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Chronic Effects of Neurotrauma Consortium (CENC)

PRINCIPAL INVESTIGATOR: David Cifu

RECIPIENT: Virginia Commonwealth University
Richmond, VA 23284

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Technical Abstract

Background: The Chronic Effects of Neurotrauma Consortium (CENC) is a coordinated, multicenter collaboration linking basic science, translational, and clinical neuroscience researchers from the VA, military, and academia to effectively address the diagnostic and therapeutic ramifications of traumatic brain injury (TBI) and its long-term effects. This Consortium is uniquely positioned because of its centralized organization provided by an experienced, professional Coordinating Center directed by senior academic TBI leaders of VA and DOD; 2) linkages between major eight VA TBI/Polytrauma Centers with multiple DoD Centers, and academic research centers 3) extensive, longer term track record of collaborative TIB research 4) access to large military/VA relevant research subject populations and six innovative and intersecting research projects that are designed to change proactively in the near term and lay the groundwork for subsequent investigation. This consortium brings together a nationwide group of researchers who have extensive track records of internal and external collaborations, demonstrated productivity in knowledge translation and dissemination, and the proven ability to recruit and follow up with research subjects.

Objectives: The chronic effects from TBIs, whether single or repeated, on chronic disabling symptoms, on recovery from combat and trauma-related comorbidities, and on long-term brain function in veterans and service members are not known. The overarching goals of CENC are to examine the critical issues related to the identification and characterization of the anatomic, molecular and physiological mechanisms of chronic brain injury and potential neurodegeneration. The specific research studies have been designed to directly address the proposed consortium objectives and focus areas, to build on and leverage existing TBI research activities across the network, to provide meaningful answers to the current questions facing individuals and organizations affected by neurotrauma, and to identify and lead a way ahead.

Research Plan: Current approved studies include the following:

1. A large, prospective, longitudinal investigation comparing veterans with OEF-OIF combat-related mTBI to non-TBI, combat-exposed controls, from 2003 to the present, with varying degrees of chronic symptoms and comorbidities, which will be comprehensively evaluated on a regular basis for change in status and performance using clinical testing, neuroimaging, genomics, biomarkers, and neuropathology.
2. A basic science project to identify the key molecular events in the processing of tau after TBI in rodents and humans, with the goal of developing novel biomarkers tools to assess tau dysregulation after TBI.
3. A coordination and comprehensive analysis of existing VA, DOD and other federal datasets of individual with TBI and comorbid conditions
4. A prospective case-controlled study to determine the effect of vestibular dysfunction on balance, gain and quality of life in veterans at the Mountain Home VA Medical Center
5. A follow up to a prospective case controlled study using advanced MR imaging and clinical outcomes measures 3-5 years after concussive traumatic brain injury (TBI) in US military personnel injured during deployment in which earlier clinical and imaging data exists.
6. An observational study to provide a means for the many different scanners across the VA hospital system to provide the same imaging answer in suspected TBI patients.

Military/VA Benefit: This project is specifically designed to understand the linkages between blast exposures with TBI, chronic effects, and neurodegeneration to assist in providing current and future care, guide the development of novel interventions to prevent or mitigate cognitive and behavioral decline, and contribute to long-term planning for service member and veterans.

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1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words):

TBI

Tau

Blast injuries

Brain concussion

Military personnel

Veterans

Rehabilitation

Otolith Dysfunction

Postural Stability

Diffusion Tensor Imaging

OIE/OIF

Neurosensory

Novel White Matter

Neuroimaging

Sensory Impairments

3. **OVERALL PROJECT SUMMARY:** Summarize the progress during appropriate reporting period (single annual or comprehensive final). This section of the report shall be in direct alignment with respect to each task outlined in the approved SOW in a summary of Current Objectives, and a summary of Results, Progress and Accomplishments with Discussion. Key methodology used during the reporting period, including a description of any changes to originally proposed methods, shall be summarized. Data supporting research conclusions, in the form of figures and/or tables, shall be embedded in the text, appended, or referenced to appended manuscripts. Actual or anticipated problems or delays and actions or plans to resolve them shall be included. Additionally, any changes in approach and reasons for these changes shall be reported. **Any change that is substantially different from the original approved SOW (e.g., new or modified tasks, objectives, experiments, etc.) Requires review by the Grants Officer's Representative and final approval by USAMRAA Grants Officer through an award modification prior to initiating any changes.**

For clarity, each principal activity is detailed separately below by key Scope of Work domain pertinent to Year 2 activities and requirements.

