*
- *Describe your facilities.*
- *Describe the availability of medical or psychological resources that subjects might need as a result of an anticipated consequences of the human research.*
- *Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.*

26.0 Multi-Site Research*

Not Applicable

27.0 Protected Health Information Recording

1.0 Indicate which subject identifiers will be recorded for this research.

☒ Name
☒ Complete Address
☒ Telephone or Fax Number
☐ Social Security Number (do not check if only used for ClinCard)
☒ Dates (treatment dates, birth date, date of death)
☒ Email address , IP address or url
☒ Medical Record Number or other account number
☐ Health Plan Beneficiary Identification Number
☐ Full face photographic images and/or any comparable images (x-rays)
☐ Account Numbers
☐ Certificate/License Numbers
☐ Vehicle Identifiers and Serial Numbers (e.g. VINs, License Plate Numbers)
☐ Device Identifiers and Serial Numbers
☐ Biometric identifiers, including finger and voice prints
☐ Other number, characteristic or code that could be used to identify an individual
☐ None (Complete De-identification Certification Form)

2.0 Check the appropriate category and attach the required form* on the Local Site Documents, #3. Other Documents, page of the application. (Choose one.)

☒ Patient Authorization will be obtained. (Include the appropriate HIPAA language (see Section 14 of consent template) in the consent form OR attach the HRP-900, HIPAA AUTHORIZATION form.)

- ☐ Protocol meets the criteria for waiver of authorization. (Attach the HRP-901, WAIVER OF HIPAA AUTHORIZATION REQUEST form.)
- ☐ Protocol is using de-identified information. (Attach the HRP-902, DE-IDENTIFICATION CERTIFICATION form.) (Checked "None" in 1.0 above)
- ☐ Protocol involves research on decedents. (Attach the HRP-903, RESEARCH ON DECEDENTS REQUEST form.)
- ☐ Protocol is using a limited data set and data use agreement. (Contact the Office of Technology Commercialization to initiate a Limited Data Use Agreement.

***Find the HIPAA forms in the IRB Website Library, Templates.**

Attach the appropriate HIPAA form on the "Local Site Documents, #3. Other Documents", page of the application.

3.0 How long will identifying information on each participant be maintained?

For duration of the study (two years) plus five additional years for publication, revision, and potential external inquiries/requests for re-analyzing data as part of the reproducible research effort.

4.0 Describe any plans to code identifiable information collected about each participant.

Eligible subject information will be entered on a hospital approved password protected computer password protected data registry in a locked research office. Enrolled subjects will be assigned a study ID number which will be how all study documents are labeled. The PI and limited trained research staff will be responsible for maintaining all components of the research record containing participants' identifying information.

5.0 Check each box that describes steps that will be taken to safeguard the confidentiality of information collected for this research:

ALL

Research records will be stored in a locked cabinet in a secure location
Research records will be stored in a password-protected computer file
The list linking the assigned code number to the individual subject will be maintained separately from the other research data
Only certified research personnel will be given access to identifiable subject information

6.0 Describe the provisions included in the protocol to protect the privacy interests of subjects, where "privacy interests" refer to the interest of individuals in being left alone, limiting access to them, and limiting access to their information. (This is not the same provision to maintain the confidentiality of data.)

1. Research staff will be trained in the importance of protecting participants' privacy.
2. Each participant will be identified by a unique ID number rather than by name or medical record number. Participants' names will not appear on materials used during data analysis. The master list of participants' names and corresponding numbers will be kept only in electronic format in a password protected file in a secure folder on password protected computers.
3. All electronic data files will be stored in secure folder on a password-protected computer in a locked research office. Only members of the research team will have access to the files.
4. All hard copies of the data will be kept in a locked file cabinet in a locked office. No hard copies will be kept of the master list of participants' names and corresponding numbers. Only study staff will have access to these documents.
5. Publications of reports will not identify participants in the study or contain information leading to the identification of participants.

We have no plans to contact subjects after their study participation or to share their PHI with other investigators.

Confidential Health Information

1.0 Please mark all categories that reflect the nature of health information to be accessed and used as part of this research.

☒ Demographics (age, gender, educational level)
☒ Diagnosis
☐ Laboratory reports
☐ Radiology reports
☒ Discharge summaries
☒ Procedures/Treatments received
☒ Dates related to course of treatment (admission, surgery, discharge)
☐ Billing information
☐ Names of drugs and/or devices used as part of treatment
☒ Location of treatment
☒ Name of treatment provider
☐ Surgical reports
☐ Other information related to course of treatment
☐ None

2.0 Please discuss why it is necessary to access and review the health information noted in your response above.

Diagnosis will be used to identify patients. Age, gender, race, injury severity scores, including Glasgow Coma Scale score and Rancho Scale level, time spent in therapy, and neuropsychological testing results will be obtained from patient's

individual medical records as control variables in the statistical analyses of this study so that potential confounding factors can be accounted for. Location of treatment (floor/room) is needed to locate the patient for participant recruitment purposes.

A Microsoft Excel spreadsheet will be created for use by the study recruiters in order to keep track of patients that fit the inclusion criteria and are recruited, and also of patients who meet exclusion criteria and are not recruited. The spreadsheet will include the following variables: first and last initial, age, gender, date screened, approached (Y/N), recruited (Y/N), and reasons for exclusion. If the patient is recruited, the spreadsheet will also include: MRN, patient name, guardian name(s), telephone number(s), email address(es), study ID number, study group (intervention or control), dates of VR therapy, and times of VR therapy. The rationale behind the eligibility spreadsheet is to track how many pediatric TBI patients are treated, and of those, how many are willing to participate in our study. This spreadsheet will be helpful for research project planning in order to guide our enrollment number prediction and also to reach out to families after discharge in order to schedule their follow-up research appointments (within 6 months). This password protected spreadsheet will be kept in a secure file folder on password protected computers in the Research Institute at Nationwide Children's Hospital. Only researchers on the IRB will have access to the secure folder where the file is located.

3.0 **Is the health information to be accessed and reviewed the minimal necessary to achieve the goals of this research?** ☒ Yes ☐ No

4.0 **Will it be necessary to record information of a sensitive nature?**
☐ Yes ☒ No

5.0 **Do you plan to obtain a federally-issued Certificate of Confidentiality as a means of protecting the confidentiality of the information collected?**
☐ Yes ☒ No