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TITLE: Improving Balance in TBI Using a Low-Cost Customized Virtual Reality Rehabilitation Tool

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CONTRACTING ORGANIZATION: Kessler Foundation

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14. ABSTRACT

The proposed study will implement and evaluate a novel, low-cost, Virtual Reality (VR) rehabilitation tool (Island Quest; IQ) targeting somatosensory, vestibular, and vision systems through a double-blind RCT. Given the importance of dual-task skills for real-world functioning, we will also evaluate the relative effectiveness of dual task (balance and cognitive) VR training to improve balance.

A total of 180 participants (Service Members, Veterans, civilians) with mild to severe TBI and documented balance impairments will be randomly assigned into one of three balance treatment groups: 1) Standard of care (control condition); 2) IQ; 3) IQ dual task (balance plus cognitive). All groups will undergo 2 treatment sessions/week x 6 weeks. Following completion of the treatment protocol, participants in the IQ training group will be randomly assigned to a maintenance training group (2 sessions/month x 4 months) or a non-maintenance group. All participants will undergo baseline, immediate (6 weeks), and long-term (4 months) follow-up assessments of: 1) static and dynamic balance and 2) community integration, self-efficacy, quality of life, and cognitive function. This design will allow us to assess the efficacy of IQ as a customizable balance treatment in TBI, and to evaluate the impact of this remediation program on overall functioning.

15. SUBJECT TERMS
Virtual reality, balance dysfunction, dual task, traumatic brain injury, multisensory, cognitive, motor

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1. **INTRODUCTION:**

The proposed study will implement and evaluate a novel, low-cost, Virtual Reality (VR) rehabilitation tool (Island Quest; IQ (recently renamed from Mystic Isle) targeting somatosensory, vestibular, and vision systems through a double-blind RCT. Given the importance of dual-task skills for real-world functioning, we will also evaluate the relative effectiveness of dual task (balance and cognitive) VR training to improve balance. A total of 180 participants (Service Members, Veterans, civilians) with mild to severe TBI and documented balance impairments will be randomly assigned into one of three balance treatment groups: 1) Standard of care (control condition); 2) IQ; 3) IQ dual task (balance plus cognitive). All groups will undergo 2 treatment sessions/week x 6 weeks. Following completion of the treatment protocol, participants in the IQ training group will be randomly assigned to a maintenance training group (2 sessions/month x 4 months) or a non-maintenance group. All participants will undergo baseline, immediate (6 weeks), and long-term (4 months) follow-up assessments of: 1) static and dynamic balance and 2) community integration, self-efficacy, quality of life, and cognitive function. This design will allow us to assess the efficacy of IQ as a customizable balance treatment in TBI, and to evaluate the impact of this remediation program on overall functioning.

2. **KEYWORDS:** *Virtual reality, balance dysfunction, dual task, traumatic brain injury, multisensory, cognitive, motor*

3. **ACCOMPLISHMENTS:**
   - **What were the major goals of the project?**

Project Milestones & Deliverables	**Timeline**	
Phase I - Project Kick-off	***9/30/14 - 3/30/15***	***% Complete***
Subtasks Phase I:		
1. Submit Administrative Approval requests - regulatory review and approval processes to include local Institutional Review Board (IRB) and DoD Human Research Protection Office.	09/30/14 - 03/30/15	100%
2. Coordinate with CRMRP, USC ICT, NICoE ISO (Fort Belvoir) and VANJHCS.	09/30/14 - 03/30/15	100%
3. Purchase study equipment and supplies, configure for study methods, and set up at study sites.	09/30/14 - 03/30/15	100%
4. Advertise for, interview, and hire study personnel.	09/30/14 - 03/30/15	100%
5. Prepare study assessment and outcome measures, organize participant folders (e.g., case report forms) and paperwork.	09/30/14 - 03/30/15	100%
6. Train study personnel in study methods, including evaluation of balance, global functioning, and cognition.	12/31/14 - 03/30/15	100%
7. Train study personnel in double-blind RCT procedures.	12/31/14 - 03/30/15	100%
8. Train study personnel in administering study treatment conditions.	12/31/14 - 03/30/15	100%
9. Set up study database.	01/31/15 - 03/30/15	100%
10. Finalize project-related modifications to the balance treatment protocols.	01/31/15 - 03/30/15	100%

Phase II - Clinical Trial (Years .5 to 3.5)	***3/31/15 - 09/29/19***	***% Complete***
Subtasks Phase II:		
1. Conduct telephone and in-person screening to evaluate for inclusion/exclusion criteria.	03/31/15 - 09/29/19	100%
2. Begin Clinical Trial Recruitment and Enrollment.	03/31/15 – 09/29/19	100%
3. Randomize participants into Standard of Care Balance (control), Island Quest (IQ; experimental), or IQ Dual Task (experimental) treatment.	03/31/15 – 09/29/19	100%
4. Conduct Balance, Global Functioning, and Cognition baseline assessments.	04/30/15 - 09/29/19	100%
5. Review sessions to evaluate treatment fidelity.	03/31/15 - 00/29/19	100%
6. Conduct immediate follow-up Balance, Global Functioning, and Cognition assessments.	07/31/15 – 09/29/19	100%
7. After completion of the treatment protocol, randomize single task IQ group participants into Maintenance or Non-Maintenance group.	07/31/15 - 09/29/19	100%
8. Conduct Maintenance sessions.	07/31/15 - 09/29/19	100%
9. Conduct long-term follow-up Balance, Global Functioning, and Cognition assessments.	07/31/15 - 09/29/19	100%
Phase III: Project Completion (Final 12 Months)	***09/30/15 - 09/29/19***	***% Complete***
Subtasks Phase III:		
1. Conclude data collection.	09/30/17 - 09/29/19	100%
2. Conduct data analysis.	03/31/18 - 09/29/19	34%
3. Prepare final report and manuscripts for publication, and other dissemination efforts to military and civilian consumers and professionals.	03/31/18 - 09/29/19	22%
Phase I, II, and II Outcomes, Products and Deliverables:	***09/30/14 – 5/29/19***	***% Complete***
• Personnel hired and trained.	09/30/14 - 03/30/15	100%
• Equipment and methods set up and implemented at study sites.	09/30/14 - 03/30/15	100%
• Full IRB approval and DoD Human Research Protection Office.	09/30/14 - 09/29/15	100%
• Subjects run according to the methodological plan.	03/31/15 - 09/29/19	100%
• Data entered, analyzed, interpreted and presented (progress reports, manuscripts).	03/31/18 - 05/29/20	28%