- I. VCU Coordinating Center: The Coordinating Center at VCU serves both to implement a specific program of research designed to provide clinically relevant answers and interventions for current service members (SMs) and Veterans and provides leadership in developing innovative research proposals and programs to define the long-term solutions to the chronic

effects of TBI, which specifically address the research gaps highlighted in our proposal and subsequent roadmap documents provided to our Government Steering Committee (GSC). The Coordinating Center at VCU insures the overall function of all components of the CENC and will be the primary point of contact to the sponsors. The primary goal of the VCU Coordinating Center is to insure completion of all activities, sponsor required reporting, and compliance for the CENC.

- a. Established subcontract for approved studies and sites
- b. Assured all IRB and IACUC protocols were obtained and maintained.
- c. Ensured that relevant regulatory, reporting and fiscal documents were completed and submitted.
- d. Hosted the annual meeting in conjunction with the MHSRS conference,
- e. Hosted all telecommunications between consortium members and appropriate parties.
- f. Hired Lt. Col Ret. Kevin Sickinger to assist in the recruitment of Veterans and active duty military personnel across all studies in the consortium
- g. Held meetings of the Consumer Advisor Board and the Scientific Advisory Board
- h. Published research and presented on CENC at major conferences (see below).
- i. Initiated newly approved studies and sites including CENC0020- Novel White Matter, CENC 0034- Structural and Functional Imaging, CENC0049 Clinical and Neuroimaging Correlates of Neurodegeneration, and CENC 0056 Visual Sensory Impairments.
- j. “Vestibular Sensory Deficits and Cognitive Adaptation in mTBI” study was approved by the GSC. The Study PI, Eliana Klier, ended employment with the Baylor College of Medicine. An alternate PI that was acceptable to the Consortium and the GSC was unable to be identified, and thus the study was terminated.

II. Neuroimaging Core: The Neuroimaging Core, located at the Baylor College of Medicine (BCM) and the Michael E. DeBakey Medical Center. It is led by Drs. Elisabeth Wilde and Harvey Levin, includes experts from the fields of neuroradiology, neuropsychology, magnetic resonance imaging (MRI) physics, information technology (IT) and computer programming, and statistics. The Core has facilitated sequence development and pulse programming, training and supervision of technologists and support personnel, and quality assurance (QA) in support of CENC. At the time of this report, the Core has:

- a. Expanded the Neuroimaging Core, to include work performed at the Michael E. DeBakey VA Medical Center.
- b. Worked with all new CENC investigators to standardize imaging policy and procedure where applicable, as well as advise on key imaging components of the new studies.
- c. Performed site qualification visits for all new studies and sites that involve an imaging component.

- d. Core personnel have continued testing of the imaging sequences at the Houston, Richmond, Tampa and San Antonio sites. To date, imaging quality has generally been deemed good, though there have been few issues with subject motion or artifacts, which have been addressed with the PIs of the sites where the patient motion issues occurred, In most cases, it was decided that rescanning would not likely result in acquisition of better data since the motion occurred on several of the sequences.
- e. Reviewed quality assurance data provided by sites.
- f. Ensured that all subject data was read for clinical and incidental findings
- g. Ensured all new study sites had ADNI and BIRN phantoms.

III. Bio-marker Core: The Biomarker Core is located at USUHS, and is led by Dr Ramona Diaz-Arrastia and Dr. Kimbra Kenny. During the fiscal year the Core has:

- a. Received biomarker samples from all Longitudinal Study sites.
- b. Provide information to each site regarding quality control, and process issues with the samples.

IV. Neuropathology Core: The Neuropathology Core is located at USUHS, led by Dr. Daniel Perl, where a new, state-of-the-art brain bank facility within the auspices of the DoD has been established. The Neuropathology Core will manage the collection of brain specimens from participants using an existing national network of dieners and neuropathologists. During this fiscal year, the Core has:

- a. Received GSC approval to expand to include the Boston VA, under the direction of Dr. Ann McKee.
- b. Receive GSC approval to rebudget funds from the USUHS core funding to support Dr. Goldstein perform electron micrographic analysis at Boston University.

V. Biostatistics [B], Data Management [DM], and Study Management [SM] Core: The Biostatistics, Data Management, and Study Management Core (BDMSM) is located at RTI and led by Dr. Rick Williams. The Core serves as a statistics support and study management resource for the CENC and all consortium members. During this fiscal year, the BDMSM Core has:

- a. Held Data Monitoring Committee meetings
- b. Established and updated the publication committee and review process
- c. Enhanced and improved the CENC website
- d. Worked on data mapping and transmission of data into FITBIR
- e. Developed a consortium wide statistical and analysis plan.
- f. Worked with new sites to build data capture infrastructure,

VI. Peer Review Program: The Peer Review Program (PRP) is designed to support the development of additional studies within the consortium including demonstration and feasibility studies. Such studies will address focused

questions, develop preliminary data, and provide an avenue for new researchers and novel research approaches to contribute to the overall Consortium program of study, as well as studies meant to replace those submitted as Core Studies in our application but which were not approved by the GSC. In addition to providing funding, the PRP provides support in the form of mentorship and resource sharing, as appropriate and needed, via each of the consortia sites. During this fiscal year, the PRP program:

- a. Reviewed the proposals that were submitted for the RFA in the previous fiscal year. As a result four additional studies were approved by the GSC for addition into the Consortium.

VII. CENC0001C - Observational Study on Late Neurologic Effects of OEF/OIF/OND Combat: This study's goal is to establish a large cohort (880) of former U.S. OEF/OIF/OND combatants who have had at least one mild Traumatic Brain Injury (mTBI), and follow the members of the cohort long-term to assess specific areas of their physical and mental health. Given the unclear role of mTBI(s) on long term health and the frequent co-occurrence of posttraumatic stress disorder (PTSD) in warfighters, the study will include a group of participants (220) who have experienced combat but have not had an mTBI. During this fiscal year, this study has:

- a. Developed QA/QC sub-committee to ensure data quality and consistency
- b. Consented 172 subjects, and fully enrolled 163 subjects.
- c. Worked to on Board Ft. Belvoir as a new study site.

VIII. CENC0004C - Epidemiology of mTBI and Neurosensory Outcomes- The primary objective of this project is to integrate and analyze existing VA healthcare data to study the chronic effects of mild traumatic brain injury (mTBI) on neurodegenerative disease and other comorbidities, and the methods to treat and rehabilitate adverse effects of mTBI, in Veterans over time. During this fiscal year this study has:

- a. Received access to all required datasets.
- b. Continued to pull and merge data from datasets, and run, test and finalize macros
- c. Began analysis for publications
- d. The San Antonio site completed the mTBI determinations based on the mTBI comprehensive TBI evaluation data, and identify individuals with historical resolved TBI.
- e. Planned for a stakeholder meeting to be held in the next fiscal year for the NCDR.

IX. CENC0005C - Tau Modifications Study- The goal of this study is to develop an animal model of repeated mTBI model that will allow the tracking of progressive intraneuronal tau alterations that can be correlated with behavioral dysfunction, fluorescent in situ hybridization, and gene expression signatures. The model could then be used to assess the effects of interventions. The observations

made in the animal model will be tested for agreement in soldiers who have died after sustaining repeated mTBI. During this fiscal year, the study has:

- a. Continued breeding in the hTau colony and assignment of mice to the different cohorts (ages and time points post injury) as described in the original protocol, with a focus on the repetitively injured cohorts at this time.
 - b. Injuries/sham injuries were performed on aged mice (12 months old) of both genders, with behavioral testing followed by euthanasia at 15 days as per the protocol. This sub study (12 mice per group r-mTBI/r-sham, male/female).
 - c. Colony status as of September 29th 2015: Mouse pups - 70; Adult mice – total 240. Mice aged 4-6 months - 61; Mice aged 7-9 months - 53; Mice aged 10-12 months - 27; Mice aged >12 months – 99.
 - d. Brains have been/are being processed from the mice assigned to the young/aged, male/female, 15 day study; to reduce variability and ensure consistency of staining across groups we plan for neuropathological analyses once brains from all cohorts have been collected.
 - e. Data from our 5-r-mTBI model shows neurobehavioral changes and progressive neuroinflammation, but no persistent TBI-dependent tau pathology unless the injuries are administered to mice with existent tau pathology (e.g. 18 month old hTau mice as in our work by Ojo et al., 2013). The neuroinflammatory aspects of TBI are clearly common to all preclinical models and all human cases and are thus highly relevant; in addition the Roskamp team has used discretionary funds (non CENC) to continue to explore additional injury paradigms with varying frequency and chronicity of injuries, for evidence of persistent tau pathology.
 - a. Ongoing exploration of additional repetitive mTBI models reveals some evidence of TBI-dependent tau pathology (increased total tau (DA9), pTau Thr231 (RZ3) and tau oligomers (TOC-1)) in young mice receiving 3-4 months of injuries at a frequency of 2 mTBI per week. Dr. Mufson analyzed tissue samples.
 - b. Optimization of the Optomotor test of visual acuity has been completed, with TBI mice demonstrating significant differences in visual function as compared to uninjured/sham mice.
- X. CENC0008P - Otolith Dysfunction and Postural Stability- This research study is part of a long-term goal to establish a unique treatment platform to diagnose, localize, and treat dizziness and imbalance related to inner ear balance issues associated with mTBI. In the recent wars in Iraq and Afghanistan, many soldiers have been exposed to blasts from IEDs or roadside bombs, and TBI has been called the signature condition of Operation Enduring Freedom and Operation Iraqi Freedom (OEF/OIF) combat Veterans. The objective of the study is to determine the effect of inner ear balance (vestibular) dysfunction on balance, gait and quality of life. The primary function of the inner ear balance function is to keep vision steady when the head is in motion and to maintain balance. Loss of inner ear balance function can result in dizziness and/or imbalance, and

individuals with these symptoms are at risk of falling. The incidence of dizziness and imbalance increases in two populations relevant to VA and military healthcare: older individuals and individuals who have suffered a head injury or blast exposure. During this fiscal year, the study has:

- a. Has enrolled 28 study participants to date.

XI. CENC0020P - Novel White Matter Imaging to Improve Diagnosis of Mild TBI:

- a. Developed and gained GSC approval of the protocol for the project
- b. Submitted and received all required regulatory approvals.

XII. CENC0025P - ADAPT/EVOLVE: The overall goal of this study is to investigate advanced MR imaging and clinical outcome measures of concussive traumatic brain injury (TBI) in US military personnel injured during deployment. As part of previous collaborative efforts, we completed early prospective, longitudinal studies enrolling active-duty US military at 0-7 days, 0-30 days, and 0-90 days post injury. All subjects met the DoD definition for mild uncomplicated traumatic brain injury. Non-brain injured control (CTL) subjects were also enrolled at each time point for comparison. Early advanced MR imaging and clinical information was collected before these subjects were followed to 6-12 months. At 6- 12 months, advanced MR imaging was repeated and a battery of neurological, neuropsychological and psychiatric evaluations were completed. In total, 591 subjects were enrolled through these efforts; 54% TBI, 46% control. This study will re-examine these subjects now 3-5 years post-injury and compare their current clinical and imaging presentation with the previously acquired longitudinal data. During this fiscal year the study has:

- a. Enrolled 54 study participants to date

XIII. CENC0034P - Structural and Functional Neurobiology of Veterans Exposed to Primary Blast Forces

- a. Developed and gained GSC approval of the protocol for the project
- b. Applied for and received all required regulatory approval.