- **What was accomplished under these goals?**

Phase I - Project Kick-off **Major Activities**	**% Complete**	**Specific Objectives Achieved**
1. Submit Administrative Approval requests - regulatory review and approval processes to include local Institutional Review Board (IRB) and DoD Human Research Protection Office.	100%	• Kessler's initial IRB application submitted to Kessler Foundation (KF) IRB (05/5/2014); Approval received (6/13/14). • IRB amendment submitted to reflect changes in protocol consistent with DoD grant application methodology (08/26/2014); e.g., addition of veteran and military personnel to protocol; Approval received (9/3/14). • IRB amendment submitted with minor clarification changes (9/11/14); Approval Received (9/18/14). • IRB amendment submitted with changes to be in compliance with the requirements of the U. S. Army Medical Research and Material Command (USAMRMC) (9/24/14); Approval received (9/29/14). • Kessler's initial IRB application submitted to HRPO (11/4/2014); Received request for clarification from HRPO (1/13/15); Responded to HRPO's requests for clarification (1/30/15) and submitted memo to local IRB to request risk determination (1/30/15) in reference to HRPO's 1/13/15 email correspondence; IRB determined non-significant risk (3/2/15); Submitted IRB non-significant risk determination to HRPO (3/2/15); Received additional requests for clarification from HRPO (3/4/15); Responded to HRPO's requests for clarification (4/8/15); Received additional requests for clarification from HRPO (5/14/15); Responded to HRPO's requests for clarification (6/4/2015); Received permission from HRPO to submit changes to local IRB (6/15/15); Submitted local IRB approval of changes to HRPO (6/23/15); Received request for clarification of protocol version number from HRPO (6/30/15). • Established IRB Agreement with USC ICT, with USC ICT acting under Kessler's FWA (04/01/15). • Submitted recruitment flyer to local IRB (4/7/15); Received approval from local IRB for flyer (4/8/15) • Submitted flyer to VANJHCS IRB contact person to seek guidance on steps to gain approval to post flyer for Veteran recruitment on VANJHCS campus. • Submitted yearly review/continuation application to local IRB (5/1/15); Received continuation approval (5/5/15). • Submitted amendment with HRPO changes to local IRB (6/19/15); Received approval of changes from local IRB (6/23/15).

		• Submitted amendment to add required VANJHCS language to flyers to local IRB (7/16/15). Received approval (7/17/15). • Ft. Belvoir site specific amendment (SSA) submitted to Ft. Belvoir IRB Manager for initial review (7/30/15) and forwarded for administrative review on 7/31/15. • Teleconference between the Defense Health Agency (DHA), Ft. Belvoir Research Staff, and Dr. Zhang in order to discuss the need for a Data Sharing Agreement (DSA) between the DHA and Kessler Foundation/System Security Verification (SSV) for data capture system (8/6/15). It was later established that neither a DSA or an SSV would be required. • Scientific Review completed by the Scientific Review Chair at Ft. Belvoir (8/25/15). • Submitted amendment adding names of recently hired physical therapists and personnel from collaborating sites to local IRB (9/3/15). Received approval (9/4/15). • Sarah Rule, NICoE ISO Fort Belvoir Community Hospital's (FBCH) Research Compliance Officer agreed to rely on Kessler's IRB review for NICoE ISO approval (9/25/15). The IRB reliance agreement (IAIR) is currently being routed for signature at the FBCH Command Suite level. • IRB manager compiled a list of suggested revisions and additional documentation required for the new project submission and sent it to the Fort Belvoir (FB) Research Coordinator for review and editing (9/9/15). • Received draft marketing project (study advertisement to be displayed in hospital/TBI NICoE ISO clinic and on electronic display board in hospital), (9/18/15). FB RC made final edits to this document and received final version on 9/22/15. • DRP Administrative Review is completed for NICoE ISO (9/25/15). • The Office of the Undersecretary of Defense for Personnel and Readiness Research Regulatory Oversight Office (R2O2) delegated that the Component Level Administrative Review (CLAR) be performed by Sarah Rule, Acting Chief Department of Research Programs, Human Protections Administrator, and Research Oversight & Compliance Officer at Fort Belvoir Community Hospital (FBCH) (10/8/15). • A request was submitted from the Fort Belvoir Department of Research Programs to the Kessler IRB for clarification regarding the risk determination of the protocol and Fort Belvoir study staff was subsequently notified that the protocol was determined to be greater than minimal risk and as a result of this determination a DoD Research Monitor

		(RM) would need to be assigned to oversee the protocol (10/23/15). • A research monitor was identified by the PI and study coordinator at Fort Belvoir and following completion of human subjects training (CITI) was added to the protocol. The updated SSA and supporting documentation were then submitted to the Fort Belvoir IRB Manager for review (12/3/15). • The CLAR was completed by Sarah Rule at Fort Belvoir (12/7/2015) and then forwarded to R2O2 for review (12/8/2015). • Submitted amendment adding alternate test (Bilingual Aphasia Test: Verbal Comprehension) to Token Test for individuals with color vision impairment (12/9/15). Received approval (12/15/15). • Fort Belvoir forwarded IRB documents to KF IRB for review (12/22/15). • Fort Belvoir SSA was approved by the Kessler IRB on 12/24/2015 and approval documents were sent to Fort Belvoir (1/15/2016). • Face-to-face PI Responsibilities meeting between Sarah Rule and Dr. Purohit, FB RC also in attendance (1/29/2016). • Sarah Rule sent email to Kessler PI, Karen Nolan, requesting clarification on the risk determination on 2/2, and received clarification from Dr. Greene regarding the risk determination. The Kessler IRB determined the risk of the research protocol to be no greater than minimal risk (2/816). • IRB amendment submitted correcting medical therapy section of the protocol (2/9/16); Approval Received (2/11/16). • Submitted protocol amendment (Amendment #1) after receiving clarification in risk from Kessler; updated SSA to reflect this change from greater than minimal risk to minimal risk and to remove DoD Research Monitor. Also, updated Dr. Chae's status from Collaborator to Associate Investigator (2/11/16). • Received required revisions back from FB IRB Manager along with notification that adding Dr. Chae as an AI on the protocol would require the leadership signature to go up a level to LTC Waits, the Director of Behavioral Health and Dr. Chae's supervisor at FBCH (2/17/16). • LTC Waits signed off on the protocol and all required revisions and documentation were submitted to the Fort Belvoir IRB (2/26/16). • Amendment #1 and all supporting documents sent to Kessler IRB for review (3/3/16). • Amendment #1 was approved by the Kessler IRB on 3/3/2016 and the approval letter was forwarded to Ft. Belvoir investigators (3/8/16).

		• Fort Belvoir's protocol package submitted to USAMRMC HRPO (3/9/16). • Deferral of Headquarters-Level Review and Oversight to the Fort Belvoir Community Hospital, Department of Research Programs for the protocol (3/23/16). • Fort Belvoir study staff received notification that the Headquarters-Level Review had been completed and the NICoE ISO site was granted approval by FBCH to initiate the research protocol (3/29/16). • Annual IRB review submitted (4/11/16). Approval pending minor revisions received (4/12/16). Revisions submitted and final approval received (4/14/16). • Continuation submitted to HRPO (5/3/16). HRPO approval received (5/4/16). • Amendment submitted to IRB to allow questionnaires to be administered via telephone (5/13/16). Approval received (5/14/16). • Annual IRB review submitted (3/6/2017). Reviewed 3/29/17. Approval pending minor revisions received (4/3/2017). Revisions submitted (4/6/2017) and final approval received (4/10/2017). Continuation submitted to HRPO (4/20/17). HRPO approval received (5/22/17). • Annual IRB review submitted (2/2/2018). Reviewed 2/28/2018. Approval pending minor revisions received (3/13/2018). Revisions submitted (3/15/2018) and final approval received (3/16/2018).
2. Coordinate with CRMRP, ICT, NICoE ISO and VANJHCS.	100%	• Established communication with DoD Science Officer (07/29/2014). • Contract negotiations completed; award date established by DoD Contracting Officer (09/17/2014). • A subcontract was established with the University of Southern California, Institute for Creative Technologies (USC ICT; agreement executed 11/19/2014). • A subcontract was initiated with Geneva for collaboration with NICoE ISO (signed by Geneva on 12/1/2014). • Conducted first site visit (3/11/2015) at Fort Belvoir (Karen Nolan and Denise Krch, Co-PIs; Irene Ward, Treatment Intervention Liaison). • Established communication with VANJHCS regarding recruitment through consultant Glenn Wylie • Began discussing steps required to obtain IRB approval to post Veteran recruitment flyer on VANJHCS campus as well as those steps required to submit an IRB application to gain access to the VANJHCS subject recruitment database. • Began recruiting veterans in coordination with KF's dedicated recruitment coordinator, Justin Stanley, who has previous experience recruiting veterans with TBI for KF. • Supported IRB application preparation activities at

		NICoE ISO through regular communication with NICoE ISO's research coordinator (RC). • Conducted site visit (3/10/2017) at FBCH (Karen Nolan and Denise Krch, Co-PIs; Irene Ward, Treatment Intervention Liaison) to evaluate treatment fidelity and to ensure successful transition of Site PI from Maulik Purohit to Melissa Guerra. • New recruitment coordinator, Samantha Schmidt hired to replace Justin Stanley. Will work with Ms. Schmidt to continue recruitment efforts targeted at veterans.
3. Purchase study equipment and supplies, configure for study methods, and set up at study sites.	100%	• Purchase orders for KF neuropsychological tests submitted end of December, 2014. • Created neuropsychological testing administration binder. • Created data collection worksheets, sample subject binder, clinical trial regulatory binder, and IRB communication binder. • Conducted ongoing meetings with KF, Kessler Institute for Rehabilitation (KIR), and USC ICT regarding study methodology. • Completed POs for balance intervention equipment. • Received office supplies, computer equipment (including monitor and Microsoft Kinect), patient hi-low table, and Mini Mental Status Examination to determine capacity to consent. • Balance intervention equipment ordered for KF. All equipment received.
4. Advertise for, interview, and hire study personnel.	100%	• Kathleen Goworek Chervin was assigned as the Research Coordinator (RC) at KF. • Lea Frank, Research Assistant (RA), was hired at KF. • NICoE ISO placed ad for RA. • Fort Belvoir hired Caitlin Jones, RC (start date 3/30/15). • Kelli Sullivan was assigned the RA at NICoE ISO. • Advertised for Physical Therapist position at KF. • Hired PTs Adam Kesten and Christina Cording at KF. • Lea Frank, RA, left KF for graduate school. • Hired Rebecca Spero to replace Lea Frank as RA at KF. • Hired second RA for KF, Sharon Gute. • Fort Belvoir hired Sara Salkind and Haymanot Yalewayker. Cross-trained staff on study protocol. • Sara Salkind left her position with Fort Belvoir. Dr. Guerra is actively looking for a replacement.
5. Prepare study assessment and outcome measures, organize participant folders (e.g., case report forms) and paperwork.	100%	• Created scoring algorithm spreadsheet and hard copy summary sheet for patient testing. • Study statistician completed first version of electronic case report form system. • Study statistician optimized electronic case report form system for data collection and randomization.
6. Train study personnel in study methods, including evaluation	100%	• All KF and KIR personnel completed CITI training. • Kessler RC and RA trained to use Mystic Isle.