XIV. CENC0039P - DTI Phantom Study: Diffusion imaging has gained importance in the past decade as a valuable means of depicting white matter injury caused by various disease processes. Diffusion imaging holds particular promise for evaluation of individuals who have experienced traumatic brain injury (TBI) because damage to white matter pathways is considered to be an important component in the causation of the many types of neurocognitive impairment that can result from TBI. Diffusion imaging can be performed using a number of different imaging techniques, and no single technique is universally recognized as the single best method. As a result, development of large pools of data is hampered by the fact that combining imaging studies obtained by multiple techniques results in an inhomogeneous data set that is difficult to analyze. If diffusion imaging is to be developed as a means to evaluate Veterans with suspected TBI, a uniform type of image acquisition is needed across the different types of imaging systems available within the VA

hospital network. To construct such a system, a means is needed to establish exactly how one scanner differs from another (or from itself over the course of time). Then, modification of imaging sequences and, as needed, hardware and software components, can be performed to allow more uniform data acquisition across scanners. This study uses diffusion imaging phantoms to evaluate differences between scanners with the goal of providing acquisition techniques that will allow data to be compared across different patient groups and combined into large data collections. The objective is to provide a means for the many different scanners across the VA hospital system to provide the same imaging answers in a suspected TBI patient. During this fiscal year, this study has:

- a. Finalized construction plans resulted in the production of the set of 4 initial phantoms by August 30, 2015. The first phase of the phantom construction has included components for testing isotropic and anisotropic diffusion components.
- b. submitted a DURIP application for additional phantoms that could be tested a large network of academic, government, military and VA sites that are not currently included in this effort
- c. Received necessary regulatory approval to test the phantoms at VA CENC scanning sites.

- XV. CENC0049P - Clinical and Neuroimaging Correlates of Neurodegeneration in Military mTBI: The objective of this study is to test several psychological and biological measures for utility as markers of mTBI-related neurodegeneration, and characterize the utility and limitations of self-report measures in the context of mTBI and comorbid psychopathology. During this fiscal year this project has
- a. Developed and gained GSC approval of the protocol for the project.
 - b. Submitted IRB approval for all study sites.

- XVI. CENC0056P - Visual Sensory Impairments and Progression Following Mild Traumatic Brain Injury: The objective of this project is to identify the spectrum of visual sensory disturbances after mTBI by utilizing new imaging technology. During this fiscal year this project has:
- a. Developed and gained GSC approval of the protocol for the project.
 - b. Submitted IRB approval for all study sites, and obtained IRB approval at the Iowa and Palo Alto VA Hospitals.

4. KEY RESEARCH ACCOMPLISHMENTS: Nothing to report.

5. CONCLUSION: Nothing to report.

6. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:

- a. List all manuscripts submitted for publication during the period covered by this report resulting from this project. Include those in the categories of lay press, peer-reviewed scientific journals, invited articles, and abstracts. Each entry

shall include the author(s), article title, journal name, book title, editors(s), publisher, volume number, page number(s), date, DOI, PMID, and/or ISBN.

(1) Lay Press: None to report

(2) Peer-Reviewed Scientific Journals:

Cifu DX, Hoke KW, Wetzel PA, Wares JR, Gitchel G, Carne W. Effect of hyperbaric oxygen on eye tracking abnormalities in males after mild traumatic brain injury. *J Rehabil Res Dev*

Wares JR, Hoke HW, Walker W, Franke LM, Cifu DX, Carne W, Ford-Smith C. Characterizing effects of mild traumatic brain injury and posttraumatic stress disorder on balance impairments in blast-exposed service members and Veterans using computerized posturography. *J Rehabil Res Dev* 2015; 52 (5): 591-604

Cifu D, Diaz-Arrasita R, Williams R, Carne W, West SL, McDougal M, Dixon K. The VA/DOD Chronic Effects of Neurotrauma Consortium: An Overview at Year 1. *Federal Practitioner*. 2015 August;32(8):44-48.

(3) Invited Articles: None to report

(4) Abstracts: See below for abstracts related to MHSRS

- b. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.

Walter Schneider	Abstract # MHSRS-15-1048 - Neurotrauma/Brain Injury - A Novel Universal Phantom and Diffusion Tensor Imaging Standardization to Provide Cross-Vendor and Site-Calibrated Quantification of MR-Based White Matter Imaging	Poster
Alicia Swan, Carlos Jaramillo, Blessen Eapen, and Mary Jo Pugh	Abstract # MHSRS-15-0535 - Neurotrauma/Brain Injury - Tinnitus and vestibular dysfunction in Iraq and Afghanistan veterans: Prevalence and associated comorbidities	Poster
Heather Belanger	Mass TBI Screening in VHA: Is There Evidence?	Oral Presentation
Heather Belanger	Abstract # MHSRS-15-0523 - Is the Neurobehavioral Symptom Inventory (NSI) a Good Outcome Measure? A Chronic Effects of Neurotrauma Consortium (CENC) and VA TBI Model System Study	Poster
Mary Newsome, Elisabeth Wilde, Harvey Levin	Abstract # MHSRS-15-1161 - Psychological Health/Resilience - Altered Functional Connectivity in Veterans with mTBI: Preliminary Data	Poster
Harvey Levin	Abstract # MHSRS-15-1137 - Neurotrauma/Brain	Oral

	Injury - Is Diffusion Tensor Imaging a Biomarker for Mild TBI?	Presentation
Courtney Hall, Faith Akin	Abstract # MHSRS-15-0321 - Sensory Issues/Vision, Hearing & Balance - Otolith Dysfunction and Postural Stability	Poster
Risa Richardson	Abstract # MHSRS-15-0538 - Neurotrauma/Brain Injury - Neuropsychological Testing is predictive of severity of disability following Traumatic Brain Injury: Findings from the VA TBI Model Systems & Implications for the Chronic Effects of Neurotrauma Consortium. Presenter – Tamara McKenzie-Hartman Abstract # MHSRS-15-0443 - Psychological Health/Post Traumatic Stress Disorder - Injury and Psychological Predictors of Employment Stability in Veterans and Service Members with TBI: A VA Brain Injury Model Systems Study – Presenter: Risa Nakase-Richardson or Adam Haskin Abstract # MHSRS-15-0441 - Neurotrauma/Brain Injury - Feasibility of Enrollment and Tracking of Longitudinal Outcomes Following TBI: A VA TBI Model System Study – Presenter: Risa Nakase-Richardson	Poster
Douglas Theriaque (RTI)	Abstract # MHSRS-15-0553 - Neurotrauma/Brain Injury - Informatics Best-practices to Facilitate Data Sharing Using the Federal Interagency TBI Research (FITBIR) Informatics System	Poster
Casey Gilmore	Abstract # MHSRS-15-0442 - Neurotrauma/Brain Injury - Deficits in Visual System Functional Connectivity after Blast-Related Mild TBI are Associated with Injury Severity and Executive Dysfunction	Poster
Kimbra Kenney, Ramon Diaz- Arrastia	Abstract # MHSRS-15-0282 - Neurotrauma/Brain Injury - Assessment of Cerebrovascular Dysfunction after Traumatic Brain Injury: MRI-BOLD versus NIRS	Poster
Ramon Diaz- Arrastia, Jessica Gill	Abstract # MHSRS-15-0989 - Neurotrauma/Brain Injury - Peripheral Concentrations of Total Tau are Increased in Military Personnel who Sustain Traumatic Brain Injuries During Deployment	Oral Presentation
Mary Jo Pugh	Abstract # MHSRS-15-1093 - Psychological Health/Resilience - Trajectories of Comorbidity in Iraq and Afghanistan Veterans: Long-term outcomes	Poster
Fiona Crawford	Benoit Mouzon - The role of tau and other pathologies in an animal model of repetitive mild traumatic brain injury.	Poster