of balance, global functioning, and cognition.		• KF RC completed training the RA and engineer on balance and mobility assessments. • KF RA completed training on administration of cognitive and global functioning evaluation tools. • NICoE ISO Site PI and RC completed CITI training. • KF PTs completed CITI training. • NICoE ISO RC completed training on administration of cognitive and global functioning evaluation tools. • KF RAs (Spero and Gute) completed training on administration of cognitive and global functioning evaluation tools, as well as mobility assessment.
7. Train study personnel in double-blind RCT procedures.	100%	• Reviewed RCT procedures with Kessler study staff; briefed Fort Belvoir on double-blind procedures during site visit. • Finalized RCT procedures with KF study staff.
8. Train study personnel in administering study treatment conditions.	100%	• Kessler study staff was briefed on administration of treatment conditions. • Continued progress in treatment protocol manual to be provided to all study staff to ensure standardization of treatment administration across personnel and sites. • Finalized implementation of treatment conditions using IQ with USC ICT. • Finalized manualization of Standard of Care treatment. • KF PTs were trained to use IQ. Clinical review of SOC and IQ treatment conditions resulted in additional required software refinements. Coordinated with USC ICT to begin implementing these refinements. • Completed software refinements. • Finalized manualization of IQ treatment conditions. • NICoE ISO PT completed onsite training at KF to review SOC and IQ treatment conditions. • Coordinated with NICoE ISO study staff to prepare for enrollment and data collection launch at NICoE ISO.
9. Set up study database.	100%	• Study statistician completed first version of electronic case report form system. • Study statistician optimized electronic case report form system for data collection and randomization. • Neuropsychological data entry sheets were added to the electronic data capture system. • Secondary randomization time point was implemented. • KF RC and RA implemented procedures for data entry and randomization of subjects.
10. Finalize project-related modifications to the balance treatment protocols.	100%	• Finalizing implementation of treatments conditions using Mystic Isle with USC ICT. • Finalized manualization of Standard of Care treatment. • Continued progress in treatment protocol manual to be provided to all study staff to ensure standardization of treatment administration across personnel and sites.

		• Initial delivery of the updated Island Quest (previously Mystic Isle) software from USC was delayed. Upon delivery, KF's study team conducted a thorough review of the software and identified areas in need of refinement. Since then, we have been working diligently with USC to implement these refinements to bring the software in line with the SOC treatment. • All treatment conditions finalized and implemented.

Phase II - Clinical Trial **Major Activities**	**% Complete**	**Specific Objectives Achieved**
1. Conduct telephone and in-person screening to evaluate for inclusion/exclusion criteria.	100%	• Ongoing telephone and in-person screening
2. Begin Clinical Trial recruitment and enrollment.	100%	• 99 participants have been enrolled to date.
3. Randomize participants into Standard of Care Balance (control), Island Quest (IQ; experimental), or IQ Dual Task (experimental) treatment.	100%	• 73 participants have been randomized into treatment
4. Conduct Balance, Global Functioning, and Cognition baseline assessments.	100%	• 73 participants have completed baseline assessments
5. Review sessions to evaluate treatment fidelity.	100%	• KF PT is completing clinical documentation after each treatment session to allow the PIs to monitor treatment fidelity and ensure systematic treatment delivery
6. Conduct immediate follow-up Balance, Global Functioning, and Cognition assessments.	100%	• 55 participant have completed immediate follow-up assessments
7. After completion of the treatment protocol, randomize single task IQ group participants into Maintenance or Non-Maintenance group.	100%	• 55 participants, who have completed follow-up assessment, have been potentially randomized. Participants will always be randomized (if relevant to treatment arm) or sham randomized (when not relevant to treatment arm) – in order to maintain blinding.
8. Conduct Maintenance sessions.	100%	• Where appropriate, maintenance sessions were conducted.
9. Conduct long-term follow-up Balance, Global Functioning, and Cognition assessments.	100%	• 46 participants have completed long-term follow-up assessments.

Phase III - Project Completion **Major Activities**	**% Complete**	**Specific Objectives Achieved**
1. Conclude data collection.	100%	
2. Conduct data analysis.	34%	

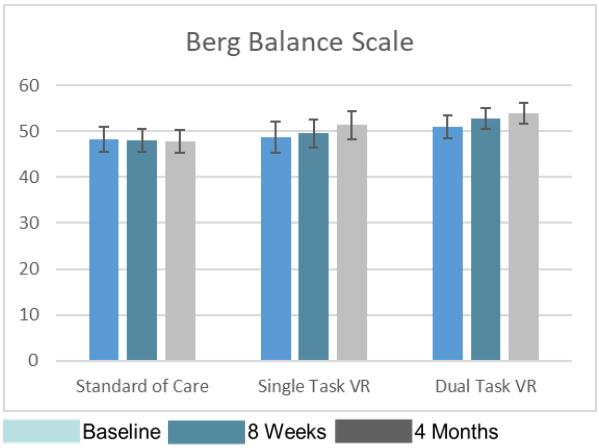
3. Prepare final report and manuscripts for publication, and other dissemination efforts to military and civilian consumers and professionals.	22%	• Abstract submitted and accepted for poster presentation at the American Congress of Rehabilitation Medicine annual conference in October, 2016: Krch, D., Ward, I., Lange, B., Kesten, A. G., Cording, C. M., Frank, L. E., Mejia, M., Chervin, K., König, S., Chang, C., Rizzo, A., Jasey, N. J., & Nolan, K. J. (2016). A Systematic Delivery for Multisensory Balance Impairment using Virtual Reality in TBI. *Archives of Physical Medicine and Rehabilitation - ACRM Annual Conference 2016, 97*(10). • Nolan, K. J., Krch, D. (June, 2018). *Treating Common Symptoms following TBI: Treating Balance Dysfunction via Dual Task Methodology in TBI.* In Chiaravallotti, N. D. *New Research in Treating Common Symptoms Following TBI*. Symposium conducted at the 4th Federal Interagency Conference on TBI, Washington, DC. • See Products section below for additional dissemination.

- ***Significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative).***

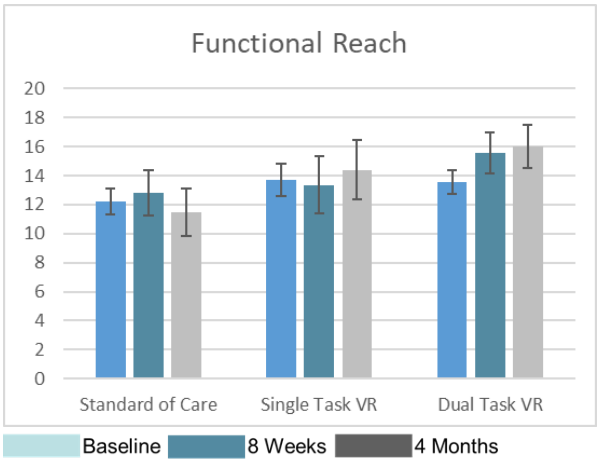
	Kessler Foundation	**Fort Belvoir**	**Total**
Recruited	188	97	285
Screened	114	48	162
Enrolled	67	43	110
Baseline	62	34	96
Short Term F/U (8wk)	55	22	77
Long Term F/U (4mo)	52	17	69
Completed	52	17	69

	Kessler Foundation	**Fort Belvoir**	**Total**
Gender	Male 46 Female 21	Male 36 Female 7	Male 82 Female 28
Age	48.41	44.20	46.31
Time since Injury	6.97	8.83	7.90
Severity of Injury	Mild 10 Moderate 16 Severe 41	Mild 36 Moderate 5 Severe 2	Mild 46 Moderate 21 Severe 43

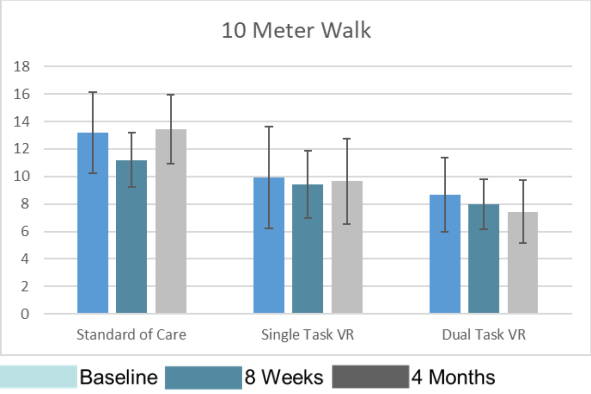
Preliminary Data Analysis (n=35)
September, 2018



The Berg Balance Scale is a 14-item scale designed to measure balance activities, including sitting, standing, single leg standing, and postural transitions with eyes open and closed. The total score ranges from 0 to 56, with higher scores indicating independence. Scores less than 42 are associated with an increased risk of falls. There were no significant differences between the three treatment groups (standard of care, single task VR and dual task VR) at post-treatment or at 4-months long-term follow-up.



The Functional Reach Test assesses stability by measuring the maximum distance an individual can reach forward while standing in a fixed position. Results demonstrated significant increases in the VR dual task group's functional reach ability relative to the other two groups. This differences was noted both at post-treatment and at 4-months long-term follow-up.



The 10 Meter Walk Test is a measure of functional ambulation. A decrease in time indicates an improved walking speed. Results showed that the Standard of Care group was slower overall relative to both VR groups, with the most gains achieved by the VR Dual task group.

Data Analysis Update (n=55)
September, 2019

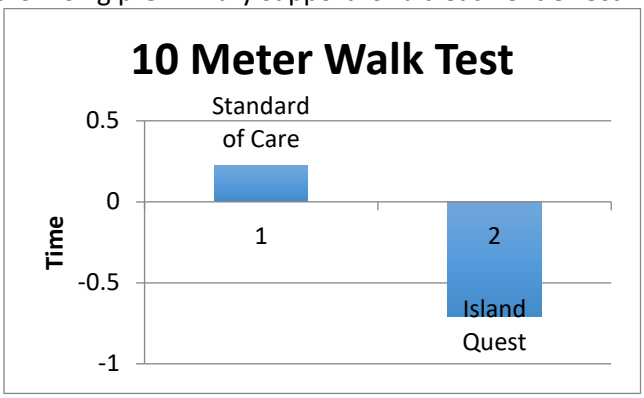
Data Screening and Cleaning. The following tasks are ongoing on the full (completed) data set in order to prepare for data analysis and dissemination:

- Evaluated incomplete participants and dropouts at both data collection sites for missing or incomplete follow-up data.
- Ran Mahalanobis distance across all used variables to find extreme response patterns and exclude these outliers at $p<0.001$ – no exclusions were made (28df).
- Computed scaled Median Average Distance (as available in MATLab) to identify univariate outliers. Outliers that existed at baseline or 8-week follow-up were either consistent (or consistently extreme) and thus were not considered errors due to data entry and appropriate for exclusion.
- Ran Mahalanobis distance prior to each analysis for baseline and 8-week follow-up variables (2df, $p<0.001$). This excluded a number of participants, but no more than 5 participants per variable-pair/analysis.
- Replaced outliers and individual missing data points that, to the best of our knowledge, are missing at random with mean substitution. Given the small number of data points that were replaced, mean substitution was an appropriate approach.

Preliminary Findings. As per the primary aims and planned analyses, 3 ANCOVAs have been conducted: functional mobility (10 Meter Talk), physical impairment (Functional Independence Measure, FIM), and static balance (Berg Balance Scale, BBS). Dynamic balance (Sensory Organization Test, SOT) analyses are still being compiled and further analysis is ongoing. In all cases, baseline values are used as covariate and post-treatment scores as the dependent variable.

- The 10 Meter Walk Test is a measure of functional mobility. Shorter times indicate faster walking speed. From pre- to post-treatment, the VR groups showed a decrease in walking speed (0.67” faster) relative to the Standard of Care group (who actually increased in speed; 0.22”), a statistically significant group difference, $F(1, 66) = 4.090$, $p = .047$. It is notable that these

findings are consistent with the analysis conducted one year ago on a smaller sample, providing promising preliminary support for a treatment effect in the Island Quest treatment conditions.



- There were no group differences found on the FIM and BBS outcomes. We are currently evaluating for potential moderators variables (baseline factors that define subgroups of responders and non-responders) and mediator variables (factors occurring during treatment that explain how or why the intervention is exerting its effects) that may have impacted the lack of an overall treatment effect.

- **What opportunities for training and professional development has the project provided?**
  - *KF PT, Adam Kesten, conducted vestibular rehabilitation and technology inservice to Kessler Institute for Rehabiliation Brain Injury PTs July, 2016.*
  - *Co-PI Krch presented Virtual Reality didactic lecture for Rutgers, KF, and Children's Specalized Hospital post-doctoral fellows April, 2016.*
  - *KF PT, Adam Kesten, pursued and obtained a neuroclinical specialist certification in March, 2017 was directly related to experience gained in association with this project.*

- **How were the results disseminated to communities of interest?**
  - We are actively disseminating information about the project and creating increased awareness about balance deficits and the use of virtual reality in rehabilitation in TBI to various communities of interest. Please see the Products section below for a details regarding publications, conference papers and presentations to Kessler Foundation Stakeholders, industry collaborators, clinical and academic audiences, scientific venues, and the general public.

- **What do you plan to do during the next reporting period to accomplish the goals?**
  - Conduct data analysis and prepare findings for presentations and publications.
  - Continue to transfer the VR treatment to a mobile, immersive VR environment using the HTC Vive for later deployment in telerehabilitation applications.

- **IMPACT:**
  - **What was the impact on the development of the principal discipline(s) of the project?**
    - *For the purposes of this project, we utilized existing balance treatment strategies and synthesized them into a multisensory treatment protocol to be delivered systematically through a virtual environment approach. Balance dysfunction is the result of damage or deficits to multiple systems, however, these integrated systems are often not treated systematically. Our experimental protocols treat the various components of balance dysfunction individually, and then as integrated system, thus enabling us to target impairments in their individual domains as well as holistically. The systematic delivery of this approach is accomplished through the use of virtual reality technology. These features are what elevates the treatment protocol to have greater potential than existing treatments for balance dysfunction.*
  - **What was the impact on other disciplines?**
    - *The additional utilization of a dual task treatment protocol will enable us to extend the research question to the field of neuropsychology. Implementing a dual task condition will enable us to better understand whether challenging the brain to attend to cognitive and motor demands will effect a significantly greater change in the target system of interest (i.e., balance) relative to treatment of that system alone.*
  - **What was the impact on technology transfer?**
    - *We believe the prototype system that we now have would be considered to be at DOD Technology Readiness Level (TRL) 7: "System prototype demonstration in an operational environment". We anticipate that the results from this investigation will produce evidence for the IQ system at TRL 9 through empirical clinical and objective support for its widespread application as a standard efficacious clinical and research tool. A customizable tool, such as IQ, could be offered as a rehabilitation treatment to clinics or health care providers. A number of health care providers and small businesses have demonstrated interest in the existing VR-based prototype tool. We expect IQ's greater efficacy and cost effectiveness, decreased lab space requirement, and decreased requirement for sophisticated equipment and skilled technicians, to further adoption/transition of our system as a standard treatment tool for balance. Further adoption/transition of this system will be facilitated by efforts to transfer the VR treatment to a mobile, immersive VR environment using the HTC Vive for later deployment in telerehabilitation applications.*
  - **What was the impact on society beyond science and technology?**
    - *Island Quest has implications as a telerehabilitation application, which would enable Service Members and Veterans in distant locations to independently use the training system with remote clinical supervision. This would also represent a great benefit to rural patients as well as patients with transportation barriers.*

The ability to reach far more patients than would ordinarily be able to present themselves to a rehabilitation facility translates into significantly improved overall quality of care and health care outcomes, and thus, is beneficial in reducing healthcare costs and burden to the healthcare system. In order this impact, we are actively taking steps transfer Island Quest to a telerehabilitation application.

- **CHANGES/PROBLEMS:**
    - **Changes in approach and reasons for change**
        - Nothing to report
    - **Actual or anticipated problems or delays and actions or plans to resolve them**

1. None foreseeable in the data analysis phase.

    - **Changes that had a significant impact on expenditures**
        - *Nothing to report.*
    - **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
        - *Nothing to report.*
    - **Significant changes in use or care of human subjects**
        - *Nothing to report.*
    - **Significant changes in use or care of vertebrate animals.**
        - *Nothing to report.*
    - **Significant changes in use of biohazards and/or select agents**
        - *Nothing to report.*
- **PRODUCTS:**
    - **Publications, conference papers, and presentations**
        - **Journal publications.**

          Larkin, M. (2017). Exploring virtual environments for cognitive and physical rehabilitation. The Journal on Active Aging. 16(5): 44-51.]

        - **Books or other non-periodical, one-time publications.**

          Nothing to report.

- **Other publications, conference papers, and presentations**

- Industry Collaborators:
  - Nolan, K.J., Krch, D. (2016). *Multisensory Balance Treatment Using a Virtual Environment*, Presentation to MotekForce Link, West Orange, NJ. January, 2016.
  - Rizzo, A.A. (2017). Clinical Virtual Reality: A Brief Review of the Future! Keynote Invited Address to the Dell Corporate Group. Austin, TX. March, 2017.
  - Nolan, K.J., (2016). *Brain Injury Mobility Research*, Presentation to Parker Hannifin, West Orange, NJ. April, 2016.
  - Rizzo, A.A. (2016). Clinical Virtual Reality: A Brief Review of the Future! Invited Featured Speaker at the Annual VR Days Europe Conference. Amsterdam, NL. November, 2016.
  - Nolan, K.J., Krch, D. (2017). Demonstration of new VR technology. Presentation to VRHealth. September, 2017
- Clinical Dissemination:
  - Kesten, A., Vestibular rehabilitation and technology inservice presented to to Kessler Institute for Rehabilitation Brain Injury Physical Therapists. July, 2016.
  - Krch, D., Virtual Reality. Presentation to Rutgers, KF, and Children's Specalized Hospital postdoctoral fellows, April, 2016.
  - Krch, D. (2017). Using VR in Rehab. Panelist presentation at Health 2.0 NYC – The New York Healthcare Innovation Group Shades of Reality: Virtual, augmented & mixed reality in healthcare. May, 2017 (Link to YouTube video of presentation: http://bit.ly/2vazNHk)
  - Rizzo, A.A. (2017). Advances in Virtual Reality and New Tehcnologies for Childhood Health Conditions, Children's Specalized Hospital Grand Rounds, Mountainside, NJ. January, 2017.

- Academic:
  - Rizzo, A.A. (2017). Virtual Reality for advancing the assessment of brain function and psychological health. Brain Research Symposium. University of Auckland, Auckland New Zealand, April, 2017.
- Scientific Collaborators:
  - Krch, D., Ward, I., Lange, B., Kesten, A. G., Cording, C. M., Frank, L. E., Mejia, M., Chervin, K., König, S., Chang, C., Rizzo, A., Jasey, N. J., & Nolan, K. J. (2016). A Systematic Delivery for Multisensory Balance Impairment using Virtual Reality in TBI. Archives of Physical Medicine and Rehabilitation - ACRM Annual Conference 2016, 97(10), e139-e140.
  - Rizzo, A.A. (2017). Clinical Virtual Reality: A Brief Review of the Future! *American Psychiatric Association* Convention, San Diego, CA. May, 2017.
  - Rizzo, A.A. (2017). Virtual Reality, Memory, and Immersion and PTSD! Keynote Address at the Annual Conference of the *Institute for Functional Medicine*. Los Angeles, California, June, 2017.
  - Krch, D., Nolan, K.J. "*Treating Balance Dysfunction via Dual Task Methodology in TBI"*. In Symposium: Chiaravalloti, N.D. "*New Research in Treating Common Symptoms Following TBI."* Abstract submitted for presentation at the 4th Federal Interagency Conference on TBI in June, 2018.
  - Nolan, K. J., Krch, D. (June, 2018). *Treating Common Symptoms following TBI: Treating Balance Dysfunction via Dual Task Methodology in TBI.* In Chiaravallotti, N. D. *New Research in Treating Common Symptoms Following TBI*. Symposium conducted at the 4th Federal Interagency Conference on TBI, Washington, DC.

- Kessler Foundation Stakeholders
  - Nolan, K.J., Krch, D. (2014). Improving Balance in TBI using a Low-Cost, Customized, Virtual Reality Rehabilitation Tool. Presentation to Kessler Foundation's Scientific Advisory Board.
  - Krch, D., Nolan, K.J. (2014). Improving Balance in TBI using a Low-Cost, Customized, Virtual Reality Rehabilitation Tool. Presented to the Kessler Foundation's Board of Directors Meeting.
- General Public
  - Social media and press releases by KF's Communications Department.
  - Krch Invited to present at the 22nd Annual Government Video Expo, Washington, DC. Presenting "VR: Changing the Game in Rehabilitation".

- **Website(s) or other Internet site(s)**

  www.kesslerfoundation.org - Official website of Kessler Foundation, a non-profit research organization dedicated to improving the lives of persons with disabilities. This website provides information about current research (with links to related press releases), publications and presentations, and community outreach. (Kessler Foundation is the primary research site).

  Article published in Streaming Media Magazine [Dreier, T. (2017). *Virtual Reality, Real Medicine: Treating Brain Injuries with VR. Streaming Media Magazine*.] September. http://www.streamingmedia.com/Articles/Editorial/Featured-Articles/Virtual-Reality-Real-Medicine-Treating-Brain-Injuries-With-VR-120738.aspx

  Health 2.0 NYC – The New York Healthcare Innovation Group. Krch presented at Shades of Reality: Virtual, augmented & mixed reality in healthcare, May, 2017 (Link to YouTube video of presentation: http://bit.ly/2vazNHk)

- **Technologies or techniques**

  Nothing to report.

- **Inventions, patent applications, and/or licenses**

  Nothing to report.

- **Other Products**

  - *Software:* For the purpose of this project, Island Quest (previously known as Mystic Isle) software was modified from a game-based exercise/rehabilitation tool to a multisensory balance treatment software that can be systematically delivered to individuals with neurological conditions.

  - *Clinical interventions: For the purposes of this project, a Standard of Care multisensory balance treatment protocol was synthesized and manualized.*

- **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

  - **What individuals have worked on the project?**

Kessler Foundation

Name:	*Denise Krch, PhD*
Project Role:	*Co-Principal Investigator*
Researcher Identifier:	*N/A*
Nearest person month worked:	*3.6*
Contribution to Project:	*Dr. Krch contributed to personnel hiring and training, study organization and set-up, and acted as a liaison between personnel across study sites. Dr. Krch provided guidance and oversight to treatment study software refinements. Dr. Krch facilitated training study staff on administration of the cognitive testing protocol. Dr. Krch is responsible for determining cognitive dual task difficulty level for participants.*
Name:	*Karen J. Nolan, PhD*
Project Role:	*Co-Principal Investigator*
Researcher Identifier:	*orcid.org/0000-0002-4667-0873*
Nearest person month worked:	*3.6*
Contribution to Project:	*Dr. Nolan contributed to personnel hiring and training, study organization and set-up, and acted as a liaison between personnel across study sites. Dr. Nolan provided guidance and oversight to treatment study software refinements. Dr. Nolan (unblinded) oversees treatment intervention sessions.*
Name:	*Kathleen Goworek Chervin, PhD*
Project Role:	*Research Coordinator*
Researcher Identifier:	*N/A*
Nearest person month worked:	*10.2*
Contribution to Project:	*Ms. Chervin managed administrative and IRB tasks as well as organized the regulatory and IRB documentation for KF and HRPO. Ms. Chervin trained RAs and engineers on the mobility outcome measures. Ms. Chervin provides guidance for all study activities at NICoE ISO. She also manages the electronic capture system.*
Name:	*Rebecca Spero, BA*
Project Role:	*Research Assistant*
Researcher Identifier:	*N/A*
Nearest person month worked:	*6*
Contribution to Project:	*Ms. Spero assisted Ms. Chervin in administrative activities and ordering study supplies. She became proficient in administering the study balance assessments. Ms. Spero conducts screening and study balance and cognitive assessments. She is responsible for entering data into the data capture system.*
Name:	*Christina Cording, DPT*
Project Role:	*Physical Therapist*
Researcher Identifier:	*N/A*
Nearest person month worked:	*4.5*
Contribution to Project:	*Christina Cording is responsible for administering all balance treatment sessions at KF.*
Name:	*Melvin Mejia, B.S.*
Project Role:	*Biomedical Engineer*

Researcher Identifier:	*N/A*
Nearest person month worked:	*4.8*
Contribution to Project:	*Melvin Mejia conducts balance assessments and assists the PT with treatment administration. His technological expertise is utilized in various aspects of this technology-based research study.*
Name:	*Sharon Gute, B.S.*
Project Role:	*Research Assistant*
Researcher Identifier:	*N/A*
Nearest person month worked:	*6*
Contribution to Project:	*Ms. Gute became proficient in administering the study balance assessments. She conducts screening and study balance and cognitive assessments and is responsible for entering data into the data capture system.*
NICoE ISO	
Name:	*Melissa Guerra, MD,*
Project Role:	*Principal Investigator*
Research Identifier:	*N/A*
Nearest person month worked:	*0.6*
Contribution to Project:	*Dr. Guerra assists with personnel hiring, study organization and manages all study activities at NiCoE ISO. She also liaises with Drs. Krch and Nolan between personnel across study sites.*
Name:	*Caitlin Jones*
Project Role:	*Research Coordinator*
Researcher Identifier:	*N/A*
Nearest person month worked:	*12*
Contribution to Project:	*Ms. Jones manages all administrative and IRB tasks at NICoE ISO. She administers the mobility outcome measures and as well as the cognitive outcome measures. Ms. Jones works closely with the KF RC, Kate Chervin to ensure standardization across sites.*
Name:	*Lara Chase*
Project Role:	*Physical Therapist*
Research Identifier:	*N/A*
Nearest person month worked:	*3*
Contribution to Project:	*Lara Chase is responsible for administrating all balance treatment sessions at NiCoE ISO.*

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
  - *No.*
- **What other organizations were involved as partners?**
  - *Kessler Institute for Rehabilitation*, West Orange, NJ, USA

- *Significant contribution to the manualization of the Standard of Care and the Mystic Isle treatment protocols.*
- *Training clinical staff and refining and standardizing treatment delivery across treatment sites*

- *University of Southern California, Institute for Creative Technologies, Los Angeles, CA, USA*
  - *Modification of the Island Quest software from a game-based exercise/rehabilitation tool to a multisensory balance treatment*
  - *Will provide software support and assistance with data extraction from the Island Quest system.*

- *National Intrepid Center of Excellence, Intrepid Spirit One, Fort Belvoir Community Hospital, Fort Belvoir, VA, USA*
  - *Study data collection site for active duty military population*
  - *Provided input on refining treatment protocols for military populations*

- **SPECIAL REPORTING REQUIREMENTS**.
  - **QUAD CHARTS:** *See below in Appendices.*
- **APPENDICES:**
  - Quad Chart.

Improving Balance in TBI using a Low-Cost Customized Virtual Reality Tool

MR130466

W81XWH-14-2-0150

PI: Denise Krch, PhD and Karen J. Nolan, PhD **Org:** Kessler Foundation **Award Amount:** $2,987,537

Study/Product Aim(s)

•**Objective 1:** Evaluate the effectiveness of Virtual Reality (VR)-based balance training using Island Quest (IQ) to improve balance in individuals with TBI.
•**Objective 2:** Evaluate the improvement on measures of global functioning following the VR balance training customized for a rehabilitation setting.
•**Objective 3:** Evaluate the effectiveness of VR-based dual task (balance and cognitive) training to improve balance in individuals with TBI.
•**Objective 4:** Evaluate the long-term efficacy of VR-based balance training through the inclusion of a 4-month, follow-up assessment examining balance and functional gains.
•**Objective 5:** Evaluate utility of maintenance training.

Approach

Participants (n=180) will be enrolled into a double-blind RCT at Kessler Foundation/Kessler Institute for Rehabilitation and the National Intrepid Center of Excellence: Intrepid Spirit One (NICoE ISO) Fort Belvoir Community Hospital. Individuals with TBI will be randomly assigned into 1 of 3 balance interventions (2 sessions/week x 6 weeks): 1) Standard of Care; 2) IQ; 3) IQ + dual task (balance and cognitive).

Service member using Island Quest, the customized, low-cost virtual reality rehabilitation tool. This tool has been developed with input from military and civilian clinicians and patients with neurological injury and will undergo evaluation in the proposed study.

Timeline and Cost

Activities / CY	14/15	15/16	16/17	17-20
IRB submittal and study prep				
Study staff training				
Recruitment and Data collection				
Data analysis				
Estimated Budget ($K)	**$647k**	**$804k**	**$796k**	**$741k**

Updated: September 28, 2019

Goals/Milestones

CY14 Goal – Study preparation
☑IRB submittal
☑Preparation of study materials
☑Clinician Training with Island Quest system
CY15 Goal – Study preparation and staff training
☑Refine software to be aligned with initial treatment conceptualization
☑HRPO submittal; Initiate participant recruitment
☑Training study staff in testing and intervention procedures
☑I**CY 2016-2020 Goals** – Data collection
☑Recruit and enroll participants from KF/KIR and NICoE ISO
☑Apply for EWOF
☐Data analysis and Dissemination

Comments/Challenges/Issues/Concerns

- Phases 1 and 2 of the Project completed.