	<p>Scott Ferguson - Screening potential TBI therapeutics in a Pre-Clinical Model of Repetitive mild TBI</p> <p>Joseph Ojo - Modeling PTSD and repetitive concussive injury in animal models</p> <p>Radouil Tzekov - Morphological and immunohistochemical characteristics of optic nerve damage post repeated traumatic brain injury</p> <p>Tanja Emmerich - Translational plasma lipidomic profiling in military populations with TBI, PTSD and TBI+PTSD and correlation to mouse models of these conditions</p>	
Christine Mac Donald	<p>Abstract # MHSRS-15-0036 - Neurotrauma/Brain Injury - Outcome Trends Following US Military Combat Concussive</p> <p>Traumatic Brain Injury: A comparison of prospectively enrolled Service Members before and after implementation of the 2010 TBI Directive Type Memorandum (DTM 09-033)</p>	Poster
Daniel Perl	<p>Abstract # MHSRS-15-0721 - Psychological Health/Resilience - Single Iatrogenic Episode of Severe Axonal Injury in Humans is Associated with Neuropathology Resembling Chronic Traumatic Encephalopathy</p>	Poster
Randy Kardon, Casey Gilmore	<p>Abstract # MHSRS150442 Neurotrauma/Brain Injury Deficits in Visual System Functional Connectivity after Blast Related Mild TBI are Associated with Injury Severity and Executive Dysfunction</p>	Poster

7. INVENTIONS, PATENTS AND LICENSES: Nothing to report.

8. REPORTABLE OUTCOMES:

Below are a list of grant applications that are a result of CENC funding. These were submitted with the GSC directed aim of establishing CENC beyond current governmental funding:

Grant Applications:

Funded:

1. TBI Endpoints Development (TED). USUHS Site PI: Diaz-Arrastia, R.; VCU Site Investigators: Cifu, DX & Merchant RS. Funded, DoD/USAMRAA.

2. Blood Biomarker Profile of TBI-Associate Cognitive Impairment Among Old and Young Veterans. PI: Diaz-Arrastis, R. Funded, DoD/MRMC.
3. Fieldable Multiplex Test for TBI Assessment. PI: Diaz-Arrastis, R. Funded, DoD/BAA.
4. Multimodal Biomarker Assessment in Acute and Chronic TBI with Ultrasensitive Digital Immunoassays. PI: Diaz-Arrastia, R. Funded, GE/NFL.
5. Neuropathology of Chronic Traumatic Encephalopathy and Late Effects of TBI: Towards in-vivo diagnosis. PI: Diaz-Arrastia, R. Funded, NIH/NINDS.
6. Identification of Traumatic Brain Injury using Abnormal Speech Audio Processing (TBI-ASAP). PI: McMahon, BT & Cifu DX. Funded, ViGYAN Inc. (DoD SBIR flow-through).

Submitted:

1. Biomarkers of Chronic TBI. PI: Diaz-Arrastia, R. Pending, ImmunArray, Inc.
2. Cerebrovascular reactivity as a marker for traumatic vascular injury in the chronic stage after TBI. PI: Diaz-Arrastia, R. Pending, CDMRP.
3. The Epidemiology of Epilepsy and Traumatic Brain Injury: Severity, Mechanism, and Outcome. PI: Pugh, MJ. Pending, CDMRP.
4. Developing a Predictive Algorithm for Mild TBI Recovery Trajectory. PI: Belanger, HG. Pending, NIH/NINDS.
5. MRI Phantom Calibrating a Network of Traumatic Brain Injury Innovation and Diagnostic Research Centers. PI: Wilde, EA. Pending, Defense University Research Instrumentation Program.
6. INHIBIT – Improving Neuropathology and Headaches Immediately after Brain Injury Trauma. PI: Dixon, KS. DoD/USAMRAA/BAA.

Not Funded:

1. Consortium on Impulsivity as a Target for Medication development in alcohol and substance use Disorder (CITMAD). PI: Moeller, FG & Cifu, DX. Submitted to DoD/USAMRAA, Not Funded.

9. OTHER ACHIEVEMENTS:

10. REFERENCES: List all references pertinent to the report using a standard journal format (i.e., format used in *Science*, *Military Medicine*, etc.).

11. APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

QUAD CHARTS: