AWARD NUMBER: W81XWH-19-2-0067

TITLE: Long-term Impact of Military-Related Brain Injury Consortium

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CONTRACTING ORGANIZATION: Virginia Commonwealth University

REPORT DATE: October 29th, 2020

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	**2. REPORT TYPE**	**3. DATES COVERED**
29 October 2020	Annual	29 Sep 2019 – 29 Sep 2020

4. TITLE AND SUBTITLE

Long-Term Impact of Military-Related Brain Injury Consortium

5a. CONTRACT NUMBER
W81XWH-19-2-0067

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

PH-TBI

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The Long-Term Impact of Military-Relevant Brain Injury Consortium (LIMBIC) is a coordinated, multicenter, nationwide translational research collaboration that is studying the effects of mild, combat-related TBIs, whether single or repeated, on chronic disabling symptoms, recovery from combat and trauma-related comorbidities, and long-term brain function. This Consortium builds upon the accrued experience of the previous Chronic Effects of Neurotrauma Consortium (CENC) funding cycle (2013-2019), where an Executive Leadership team, a Study Coordinating Center, centralized research Cores (Database and Biostatistics, Imaging, Biomarker), Scientific and Community Advisory Boards, a large, nationwide, multi-level, Prospective Longitudinal Study (PLS) and a multi-site, Retrospective Database Study (RDS) were all established and implemented. These essential elements of CENC have been carried over to LIMBIC and key enhancements of the PLS and RDS have been implemented. The LIMBIC team has completed all regulatory activities, personnel hiring, technical upgrades and documentation adjustments needed for the PLS to initiate follow-up evaluations on all extant participants and also recommence new recruitment of participants, with the easing of COVID-19 research restrictions. The LIMBIC PLS will specifically; 1) expand the current, well-characterized participant cohort with a history of deployment and combat exposure from 1,500 individuals exclusively from the OEF-OIF conflicts to 3,000 participants from all combat-eras to allow for greater statistical opportunities and flexibility in evaluating outcomes in both cross-sectional and longitudinal studies, 2) expand recruitment and testing of active duty and Veteran service members from 2 military/7 Veteran sites to 8 military/9 Veteran sites to increase recruitment of active duty service members, 3) refine existing and add new outcome measures to better evaluate the long-term effects of the number and types of blasts exposures, 4) add a well-utilized and accepted dementia measure that incorporates both participant and informant feedback to gain a better understanding of how TBI effects the development of dementia and which individuals may be more susceptible, 5) continue to refine and validate the standardized potential concussive event and concussion diagnostic interview formats, thereby allowing the field to use a common approach for evaluating concussive history which will enable better harmonization across study efforts, and 6) seek to identify specific neuroimaging and fluid biomarkers that are associated with combat-concussion and risk for poor outcome. The LIMBIC RDS has augmented and refine the CENC mega-database from 1.6 million military Veterans to more than 2.2M unique participants, with all data through 2019, of all TBI diagnoses (using ICD-10) and a random sample of non-TBI, all-era Veterans and identified subgroups with respect to risk/resilience, to 1) examine the complex association between comorbidities and TBI, 2) develop prognostic models for co-morbidity and poor outcomes, 3) identify TBI phenotypes that incorporate acute injury, mechanism of injury and blast exposure, 4) compare differences in health services utilization and costs for individuals with and without Traumatic Brain Injury (TBI) and within distinct TBI phenotypes accounting for comorbidities, 5) compare differences in service-connected disability costs for individuals by TBI status, and 6) extrapolate DoD and VA health services and disability cost estimates to provide DoD and VA annual budgetary impact of TBI accounting for comorbidities and within subpopulations of interest

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
					USAMRMC
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**	Unclassified		**19b. TELEPHONE NUMBER** *(include area code)*
Unclassified	Unclassified	Unclassified			(804) 828-4231

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

Background: The Long-Term Impact of Military-Relevant Brain Injury - Chronic Effects of Neurotrauma (LIMBIC-CENC) Consortium is a coordinated, multicenter, nationwide collaboration linking and utilizing 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 psychological, health and cognitive impacts on our active duty service members and military veterans. This Consortium builds upon the accrued experience of the previous CENC 5-year funding cycle and expands its reach and value. LIMBIC-CENC continues to be distinctively positioned because of 1) a coordinated and centralized organization directed by senior academic TBI leaders of the VA and DOD and effectively supported by an highly experienced, professional Coordinating Center; 2) close linkages between twelve major VA TBI/Polytrauma Centers with eight DoD Centers, and fourteen University research centers 3) proven ability to access large military and Veteran- relevant research subject populations and to work effectively with command personnel at those sites 4) an extensive, long term track record of collaborative TBI research 5) the ability and motivation to coordinate with other large scale TBI projects (currently over a dozen) throughout the country and collaborate to leverage resources and to achieve significant results faster 6) the establishment of a fully functioning Knowledge Translation (KT) Center that synthesizes and disseminates LIMBIC-CENC findings to all stakeholders (investigators, collaborators, community scientists, and participants) in varied formats and levels of depth allowing for easy comprehension 7) the maintenance and functional expansion of three study cores (data and biostatistics, biomarkers and neuroimaging) that support LIMBIC-CENC efforts in achieving its goals.

Objectives: The 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 fully understood. The overarching goals of LIMBIC-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, particularly chronic traumatic encephalopathy and dementia. 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: Six current studies are underway:

The Prospective Longitudinal Study (PLS) builds upon CENC's highly successful Observational Study on Late Neurologic Effects of OEF/OIF/OND Combat in several important ways: 1) by expanding the current well-characterized participant cohort of 1500 individuals to 3000 participants with a history of deployment and combat exposure from all eras of combat-exposure, which will allow for greater statistical opportunities and flexibility in evaluating outcomes in both cross-sectional and longitudinal studies 2) by refining existing and adding new outcome measures to better evaluate the long-term effects of number and types of blasts 3) by specifically adding a well-utilized and accepted dementia measure that incorporates both participant and informant feedback to gain a better understanding of how TBI effects the development of dementia and which individuals may be more susceptible 4) by continuing to refine and validate the standardized potential concussive event and concussion diagnostic interview formats, thereby allowing the field to use a common approach for evaluating concussive history which will enable better harmonization across study efforts

The Retrospective Database Study (RDS) continues to maintain, augment, and refine a growing database (2.2M Veterans) of all TBI diagnoses (including converting ICD-9 diagnoses to ICD-10) and a random sample of non-TBI, all-era Veterans and identified subgroups with respect to risk/resilience. The study examines the complex association between comorbidities and TBI and will develop prognostic models from the data.

The Novel Neuroimaging Study aims to utilize neuroimaging to understand the relation between and variability in neurodegenerative dx and/or comorbidities in those with TBI by assessing available methods for overcoming variability and by harmonization across sites to incorporate elements of advanced statistical analysis and multimodal imaging in conjunction with other injury, demographic and outcome data and to 2) actively investigate new and established tools, share methodology and compare results using different approaches by critically examining and comparing strengths and limitations of analysis methods, by evolving existing analytic pipelines and creating novel analytic approaches where gaps exist

The Biomarker Discovery Project seeks to identify biospecimen markers that are predictive of the long-term impact from concussive forces and which biomarkers may signal resilience despite experiencing TBI. Specifically, the study collects blood and saliva biomarker assays from all subjects with baseline specimens in the biorepository.
Biomarker correlations with TBI status (repetitive versus mTBI with LOC versus blast versus no TBI), pre-deployment/pre-injury biomarker levels, neurobehavioral symptoms, advanced imaging, neuropsychological testing, serial biomarker levels among small cohort with incident neurodegenerative disorder (e.g., dementia) are evaluated.
Intent is to develop panel of prognostic biomarkers for each phenotype of chronic neurotrauma (e.g. dementia, headache, PTSD, sleep disorder).

The Phenotypes Study extends the existing CENC Warfighter Cohort with respect to scope, duration of observation, and types of data included from both deployed and non-deployed participants. New types of data (e.g., radiology results, behavioral health screening, VA/DoD Suicide Data Repository, VA Homelessness Registry, text notes, vital signs, cost of care, etc.) have been added to the outcome measures to extend the validity of the phenotype attempt. The TBI severity algorithm has been extended to identify TBI phenotypes that incorporate acute injury, mechanism of injury and blast exposure. The study aims to compare the prevalence of key comorbidities by TBI severity and study group, and then use deep learning models that incorporate mTBI phenotype, acute and chronic treatment approaches, and emergence of diverse comorbidities to develop risk scores for poor military outcomes, and risk for developing key comorbidities.

The Health Economics Study seeks to compare differences in health services utilization and costs for individuals with and without Traumatic Brain Injury (TBI) and within distinct TBI phenotypes accounting for comorbidities. Further it aims to compare differences in service-connected disability costs for individuals by TBI status. Finally, it will extrapolate DoD and VA health services and disability cost estimates to provide DoD and VA annual budgetary impact of TBI accounting for comorbidities and within subpopulations of interest

CORES:
The Coordinating Center, comprised by the key operations personnel at VCU, will work under the guidance and supervision of the VCU LIMBIC leadership team. This Coordinating Center will be responsible for most day-to-day VCU LIMBIC organizational and management issues. Principal among these functions will be establishing and maintaining the necessary infrastructure, personnel and procedures to successfully implement and complete the primary VCU LIMBIC objectives. The Coordinating Center shall be responsible for maintaining all SOPs and MOPs necessary for the operation of all studies. The Coordinating Center will ensure that all regulatory paperwork is submitted in a timely fashion and updated as required. The Coordinating Center will further ensure that study personnel are properly trained and certified in appropriate regulatory, ethical and legal research procedures, and that all personnel are credentialed by internal subject matter experts in the administration of tests and study procedures. Further, the Coordinating Center will implement tracking procedures to confirm that sites meet enrollment goals as well as monitor followup evaluation sessions of already enrolled participants. This information will be obtained through biweekly site telephone conferences, regular email exchanges, dashboard metrics and site visits as required.

The Data and Biostatistics Core establishes procedures to receive, share, and adjudicate requests related to

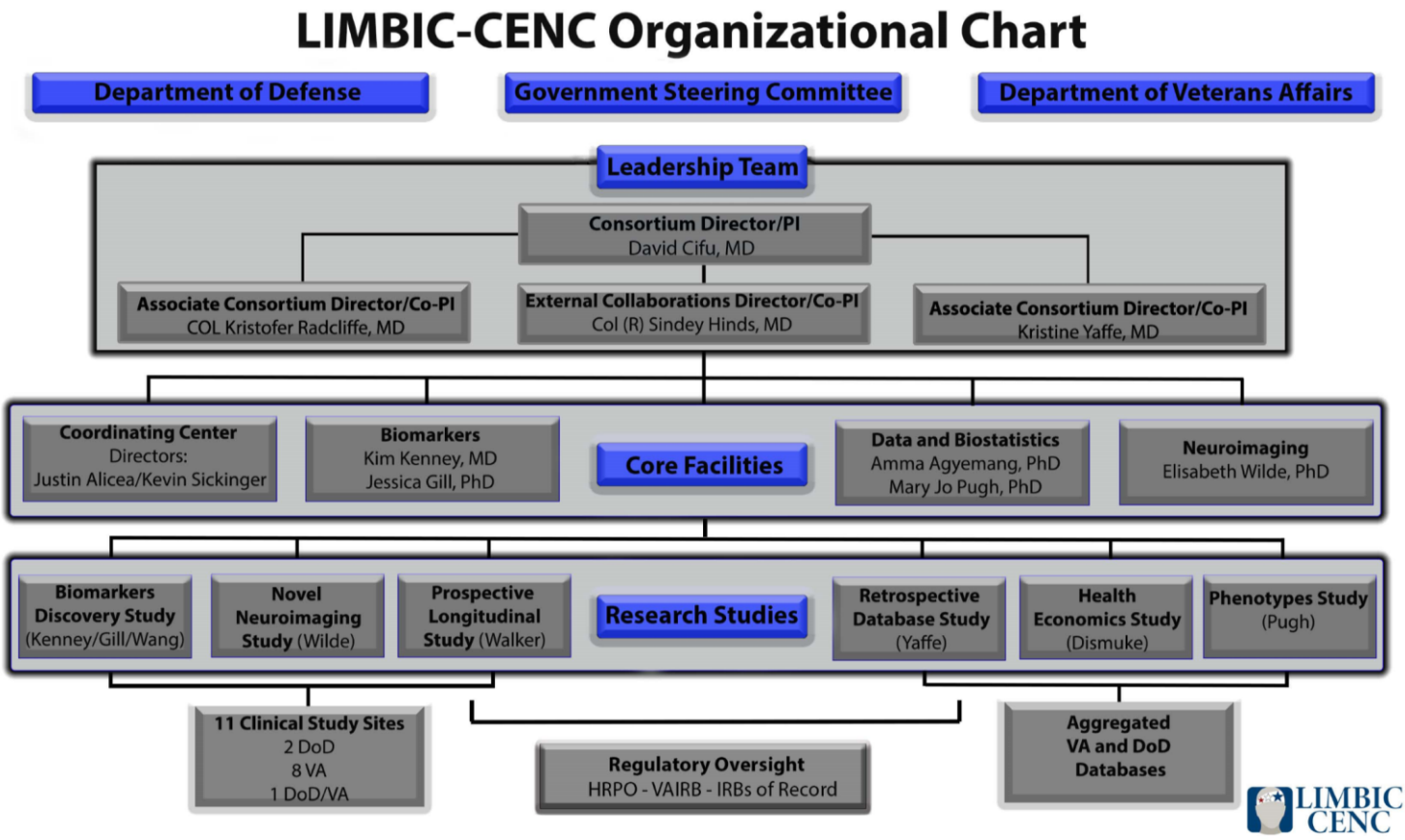
imaging data. It creates and implements efficient logistics for data-sharing both within and outside of the consortium. It develops and refines procedures for data collection and QA/QC, storage and management, and dissemination, while managing data capture (primarily through Medidata), and efficiently and securely storing all clinical data, and biospecimen and neuroimaging data for the Prospective Longitudinal Study. It performs QA and QC processing for all clinical data and works with Neuroimaging and Biorepository Cores to QA neuroimaging and biospecimen data. It disseminates requested data to investigators, provides analytical support for manuscripts, presentations, and other dissemination products, and submits data to FITBIR.

The Neuroimaging Core maintains an organized and well-characterized imaging dataset using standardized techniques of analysis and creates and manages the premiere database for military-relevant brain injury imaging data to identify indicators of neurodegeneration. Further, the core oversees and coordinates image procurement and promotes high-quality, accurate and consistent data collection. The core also establishes procedures to receive, share, and adjudicate requests related to imaging data. It actively creates and implements efficient logistics for data-sharing both within and outside of the consortium.

The Biomarker Core coordinates with appropriate LIMBIC-CENC personnel to submit relevant NED, APOE data to FITBIR. It conducts DNA extraction and APOE genotyping (in batches of 100-200) based on acquired consents for genetic testing. It continues to perform LIMBIC-CENC service operations-limited genotyping and NED screens through CLIA-certified lab (including complete set up for NED testing at 3 new LIMBIC sites). The Core provide samples for approved research specimen requests (LIMBIC and external investigators) once full regulatory documents are in place. Blood and saliva biomarker assays from all subjects with baseline specimens in the biorepository are performed. The core regularly carries out candidate biomarker correlations with TBI status (repetitive versus mTBI with LOC versus blast versus no TBI), pre-deployment and pre-injury biomarker levels, neurobehavioral symptoms, advanced imaging, neuropsychological testing, serial biomarker levels among small cohort with incident neurodegenerative disorder (e.g. dementia). The core is developing a panel of prognostic biomarkers for each phenotype of chronic neurotrauma (e.g., dementia, headache, PTSD, sleep disorder).

Military/VA Benefit:
LIMBIC-CENC is specifically designed to demonstrate the linkages between TBI, direct effects (cognitive, general health, behavioral) and chronic neurodegeneration. This knowledge will aid in providing clinical care that guides the development of novel interventions that prevent or mitigate cognitive and behavioral decline and contributes to long-term planning for service member and veterans.

See LIMBIC-CENC Organizational Chart Below.



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

chronic effects prognostic biomarker NfL Tau miRNA FITBIR MRI neuroepidemiology phenotype chronic pain pharmacoepidemiology mTBI epidemiology neurodegeneration dementia comorbidity cognition obstructive sleep apnea

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Cores

Coordinating Center:
This Coordinating Center is responsible for most day-to-day VCU LIMBIC organizational and management issues. Principal among these functions will be establishing and maintaining the necessary infrastructure, personnel and procedures to successfully implement and complete the primary VCU LIMBIC objectives. The Coordinating Center shall be responsible for maintaining all SOPs and MOPs necessary for the operation of all studies. The Coordinating Center will ensure that all regulatory paperwork is submitted in a timely fashion and updated as required. The Coordinating Center will further ensure that study personnel are properly trained and certified in appropriate regulatory, ethical and legal research procedures, and that all personnel are credentialed by internal subject matter experts in the administration of tests and study procedures. Further, the Coordinating Center will implement tracking procedures to confirm that sites meet enrollment goals as well as monitor followup evaluation sessions of already enrolled participants. This information will be obtained through biweekly site telephone conferences, regular email exchanges, dashboard metrics and site visits as required.

Data and Biostatistics Core:
The Data and Biostatistics Core is a collaborative effort of two sites with expertise working at HHMVANMC/VCU and VASLCHCS/UU. The Richmond group will manage data collection for the clinical studies via Medidata Rave, NIH toolbox and other mechanisms (i.e., Otogram, EEG/ERP), as well as ensure data quality and timely submission of data to FITBIR. The Salt Lake City team will provide analytic leadership, biostatistics and informatics expertise, and facilitate data distribution and manuscript development for the clinical studies, in addition to facilitating manuscript development by consortium members from the other five Research Studies. This Core will also collaborate with the Coordinating Center and Clinical Studies Core to conduct data checks, queries, auditing, and other data quality assurance activities. This Core Facility allows for both a centralized repository for all VCU LIMBIC data and efficient access to the data for accelerated knowledge translation and readily deployable research products.

Neuroimaging Core:
The Neuroimaging Core, at the VA Salt Lake City Health Care System (VASLCHCS) and the University of Utah, will facilitate acquisition, review, transfer, collation, tracking, analysis, integration, reporting, storage, and interpretation of all CENC and VCU LIMBIC neuroimaging data. Neuroimaging Core Specific Aims are to:
Task 1: Maintain the established CENC/LIMBIC neuroimaging database using the standardized techniques of image procurement, standardization and quality assurance.
Task 2: Oversee and coordinate the image procurement at each clinical study site.
Task 3: Establish procedures in collaboration with the Research Committee to receive and adjudicate requests for studies utilizing imaging data specimens.
Task 4: Establish priorities, policies and procedures to make imaging data accessible to VCU LIMBIC and associated researchers.

Biomarkers Core:
The Biomarkers Core, located at CNRM at USUHS, will manage the storage and processing of blood and saliva samples collected through the Prospective Longitudinal Study. Blood samples consist of plasma, serum, and cells, which will be processed to extract DNA. These biological fluids will be cataloged and tracked, and

stored at -80oC in a dedicated Biorepository Facility maintained by the Center for Neuroscience and Regenerative Medicine. The work will involve faculty and staff processing lab work on thousands of samples. Finally, the Core will administer requests for use of these biological samples from investigators inside or outside LIMBIC, according to the data and sample sharing policies of the Consortium. Biomarkers Core Specific Aims are to:

Task 1: Maintain the established a Biospecimen Biorepository with standardized methods of collection, local processing, and shipment of blood and saliva from VCU LIMBIC study sites to a centralized Biorepository where samples are collected, stored and curated.

Task 2: Screen all clinical study participants at baseline for neuroendocrine dysfunction (NED) through a CLIA-certified Laboratory.

Task 3: Carry out Deoxyribonucleic Acid (DNA) extractions and Apolipoprotein genotyping on study consented participants.

Task 4: Establish procedures in collaboration with the Research Committee to receive and adjudicate requests for studies utilizing Biorepository specimens.

Task 5: Establish priorities, policies and procedures to make Biorepository specimens accessible to VCU LIMBIC and associated researchers.

Task 6: Retrieve and ship requested samples to approved projects for study.

Studies

Prospective Longitudinal Study:

The CENC Prospective Longitudinal Study (PLS) established an active multicenter cohort of 1550 Service Members and Veterans who have all undergone comprehensive evaluation. The overall goal of the LIMBIC-CENC PLS is to maintain, expand and serially assess this multicenter cohort to anchor the solicited single Consortium of a large, longitudinal study, supporting sub-studies to analyze a large mild tramatic brain injury (mTBI) cohort including servicemembers (SMs), veterans (Vs), and relevant populations, and through a series of scientific analyses it will fulfill all of the required LIMBIC-CENC research elements. Under LIMBIC, this includes targeted expansion of pre-911 era SMs, current SMs, and heavily blast exposed populations. Initial and longitudinal data are collected under TBI CDE guidelines using comprehensive assessments and submitted to the FITBIR. Scientific analyses investigate mTBI co-morbidities and neurologic outcomes including change over time. Though this process, the PLS will identify potential differences in outcomes between SMs & Vs with various histories of lifetime mTBI and repetitive low-level blast exposures, identify pathophysiological and biomarker signatures for chronic mTBI subgroups of recovery patterns and neurodegeneration susceptibility, and evaluate neuroimaging techniques to understand the relationships between mTBI and neurodegenerative disease and other co-morbidities.

Retrospective Database Study:

The primary objective of this project is to integrate and analyze existing VA healthcare data to study the long-term effects of traumatic brain injury (TBI) on neurodegenerative disease, mental health, and other outcomes. Our group of experts in TBI and epidemiology created a highly pragmatic national analytic database of over 2 million Veterans. In LIMBIC-CENC, we are rapidly investigating unanswered questions related to health risks associated with TBI:

Task 1: Planning and regulatory review, data updating, and variable creation (Months 1-12)

Task 2: Analysis assessing the role of mental health comorbidities on the association between mTBI and long-term outcomes such as dementia and other neurodegenerative diseases (Months 6-30)

Task 3: Analyses assessing the role of demographics and socioeconomic status to the risk of developing dementia and examining the characteristics and longitudinal course of younger veterans (<55) with cognitive impairment after mTBI (Months 24-50)

Task 4: Develop prognostic models to better determine risk of dementia and mortality and associations with risk factors in veterans with mTBI; create and validate clinical tool determining risk of poor short-term and long-term outcomes in patients with mTBI (Months 24-60)

Phenotype Study:
Study staff and investigators will compile the DoD-VA data to expand the CENC Warfighter cohort, extend the observation period and provide data to 1) describe the population of SMs and Vs with mTBI, no TBI and TBI of other severities; 2) identify phenotypes and risk for specific phenotypes accounting for baseline characteristics, acute injury characteristics, and acute and chronic treatment patterns. The study aims to compare the prevalence of key comorbidities by TBI severity and study group, and then use deep learning models that incorporate mTBI phenotype, acute and chronic treatment approaches, and emergence of diverse comorbidities to develop risk scores for poor military outcomes, and risk for developing key comorbidities. The major goals for this study are as follows:
Task 1: Update data repository annually with latest VA data and merge with relevant DOD datasets and add additional DoD data to enhance acute TBI identification. Once assembled, perform quality checks and continue maintenance throughout study.
Task 2: Conduct phenotype analysis by deployment strata to examine the role of mTBI in emergence of neurodegenerative disease, psychological health status, neurosensory deficits and pain over time.
Task 3: Use phenotypes and mTBI to develop risk scores for military outcomes, neurosensory/neurodegenerative disease, and adverse outcomes by deployment.
Task 4: Examine association of phenotypes with TBI and risk for repetitive low-level blast by deployment strata.

Health Economics Study:
Study staff and investigators will compile the DoD-VA data to expand the CENC Warfighter cohort, extend the observation period and provide data to 1) describe the population of SMs and Vs with mTBI, no TBI and TBI of other severities; 2) identify phenotypes and risk for specific phenotypes accounting for baseline characteristics, acute injury characteristics, and acute and chronic treatment patterns; 3) economic impact of phenotypes from the perspective of the DoD, the VA, and society. Along with the phenotypes study, the Health Economics Studies will develop a merged DoD and VA cohort that includes individuals who were on active duty after September 11, 2001 through the end of FY19 via DaVINCI, a portal that allows sharing of VA and DoD data for all SMs and Vs (including deployed National Guard/ Reserve members), as we have done for several previous studies. Based on MHS data included in the Mental Health Data Cube compiled by Kennel Associates, we will identify individuals who were deployed to combat theatre and those who were not deployed. We will then merge the DoD data with data from the Veterans Health Administration and Veterans Benefits Administration to identify individuals who have connected with the VA for Health and/or Benefits in order to assess the long-term disability and health status impact and classify the cohort into our study groups stratified by deployment and VA health care use status: Deployed+VA, Deployed-No VA, Non-deployed+VA, Non-deployed-No VA. We will identify our cohort through FY19, and with follow-up observation through FY23.
For the Longitudinal prospective cohort, the major goals are:
Task 1: Merge up to 4000 records from the Prospective Study, veterans and service members, with VA health service connected disability, VA diagnoses, VA health services utilization and VA cost data as data are provided from the Prospective Study PI.
Task 2: Examine the association of self-reported combat and training mechanism of injuries with VA service connected disability ratings and costs by TBI status and severity.
Task 3: Examine the association of self-reported combat and training mechanism of injuries with VA health services utilization and costs by TBI status and severity.
Task 4: Examine the association of self-reported combat and training mechanism of injuries with VA diagnoses by TBI status and severity.

Novel Neuroimaging Study:
In addition to supporting Prospective Longitudinal Study, the Neuroimaging Core will utilize neuroimaging to understand the relationship between and variability in neurodegenerative disease and/or comorbidities in those with mTBI. The Novel Neuroimaging Study will actively investigate new and established tools, share methodology, and compare results using different approaches; this will enable us to evolve analytic pipelines based on these investigations, and create novel analytic approaches where gaps exist. Novel Neuroimaging

Study Major Tasks are as follows:
Task 1: Assess available methods of overcoming variability introduced by differences in scanner hardware and software.
Task 2: Critically examine and compare strengths and limitations of commonly used imaging analysis pipelines.
Task 3: Develop and test aspects of pre-processing which enhance accuracy and consistency.
Task 4: Create and refine novel, automated pipelines to address aspects of imaging analysis which are currently absent or incomplete.
Task 5: Incorporate elements of advanced statistical analysis (e.g., Bayesian analysis, machine learning) to utilize multi-modality imaging data in conjunction with other injury, demographic and outcome data to develop subgroups/phenotypes and identify related variables in those at highest risk for poor outcome.
Task 6: Assess merits and challenges of existing methods of "individualized" data analysis.
Task 7: Share data with external investigators; Biannual submission to FITBIR (March and September)

Biomarker Discovery Study:
In addition to supporting the Prospective Longitudinal Study, the Biomarkers Core will carry out projects in collaboration with the other VCU LIMBIC Cores to address the following objectives:
Task 1: Identify biologic signatures that may be predictive (prognostic biomarkers) of long-term TBI outcomes or maintenance of symptoms. Identify novel biomarkers for chronic mTBI; characterize mTBI subgroups based on recovery and neurodegeneration.
Task 2: Collaborate with Dr. Wang (Gainesville VA) to develop and validate a rapid throughput multiplex immunoassay of candidate chronic TBI biomarkers for commercialization.
Task 3: To collaboratively carry out GWAS within the CENC/LIMBIC cohort (N = 3,000) in collaboration with the Genetic Association in Neurotrauma (GAIN) consortium that has data from >10,000 participants.
Task 4: To expand the miRNA study and to be the first to carry out a DNA methylation study in chronic TBI patients.

What was accomplished under these goals?
For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Cores

Coordinating Center:
Major Task 1: Transition and Expand CENC to LIMBIC:

1. Submission of IRB approved master protocol.
   Month(s): 1 - 3
   Progress: Completed in the 1st Quarter,

2. Delivery of expanded Consortium SOP.
   Month(s): 1 - 3
   Progress: Completed in the 1st Quarter.

3. Submission of timeline for onboarding performance sites.
   Month(s): 1 - 3
   Progress: Completed in the 1st Quarter and briefed during our GSC Meeting in February. Please see Appendix #1 (February GSC Meeting) for the information on the timeline for onboarding the new performance sites.

4. Establishment of Data Sharing Agreement with DHA for access and use of MHS data at VCU CC and appropriate sites.

Month(s): 1 - 4

Progress: This has been completed for some of the studies like the Phenotype and Health Economics but is still in the works for others.

5. HRPO Approval of Master Protocol.

Month(s): 1 - 6

Progress: We have gained HRPO approval for almost all of the Prospective Longitudinal Study (PLS) sites except for just a few like Fort Gordon. We recently got their IRB approval through the Walter Reed IRB and now have their HRPO approval submitted and awaiting response. Biomarker Discovery Study/Core and Neuroimaging Study/Core are different story. The PIs and the Coordinating Center were under the impression that had HRPO approval because HRPO had previously declared that Imaging and Biomarkers didn't need HRPO approval since they were deemed as not being human research. We were wrong in our assumptions and have already submitted the Biomarker Core HRPO request and are in the process of submitting the Biomarker Study, Imaging Core, and Novel Neuroimaging Study requests to HRPO.

6. IRB/HRPO/JIT approvals for all performance sites and consortium cores.

Month(s): 1 - 12

Progress: All IRB and JIT submissions were submitted and approved. See above for HRPO approvals.

7. Hiring, training and certification of subaward personnel, particularly subaward clinicians and associate researchers.

Month(s): 1 - 6

Progress: We have assisted all of the PLS sites with the hiring, training and certification of all personnel. We still have training and certification to complete for our new Audiostar equipment at a couple locations but that is being completed just prior to sites coming back on line from their COVID-19 restrictions.

Major Task 2: Add three new additional Prospective Study Enrollment Sites:

1. Onboard 3 new enrollment sites (Salisbury/San Diego/Fort Gordon).

Month(s): 1 - 6

Progress: This was completed on time, well before the end of the 2nd Quarter.

2. Assist with hiring, training and certifying staff.

Month(s): 1 - 6

Progress: We assisted with the hiring, training and certifying of staff for the three new sites but we still have a couple tasks that the new sites need training and certification on. We held off on training several of the more complicated/technical tasks until weeks prior to the sites initiating in-person research. We didn't want to train and certify them on a couple of the tasks to have them lose proficiency waiting on the go ahead for in person research to resume.

3. Assist with regulatory approvals to include IRB and HRPO.

Month(s): 1 - 6

Progress: All IRBs have been approved and all sites except Fort Gordon have HRPO approval. The Fort Gordon request is at HRPO awaiting approval.

Major Task 3: Conduct Call Center operations:

1. Assist with hiring, training and certifying staff.

Month(s): 1 - 60

Progress: We have had some turnover in the Call Center but we are fully manned and operational. We replaced the Supervisor with our best caller and then had to hire, train and certify her replacement. That has been completed but we also promoted another of our callers to a coordinator position and have just completed that hiring process and are in the process of completing her training and certification.

2. Conduct liaison between enrollment sites.

Month(s): 1 - 60

Progress: The hiring of a new Call Center Supervisor coupled with the launch of the Call Center Application by our Data and Biostatistics Core has greatly increased the liaison between the Call Center and the enrollment sites. We are in a great position to excel once the COVID restrictions are lifted and enrollment takes off.

3. Conduct all necessary follow-up calls to include BTACTs and Annual Telephone Assessments for Prospective Longitudinal Study.

Month(s): 1 - 60

Progress: The call has attempted to conduct all necessary follow-up calls to include Annual Follow Up Assessments and BTACTs. The BTACT completion percentage is 85% while the Annual Follow Up Assessment percentage is at 71%.

Major Task 4: Attend Semi-Annual GSC meetings with DoD and VA sponsors:

1. Coordinate with CDMRP Science Officer to make tentative schedule for semi-annual GSC meetings.

Month(s): *4 - 60*

Progress: Completed one GSC meeting within the reporting period (February) and coordinated another meeting during the period but the meeting was conducted in year two of the Period of Performance. See Appendix #1 for the February GSC Meeting presentations.

2. Coordinate with all performance site PIs to ensure that their schedules permit attendance at meetings.

Month(s): *4 - 60*

Progress: We were able to get almost all of the primary PIs to attend the in person meeting in February.

3. Provide CDMRP Science Officer with all required meeting materials in accordance with approved schedule.

Month(s): *4 - 60*

Progress: We were able to get all of the required meeting materials for the first meeting in February but we were a day late for the second meeting. We have instituted a new timeline for meeting materials that will not only ensure meeting the turn-in suspense but also allow for review time for our Science Officer to ensure that we are also on target.

Major Task 5: Set and publish all Performance Site Metrics to include (recruiting/retention/reporting/data collecting/FITBIR reporting):

1. Establish Site Metrics.

Month(s): *1 - 60*

Progress: This task has been completed. The DBC has been reporting their portion of the Metrics to sites on a monthly basis but the Coordinating Center postponed any reporting on recruiting since we were not able to recruit and the new sites were mostly concentrating on standing up.

2. Establish recruitment and retention goals as well as the overall plan.

Month(s): *1 - 60*

Progress: This was completed during the negotiation phase of the project, however, we have adjusted the site recruitment goals based on the fact that the sites were not able to recruit during

the first year. Fortunately, we had planned to meet our goal within year four which has now allowed us to shift the recruitment goals on the calendar to the right by a year. See table below for the new recruitment goal:

Projected Quarterly New Enrollments for Study A: Prospective Longitudinal Study

Subject enrollment will be expected at a rate of 2-5 per month for the duration of the study period

	Year 1				Year 2				Year 3				Year 4				Year 5				
Target Enrollment Study A	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Total**
(01) Hunter Holmes McGuire	0	0	0	0	9	9	9	9	9	9	9	9	9	9	8	8	4	3	3	0	116
(02) Michael E. DeBakey	0	0	0	0	9	9	9	9	6	6	6	6	6	6	6	6	4	4	2	0	94
(03) James A. Haley	0	0	0	0	9	12	12	12	12	12	12	12	8	8	8	8	4	4	2	0	135
(04) South Texas Veterans	0	0	0	0	9	9	9	9	9	9	9	9	9	9	9	9	5	5	4	4	126
(05) Fort Belvoir	0	0	0	0	9	9	9	9	9	9	9	9	9	9	9	9	6	6	6	0	126
(06) Portland Health Care	5	6	0	0	10	15	15	15	15	15	15	15	12	12	12	12	4	4	1	0	183
(07) Minneapolis VA	0	0	0	0	10	15	15	15	15	15	15	15	15	15	12	12	10	10	8	0	197
(08) Boston Healthcare System	0	0	0	0	10	12	12	12	12	12	12	12	12	12	12	12	12	12	12	6	184
(09) W.G. (Bill) Hefner VA	0	0	0	0	10	15	15	16	16	16	16	16	16	16	16	16	16	16	15	11	242
(10) Dwight D. Eisenhower	0	0	0	0	10	15	15	15	15	15	15	15	15	15	15	15	15	15	15	6	226
(11) San Diego Healthcare System	0	0	0	0	10	14	14	14	14	14	14	14	14	14	14	14	14	14	8	0	200
Target Enrollment (cumulative)	5	6	0	0	105	134	134	135	132	132	132	132	125	125	121	121	94	93	76	27	1829

3. Monitor and report site performance.

Month(s): *1 - 60*

Progress: This has been completed throughout the year to include monthly feedback to the sites.

4. Maintain and establish regular communication through meetings, teleconferences, e-mails, site visits and other methods to maintain consortium function.

Month(s): *1 - 60*

Progress: We have not had any in-person meetings since March but we have established and maintained regular communications through teleconferences, emails and other calls as needed. We have not been able to conduct site visits due to travel restrictions and safety precautions due to COVID-19 but will resume travel once it is deemed safe.

Major Task 6: Collect required information, prepare and submit Quarterly, Annual and Final Reports.

Month(s): *1 - 60*

Progress: Competed the three Quarterly Reports on time and to standard.

Major Task 7: Conduct Consumer Advisory Board Meetings:

1. Select Board Members and attain GSC approval of the selectees.

Month(s): 1 - 3

Progress: We selected the members for the Consumer Advisory Board (CAB) and requested approval at the GSC Meeting in February. Our initial submission had nine members, six of which were on the CENC CAB and three new members. We were asked by the GSC to look at adding another clinician which we did and we gained approval for the CAB members that we requested. However, we are looking for another active service member clinician to join the board as requested by the GSC in their approval notification.

2. Publish the LIMBIC CAB Charter.

Month(s): 1 - 6

Progress: The LIMBIC-CENC CAB Charter was approved during the first CAB meeting on 14 August 2020. Please see **Appendix #2** for the CAB Charter.

3. Publish the LIMBIC CAB Meeting Schedule.

Month(s): 1 - 6

Progress: The LIMBIC-CENC CAB meeting calendar was approved during the first CAB

meeting on 14 August 2020. Please see **Appendix #3** for the CAB meeting calendar.

4. Conduct the meetings, provide appropriate feedback to Consortium Leadership and implement approved feedback.

Month(s): 6 - 60

Progress: We conducted our first meeting on 14 August 2020. The main emphasis for this meeting was an introduction to LIMBIC-CENC from Dr. Cifu, review and approval of the Charter and Calendar. There wasn't any feedback at this time but will ensure that provide appropriate feedback from future meetings. Please see **Appendix #4** for the presentation given during the CAB meeting.

Major Task 8: Ensure maximum Consortium PI involvement in scientific conferences:

1. Ensure maximum Consortium PI involvement in scientific conferences.

Month(s): 1 - 60

Progress: We had several Consortium PIs who were going to attend the MHSRS meeting this summer but this conference and all others were canceled due to COVID-19. However, we have included several of the approved abstracts from the MHSRS in our Appendices.

Major Task 9: Management of Fiscal Resources:

1. Establish appropriate approved sub contractual arrangements.

Month(s): 1 - 3

Progress: Completed in the 1st Quarter.

2. Establish CRADA and other agreements as required, provide copies to the GOR, and update as necessary.

Month(s): 1 - 3

Progress: The LIMBIC-CENC Team has been in routine contact with all the administrative contacts responsible for the CRADA process. An unexpected personnel change at Ft. Belvoir occurred in the 2nd quarter which delayed the administrative process. Precipitously in the 3rd quarter all parties involved were abruptly impacted by COVID-19 shutdowns. In the 4th quarter the CRADA was reverted from Walter Reed to USUHS in a request to add them as a party to the agreement. A meeting occurred on Monday, September 28th between Walter Reed and USUHS to resolve concerns.

3. Monitor overall and individual site finances.

Month(s): 1 - 4

Progress: We have closely monitored individual site finances to include expenditures and personnel effort. We also worked with each and every individual site in order to work on redoing their budgets since COIVD-19 greatly affected their expenditures since they were not allowed to enroll new participants or hire some personnel.

4. Develop strong working relationship with both the DoD and VA Contract Personnel to ensure 100% financial regulatory compliance.

Month(s): 1 - 60

Progress: See task #3. We strengthened our relationship with the VA Contract Personnel and have initiated a working relationship with our DoD counterpart.

5. Provide Quarterly and Annual Financial Reports to be included in the Consortium's Quarterly and Annual Reports.

Month(s): 1 - 60

Progress: Completed.

Major Task 10: Publication of methodology, preliminary, and final study results and methodology:

1. Develop plan for analysis of study data, and reporting.

Month(s): 12 - 24
Progress: These activities are ongoing for the entire consortium. However, Dr. Walker provides a detailed analysis plan within the PLS section and his Analysis Plan is also included as an attachment to the report since it is an Excel Spreadsheet.

2. Assist Consortium PIs in publishing of results in both Scientific Journals and Conferences.
Month(s): 24 - 60
Progress: Although this wasn't scheduled to happen until year #3, our Consortium PIs have published a few manuscripts in the first year of this grant. All of these are included as Appendices.

3. Conduct Knowledge Translation in order to transform the findings from research to practice.
Month(s): 36 – 60
Progress:
Updated Website with Core Online Products (On-going):
- 35 plain language abstracts and key points for published research articles.
- Evidence update for clinician "clinical pearls".
- Regularly updated LIMBIC-CENC banner material and major news announcements.
- Regular announcements for the general public and consumers using LIMBIC-CENC Facebook, Twitter, and Instagram.
- Added 115 peer-reviewed publications to website.
- VCU Foundation Article on LIMBIC-CENC Grant.

Created Prospective Longitudinal Study Data Visualization Dashboard:
- Visual display that provides a summary overview of the LIMBIC-CENC Prospective Longitudinal Study enrolled participants including sample size and date range for data presented.
- Provides "at a glance" summary display of LIMBIC-CENC Prospective Longitudinal Study participants' key findings and quick links to each of four areas: Demographics, Military Status, TBI Characteristics, and Key Outcomes.

Developed Prognostic Dementia Risk Tool Prototype for Service members, Veterans and their Clinicians:
- Has two primary products: a brief Dementia Risk Survey and a personalized 'My Dementia Risk Profile'.
- Used LIMBIC-CENC and other longitudinal published findings to identify evidence-based, (modifiable) risk and protective factors for dementia.
- The Dementia Risk Survey features 15 questions that screen for dementia risk and protective factors.
- Veterans usability feedback on the Dementia Risk Survey indicates it takes an average of two minutes to complete and is very easy to do.
- Evidence-based algorithms and programming translate Dementia Risk Survey responses into a personalized 'My Dementia Risk Profile' report.
- The 'My Dementia Risk Profile' provides a summary of each dementia risk factor identified reported along with "basic" and "advanced" evidence-based, recommended actions to reduce each dementia-related risk.

Created LIMBIC-CENC Searchable Journal Database
- Created searchable database of LIMBIC-CENC and affiliated author publications to meet long-term research publication storage, access and knowledge translation needs.
- 'Basic search' filter allows users to type in search keyword(s) to filter publications of interest.
- 'Advanced search' allows users to select search categories from drop-down lists to do

more targeted filters of publications.

- A table of filtered articles allows users to sort the table by Title, Author(s), Publication Journal, or Year Published.
- A detailed APA Citation and Structured Abstract is provided for each published article.
- A 'Full Text Link' allows users to download the full article.

LIMBIC-CENC/Biogen Dementia Awareness, Education and Prevention Campaign

- Proposed $1.5 million project to fully inform Servicemembers, Veterans, families, clinicians and advocates about dementia prevention and treatment strategies, and Biogen's medications and research studies.
- Raise universal military and Veterans awareness and knowledge of Alzheimer's disease (AD) including: (1) risk factors and prevention strategies; (2) signs and symptoms of AD; (3) FDA approved medication treatments; and (4) how pharmaceuticals fit into early, moderate and advanced AD management.
- Develop and pilot 'Treat'D Right', a 'Treat Dementia Right' clinical delivery education program that would give Veterans and Servicemembers with pre-dementia or dementia the right treatment information for the right diagnosis at the right time. Servicemembers, Veterans and families who are 'Treat'D Right' will feel knowledgeable, fully weigh their options, and make informed decisions to personalize treatment and maximize life quality.
- The proposal received first level approval and is being considered for final funding decision with executive/finance board members.

Major Task 11: Interface with other researchers, entities, and consortiums as directed by the Government Steering Committee and Program officer.

Maximum participation in conferences, with a minimum attendance at 1 scientific conference per year and at 2 military conferences (DoD or VA-sponsored) over 5 years.

Month(s): 1 - 60

Progress: During the first year of LIMBIC-CENC, the senior leadership decided to formalize its external collaboration efforts process. LIMBIC-CENC created a consortium operation plan to capitalize on the innate desire of the LIMBIC-CENC cores, researchers and leaders to work with other like-minded individuals and organizations, to improve the fields of mild traumatic brain injury and the discovery of risk factors which may lead to neurodegeneration.

Recognizing that there are limitations to the consortium's time, finances, and space resources, LIMBIC-CENC created a framework to maximize and prioritize its external interactions. The LIMBIC-CENC consortium operation plan takes a tiered approach to prioritize the efforts in which it will be involved. For example, the highest level of external collaboration efforts consume the most resources to cultivate and may also have the highest impact. Data sharing agreements, creation of a research proposal, or preparation for an evidence-based consensus conference represent the highest level, or tier 1, LIMBIC-CENC activities.

In addition, the LIMBIC-CENC consortium operation plan describes the tangible outputs/deliverables to share, advance, and create knowledge, which when accomplished will improve the overall mild traumatic brain injury and neurodegeneration practices in research and clinical care. These collaborative outputs include but are not limited to manuscripts, clinical recommendations, research proposals, clinical practice guidelines, letters of understanding, data sharing agreements, specimen sharing agreements, and knowledge and technical products. During fiscal year 2020 LIMBIC-CENC has continued its external collaborations as the development of the consortium operation plan for external collaborations was being created. This year's external collaborations included selecting and on-boarding of the new DoD co-PI, Col. Kristopher Radcliffe. This involved an extensive search for a military co-PI with the highest experience and credentials in the fields of neurotrauma and neurodegeneration; an individual with military medical and combat experience; and experience with the higher echelons of military medical administration. LIMBIC-CENC leadership coordinated with Col. Radcliffe's

command, over the course of numerous meetings to ensure a seamless assumption of duties. Not only will Col. Radcliffe be instrumental in guiding research efforts, but also he will be a critical leader in knowledge translation endeavors.

During this year, LIMBIC-CENC continued processing and approving data and specimen sharing agreements; creation of manuscripts and presentations; hosting and participating in virtual external collaboration working meetings; and iterative meetings to create research proposals aligned with the LIMBIC-CENC mission.

LIMBIC-CENC continued interactions:

- TRACK-TBI
- NCAA Care Consortium
- InTBIR
- Veterans Against Alzheimer's
- ENIGMA
- University of Pennsylvania
- Concussion Legacy Foundation
- DVBIC

LIMBIC-CENC began collaborative work:

- Harvard's Football Player's Health Study investigators
- Million Veterans Program
- Biogen
- CONNECT-TBI
- Operation Backbone
- University of Virginia
- Perspecta
- University of Utah

LIMBIC-CENC will continue to foster external collaborations which will provide the most impactful achievements, and which will propel the expansive knowledge in the fields of neuroscience, neurotrauma, neurodegeneration and rehabilitation forward. For more details on External Collaborations, please see our Collaboration Tracker located at **Appendix #5**.

2. Addition of other consortium members on our Advisory Boards.

Month(s): 1 - 60

Progress: We currently do not have any other consortium members on our Advisory Boards but we will continue to look into how we can make this happen.

Data and Biostatistics Core:

Major Task 1: Hire and maintain DBC staff.

Month(s): *1 - 60*

Progress: All Core staff (1 data manager, 1 project manager, 3 data scientists, 1 data analyst, 1 full stack developer, 1 research associate) were hired, onboarded and trained by the end of the 2nd quarter of LIMBIC-CENC.

Major Task 2: Collect data using Medidata RAVE and supplementary platforms; clean and check data quality; share data with internal investigators as requested.

Month(s): 1 - 60

Progress: Transitioned from CENC data capture sytem in Medidata to LIMBIC-CENC system also in Medidata, including transferring all previously collected data from six years of CENC. We have optimized the system (implemented over 200 edit checks and custom functions in more than 50% of PLS 92 CRFs) to improve efficiency. In addition to Medidata, raw data files will be captured through new secure file transfer protocol. Developed new system (Study Portal) to capture and manage PLS

participant contact information and to track Call Center call completion. Added feature in Study Portal to facilitate sites' tracking of upcoming visits. Completed training of all 11 sites in all IT systems and provide ongoing support. Developed and refined system for monthly quality checks and feedback to sites on visit completion rates, data entry timing and quality, raw data uploads, FITBIR GUID and pseudo GUID tracking. Generate multiple monthly reports to track retention, comprehensive, annual telephone, and BTACT visit completion, and consent report for biofluid samples. Developed and implemented REDCap survey to enable completion of self-report questionnaires remotely. Worked with Neuroimaging Core to build system for capture of data from common data element coding of MRIs and QA/QC of data. Refined internal data request process based on feedback from investigators. Completed 15 data requests (4 in Q1, 3 in Q2, 4 in Q3, and 4 in Q4) and currently working on 4 data requests. Dveloped data dictionary to facilitate data requests and currently working on improving its searchability and making it web-based. Devloped system to release data snapshots 2x/year in conjuction with FITBIR submissions.

Major Task 3: Analyze data to evaluate cognitive decline and related late effects.

Month(s): *1 - 60*

Progress: Developed analytic data for four papers addressing these primary data analyses. Central Biostatistics core working with investigators for these analyses.

Major Task 4: Translate knowledge and disseminate knowledge products.

Month(s): *1 - 60*

Progress: Implemented first interation of searchable, comprehensive publication database of CENC and LIMBIC-CENC publications (publicationdatabase.limbic-cenc.org). Developed mock up for Prognostic Tool.

Major Task 5: Provide advanced biostatistical support to develop analysis plans, conduct analyses, and support manuscripts.

Month(s): 1 – 60

Progress: Completed analyses for 2 investigator-initiated projects. Actively conducting advanced analyses for 3 investigator-initiated projects. Awaiting datasets to conduct advanced analyses on 3 more requests. Initial development of the plan for phenotype analyses to present to the study PI and investigators.

Major Task 6: Share data with external investigators; Biannual submission to FITBIR (March and September).

Month(s): *6 – 60*

Progress: Attended biweekly meetings with FITBIR Ops. Completed in-person training with CDMRP and Neuroimaging Core. Set up FITBIR account access for LIMBIC-CENC Data and Biostatistics Core personnel for data submission and all Prospective Longitudinal Study site personnel for GUID creation. In June 2020, 92 Forms were resubmitted (i.e., CENC data up to December 2018) as a part of FITBIR study closeout for CENC and subsequently, CENC data up to December 2018 went live on July 1st 2020. In September 2020, 92 Forms were resubmitted (i.e., CENC data between Jan 2019 – Sep 2019) as part of FITBIR Study closeout and subsequently the data was approved to be shared in October 2020. In September 2020, 92 Forms were submitted encompassing data collected in the first 2 quarters of LIMBIC-CENC PLS (i.e., LIMBIC-CENC data between Oct 2019 – Mar 2020).

Major Task 7: Attendance at biannual GSC meetings.

Month(s): *4 – 60*

Progress: Attended and presented progress to GSC at both scheduled meetings.

Neuroimaging Core:

Major Task 1: Hire and maintain all research consortium staff.

Month(s): *1 - 60*

Progress: The relocation of both Drs. Wilde and Tate to the University of Utah and the Salt Lake City VA consolidated many of the personnel in the Neuroimaging Core under CENC. We have transitioned staff that were hired under CENC, including Dr. Hunsaker (quality control, imaging analysis, GitHub), Mr. Abildskov (data organization, quality control, FITBIR upload), and Ms. Velez (imaging analysis), who are now all based in the same lab in Salt Lake City. Additionally, we have hired and trained new staff members within the conjoint lab, including Dr. Lindsay (preparation of imaging data for approved requests), and Ms. Dimanche and Ms. Hovenden (data tracking, assist with clinical reads, data entry). We had a change in the MR physicist from Dr. Brian Taylor (left VCU in July 2020) to Dr. Robert Welsh (University of Utah), who is in the process of training, starting September 2020). All staff members have WOC appointments at the VA, and are current on all required CITI training for University of Utah, SLC VA, and Office of the Undersecretary of the Department of Defense. While some staff training is anticipated to continue throughout the project (as staff assume additional responsibilities or duties evolve), we have an effective and well-integrated team.

Major Task 2: IRB protocol development, submission, and continuing review. (Locally and in conjunction with Coordinating Center at VCU).

Month(s): *1 - 60*

Progress: We submitted a new IRB under LIMBIC to the University of Utah and George E. Wahlen VA and received formal determination from the IRB that activities conducted under the Neuroimaging Core were not considered human subjects research and did not require further oversight by the IRB (03 Dec 2019). The IRB for Neuroimaging Core-related work at Baylor College of Medicine and the Michael E. DeBakey VA was also resubmitted and approved. Since no continuing review is necessary, this is considered complete. We will continue to undergo annual RR&D committee approval at the VA.

Major Task 3: HRPO approval and continuing review.

Month(s): *1 – 60*

Progress: We notified the Coordinating Center at VCU on the day that we received IRB determination that the Neuroimaging Core activities did not constitute human subjects research. In the past, the CENC Neuroimaging Core activities were also determined by HRPO to not constitute human subjects research. Unfortunately, we assumed that this would continue under LIMBIC-CENC but after having found out that this was not the case for the Biomarker Core, we are now in the process of submitting this to HRPO for review.

Major Task 4: Oversee image acquisition for accuracy and consistency across sites through standardized protocols, MR and human phantom testing.

Month(s): *1 - 60*

Progress: During this reporting period, we completed initial (annual) site-specific training on imaging –related procedures for all sites that were previously involved in CENC as well as sites new to LIMBIC. Each training session focused upon review of highlights and new procedures from the revised Standard Operating Procedures manual as well as course correction notes for the site, review of parameter consistency, and review of phantom QA procedures. New quality assurance-related procedures include quarterly self-assessments performed by the sites (due January, April, July, and October) as well as semiannual assessments performed by the Core (due April and October). These assessments address adherence to established procedures and are detailed in the SOP. Phantom object (every two weeks) and human phantom (annual) testing will resume when COVID-19 restrictions are lifted and sites resume scanning participants. This is anticipated to be ongoing through the course of the project.

Major Task 5: Share data with external investigators; Biannual submission to FITBIR (March and September).

Month(s): *6 - 60*

Progress: During this reporting period, we recruited Dr. Hannah Lindsay to assist in

pulling/distributing data for approved data requests from investigators within and outside the consortium as well as creating custom composites and analyses, as needed. We have also established a GitHub repository for all imaging data. GitHub is a well-known and widely-used platform in the imaging communand development, which allows for collaborative work (particularly important in this social distancing era). Most importantly, GitHub allows for detailed documentation of version and enhanced communication (we can track who made changes and when changes occur every time a change is made). We have assisted in providing imaging data for 8 data requests during this reporting period (Richardson/Garcia, Newsome, Tate/Wade, Dennis, Levin, Fino, Kenney, and Hodges).

We have also completed scheduled data uploads of the raw imaging data to FITBIR (most recent was October 2020). We also assist in the data entry and review for the results of the imaging Common Data Elements based on the clinical reviews by the neuroradiologists. We meet weekly with the Data Core, and participate in other subgroup calls, as needed.

We are preparing to submit previously collected imaging data for non-Prospective Longitudinal Study studies but that would be very beneficial to the current project since it was collected at sites that have since been incorporated into the PLS. This is anticipate to be complete by April 2021.

Major Task 6: Review MRI sequence parameters adherence and bi-monthly testing with research phantoms. Annual and pre-/postupgrade human phantom testing.

Month(s): *1 - 60*

Progress: From the period between October 2019 and March 2020, the Neuroimaging Core was actively reviewing the phantom data that was collected from sites that were actively enrolling. We will resume phantom data review at all sites as they are cleared to resume scanning and when COVID restrictions are lifted. Annual human phantom data collection will resume once COVID-19 –related restrictions are lifted. This is anticipated to be an ongoing activity throughout the course of the project.

Major Task 7: Perform qualitative and quantitative QA review of imaging data.

Month(s): *1 - 60*

Progress: We perform visual (qualitative) inspection of data to assess data quality at a preliminary review level. However, we have also instituted quantitative QA procedures that assess metrics such as motion, signal to noise, contrast to noise, etc. These parameters are assessed in a 7-page report that is generated for each scan. This is anticipated to be an ongoing activity throughout the course of the project.

Major Task 8: Review quantitative testing for T1-weighted, diffusion, and functional connectivity QA, and qualitative data.

Month(s): *1 - 60*

Progress: In addition to reports that are generated for each participant/scan, we have created a system to compile aggregate group reports which graph the data distribution in violin plots, both for each site and the data as a whole; this enables identification of outliers and provides a snapshot of the data quality overall. To date, data quality has generally been good. This is anticipated to be an ongoing activity throughout the course of the project.

Major Task 9: Review imaging data for clinical and incidental findings, and code imaging data according to the Inter-agency CDE for Imaging.

Month(s): *1 – 60*

Progress: Because coding provides context for future data collection on subjects that are followed over time, we have also reviewed the consolidation of the CDE data transferred from the older CENC system into the newer one which will be used in LIMBIC and reconciling and monitoring CDE codings in this review period. Reading of scans collected during January 2019-September 2019 was initially prioritized, and we have been working on completion of reads for outstanding scans acquired 2013-2018 and post September 2019. For scans collected 2013-2018, we have been working with the Data Core as well as individual sites to verify that data was/was not collected. We noted that some of the previously completed forms were missing fields, so we have been reviewing all data and adding

new information, as required. We have completed initial training with Dr. Robert Shih (Walter Reed) who will be performing additional CDE codings in addition to Drs. Gerry York, Aaron Betts, and Tim Duncan).

Major Task 10: Ongoing review and CDE coding of newly acquired conventional sequence data by neuroradiologists.

Month(s): *1 - 60*

Progress: See above description under item 9.

Major Task 11: Pre-process and analyze volumetric, diffusion, perfusion, and functional connectivity data, using pipelines for longitudinal analysis.

Month(s): *1 - 60*

Progress: The preprocessing of imaging data maintained by the Neuroimaging Core is largely up-to-date for the standard analysis pipelines (including recent versions of FreeSurfer (v7.1) and ENIGMA diffusion processing which were released during this review period); we have also instituted some additional longitudinal pipelines, which are in process. This is anticipated to be an ongoing activity throughout the course of the project.

Major Task 12: Quarterly update of analyzed, summary imaging data provided to Data Core.

Month(s): *3 - 60*

Progress: The analyzed summary data are available on our GitHub repository site to maintain version control and documentation of changes. The Neuroimaging Core presents weekly reports to the Data Core regarding CDE coding completion. This is anticipated to be an ongoing activity throughout the course of the project.

Major Task 13: With other Prospective Longitudinal Study investigators, examine imaging data in relation to demographic, injury, and biomarker data.

Month(s): *1 - 60*

Progress: Drs. Wilde and Tate and Mr. Abildskov have been attending regularly scheduled teleconference meetings with the FITBIR and Data Core teams.

We are in the process of assisting in the analysis of an approved request by Kimbra Kenney related to the relation between biomarker and imaging data.

We have continued to work with other investigators with outstanding analysis requests to facilitate access to data and to assist in analysis and data dissemination including, but not limited to, 1) Drs. Stone, Tustison and Avants, 2) Dr. Mary Newsome, 3) Dr. Cooper Hodges, 4) Drs. Risa Richardson and Amanda Garcia, 5) Dr. Harvey Levin, 6) Dr. Emily Dennis, 7) Dr. David Tate, 8) Dr. Ben Wade, 9) Drs. Kenney/Werner/Gill.

We have submitted a manuscript on the relation between hippocampal and amygdala subfields and symptoms of PTSD and mood disorders (lead author: Benjamin Wade) and are in the process of preparing drafts for 4-5 others.

Members of the Imaging Core have also participated in manuscripts associated with the larger consortium (lead authors: Amanda Garcia, Maya O'Neill)

Major Task 14: Organize, transfer, archive, and securely store neuroimaging data.

Month(s): *1 - 60*

Progress: We have updated and reconfigured hardware for the imaging databases to increase storage capacity and enhance security, and enabled accounts for investigators and staff with a need to upload or download data [complete November 2020]. We have also reconfigured the Core-specific PACS system that uses dicom formatted data for the neuroradiologists' clinical coding [complete November 2020]. We have updated software to ensure use of the most current versions of the primary analysis pipelines (FreeSurfer, ENIGMA) which have been released during this review period [June 2020). Additionally, we have reformatted all raw imaging data in BIDS format to enhance consistency not only within the consortium but also as we prepare to shre data with investigators outside the

consortium. We renamed all CENC raw data (millions of files) to assure continued consistency with LIMBIC and all other clinical and outcome data [complete July 2020]. Finally, we have performed an intensive audit to cross check consistency between the data available on the Imaging Core Server, the PACS system, and the Medidata database [initial audit complete April 2020, but this is anticipated to be an ongoing activity throughout the course of the project].

Major Task 15: Attendance at biannual GSC meetings.

Month(s): *6 - 60*

Progress: Dr. Wilde attended and presented at the GSC meeting scheduled during this review period (February).

Biomarkers Core:

Major Task 1: Maintain consistent infrastructure, management, and centralized resources for longitudinal collection and curation of bio specimen.

Month(s): *1 - 60*

Progress: The Biorepository director and staff remain consistent. Continued to receive and distribute samples. Renewed Contract with CLIA-certified lab (Quest) for NED screen (IGF-1, testosterone, TSH). Addition of 3 new sites from where blood samples will be shipped VA San Diego Health Care System, San Diego, CA, Salisbury VA Health Care System, Salisbury, NC, and Eisenhower Army Medical Center, Fort Gordon, GA.

As of 31 AUG 2020, BR has collated/stored processed/aliquoted biospecimens (DNA/buffy coat, plasma, serum, saliva, RNA (PaxGene) from 1,494 Study 1 (423 F/U) subjects, as well as samples from 143 Study 49 (2005 aliquots) & 20 Study 20 subjects (300 aliquots) for current total 28,815 aliquots of in the biorepository available for analysis.

Received 7 shipments from LIMBIC sites from 2/1/2020 thru 9/20/2020.

Major Task 2: IRB protocol development, submission, and continuing review. (Locally and in conjunction with Coordinating Center at VCU).

Month(s): *1 - 60*

Progress: Local regulatory approvals complete. HRPO approval pending. Our continuing review was approved by USUHS IRB, 3-30-2020. A mod was approved by IRB to change the number of specimens to be collected from 2,500 and 2,000 to 3,500 and 3,000 respectively to include those specimens to be collected from the new sites and change PI from Cox to Werner on 12-9-2019.

Major Task 3: HRPO approval and continuing review.

Month(s): *1 - 60*

Progress: See answer above in Major Task #2.

Major Task 4: Share data with external investigators; Biannual submission to FITBIR (March and September).

Month(s): *6 - 60*

Progress: NED and APOE data entered into FITBIR in March and September by the VCU LIMBIC informatics data managers.

Major Task 5: Carry out genotyping assays of common genetic variants associated with the chronic effects of neurotrauma.

Month(s): *1 - 60*

Progress: No genotyping carried out because no new enrollments in LIMBIC prospective study in Year 1.

Major Task 6: Carry out service operations (limited genotyping and neuroendocrine screen through CLIA-certified lab).

Month(s): *1 - 60*

Progress: No NED screening through Quest was conducted because no new enrollments in LIMBIC prospective study in Year 1. However, we are collaborating with Dr. Bill Walker for evaluation of NED screen in Longitudinal sample

Major Task 7: Manage biospecimen sharing with CENC and external investigators.

Month(s): *1 - 60*

Progress: MTA for Research committee approved and signed (collaborative project submitted by Roskamp Institute, Fiona Crawford and colleagues) for lipidomic analysis of samples studied with proteomic analysis by CENC biomarker discovery project. March 2020. COVID restrictions just lifted and samples shipped June 29 and received by Roskamp Inst. on June 30.

MTA for project with Dr. Nakase-Richardson, and her team at the Tampa VA in process.

Major Task 8: Provide biospecimens for approved LIMBIC biomarker projects.

Month(s): *1 - 60*

Progress: Samples shared with Roskamp Institute, Fiona Crawford for lipidomic analysis (in process)

Major Task 9: Attendance at biannual GSC meetings.

Month(s): *6 - 60*

Progress: Dr. Kenney attended and presented at the GSC meeting scheduled during this period of performance (February).

Studies

Prospective Longitudinal Study:

Major Task 1: Hire and maintain all research consortium staff.

Month(s): *1 - 60*

Progress: 100% met; ongoing to maintain. New PLS all sites biweekly virtual meeting format deployed that combines operational issues and scientific presentations/discussions

Major Task 2: IRB protocol development, submission, and continuing review.

Month(s): *1 - 60*

Progress: 100% met; ongoing to maintain. New PLS assessments deployed (Clinical Dementia Rating, Repetitive low level blast exposure questionnaire, COVID-19 impact questionnaire).

Major Task 3:HRPO approval and continuing review.

Month(s): *1 - 60*

Progress: 91% met; we are still working on getting HRPO approval for our Fort Gordon site. HRPO sent our first request back with a couple recommended changes to the ICF. Changes were made and it is now back at the Walter Reed IRB. Upon IRB approval, we will forward it back to HRPO for final approval.

Major Task 4: Onboard 3 new recruitment sites.

Month(s): *1 - 4*

Progress: 100% met; New QA/QC procedures developed and deployed; Trainings and re-trainings conducted across all sites.

Major Task 5: Conduct follow-up Assessments to include phone assessments.

Month(s): *1 - 60*

Progress: 100% met for all willing participants.

- New comprehensive and annual phone follow-up assessments completed from Oct 01, 2019 to Aug 31, 2020 was 205 and 726 respectively for a completion rates of 78% and 72.7%
- BTACT assessment completed from Oct 01, 2019 to Aug 31, 2020 was 183 for a completion

rates of 85.1%.

Major Task 6: Report descriptive data.

Month(s): *1 - 60*

Progress: 100% met; ongoing to maintain.

Major Task 7: Acquire, safely store and analyze eye tracking data.

Month(s): *1 - 60*

Progress: 100% met for willing participants prior to in-person research being shut down for COVID. Once the restriction is lifted, we will continue on an ongoing basis.

Major Task 8: Acquire, safely store and analyze Balance Master data.

Month(s): *1 - 60*

Progress: 100% met for willing participants at sites with testing capability prior to in-person research being shut down for COVID; ongoing to maintain.

Major Task 9: Acquire, safely store and analyze hearing test data.

Month(s): *1 – 60*

Progress: 100% met for willing participants prior to in-person research being shut down for COVID; ongoing to maintain.

Major Task 10: Administer and interpret neuropsychological data.

Month(s): *1 - 60*

Progress: 100% met for willing participants; ongoing to maintain. New data capture system developed and deployed;

Major Task 11: Acquire, safely store and analyze biospecimens.

Month(s): *1 – 60*

Progress: 100% met for willing participants prior to in-person research being shut down for COVID; ongoing to maintain.

Major Task 12: Acquire, safely store and analyze imaging data.

Month(s): *1 – 60*

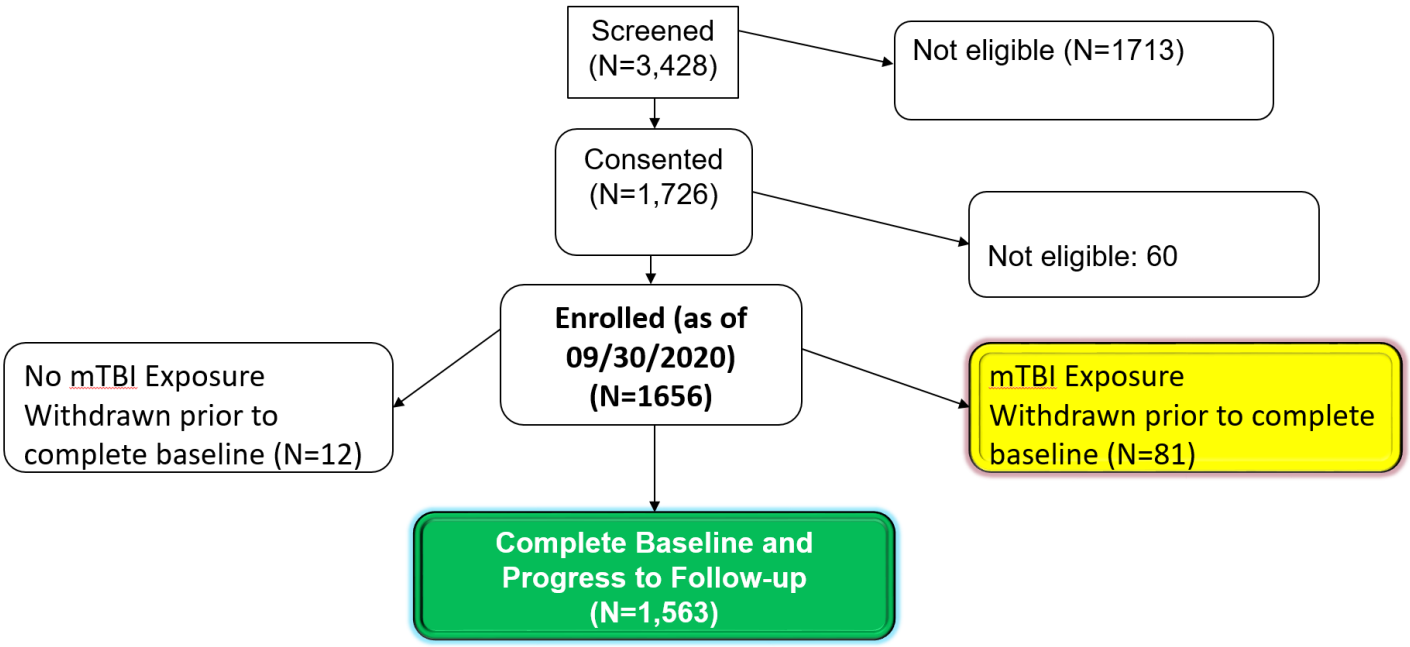
Progress: 100% met for willing participants prior to in-person research being shut down for COVID; ongoing to maintain.

Major Task 13: Recruit study total of not less than 3000 subjects.

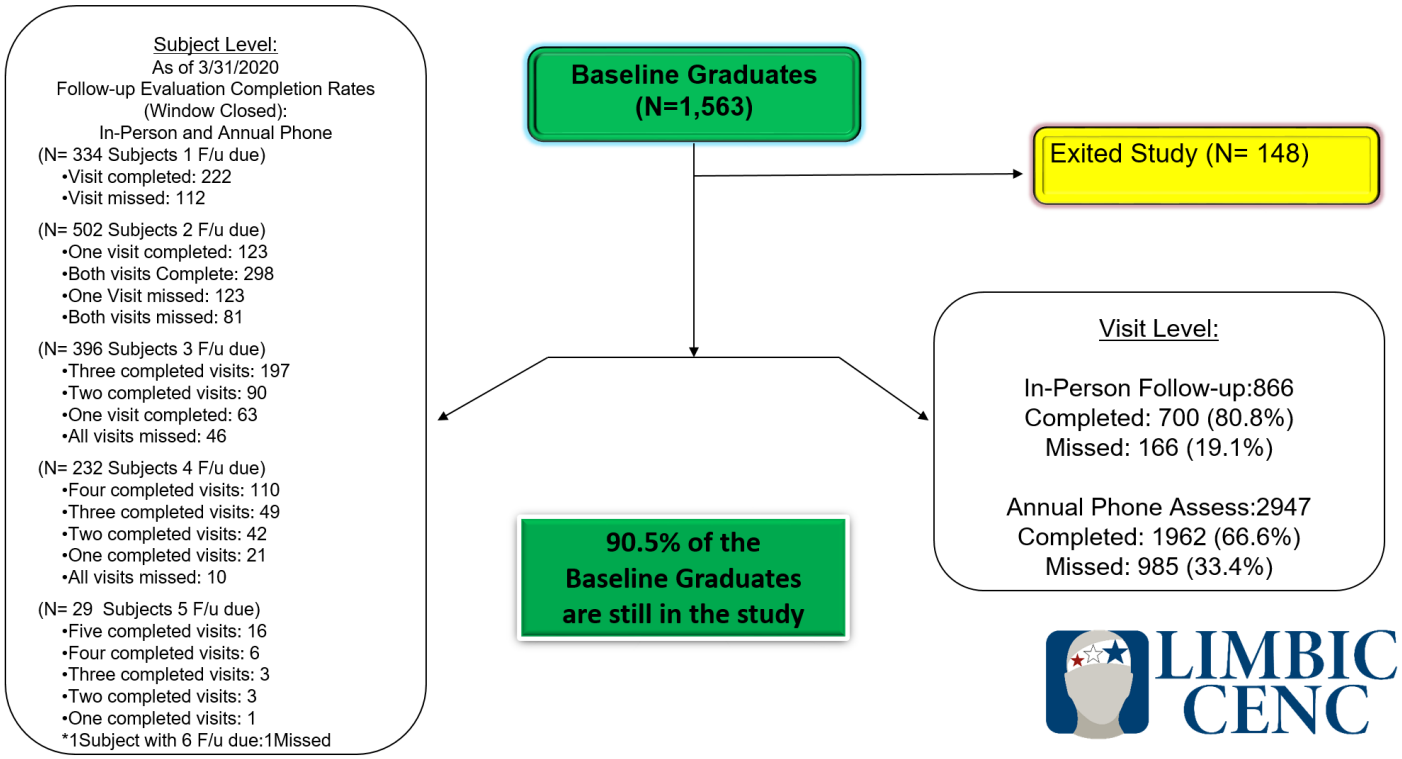
Month(s): *1 - 60*

Progress: Ongoing. Through the course of the study (from CENC to LIMBIC-CENC), a cumulative total of 700 comprehensive and 1962 annual follow-up assessments have been completed for overall rates of 80.8% for comprehensive and 66.6% for annual telephonic. The two tables below better illustrate participant numbers for the duration of both CENC and LIMBIC-CENC:

Study Consort Diagram for Initial Evaluations



Study Consort Diagram for Longitudinal Evaluations



LIMBIC CENC

Major Task 14: Develop site-wide recruitment and retention plan.

Month(s): *1 - 60*

Progress: 100% met; See more details about the recruitment plan and changes made due to COVID in the Coordinating Center section.

Major Task 15: Implement recruitment and retention plan.

Month(s): *1 – 60*

Progress: 100% met; See more details about the recruitment plan and changes made due to COVID in

the Coordinating Center section.

Major Task 16: Analysis & Publication of Cross-sectional Data.

Month(s): *12 - 60*

Progress: Ahead of schedule. We established collaborations with multiple external groups and consortia.

- Seattle VAMC and University of Washington TBI: planning for joint TBI fellowship linked to LIMBIC with a goal of RR&D CRA.
- NCAA-DoD Concussion Assessment, Research and Education (CARE) Consortium: Dialogue underway for collaboration opportunities. Tentatively planning a comparison analysis of study participant characteristics and overlapping variables and outcome measures.
- Football Players Health Study (FPHS), Harvard, R. Zafonte; Status: ongoing discussions for shared interests and specific combined analysis and RFA opportunities
- VA Cooperative Studies Program; Growth Hormone Stimulation in mTBI RCT
- Invisible Wound Clinic. to provide a whole-health, integrative wellness program for Service Members with persistent difficulties after mTBI (and more). Status: discussion underway for program development and integration across VA-DoD.
- Million Veterans Program (MVP). Status: ongoing discussions for shared interests and specific combined analysis and RFA opportunities.
- Biogen. Alzheimer's Disease Therapeutic Trials. Status: ongoing discussions for shared interests and clinical trial opportunities.
- University of Virginia, Network of 18 NCAA Athletic & ROTC programs, Perspecta. Dr. Jacob Resch. DHA MTEC Warfighter Brain Health RFA. Standardizing Management of Acute and Repeated mild Traumatic Brain injuries using Artificial Intelligence solutions (SMART BRAINS). Status: full application pending.
- DVBIC. Characteristics Comparison Analysis & ongoing collaboration. Status: Data-sets released; analysis ongoing.
- DVBIC-IMAP. Direct Involvement by Dr. Walker and others in LIMBIC.
- NIDILRR TBI-MS. Direct Involvement by Dr. Cifu, Dr. Walker, and others in LIMBIC.
- Seattle VAMC and University of Washington TBI: planning for joint TBI fellowship linked to LIMBIC with a goal of RR&D CRA.
- "VA Cooperative Studies Program; Growth Hormone Stimulation in mTBI RCT. Ricardo E. Jorge MD. Michael E DeBakey VA Medical Center. Status: scored in fundable range; awaiting final approval. "

We collaborated on multiple derivitative studies with external funding approved or submitted for:

- Abdullah, L (Tampa VAMC). *Identifying APOE Related Lipid Biomarkers for Diagnosing Chronic Neurocognitive Deficits in TBI Patients*. Funding: VA RR&D. Status: Funding approved. Key collaborator(s): Roskamp Institute.
- Walker, WC. *Optimizing Heart Rate Variability (HRV) to Improve Sleep and Performance after Concussion in Combat Veterans in a Chronic Effects of Neurotrauma Consortium Cohort*. Submitted for CDMRP CTA funding. Funding status: Chosen for alternate; notified no funding available. Key collaborator(s): Columbia, SC VAMC and Univ of South Carolina.
- Carlson, K (Portland VAMC). *Effects of Opioid and Other Psychotropic Drug Exposures on Long-term Outcomes of TBI: Developing Measurement Best Practices.* VA R&D, SPiRE. Funding status: approved.
- Pugh, MJ. *The Epidemiology of Epilepsy and Traumatic Brain Injury: Severity, Mechanism, and Outcomes".* Funding awarded. Dept. of Defense, Epilepsy Research Program, Idea Development Award.
- Agyemang, A (Richmond VAMC). *The mediational role of sleep quality in the relationship between chronic mTBI and cognitive functioning.* Funding awarded. NIH Diversity Supplement grant.
- Roskamp Institute. Biospecimen request analysis [defer to Dr. Kenney's Biomarker Core section of report].
- Dr. Randel Swanson. Corporal Michael J. Crescenz VA. VA R&D Career Developlment Award. Relationship between Diet, Nutrition and mTBI outcomes in LIMBIC-CENC PLS. Status: ongoing

discussions for shared interests and specific secondary analyses in PLS, and preparing CDA application.

- Dr. Christina Sheerin, VCU. K01 Award Supplement. Will examine the impact of the COVID-19 pandemic on alcohol phenotypes (e.g., consumption, binge drinking, problems, AUD symptoms) in LIMBIC-CENC PLS. Status: funded.
- Dr. Jacob Resch. University of Virginia. Commonwealth Health Research Board grants program; Pituitary dysfunction after repetitive mTBI. Status: Pre-proposal submitted.
- Maya O'Neil PI. Portland VAMC. CDMRP W81XWH-19-PHTBIRP-FITBIRA. FITBIR: Accelerating Synthesis of TBI Research Using Novel Methods" (FAST RUN Methods). Status: funded.
- Maya Troyanskaya, Houston VAMC. VA R&D SPiRE. Mild Traumatic Brain Injury and Moral Injury in Combat Veterans; will assess Personality Traits and Brain Matter Aberrations as potential markers for mTBI and PTSD in CENC Study 1 cohort. Status: revision application submitted.

The following analytic projects were presented on the biweekly LIMBIC-CENC PLS All-Sites audiovisiual meeting/conferences:

- 5/4/2020 = McDonald and Oneil. Mild TBI and PTSD among Combat-Exposed Military Personnel are Associated with Neurobehavioral Quality of Life.
- 5/4/2020 = V. Guedes. Exosomal MiRNAs and Proteins are Linked to Chronic PTSD Symptoms in SMs and Veterans with mild TBI.
- 6/1/2020 = A. Garcia. CENC OSA risk.
- 6/15/2020 = T. Pogoda and K.Carlson. Causal Analysis of Employment Status in Post-9/11 combat Veterans with or without mild TBI.
- 6/29/2020 = B.Wade. Dissociating Contributions of PTSD & Depression Symptoms to Hippocampal & Amgydala Subregional Volumes.
- 7/13/2020 = C. Dismuke. A Prediction Model of Military Combat and Training Exposures on VA Service Connected Disability: A CENC Study
- 8/10/2020 = D. Tate. Predicting TBI exposure history using biomarker and neuroimaging variables: A CENC Study.
- 8/24/2020 = L. Franke. The role of psychological distress and sensory loss in auditory event-related potentials after mTBI.
- 9/21/2020 = S. Martindale. Influence of blast exposure on cognitive functioning in combat veterans.

Major Task 17: Analysis & Publication of Longitudinal Data.

Month(s): *24 - 60*

Progress: Ahead of schedule. Preparation & pilot work underway. See below sections and appendices for details: With regard to progress on specific analyses, publications, and scientific meeting presentations, please refer to PLS Appendix #1 LIMBIC-CENC PLS analysis and dissemination tracker, as well as the LIMBIC-CENC Publication Database and Current LIMBIC-CENC Tracking Excel spreadsheets in the Appendix. To summarize, we finished analysis and dissemination of some data collected under CENC and began multiple scientific analyses (see appendices for details). Dissemination efforts included scientific meeting presentations, peer-reviewed journal publications, developing and cataloguing Key Points summary of each publication and national webinars and other presentations as well as working closely with the LIMBIC-CENC knowledge translation (KT) center on the website and other KT products.

Retrospective Database Study:

Major Task 1: Investigators already have access to databases to be accessed. They will annually renew IRB/VA data access approvals.

Month(s): *1 - 60*

Progress: We submitted and received all the required regulatory approvals. The LIMBIC Epidemiology Study was approved through UCSF IRB on 25-OCT-2019, the SF VA Medical Center on 8-NOV-2019 and approved through HRPO on 31-DEC-2019.

Major Task 2: Annually update database; merge with DOD data; perform quality checks and continue maintenance throughout study.

Month(s): *1 - 60*

Progress: We updated our database, which was a monumental task. We first requested, downloaded, and cleaned data for all TBI cases FY2016-2019. We then requested, downloaded, and cleaned data for the updated 2% random sample of Veterans. All the new data was merged with the old data, requiring extensive processing time due to the size of the database, compounded by difficulty working remotely due to Covid. We added medication data for all 2.2 million Veterans, for use in defining outcomes, comorbidities, and examining treatment.

Major Task 3: Create, define, and refine variables (i.e, TBI).

Month(s): *1 - 12*

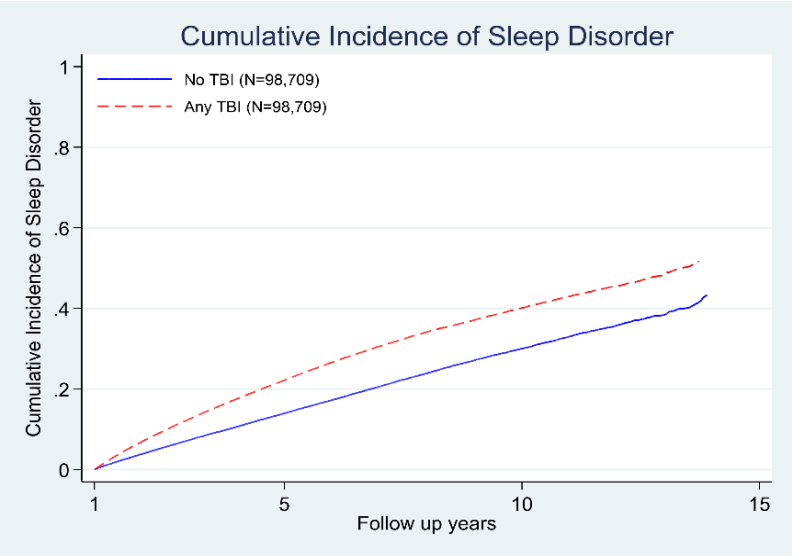
Progress: All diagnosis codes were updated with ICD-10 codes (TBI, dementia, comorbidities, etc.) in addition to ICD-9 codes. For TBI alone, there are over 450 ICD-10 codes, so this was an extremely time-consuming task.

Milestone: Data repository ready for analysis: The updated database, consisting of 2.2 million Veterans, including 426,643 with TBI, was completed in September of 2020.

Major Task 4: Analyze data assessing mental health comorbidities in association between TBI and late effects (i.e., dementia).

Month(s): *1 – 24*

Progress: We recently investigated the association between TBI and incident sleep disorders in veterans. Development of sleep disorders was defined as any inpatient or outpatient diagnosis of sleep apnea, hypersomnia, insomnia or sleep-related movement disorders based on ICD-9 codes. The study included 182,247 veterans with TBI and 182,247 age-matched veterans without TBI (aged 48.6±19.8y). Individuals with prevalent sleep disorders at baseline were excluded, and all had at least one year of follow-up data. Veterans with TBI were 41% more likely to develop any sleep disorder, adjusting for demographics and medical and psychiatric conditions: HR=1.41 (1.37-1.44). Veterans with TBI were more likely to develop sleep apnea [HR=1.28 (1.24-1.32)], insomnia [HR=1.50 (1.45-1.55)], hypersomnia [HR=1.50 (1.39-1.61)], and sleep-related movement disorders [HR=1.33 (1.16-1.52)]. Our study is the first to show a longitudinal association between TBI and risk of sleep disorders in Veterans. Additional research is needed to determine potential underlying mechanisms. Early identification and prevention strategies for sleep disorders are needed to improve quality of life and long-term outcomes in TBI patients.



We instituted regular working group meetings for in-process analyses. We are currently in the early stages of an analysis examining if cardiovascular factors increase risk of dementia after TBI.

Major Task 5: Collaborate with Dr. Dismuke on analyses to examine health care utilization and costs of mental and physical health comorbidities after mTBI.

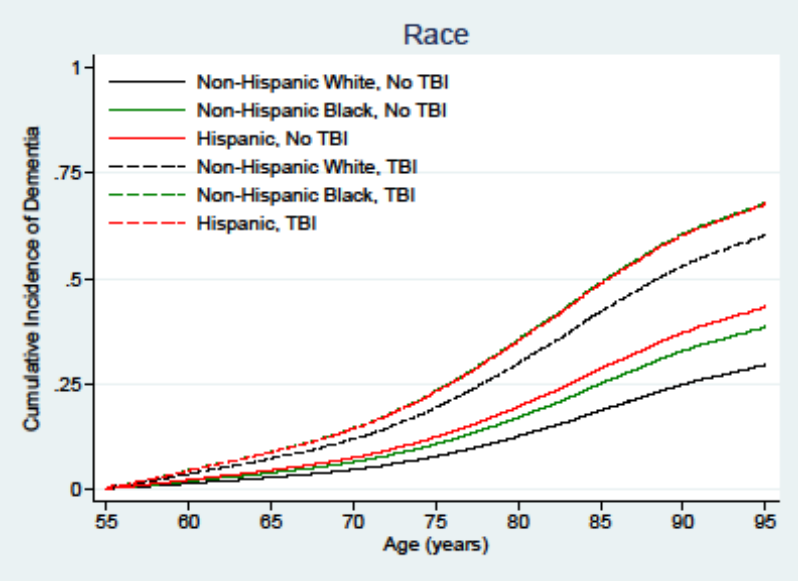
Month(s): *12 - 24*

Progress: None yet as we will start working on this task this coming FY.

Major Task 6: Analyze data assessing the role of race/ethnicity, gender, and socioeconomic status on the association between mTBI and risk of neurodegeneration (i.e., dementia).

Month(s): *24 – 36*

Progress: During the database updating, we utilized our previous database to investigate incident dementia in older veterans with TBI exposure by race and sex. Using a sample of nearly 1 million veterans with data from 2000-2015, we excluded all people with prevalent dementia. Both Male and Female veterans had more than 2X increased risk of dementia after TBI [Males HR=2.60 (2.54-2.66); Females HR=2.36 (2.08-2.69)]. There was a significant interaction effect between sex and TBI (p=0.02), however, the magnitude of differences was small and likely not clinically significant. Compared to those without TBI, Hispanic Veterans with TBI were almost two times more likely (HR: 1.74, 95% CI: 1.51-2.01), Black Veterans with TBI were over two times more likely (HR=2.15, 95% CI: 2.02-2.30), and White Veterans with TBI were nearly three times more likely to develop dementia (HR=2.71, 95% CI: 2.64-2.77). A significant interaction between TBI and race for developing dementia was observed (p<0.001). Several studies in other cohorts are looking at race differences in dementia after TBI and are finding similar results to ours. The racial differences may be due to differences in dementia risk, dementia diagnosis rates, or potentially an interaction between race, APOE, and neurotrauma. Racial differences are a novel and important finding that deserve future study. The manuscript detailing these exciting results was just published in Neurology.



Milestone: *Data analysis completed and manuscripts prepared for journal submission:* We have one manuscript published and another under review.

Major Task 7: Analyze data on the characteristics and longitudinal course of veterans with early-onset dementia after mTBI.

Month(s): *24 - 48*

Progress: We instituted regular working group meetings for in-process analyses. We are currently in the early stages of an analysis looking at risk and resilience for dementia after TBI.

Major Task 8: Examine (with Dr. Dismuke) health care utilization and costs of TBI-associated dementia vs all-cause dementia.

Month(s): *36 - 60*
Progress: None yet as this will occur during year 4.

Major Task 9: Prepare manuscripts for journal publication.
Month(s): *24 - 60*
Progress: None yet as this will occur during year 3.
Milestone: Data analysis completed and manuscripts prepared for journal submission.

Major Task 10: Develop prognostic models to better determine risk of dementia and mortality and associations with potential risk factors in veterans with mTBI.
Month(s): *24 – 48*
Progress: None yet as this will occur during year 3.

Major Task 11: Create and validate prognostication clinical tool.
Month(s): *36 - 60*
Progress: *None yet as this will occur during year 4.*

Major Task 12: Prepare manuscripts on prognostic models.
Month(s): *48 - 60*
Progress: None yet as this will occur during year 5.
Milestone: Data analysis completed, manuscripts prepared for journal submission, and clinical modeling tool ready for use.

Major Task 13: Attendance at biannual GSC meetings.
Month(s): *6 - 60*
Progress: We presented updates on our work at the February 2020. The feedback we received was informative and thoughtful.

Phenotype Study:
Major Task 1: Investigators already have access to relevant databases. Update data repository annually with latest VA data and merge with relevant DOD datasets and add additional DoD data to enhance acute TBI identification. Once assembled, perform quality checks and continue maintenance throughout study.
Month(s): *1 - 12*
Progress:
Regulatory approvals are complete as of June 2020.
We have completed compilation of VA data for the cohort and have linked DoD data for those individuals who are in VA care. We are working with the DaVINCI staff to obtain data for individuals who receive DoD care but do not matriculate to VA due to remaining on active duty, or choice of not entering VA care.
We have submitted an amendment to add the TBI Module that is available from the Joint Trauma System in addition to the DoD trauma registry. We will submit the DSAA for both data sources once the amendment is approved.

Major Task 2: Using merged DoD-VA datasets, conduct phenotype analysis by deployment strata to examine the role of mTBI in emergence of neurodegenerative disease, psychological health status, neurosensory deficits and pain over time.
Month(s): *1 - 36*
Progress:
We have identified comorbidities of interest in VA and DoD data for this cohort.
We have purchased servers that will be added to VA network as regulatory requirements are addressed.

Our preliminary data (not finalized) includes only individuals who entered VA care by the end of 2014. We linked VA and DoD data and identified demographic and DoD diagnosed health status characteristics, and compared proportions between deployed and non-deployed groups using the chi square statistic. Table 1 shows the demographic characteristics of the deployed and non-deployed cohorts.

Table 1: Demographic Characteristics of Deployed and Non-deployed Post-9/11 Veterans (entering VA care 2002-2014)

No. (%)	**Non-Deployed N=386,082**	**Deployed N=859,566**
DEMOGRAPHICS		
Age (Mean [SD]) at VA entry**)**		
17-29	46.70 (175,634)	55.08 (478,991)
30-39	21.43 (80,610)	23.83 (207,193)
40-49	23.79 (89,471)	16.83 (146,322)
50 and older	8.07 (30,367)	4.26 (37,060)
Sex: Female	26.56 (99,894)	12.90 (112,155)*
Race/Ethnicity		
White	54.73 (205,814)	62.04 (539,506)
Black	21.41 (80,532)	16.77 (145,823)
Hispanic	8.22 (30,909)	10.61 (92,250)
Asian	2.44 (9,174)	2.37 (20,637)
Native American/Pacific Islander	1.69 (6,356)	1.85 (16,106)
Unknown	11.51 (43,297)	6.35 (55,244)
Marital Status upon discharge		
Married	49.22 (185,124)	48.73 (423,774)

Chi square analyses found that those who were deployed were younger, less likely to be female, and more likely to be White non-Hispanic and Hispanic ($p<.0001$).

Table 2 shows descriptive statistics for injury data by deployment status. Those deployed were significantly more likely to have TBI, including all levels of severity ($p<.0001$) and spinal injury ($p<.0001$). Those who were non-deployed were significantly more likely to have a documented burn injury ($p<.001$), however burn severity was not identified in this analysis. While those who were deployed were significantly more likely to have amputation ($p<.01$), this small difference is due to the extremely large cohort. Future descriptions are restricted to those differences that are more clinically meaningful and $p<.0001$.

Table 2: DoD Injury Characteristics of Deployed and Non-deployed Post-9/11 Veterans (entering VA care 2002-2014)

	Non-Deployed N=386,082 % (n)	**Deployed N=859,566 % (n)**
TBI Severity		
Screen Positive no other Evidence (based on VA screening data)	1.08 (4,058)	7.26(63,102)
Mild	2.43 (9,122)	13.36 (11,6215)
Moderate/Severe	0.96 (3,607)	3.10 (26,980)
Penetrating	0.10 (369)	0.33 (2,897)
History of Code/Unclassified	2.04 (7,658)	3.98 (34,591)
No Evidence of TBI	93.40 (351,268)	71.96 (625,781)
Other Injury		
Burn Injury	8.20 (30,844)	7.50 (65,238)
Amputation Injury	0.69 (2,601)	0.73 (6,378)
Spinal Injury	2.41 (9,068)	7.63 (66,356)

Table 3 shows the proportion of deployed and non-deployed service members with diagnoses of neurosensory and pain-related conditions. Those who were deployed were significantly more likely to have blurred vision/photophobia, tinnitus, and hearing loss than non-deployed personnel ($p<.0001$). Regarding pain, deployed service members were more likely to have diagnoses of backpain and headache, while non-deployed personnel were more likely to have diagnoses of other musculoskeletal pain ($p<.0001$).

Table 3: DoD Diagnoses of Neurosensory and Pain Conditions in Deployed and Non-deployed Post-9/11 Veterans (entering VA care 2002-2014)

	Non-Deployed N=386,082 % (n)	**Deployed N=859,566 % (n)**
Neurosensory Disorders		
Blurred Vision/Photophobia	1.23 (4,632)	1.41 (12,265)
Blindness	0.74 (2,784)	0.73 (6,391)
Vestibular Dizziness	3.28 (12,342)	3.17 (27,579)
Tinnitus	5.80 (21,818)	9.79 (85,159)
Balance Problems	1.39 (5,231)	1.07 (9,339)
Hearing Loss	10.66 (40,078)	12.70 (110,398)
Pain		
Back Pain	42.44 (159,617)	45.83 (398,538)
Neck Pain	14.48 (54,438)	14.00 (121,721)
Other Musculoskeletal Pain	29.64 (111,486)	25.45 (221,286)
Headache	19.69 (74,046)	22.17 (192,806)

Table 4 shows proportions of deployed and non-deployed individuals who had diagnoses of specific mental health and substance use disorder diagnoses while in DoD care. Deployed personnel were profoundly more likely to have diagnoses of PTSD ($p<.0001$) and significantly more likely to have diagnoses of depression,

anxiety, suicidal ideation/attempt, and overdose than non-deployed service members (p<.0001). Non-deployed personnel were significantly more likely than deployed personnel to have diagnoses of bipolar disorder and schizophrenia (p<.0001). Deployed service members were also more likely to have any substance use disorder and a number of different types of substance use disorders (p<.0001). Of particular interest are alcohol use, amphetamine, cocaine, opioid and cannabis use.

Table 4: DoD Diagnoses of Mental Health and Substance Use Disorders in Deployed and Non-deployed Post-9/11 Veterans (entering VA care 2002-2014)

	Non-Deployed N=386,082 % (n)	**Deployed N=859,566 % (n)**
Mental Health		
Depression	34.10 (128,257)	38.07 (331,042)
PTSD	17.24 (64,830)	43.78 (380,737)
Anxiety	26.18 (98,452)	28.54 (248,177)
Bipolar Disorder	11.19 (42,074)	9.64 (83,843)
Schizophrenia	1.56 (5,881)	0.84 (7,344)
Suicidal Ideation/Attempt	5.54 (20,818)	6.47 (56,280)
Any Overdose	3.27 (12,305)	3.72 (32,326)
Substance Use Disorders		
Any Drug/Alcohol Abuse	19.37 (72,861)	27.33 (23,7647)
Alcohol Abuse	14.46 (54,383)	22.82 (198,472)
Amphetamine Abuse	1.82 (6,830)	2.10 (18,252)
Cannabis Abuse	6.28 (23,623)	8.06 (70,093)
Cocaine Abuse	2.27 (8,544)	2.65 (23,053)
Opioid Abuse	3.27 (12,314)	3.48 (30,234)
Sedative Abuse	1.10 (4,120)	1.16 (10,051)
Hallucinogen Abuse	0.25 (925)	0.25 (2,167)
Other Drug Abuse	5.54 (20,847)	6.85 (59,528)

Table 5 shows comparisons of deployed and non-deployed personnel on sleep and central nervous system disorders. Deployed personnel had significantly higher rates of hypersomnia, insomnia, and obstructive sleep apnea. There were also more likely than non-deployed personnel to have diagnoses consistent with any cognitive dysfunction which includes diagnoses of memory loss, mild cognitive impairment and diagnoses included in VA's dementia diagnoses (p<.0001); most diagnoses were for "memory loss". Non-deployed personnel were significantly more likely to have higher prevalence of pituitary disorders, stroke, and epilepsy/seizures (p<.0001). These data also suggest certain individuals have multiple substance use disorders that require further evaluation.

Table 5: DoD Diagnoses of Sleep and Central Nervous System Disorders in Deployed and Non-deployed Post-9/11 Veterans (entering VA care 2002-2014)

	Non-Deployed N=386,082 % (n)	**Deployed N=859,566 % (n)**
Sleep		
Hypersomnia	6.53 (24,558)	6.93 (60,252)
Obstructive Sleep Apnea	18.46 (69,423)	20.06 (174,446)

Insomnia	12.49 (46,991)	18.04 (156,856)
CNS/Cognitive Conditions		
Stroke-Cerebrovascular Disease	1.01 (3,806)	0.72 (6,295)
Pituitary Disorders	0.80 (2,999)	0.64 (5,588)
Any Cognitive Dysfunction	0.92 (3,478)	1.55 (13,461)
Epilepsy/Seizures Status		
Epilepsy	3.20 (12,044)	2.16 (18,800)
Seizure, No Epilepsy	1.91 (7,175)	1.42 (12,342)

Table 6 shows differences in chronic disease in DoD by deployment status. For all chronic diseases except liver disease, the non-deployed cohort was significantly more likely to be diagnosed in DoD ($p<.0001$). Mortality data through February 2020 revealed those who were not deployed were also significantly more likely to be deceased.

Table 6: DoD Diagnoses of Chronic Disease in Deployed and Non-deployed Post-9/11 Veterans (entering VA care 2002-2014)

	Non-Deployed N=386,082 % (n)	**Deployed N=859,566 % (n)**
Chronic Disease		
Cancer	2.58 (9,686)	1.67 (14,545)
Coronary Artery Disease	1.88 (7,088)	1.17 (10,195)
Other Cardiac Disease	7.10 (26,694)	5.05 (43,944)
Hypercholesterolemia	30.96 (116,440)	30.11 (261,865)
Chronic Lung Disease	1.14 (4,285)	0.92 (7,986)
Hypertension	25.16 (94,627)	21.33 (185,462)
Liver Disease	3.00 (11,284)	2.90 (25,204)
Kidney/Renal Failure	1.71 (6,432)	1.19 (10,343)
Obesity	24.14 (90,802)	23.36 (203,147)
Diabetes	8.92 (33,556)	6.31 (54,897)
Osteoarthritis	10.61 (39,916)	7.78 (67,636)
Mortality (As of 06 FEB 2020)	2.39 (9,006)	1.80 (15,692)

These data suggest that the non-deployed cohort experienced some injuries consistent with trauma, possibly due to motor vehicle accidents, and that they were more likely to have certain CNS related conditions, and chronic disease. Those who were deployed were significantly more likely to have TBI, traumatic injuries, mental health and substance use disorders, suggesting both physical and psychic impact of combat deployment. Further analyses will explicate the relationship of these DoD diagnoses to VA comorbidity and adverse outcomes.

Major Task 3: Use phenotypes and mTBI to develop risk scores for military outcomes, neurosensory/neurodegenerative disease, and adverse outcomes by deployment.

Month(s): *24 - 48*

Progress: None yet as this will occur during year 3.

Major Task 4: Examine association of phenotypes with TBI and risk for repetitive low-level blast by deployment strata.

Month(s): *48 - 60*

Progress: None yet as this will occur during year 5.

Milestone: *Compile VA data for Post-9/11 Veteran Cohort from existing data repository.* ***COMPLETE***
Milestone: *Convene stakeholder panel of VA and DoD operational partners.* ***VA and Veteran stakeholders are identified. We have one DoD partner and looking for one to two additional DoD stakeholders.***
Milestone: *Obtain DoD Data for Post-9/11 Veterans via DoDTR and DaVINCI.* ***DoD data for VA cohort is collected and processed.***
Milestone: *Analytic data sets for latent class/deep learning models developed.*
Milestone: *Develop DoD+VA phenotypes in: deployed VA users; nondeployed VA users; deployed no VA care; non-deployed no VA care.*
Milestone: *Compare phenotypes among sub-strata (deployed/nondeployed/VA/non-VA).*
Milestone: *Examine association of military relevant outcomes and repetitive low-level blast occupations with phenotypes.*

Health Economics Study:

Major Task 1: Obtain DoD and VA authorizations.

Month(s): *1 – 24*

Progress: We set up IRB and R&D/RDIS with Stanford IRB and VA Palo Alto Health Care System, respectively. Modifications to the IRB including adding VA COVID-19 Shared Data Resource Databases and VA Salt Lake City, VA Houston, and VA Richmond were added as collaborating institutions. Further modifications were updating the number of records from 1139 to 4000 research subjects, and adding language saying that we will merge data in VINCI with VA and Department of Defense(DoD) DaVINCI data using real SSN.

We've coordinated DART data requests. Amendments to the DART include adding VA Salt Lake City, VA Houston, and VA Richmond to the VINCI project workspace and gaining data access to the VA COVID-19 Shared Data Resource Databases.The DART was also amended to include the DUA between VA Palo Alto and VCU DBC.

A DUA between VA Palo Alto and VCU DBC was drafted and executed.

The budget, quad chart and the PI assurance were submitted for JIT approval. Funds were stationed. The study team also submitted HRPO submissions forms.

Real SSNS and associated Longitudinal study IDs were obtained from:
Richmond / Houston / San Antonio / Minneapolis / Tampa / Portland / Boston

Major Task 2: Create a joint VA/DoD database within VINCI, matching on real SSN, for all Vs using VA and diagnosed with TBI either in DoD, VA or both since 2004. Once assembled, perform quality checks and continue maintenance throughout study.

Month(s): *1 - 24*

Progress: All VINCI VA and DaVINCI DoD databases for 1550 Veterans have been obtained. Merging by study ID and stripping of PHI identifiers is in process to send databases to VCU DBC.

An analyst joined the study team and he's working with the VCU DBC data manager on:

1. Microsoft SQL Extract, load and transform processes
2. SQL database migration
3. Create SQL script file for database backup and migration

Major Task 3: Assemble a matching cohort on age of Vs without TBI. Once assembled, perform quality checks and continue maintenance throughout study.

Month(s): *1 - 24*

Progress: All VINCI VA and DaVINCI DoD databases for 1550 Veterans have been obtained. Merging by study ID and stripping of PHI identifiers is in process to send databases to VCU DBC.

Milestone: *Create a joint VA/DoD database within VINCI, matching on real SSN, for all veterans using VA and diagnosed with TBI either in DoD, VA or both since 2004 (matching cohort on age of veterans TBI(-) for*

comparisons) to include demographics, military characteristics, military exposures identified in MHS to potential concussive event mechanisms, TBI severity when diagnosed by DoD, trauma and non-trauma comorbidities identified by DoD, MHS health services utilization and costs, military readiness, disability, days of work duty limitations and time in service, date of military separation, first date of VA eligibility, VA service connected disability rating and payments, VA comorbidities, VA health services utilization and survival.

Major Task 4: Collaborate with Drs. Pugh and Yaffe on the corrected identification of TBI severity and comorbidities.

Month(s): *24 - 36*
Progress: None yet as this will occur during year 3.

Major Task 5: Request, clean and merge data within the VINCI environment.

Month(s): *24 - 36*
Progress: None yet as this will occur during year 3.

Major Task 6: Examine the impact of TBI along with mechanisms of injury (controlled detonations, uncontrolled blast exposures, impact exposures in combat and training), and its comorbidities with DoD health services utilization, cost and disability (days of military released with work duty limitations, sick at home/quarters, and failed to meet medical standards), 2004-2018.

Month(s): *36 - 60*
Progress: None yet as this will occur during year 3-5.

Major Task 7: Examine the impact of MHS neurology, imaging, polytrauma/TBI clinic, other rehabilitation, pain clinic and mental health services on time in military service, military readiness, sick days and DoD costs. MHS costs will include out-ofpocket costs incurred by individuals as well as payments to health care providers made on their behalf by Tricare.

Month(s): *36 - 60*
Progress: None yet as this will occur during year 3-5.

Major Task 8: Examine the impact of TBI and its mechanisms of injury, along with MHS health services on VA access/transition after DoD separation, survival and VA service connected disability compensation and pension benefits, 2004-2018.

Month(s): *36 - 60*
Progress: None yet as this will occur during year 3-5.

Major Task 9: Examine the impact of TBI, its mechanisms of injury, and its comorbidities on VA health services utilization and cost, 2004-2018.

Month(s): *36 - 60*
Progress: None yet as this will occur during year 3-5.

Major Task 10: Examine the impact of VA health services on survival and VA costs. VA costs will include inpatient, outpatient, pharmacy, and fee-basis payments to non-VA providers; Potential gender, racial/ethnic, and geographic inequities in MHS and VA health services utilization, SMs' military readiness and V's service connected disability and survival will be investigated.

Month(s): *36 - 60*
Progress: None yet as this will occur during year 3-5.

Milestone: Develop statistical analyses to economic and epidemiological models.
Milestone: Submit manuscripts to be reported in a series of peer-review manuscripts in journals such as Brain Injury, Journal of Neurotrauma, Military Medicine, Health Equity, and Health Services Research.
Milestone: Write reports for the Defense and Veterans Brain Injury Center (DVBIC), United States Army Medical Research and Development Command (USAMRDC), VA and CMTBIAC/VHA.
Milestone: Submit/Present results at DoD, VA, national and international TBI and neurotrauma meetings as

well as rehabilitation meetings such as the ACRM, DVBIC, USAMRDC, VA, CMTBIAC/VHA.

Novel Neuroimaging Study:

Major Task 1: Assess available methods of overcoming variability introduced by differences in scanner hardware and software.

Milestone: Examine phantom-based and statistical correction for variability introduced by scanner hardware and software.

Month(s): *1 - 60*

Progress: We have performed further analyses of the CENC data to examine the ComBat method of data harmonization to overcome site differences. Our initial analysis resulted in substantial reduction of variability across sites, but we have completed additional data to examine how this affects relationships with other clinical and outcome data. We have started to draft an initial manuscript on the results obtained to date.

We have identified another novel method of data harmonization using a technique developed by colleagues at Brigham and Women's Hospital (BWH) which is being applied in other consortia. We have discussed collaboration with this group and with others in the InTBIR and ENIGMA communities; we submitted a grant application to explore this in the LIMBIC data, but it was not selected for funding.

This task remains in progress, and we will explore additional harmonization techniques over the next review period (12 months).

Major Task 2: Critically examine and compare strengths and limitations of commonly used imaging analysis pipelines.

Milestone: Using data collected as part of CENC, results of comparisons of data analysis pipelines will be submitted as one or more manuscripts for publication.

Month(s): *1 - 12*

Progress: In addition to the standard "Core" pipelines that we have been using as part of CENC, we have identified several additional pipelines for comparison of results. These data analyses are in process at the University of Utah. We have also worked with Drs. Stone, Tustison and Avants to utilize their SyMLR method, and are in the process of reviewing and refining those results. We also submitted an NIH R61/R33 grant application to build a novel pipeline for both structural and functional imaging analysis; we have received the Notice of Award and have recently started this project. We will work, in connection with other colleagues, to develop a modified ComBat technique over the next three years.

Major Task 3: Develop and test aspects of pre-processing which enhance accuracy and consistency.

Milestone: Extend efforts to critically examine pre-processing approaches which may enhance accuracy and consistency (i.e. attenuate distortion artifacts in diffusion imaging).

Month(s): *1 - 60*

Progress: We have created a limited data set which can be used for this objective and creating a set of parameters which can be manipulated for testing. We will perform testing both using data collected as part of this consortium, but will also work with additional data in conjunction with the ENIGMA consortium.

Major Task 4: Create and refine novel, automated pipelines to address aspects of imaging analysis which are currently absent or incomplete.

Milestone: Further refine CENC pipelines including an automated analysis pipeline for detection and analysis of white matter hyper-intensities as well as pipelines for volumetric, diffusion and functional connectivity, separately as well as in combination.

Month(s): *1 - 24*

Progress: The WMH pipeline has been updated and we are in the process of applying this to a larger set of data collected under LIMBIC-CENC (and later, to a larger dataset in conjunction with

ENIGMA and NICoE). Pending receipt of additional clinical and outcome data, we will perform analysis examining the relation of these variables. We aim to complete this within the coming year of the grant.

Major Task 5: Incorporate elements of advanced statistical analysis (e.g., Bayesian analysis, machine learning) to utilize multi-modality imaging data in conjunction with other injury, demographic and outcome data to develop subgroups/phenotypes and identify related variables in those at highest risk for poor outcome.
Milestone: Initial analysis of existing CENC Study 1 data; interim and final analysis of imaging data utilizing sophisticated Bayesian and machine learning models to identify phenotypes and the most salient imaging-derived components that may predict high risk for future outcome.

Month(s): *1 - 60*

Progress: We have performed additional analyses examining the use of advanced statistical analysis in existing LIMBIC-CENC data, particularly with regard to diffusion imaging findings. This manuscript has been drafted and is in circulation among the co-authors.

We have been meeting with the Data Core and Biostatistics group as well as the Biomarkers Core to identify additional analytic plans for phenotype exploration within the imaging data, qualitative comparative analysis (QCA) and additional machine learning methods. QCA analysis was completed (Dr. Hodges). We are preparing a proposal request in conjunction with Benjamin Dunkley to examine additional machine learning strategies.

Major Task 6: Assess merits and challenges of existing methods of "individualized" data analysis.
Milestone: Perform a critical review and testing of existing methods which target "individual" analysis to determine their clinical utility for diagnosis, treatment planning and evaluation of treatment response.

Month(s): *36 - 60*

Progress: Work on this task is scheduled for a later stage in the project.

Major Task 7: Share data with external investigators; Biannual submission to FITBIR (March and September).

Month(s): *6 - 60*

Progress: We prepared and submitted the imaging data for the scheduled September submission. Please see the Neuroimaging Core report for additional information.

We are working with members of the LIMBIC Data and Biostatistics Core as well as the Biomarkers Core to propose and design additional analyses. Neuroimaging Core members are involved in a number of data request submissions.

Neuroimaging Core investigators lead and support the ENIGMA Military Working Group; we are also involved in communication with TRACK-TBI, TED, and InTBIR. Please see the Neuroimaging Core report for additional information.

Biomarker Discovery Study:

Major Task 1: Obtain pre-deployment biospecimens from the DoD biorepository to assess pre-injury levels of candidate biomarkers in the CENC longitudinal cohort.

Month(s): *1 - 36*

Progress: Still in the process of obtaining pre-injury serum samples from DoD serum biorepository. We are working with the Coordinating Center and the DBC in order to work out the final details on how to distinguish the 1556 Participants in the LIMBIC-CENC Prospective Longitudinal within the DoD Biorepository.

Major Task 2: Carry out biomarker discovery project (N = 2000) of Prospective Longitudinal Study participants, expanding initial project CENC study 1 initial participants.

Month(s): *1 - 36*

Progress: Completed assays of 4 proteins (t-tau, NfL, GFAP & UCH-L1) on 1,200 Prospective Study participants. Running inflammation panel (IL-6, IL-10, TNF-α) currently.

Published 2 manuscripts (NfL- Neurology; MiRNA- J Neurotrauma) and 1 author reply (NfL- Neurology). Produced 1 podcast of Neurology NfL manuscript with AAN. Published Chapter on TBI Biomarkers in Brain Injury Medicine, Board Review, 7-19-2020. Submitted 5 abstracts for national/international conferences (3 as oral presentations at MHSRS, 1 at Sleep and 1 at European Sleep Research Society). **See Appendices 6-16**.

2 Awards for Biomarker Core PIs

Jessica Gill RN PhD: 2020 MHSRS award Outstanding Research Accomplishment Individual/Academia, July 2020

LCDR J Kent Werner: 2020 Sleep Young Investigator Award, June 2020

Major Task 3: Examine candidate protein biomarkers in plasma/serum, centrally-derived exosomes, saliva that were tested initially from both prospectively collected chronic TBI and pre-deployment (pre-injury) samples of Prospective Longitudinal Study cohort.

Month(s): *1 - 36*

Progress: 3 manuscripts under prep (NED in mTBI, Exosome methods paper, CENC Study 49 TBI Biomarkers with Nick Davenport). 2 manuscripts under review/revision (Biomarkers of TBI, poor sleep & cognition- Sleep; MiRNA & PTSD symptoms- Translational Psychiatry)

Major Task 4: Test additional candidate protein biomarkers of chronic TBI as they are identified (e.g.orexin, c-reactive protein, among others).

Month(s): *1 - 36*

Progress: Collaborating with Roskamp Institute for lipidomic analysis on Biomarker Discovery set. Executed an MTA. Sent plasma samples from 195 subjects to Roskamp June 29, 2020 and running assays on protein biomarkers of chronic TBI.

Major Task 5: Correlate candidate biomarker levels from pre-deployment and post- TBI specimens, as well as with outcome measures (neurobehavioral, imaging, neurocognitive testing).

Month(s): *1 - 36*

Progress: Collaborating with Imaging and Informatics for Biomarker-Imaging analyses (Random Forest Biomarkers, DTI-NfL). Project is currently underway.

Major Task 6: Correlate serial candidate biomarkers (in pre-deployment and serial samples) with neurodegeneration as symptoms/signs develop among Prospective Longitudinal Study cohort to identify unique prognostic biomarkers of chronic neurotrauma outcomes.

Month(s): *1 - 36*

Progress: Correlations of candidate prognostic biomarker correlations with symptoms and outcomes underway.

- *Milestone: Carry out blood and saliva biomarker assays from all subjects with baseline specimens in the biorepository.*
- *Milestone: Carry out candidate biomarker correlations with TBI status (repetitive versus mTBI with LOC versus blast versus no TBI), pre-deployment/pre-injury biomarker levels, neurobehavioral symptoms, advanced imaging, neuropsychological testing, serial biomarker levels among small cohort with incident neurodegenerative disorder (e.g. dementia).*
- *Milestone: Develop panel of prognostic biomarkers for each phenotype of chronic neurotrauma (e.g. dementia, headache, PTSD, sleep disorder)*

Major Task 7: Carry out GWAS using case-control assessment in discovery set using multi-chip array among subset of CENC Prospective Longitudinal Study subjects and large DoD or VA GWAS databases for each chronic TBI phenotype (e.g. dementia, PTSD, etc).

Month(s): *12 - 60*

Progress: None yet as this will occur during years 2-5.

Major Task 8: Validate GWAS results in independent validation cohort of Prospective Longitudinal Study subjects for each chronic TBI phenotype studied.

Month(s): *12 - 60*

Progress: None yet as this will occur during years 2-5.

Major Task 9: Calculate risk ratios and Manhattan plot, controlling for multiple comparisons.

Month(s): *12 - 60*

Progress: None yet as this will occur during years 2-5.

- *Milestone: Carry out and complete case-control GWAS assessment.*
- *Milestone: Correlate GWAS results with individual chronic Neurotrauma outcome (e.g. dementia, headache, PTSD).*
- *Milestone: Develop polygenic risk scores (PRS) of genetic risk factors for chronic neurotrauma outcomes.*

Major Task 10: Carry out DNA methylation studies on 200 CENC samples, to examine genetic influences of unique neurobehavioral TBI outcomes (e.g. dementia, sleep disorder, PTSD).

Month(s): *24 - 60*

Progress: None yet as this will occur during years 3-5.

Major Task 11: Carry out and extend exosomal microRNA analysis of CENC Prospective Longitudinal Study cohort based on preliminary results from CENC biomarker discovery project.

Month(s): *24 - 60*

Progress: None yet as this will occur during years 3-5.

Milestone: Carry out DNA methylation study on extracted DNA from 200 subjects in longitudinal study and associate methylated genes with chronic TBI outcomes.
Milestone: Carry out validation microRNA analysis of miRNA biomarkers identified in the CENC biomarker discovery project (in process).
Milestone: Develop panel of miRNA biomarkers associated with chronic TBI outcomes.

Major Task 12: Share data with external investigators; Biannual submission to FITBIR (March and September).

Month(s): *6 - 60*

Progress: Completed by the VCU DBC team.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Prospective Longitudinal Study: Dr Walker and Dr Cifu along with other senior investigators mentored multiple LIMBIC junior investigators on analytic, publication, and dissemination work across including Dr.

Amanda Garcia, Dr. Amma Agyemang, Jonathan Yee, Dr. Susan Van der Veen and Dr. Bilal Khokhar. (see Attached LIMBIC-CENC PLS analysis and dissemination tracker for details). Dr Walker also recently began mentoring two PM&R physician residents in training on a new analytic project using PLS data. Multiple trainees and junior investigators received mentoring by senior LIMBIC investigators and worked with LIMBIC on separately funded research projects to further their scientific career including Dr C. Sheerin and Dr. C. Hodges; Dr Sheerin was just successfully awarded a supplement to her NIAAA K01 award "Examining genetic and learning-based mechanisms for AUD and PTSD" that will use LIMBIC to study "Functional relations between alcohol use and mental/physical health in the wake of the COVID-19 pandemic".

Retrospective Database Study: Two junior investigators, Erica Kornblith, PhD, and Yue Leng, PhD, have worked with the study team and completed projects resulting in manuscripts (one published, one under review). They collaborated with our experienced team of researchers, gaining knowledge about traumatic brain injury, Veteran's health, and working with large administrative datasets.

Novel Neuroimaging Study: Drs. Wade, Dennis and Kennedy are in the early stages of their careers, and have been able to access the statistical expertise of the Biostatistics Core in Dr. Pugh's group as well as the clinical and imaging expertise of Drs. Wilde, Tate and other investigators. Additionally, all have been engaged in joint analyses with Dr. Kenney's group and have been increasingly exposed to expertise in biomarker analysis.

Dr. Hodges was working in the lab of Drs. Wilde and Tate for most of this year as a graduate student. He then transitioned to VCU to work as a post-doctoral fellow.

Neuroimaging Core: Participation in training activities involves the following:
1) Personnel in our own laboratory at the University of Utah have been exposed to significant training opportunities as a result of their work on this project. We currently have 3 post-doctoral fellows (Hannah Lindsay, Paula Johnson, and Ben Wade) who are working on the project as well as 1 graduate student (Carmen Velez) and 2 undergraduate students (Josephine Dimanche and Elizabeth Hovenden). These trainees have now had specific training in and experience with numersou aspects of imaging acquisition and analysis. Until his transfer to VCU for post-doctoral work (also LIMBIC-related), another graduate student (Cooper Hodges) utilized LIMBIC data for a doctoral dissertation.
2) Dr. Wilde acted as a mentor to Sara Mithai (Jessica Gill's laboratory) on an NIH K-level application that involved both imaging and biomarkers in the LIMBIC data. Drs. Wilde, Tate, Pugh, Gill and Kenney hold regular analysis meetings which involve trainees and junior faculty at different levels.
3) Drs. Wilde and Tate have also contributed to mentorship of other local trainees and junior faculty (e.g., Peter Fino, Melisa Cortez) and assisted in formulating analysis plans and requests using LIMBIC-CENC data.
4) Drs. Tate and Wilde co-lead the Enhancing Neuroimaging and Genetics through Meta-analysis (ENIGMA) Military Working Group, which facilitates datasharing, mega- and meta-analysis, with a particular focus on assisting younger investigators and trainees.

Participation in professional development activities include the following: We note that Dr. Wilde and Tate were scheduled to attend and present at multiple conferences and workshops that were canceled due to COVID restrictions.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Data and Biostatistics Core: Knowledge translation products and other updates/information shared on LIMBIC-CENC website.

Prospective Longitudinal Study:

- Conventional scientific community dissemination activities are listed in the Appendices showing PLS peer-reviewed journal publications and scientific meeting presentations including posters, oral paper presentations, and topical seminars.
- National webinars were conducted by several LIMBIC leaders (including Dr. Cifu, Dr. Walker, and Dr. Kenney) that concerned findings and updates on the PLS. (see Appendices for full listing and more detail.)
- Additionally, a wide range of dissemination activities and product development took place in collaboration with the LIMBIC KT center targeting all stakeholders including the scientific community, SMs and Vs and their families, and the general public. Details are provided in the KT section of this report and the Appendix which can be further supplemented by visiting the Website.
- The LIMBIC Consumer Advisory Board (CAB) participated by giving feedback on the development of the KT products and website design. Details on the LIMBIC CAB is provided elsewhere in this report.

Health Economics Study: The PI presented 2 VA Cyberseminars, published 2 manuscripts and a book chapter and had a poster presented at Academy Health.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

CORES

Coordinating Center:
1. Continue working on the remaining HRPO submissions.
2. Continue working with PLS sites as we gear up to resuming In Person research.
3. Continue working with the CAB in order to garner feedback and forward recommendations to Consortium Leadership.
4. Once able to travel safely, look to schedule trips to all 11 PLS sites.
5. Re-initiate the Site Metrics as we resume enrollment.

Data and Biostatistics Core: In the next year, the DBC will accomplish the following:
1. Continue development of the interactive platform for on demand review of data.
2. Continue QA/QC of data.
3. Continue development of analytic data sets for investigator data requests.
4. Continue central biostatistics support.
5. Work on development of integration of data dictionary on the LIMBIC-CENC website.
6. Continue FITBIR Ops and preparation of FITBIR data for the next submission.

Biomarkers Core: In the next year, the Biomarkers Core will accomplish the following:
1. Continue receiving and storing locally processed LIMBIC biospecimen samples into biorepository as collected.
2. Maintain inventory of LIMBIC-CENC BR samples and validate BSI database with Medidata through VCU informatics.
3. Continue to carry out NED screening at baseline visits of participants in the Prospective Study
4. Continue to carry out DNA extraction and APOE genotyping at baseline viists of participants in the Prospective Study who give permission for genetic testing on their blood specimen
5. Continue to make CENC/LIMBIC samples available for CENC/LIMBIC-related studies as sufficient samples are obtained and as approved by the procedures outlined and approved by the USUHS IRB.

Neuroimaging Core: In the next year, the Neuroimaging Core will accomplish the following:
1. Upload of the next installment of FITBIR data, planned for March and September 2021.
2. Continue to monitor quality assurance, as above.
3. Continue to perform and update analysis of imaging data on standard pipelines, as above, with re-analyses as new software versions are released.
4. Continue to assist in preparation of data requests, distribution of data for approved requests, and integration of imaging data with other consortium data.
5. Ongoing coding of CDE imaging data
6. Annual refresher training and monitoring of site compliance with SOP
7. Continue to participate in joint meetings with the PLS study team, Data Core, Biostatistics Core, and Biomarker Core.
8. Portland will be undergoing an upgrade to their system, and before the scanner is decommissioned, we will work with the site to collect pre- and post-upgrade data as well as to create a new protocol for the Vida scanner.
9. Complete training with new physicst (Dr. Welsh) and the new neuroradiologist rater (Dr. Shih)
10. Completion of 5-6 manuscripts which are currently in preparation
11. Complete reconciliation of all outstanding CDE coding data.

STUDIES

Prospective Longitudinal Study: In the next year, the Prospective Longitudinal will accomplish the following:
1. Staged reopening of in-person research activities across the LIMBIC-CENC PLS with respect to the COVID-19 pandemic shut-down as each site eventually gets local clearance. So far, Portland and now Richmond (in the last week of September) got such clearance.
2. After reopening, we anticipate continued challenges from COVID-19 including refusals for in-person research participation and longer assessment times when conducting in-person procedures due to social-distancing, disinfecting, and other COVID-19 mitigation precaution that will be necessary.
3. Our goal is to gradually and steadily ramp up enrollments toward the original planned targets.
4. Otherwise, main goals are to continue the retention and longitudinal reassessment study activities and continued work and success with scientific analysis and dissemination.

Retrospective Database Study: In the next year, the Retrospective Database Study will accomplish the following:
1. Make incredible progress on our newest analyses; the sleep paper will be published.
2. Finalize definitions for important variables in our cardiovascular analysis and examine the role of cardiovascular disease in the relationship between TBI and dementia.
3. Work on examining why some individuals with TBI are at risk for dementia and others are resilient.
4. Continue regular group meetings between investigators and regular reporting on LIMBIC consortium calls, the DoD report, and at the Government Steering Committee meetings.

Phenotype Study: In the next year, the Phenotype Study will accomplish the following:
1. Submit the DSAA with the Joint Trauma System for the DoD Trauma Registry and TBI module.
2. Obtain DoD data for the DoD only cohort.
3. Continue acquisition of novel data including radiology reports, etc.
4. Continue to work on developing analytic data set.
5. Work to connect computer servers to VA network to facilitate machine learning capacity.

Health Economics Study: In the next year, the Health Economics Study will accomplish the following:
1. As study data is being transferred to VCU, VCU programmers are working to send Longitudinal study variables to the Palo Alto team to merge with economic data in order to conduct analyses of combat and training exposures with Service Connected Disability, health services utilization and costs.
2. Teams will be created for manuscripts to create models, estimate models and report results.

Novel Neuroimaging Study: In the next year, the Novel Neuroimaging Study will accomplish the following:
1. If allowed given the COVID travel and infection control restrictions, conduct phantom testing with the diffusion phantom to collect data for data harmonization.
2. Participate in further discussion with colleagues who are developing additional harmonization methods, and complete harmonization manuscript.
3. Within the ENIGMA pipeline, critically examine the impact of different aspects of the analysis, including use of a population-specific template, and various aspects of pre-processing.
4. Perform additional analyses using additional machine learning techniques following receipt of feedback from collaborators.
5. Continue to work with other consortia and military-relevant groups (e.g., ENIGMA, InTBIR, TED, TRACK-TBI) to collaborate on data aggregation and analysis.

Biomarker Discovery Study: In the next year, the Biomarker Discovery Study will accomplish the following:
Project 1: Continue SOW into year 2 (of 3 total for this project), as follows:
1, Obtain pre-deployment specimens from DoD biorepository, as available
2. Correlate plasma biomarker results with Neuroimaging and neurocognitive outcomes in collaboration with LIMBIC Cores and prepare results for dissemination.
3. Identify subsets of Prospective study with TBI neurodegenerative outcomes (e.g. dementia, sleep disorders, epilepsy) and analyze relevant biomarkers in these sub-cohorts
4. Continue to analyze saliva samples for protein biomarkers of chronic TBI from CENC study 1 subjects.
5. Prepare manuscript of biomarker studies once analyses complete.
Project 2: Prepare and submit a GWAS project to the research committee and initiate GWAS project once minimum 1,500 DNA samples collected with approval for genetic testing collaboratively with GAIN through the Broad Institute.

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Biomarkers Core: Significant discoveries that may translate into diagnostics: The goal is to discover biomarkers that could be used to detect mild TBI and someday be able to make judgements about prognosis for injury outcome.
1. First to examine exosomal microRNA in remote TBI; 4 miRNA significant in rTBI and 1-2 mTBI vs TBI neg analyses; associations with chronic symptoms and outcomes.
2. Remote, repetitive mTBI is associated with higher levels of exosomal p-tau, exosomal and plasma t-tau, NFL, IL-6, exoxomal IL-10.
3. Higher exosomal levels of all 5 candidate biomarkers are variably associated with chronic neurobehavioral symptom burdens.
4. With GLM, higher levels of exosomal tau, p-tau, NFL, IL-6 and plasma NFL are associated with higher scores on PCL, PHQ-9 and NSI.

Prospective Longitudinal Study: To highlight several findings of importance that were derived or disseminated during the first year of LIMBIC:
1. Three or more lifetime mTBIs are associated with poorer outcomes including evidence of neurodegeneration. This comes from mounting and converging biologic (biomarker), physiologic (posturography) and self-report

(NSI symptoms, TBI-QoL, pain related disability) evidence from multiples studies using data from the PLS. This suggests that after 2 mTBIs, SMs should be considered for removal from high risk activities and any SMs or Vs with 3 or more lifetime mTBIs need comprehensive evaluation, comprehensive treatment for all problems and modifiable factors, considered for novel treatments that might arise, and close monitoring for change over time.
2. Neurofilament Light (NfL) protein levels were increased in SMs and Vs with 3 or more mTBIs and were higher if more symptomatic. This finding is consistent with recently published data in other cohorts at other times post-injury indicating that NfL may serve as a marker of neuro-axonal damage in this population.
3. Sleep apnea has a stronger relationship to neurocognitive function than mTBI history; in a separate study, mental health conditions have a stronger relationship to pain-related disability than did mTBI history. These studies highlight the need to holistically assess and treat all comorbidities including sleep apnea and mental health conditions (e.g. depression, PTSD).

Health Economics Study: Preliminary work suggests that blast mTBI has significant impact on health services utilization and costs in the VA relative to non-blast mTBI and no mTBI. It also suggests exposures in combat and training are important predictors of Service Connected Disability and that controlled blasts possibly in training may be much more impactful. We also found that while MRI is a much more expensive per unit technology, when its benefits are taken into account, it may be much more cost-effective than previously recognized in diagnosing and managing TBI. Finally, we found that there are important racial/ethnic disparities as well as service connected disability disparities in TBI mechanism of injury which are seen in a Level 1 Trauma Center and that assault/gunshot TBI is much more expensive long-term to the VA relative to other TBI mechanism of injury in Veterans.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Prospective Longitudinal Study: The range of KT products developed and available on the LIMBIC-CENC website are intended to reach a range of disciplines and audiences. The LIMBIC CAB provides ongoing input on how best to reach wide audience groups. Ideas from the Government Steering Committee (GSC) have also been embraced and used to shape our KT planning. The audience for the national webinar by Dr. Walker included physicians, physician extenders, nurses, physical, occupational and speech therapists, psychologists, neuropsychologists, health-care administrators, and basic science and clinical researchers.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Data and Biostatistics Core: Data is submitted to FITBIR for use by the wider scientific community.

Prospective Longitudinal Study: The main impact of the PLS on technology transfer has been the ongoing upload of all data into FITBIR informatics system for sharing of LIMBIC-CENC PLS data to other investigators and interested parties. Additionally we have set up and launched a system of direct request for sharing of datasets directly from our Data and Biostatistics Center (DBC) and of biofluid specimens from our Biomarker Core.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Health Economics Study:
1. Our results on the importance of controlled detonations on service connected disability may have implications for DoD training.
2. Our results on socio-determinants of mechanism of injury in a Level 1 Trauma Center may have implications for prevention of assault and gunshot related TBI.
3. Our results on the cost-effectiveness of MRI may have implications for its use in the diagnosis and management of TBI, especially mild TBI.

5. CHANGES/PROBLEMS: *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Prospective Longitudinal Study: The COVID-19 pandemic necessitated a change in approach during the past reporting year as described below in the Problems / Delays /Plans to Resolve section. All changes were within the initially approved scope of work.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Biomarkers Core: In March of 2020, COVID-19 restrictions were instituted and the site labs closed and enrollment of new participants was halted. (Modification for no-contact procedures approved by IRB.) Sites/labs began working on limited basis for biospecimen analysis in August 2020 in the LIMBIC Biorepository laboratories at USUHS and NIH. Sites just reopened for face-to-face clinical research and sample shipping has resumed. The pandemic is a waxing and waning situation and the lab activities may stop and start more than once.

Neuroimaging Core: The initial trainings related to neuroimaging data collection were initially delayed due to regulatory issues and COVID-19 restrictions, so these were completed by web-conferencing. We have been unable to collect human phantom data, but will plan to do this once travel restrictions are lifted. We are still awaiting some CDE codings from some of the neuroradiologist central readers who have had periods of difficulty due to COVID-19 and fires.

Prospective Longitudinal Study: The main operational challenge was the COVID-19 pandemic which led to suspension of all in-person research activities at all PLS sites before new enrollments could restart under

LIMBIC with the revised PLS protocol and related new regulatory approvals secured. This prohibited any new enrollments with the exception of one site, Portland, that was able to enroll several participants before the COVID-19 shut-down and one additional subject after getting local clearance for reopening in-person research activities in September 2020; limiting new enrollments to five total from Oct 01, 2019 to Sep 30, 2020. We reacted to this challenge by modifying our comprehensive longitudinal assessments to allow virtual data collection of all elements that do not require in-person elements such as physical examination, phlebotomy, or imaging. All questionnaires can now be completed by secure web-based method from home. We continue to work on other remote methods as well to capture neuropsychological testing by audio-visual streaming and are seeking regulatory approval to conduct informed consent revision process electronically (e.g. DocuSign). Additionally, we developed and deployed a COVID-19 impact questionnaire to allow us to gauge the impact of the pandemic on our participants' lives as an additional confounder variable to consider in our scientific work.

Retrospective Database Study: Due to the Covid-19 pandemic, we experienced some minor delays in our dataset creation, merging, and early analyses due to staff working from home. The VA servers we use for our projects have been running slowly due to the increased access from home computers. We estimate that we may incur a 3-4 month delay due to the pandemic and shelter-in-place orders and may need a no-cost extension to complete the project as proposed.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Coordinating Center: We worked with the VA HQ budget person in order to roll over as much of the unspent budget into the out years as we could. We were able to increase the VA max spending for a study per year from $5M to $5.25M, thus adding small amounts of roll over for most sites on an annual basis. Add this to some shifting of projected enrollment for several sites and each site is currently situated well fiscally speaking for the coming years. However, this will get more and more difficult if the pause on in-person research isn't lifted within the next 4-6 months.

Data and Biostatistics Core: Due to the cessation of in-person visits due to COVID-19, the amount and types of data, we have not been receiving the full spectrum of data that would be expected from visits, including not having any baseline visits until the past month. It is expected that once in-person visits resume at all sites, the amount data we will be receiving and managing will increase significantly. There will be increased expenditures to support this increase in data.

Biomarkers Core: The delays in collecting and shipping samples for almost 6 months delays reaching the enrollment goals while personnel are begin paid. This may have some impact on the funding for the project.

Prospective Longitudinal Study: Due to the COVID-19 shutdown of in-person research at all sites, most sites under-spent during the first fiscal year of LIMBIC and need intact carry-over of unspent funding in order to meet the long-term enrollment targets and goals.

Significant changes in use or care of human subjects

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Nothing to report.

6. PRODUCTS: *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

See attached Publication Tracker for numerous Journal Publications.

Kornblith E, Peltz CB, Xia F, Plassman B, Novakovic-Apopain T, Yaffe K. Sex, Race, and Risk of Dementia Diagnosis after Traumatic Brain Injury among Older Veterans. *Neurology,* 2020, 95(13). **(Appendix #19)**

Dismuke-Greer, CE, Hirsch, S, Carlson, KF, Pogoda, TK, Nakase-Richardson R, Bhatnagar, S, Eapen, BC, Troyanskaya, M, Miles SR, Nolen, T, Walker, WC. Health services utilization, healthcare costs, and diagnoses by mild traumatic brain injury exposure: A 14-year longitudinal chronic effects of neurotrauma consortium study. Arch Phys Med Rehabil. 2020. **(Appendix #20)**

Dismuke-Greer, CE, SM Fakhry, MD Horner, TK Pogoda, MJ Pugh, M Gebregziabher, CL Hall, D Taber, and DA Spain. Ethnicity/race and service-connected disability disparities in civilian traumatic brain injury mechanism of injury and VHA health services costs in military veterans: evidence from a level 1 trauma center and VA medical center. Trauma. 2020;8(3), 237-265. doi:10.1177/1460408620914436. **(Appendix #21)**

Dismuke-Greer CE. Economics of traumatic brain injury biomarkers. Biomarkers for Traumatic Brain Injury. Eds Wu, AHB, Peacock WF. Elsevier. 2020.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Kenney K, Werner JK, Gill J. **Chapter 7: Genetic, Epigenetic and Proteomic Biomarkers**. In: Brain Injury Medicine: Board Review. Blessen Eappen and David Cifu editors. 1st edition: Elsevier Press; 3 Sept 2020. https://www.elsevier.com/books/brain-injury-medicine/eapen/978-0-323-65385-5.

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Wilde, EA. "Research Advances in Imaging Traumatic Brain Injury: Bridging the Gap between Research and Practice. 7th Annual Alaska Brain Institute Meeting. Feb 29, 2020 **(Appendix #26)**

Wilde, EA. "Long-term Impact of Military-Relevant Brain Injury Consortium (LIMBIC)/Chronic Effects of Neurotrauma Consortium Overview" Presentation to India. Feb 1, 2020. **(Appendix #25)**

Werner JK, Shahim P, Gill JM, **Kenney K**. Poor sleep quality predicts serum markers of neuronal injury and cognitive deficits in warriors with mild traumatic brain injury. Abstract accepted for oral presentation at 2020 International Brain Injury Association (IBIA), New Orleans, LA, FEB 27-29, 2020.

Poster presented at the European Sleep Research Society (ESRS) September 22-24, 2020).
Poor sleep is associated with increased inflammation in warfighters with mild traumatic brain injury, Josephine U. Pucci BA[1], Sara M. Mithani PhD[2], Jackie Leete BA[2], Risa Nakase-Richardson PhD[4,5,6], Chen Lai PhD[2], Kimbra Kenney MD[1], Jessica M. Gill RN PhD[2], J. Kent Werner MD PhD[1,3] Department of Neurology, Uniformed Services University of Health Sciences, Bethesda, MD; [2]National Institutes of Health, Bethesda, MD;[3]Center for Neuroscience and Regenerative Medicine, Bethesda, MD; [4]Department of Internal Medicine, Sleep and Pulmonary Division, University of South Florida, Tampa, FL; [5]Defense and Veterans Brain Injury Center, Tampa, FL; [6]James A. Haley Veterans Hospital, Tampa, FL

Kenney K, Lai C , Devoto C, Qu B , Walker W, Wilde E, Diaz-Arrastia R, Gill J. Exosomal MicroRNAs in Chronic Mild Traumatic Brain Injury: Preliminary Results from a Chronic Effects of Neurotrauma Consortium (CENC) Biomarker Discovery Project. Abstract accepted for poster presentation at 2020 International Brain Injury Association (IBIA), New Orleans, LA, FEB 27-29, 2020. **(Appendix #9)**

Kenney K, Shahim P-P, Bazarian J, Gill JM. Biomarkers and Beyond: How TBI Care Can be Transformed Through Challenging our Capacity to Use Fluid-Based Biomarkers. Invited speaker, 2020 National Capitol Area TBI Research Symposium, Bethesda, MD, MAR 5-6 2020.

Chen L, Devoto C, Qu B-X, Guedes V, Walker WC, Wilde EA, Diaz-Arrastia R, **Kenney K**, Gill JM. Exosomal MicroRNAs for Diagnosis and Monitoring of Mild Traumatic Brain Injury: Preliminary Results from a Chronic Effects of Neurotrauma Consortium (CENC) Biomarker Discovery Project. Poster presentation at the 2020 National Capitol Area TBI Research Symposium, Bethesda, MD, MAR 5-6 2020. **(Appendix #7)**

deGuedes V, Lai C, Devoto C, Qu B-X, Walker WC, Wilde E, Diaz-Arrastia R, **Kenney K**, Gill JM. Exosomal Proteins and MicroRNAs as Prognostic Biomarkers of Persistent Affective Symptoms in Veterans with History of Mild TBI. Oral Presentation at the 2020 National Capitol Area TBI Research Symposium, Bethesda, MD, MAR 5-6 2020. **(Appendix #14)**

Mithani S, Lai C, Devoto C, Qu B-X, Walker WC, Wilde E, Diaz-Arrastia R, Gill JM, **Kenney K**. Exosomal MicroRNA in Blast-Exposed Veterans with Mild Traumatic Brain Injury. Oral Presentation at the 2020 National Capitol Area TBI Research Symposium, Bethesda, MD, MAR 5-6 2020. **(Appendix #15)**

Werner JK, Shahim P, Gill JM, Nakase-Richardson R, **Kenney K**. Poor Sleep Quality Predicts Serum

Markers of Neurodegeneration and Cognitive Deficits in Warriors with Mild Traumatic Brain Injury. Oral Presentation at the 2020 National Capitol Area TBI Research Symposium, Bethesda, MD, MAR 5-6 2020. **(Appendix #13)**

Edwards K, Campbell C, Kendrick N, **Kenney K**, Diaz-Arrastia R, Gill JM1, Debad J. Ultrasensitive Blood Test for Hyperphosphorylated Tau in Military Veterans with Chronic Traumatic Brain Injury. Poster Presentation at the 2020 National Capitol Area TBI Research Symposium, Bethesda, MD, MAR 5-6 2020. **(Appendix #12)**

Werner JK, Shahim P-P, Gill J, Richardson R, **Kenney K**. Traumatic Brain Injury Warfighters with Poor Sleep have Increased Plasma Biomarkers of Neurodegeneration. Neurology Apr 2020, 94 (15 Supplement) 5261; virtual poster presentation at the 2020 annual American Academy of Neurology.

Werner JK, Pucci J, Gill JM, Nakase-Richardson R, **Kenney K**. Poor Sleep Quality Predicts Serum Markers of Neurodegeneration and Cognitive Deficits in Warriors with Mild Traumatic Brain Injury. Abstract accepted as a poster presentation at the 34th Annual Meeting of the Associated Professional Sleep Societies, LLC, Philadelphia PA, June 13-17, 2020.

Garcia A, Reljic T, **Kenney K**, Agyemang A, Troyanskaya M, Wilde E, Walker W, Nakase-Richardson R. Association between STOPBANG Risk and Sleep Quality in an mTBI Sample: A Chronic Effects of Neurotrauma Consortium Study. Abstract accepted as an oral and poster presentation at the 34th Annual Meeting of the Associated Professional Sleep Societies, LLC, Philadelphia PA, June 13-17, 2020. **(Appendix #16)**

Edwards K, Campbell C, Kendrick N, **Kenney K**, Diaz-Arrastia R, Gill JM1, Debad J. Ultrasensitive Blood Test for Hyperphosphorylated Tau in Military Veterans with Chronic Traumatic Brain Injury. Abstract accepted for poster presentation at the 2020 ***Military Health System Research Symposium (MHSRS)***, Kissimee, FL, AUG 24-27, 2020. **(Appendix #8)**

Werner JK, Pucci J, Shahim P, Gill JM, Nakase-Richardson R, **Kenney K**. Poor Sleep Quality Predicts Serum Markers of Neurodegeneration and Cognitive Deficits in Warriors with Mild Traumatic Brain Injury. Abstract accepted for oral presentation at the 2020 ***Military Health System Research Symposium (MHSRS)***, Kissimee, FL, AUG 24-27, 2020.

deGuedes V, Lai C, Devoto C, Qu B-X, Walker WC, Wilde E, Diaz-Arrastia R, **Kenney K**, Gill JM. Exosomal Proteins and MicroRNAs as Prognostic Biomarkers of Persistent Affective Symptoms in Veterans with History of Mild TBI. Abstract accepted for oral presentation at the 2020 ***Military Health System Research Symposium (MHSRS)***, Kissimee, FL, AUG 24-27, 2020. **(Appendix #10)**

Pucci JU, Mithani SM, Leete J, Nakase-Richardson R, Lai C, **Kenney K**, Gill JM, Werner JK. Poor sleep is associated with increased inflammation in warfighters with mild traumatic brain injury. Abstract accepted as e-poster at the 25th Virtual Congress of the ***European Sleep Research Society***, Sevilla, Spain, SEP 22-24, 2020.

Werner JK, Shahim P, Pucci J, Lai C, Gill J, Nakase-Richardson R, Diaz-Arrastia R, **Kenney K**. Poor sleep quality predicts plasma markers of neurodegeneration and cognitive deficits in warriors with mild traumatic brain injury. Abstract accepted as e-poster at the 25th Virtual Congress of the ***European Sleep Research Society***, Sevilla, Spain, SEP 22-24, 2020.

Werner JK, Gerstenslager B, Yeh P-H, Srikanchana A, **Kenney K**, Ollinger J. Diffusion Tensor Imaging Evidence of Hypothalamic Injury in Traumatic Brain Injury Warfighters with Sleep Dysfunction. Abstract accepted for poster presentation at the 25th Virtual Congress of the ***European Sleep Research Society***, Sevilla, Spain, SEP 22-24, 2020.

Dismuke-Greer CE (Presenter). Economics of TBI Biomarkers. Accepted for the 2020 Military Health System Research Symposium.

Eggleston B, Dismuke-Greer CE (Presenter), Pogoda TK, Denning JH, Eapen BC, Carlson KF, Bhatnagar S, Richardson R, Nolen T, Walker WC. Title: A Prediction Model of Military Combat and Training Exposures on VA Service Connected Disability: A CENC Study. VA Cyberseminar. June 18, 2020. **(Appendix #22)**

Dismuke-Greer CE. Economics of TBI Biomarkers. VA Cyberseminar. September 16, 2020. **(Appendix #23)**

CE Dismuke-Greer (Presenter) , SM Fakhry, MD Horner, TK Pogoda, MJ Pugh, M Gebregziabher, CL Hall, D Taber and DA Spain. Ethnicity/race and service-connected disability disparities in civilian traumatic brain injury mechanism of injury and VHA health services costs in military veterans: Evidence from a Level 1 Trauma Center and VA Medical Center. Presented at the 2020 Academy Health Conference. **(Appendix #24)**

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

https://www.limbic-cenc.org
https://www.limbic-cenc.org/index.php/knowledge-translation-center/

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

LIMBIC-CENC Assessment tools, including PLS Variables and Concussion Assessment Tool for identifying and diagnosing lifetime mTBI history for clinical or research use were made available and kept updated on the website (https://www.limbic-cenc.org/index.php/knowledge-translation-center/limbic-cenc-concussion-assessment-tools/)

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to report.

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *physical collections;*

- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?
Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Example:

Name: *Mary Smith*
Project Role: *Graduate Student*
Researcher Identifier (e.g. ORCID ID): *1234567*
Nearest person month worked: *5*

Contribution to Project: *Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support: *The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Name: Abelson, Tracy
Project Role: Staff
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:
Data transfer, organization, archive and storage; FITBIR submission
Funding Support: N/A

Name: Agyemang, Amma
Project Role: Principal Investigator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:
Serves as co-PI of the Data and Biostatistics Core
Funding Support: N/A

Name: Alicea, Justin
Project Role: Coordinating Center Co-Director
Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: No Change
Contribution to Project:
Serves as co-Director of the Coordinating Center
Funding Support: N/A

Name: Amuan, Megan
Project Role: Data Manager
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:
develop analytic data sets
Funding Support: N/A

Name: Bailie, Jason
Project Role: PI
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:
analytic plans and conduct statistical analyses.
Funding Support: N/A

Name: Barnes, Deborah
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID): 0000-0002-2953-4079
Nearest person month worked: No Change
Contribution to Project:
Lead multiple projects and assisting in others. Involved in data analysis,
Funding Support: N/A

Name: Blessen, Eapen
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 3
Contribution to Project:
Phenotype Study - clinical expert for interpretation of data/analyses
Funding Support: N/A

Name: Boscardin, John
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID): 0000-0003-3121-9526
Nearest person month worked: No Change
Contribution to Project:
Statistician at UCSF and will oversee the statistical analysis and assist with manuscript preparation.

Funding Support: N/A

Name: Bowles, Amy
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 3
Contribution to Project:
Phenotype Study - clinical expert for interpretation of data/analyses
Funding Support: N/A

Name: Brunson, Linda
Project Role: Biospecimen Repository Mgr.
Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: No Change
Contribution to Project:
Manages receipt and storage of biospecimen for biomarkers core
Funding Support: N/A

Name: Byers, Amy
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:
lead multiple projects and assist others. She will be involved in data analysis, interpretation and manuscript preparation.
Funding Support: N/A

Name: Carlson, Kathleen
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project: Co-Investigator phenotypes
Funding Support: N/A

Name: Carne, William
Project Role:
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:
Coordinate activities across all sites. He will aid in the recruitment of subjects, and act as liaison with VCU IT, human subjects, and awards management units. Dr. Carne will assist in the logistics associated with obtaining documentation from the various sites and providing outputs from the cores and VCU. He will
also participate in dissemination efforts.
Funding Support: N/A

Name: Carone, Brandon
Project Role: Research Assistant
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:
completed training and certification for multiple assessments, including assistance with scoring for other studies. He is completing imaging training at UCSD Keck Center for Functional MRI. He has assisted
Funding Support: N/A

Name: Cheruiyot, Ronald
Project Role: Biospecimen Repository Technician
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:
responsible for the day-to-day operations of
maintaining the biospecimen biorepository, under the direction of the Biorepository laboratory manager, and includes daily operations such as supplying the kits to the study sites, receiving the samples, logging them in and preparing shipments for approved biorepository projects.
Funding Support: N/A

Name: Cifu, David
Project Role: Principal Investigator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:
responsible for the coordination of the project's activities, obtaining IRB approval for the project, as well as implementation of the overall protocol, data analysis, and dissemination of results. He will also oversee the direction of associated personnel at the Coordinating Center and across the consortium, and ensure that protocol guidelines are adhered. Further, Dr. Cifu will coordinate all associated activities and will lead all report writing and dissemination activities. He will have final responsibility for all aspects of the project
Funding Support: N/A

Name: Clara Dismuke-Greer
Project Role: Principal Investigator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:
3 Months working with Dr. Dismuke-Greer to submit LIMBIC Health Economics protocol and CENC Health Economics Amendment to Stanford IRB and VA Palo Alto Health Care System committees. Also
Ms. Garcia helped Dr. Dismuke-Greer prepare the Quad Chart and PI Assurance.
Funding Support: N/A

Name: Cook, Larry
Project Role: Co-Investigator / Biostatistician
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project: Lead for central biostatistics team
Funding Support: N/A

Name: Dennis, Emily
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID): 0000-0001-7112-4009
Nearest person month worked:
Contribution to Project: Data analysis, QA procedures- Neuroimaging Core
Funding Support: N/A

Name: Dennis, Emily
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID): 0000-0001-7112-4009
Nearest person month worked: No Change
Contribution to Project: Data analysis, QA procedures - Neuroimaging Study
Funding Support: N/A

Name: Dimanche, Josephine
Project Role: Project Coordinator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project: assistance with CDE coding and reconciliation, update of SOP and training materials
Funding Support: N/A

Name: Fung, Kathy
Project Role: Programmer
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change

Contribution to Project: is responsible for dataset creation, updating, and cleaning. She assists with data analysis when needed.
Funding Support: N/A

Name: Garcia, Carla
Project Role: Research Assistant
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project: Works with Dr. Dismuke-Greer to submit LIMBIC Health Economics protocol and CENC Health Economics Amendment to Stanford IRB and VA Palo Alto Health Care System committees. Also
Ms. Garcia helped Dr. Dismuke-Greer prepare the Quad Chart and PI Assurance.
Funding Support: N/A

Name: Gardner, Raquel
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID): 0000-0003-4028-440X
Nearest person month worked: No Change
Contribution to Project: lead multiple projects and assisting in others. She will be involved in data analysis, interpretation and manuscript preparation.
Funding Support: N/A

Name: Green, Tom
Project Role: Biostatistician
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project: Biostatistician on central biostats team
Funding Support: N/A

Name: Henenlotter, Rebecca
Project Role: Research Associate
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project: Data Core Research Assistant
Funding Support: N/A

Name: Healy, Kyle
Project Role: Data Developer
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:
Developer for DBC, creates and manages applications
Funding Support: N/A

Name: Hoang, Tina
Project Role: Research Associate
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:
assist with manuscript preparation and submission, presentations, and reporting requirements.
Funding Support: N/A

Name: Horner, Audrey
Project Role: Fiscal Technician
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:
assist Ms. McCarthy in the set-up of the contractual arrangements with Consortium partners

and the coordination of internal VCU processes by completing internal paperwork, monitoring the status of fiscal operations, and organizing documentation for her review and approval. She will process the complex procurements for Medidata and the website services, and monitor the invoicing of these procurements. Ms. Wood will also process the extensive monthly reconciliation of all LIMBIC expenditures and assist in the preparation of financial statements and progress reports.

Funding Support: N/A

Name: Hovenden, Elizabeth
Project Role: Project Coordinator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 3
Contribution to Project:
assistance with CDE coding and reconciliation, update of SOP and training materials
Funding Support: N/A

Name: Humpherys, Jeffrey
Project Role: Co-Investigator / Biostatistician
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project: Biostatistics
Funding Support: N/A

Name: Hunsaker, Naomi
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID): 0000-0002-0462-2910
Nearest person month worked: No Change
Contribution to Project:
Volumetric and fcMRI analysis, automated QA procedures - Neuroimaging Study
Funding Support: N/A

Name: Jak, Amy
Project Role: Principal Investigator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:
Dr. Jak oversees the VASDHS and UCSD-based components of the project:
Funding Support: N/A

Name: Jaramillo, Carlos
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 1
Contribution to Project:
clinical expert for interpretation of data/analyses
Funding Support: N/A

Name: Johnson, Michael
Project Role: Call Center Assistant
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 12
Contribution to Project: Call Center Assistant
Funding Support: N/A

Name: Johnson, Paula
Project Role: Post-Doc
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project: Q&A procedures and monitoring, Data organization

Funding Support: N/A

Name: Kamineni, Sreekanth
Project Role: Research Database Analyst
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:
Data scientist- FITBIR submissions, data QC, analytical support
Funding Support: N/A

Name: Karki, Sudeep
Project Role: Data Manager
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 12
Contribution to Project:
regulatory procedures, adhering to data quality standards, and following procedures for data sharing including through FITBIR.
Funding Support: N/A

Name: Kean, Jacob
Project Role: Co-Investigator Quality Insurance
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project: Co-Investigator Quality Insurance
Funding Support: N/A

Name: Li, Yixia
Project Role: Programmer
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:
involved in the dataset creation, variable coding. She will be running the statistical analyses for this project under the direction of Dr. Byers and Dr. Yaffe.
Funding Support: N/A

Name: Lindsay, Hannah
Project Role: Post-Doctoral Fellow
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change contribution Contribution to Project:
QA procedures and monitoring, data organization
Funding Support: N/A

Name: Mack, Yasmonia
Project Role: Call Center Assistant
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project: Call Center Assistant
Funding Support: N/A

Name: Manning, Laura
Project Role: EEG Specialist
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project: subject matter expert for EEG
Funding Support: N/A

Name: McCarthy, Bonnie
Project Role: Finance Manager
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change

Contribution to Project:

support the PI and other members of the Consortium in the fiscal and administrative management of the program. Her duties will include facilitating all contractual arrangements with Consortium partners, coordinating internal administrative processes between various VCU departments and divisions, and personnel management. She will also ensure federal and state cost accounting standards are followed, approve invoices, and oversee the preparation of financial statements and progress reports.

Funding Support: N/A

Name: Mobasher, Helal
Project Role: Data Scientist
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:

Data scientist- FITBIR submissions, data QC, analytical support

Funding Support: N/A

Name: Montanari, Joseph
Project Role: Research Assistant
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:

assist LTC Sickinger in reviewing, enhancing and refining all LIMBIC human study recruitment and retention efforts on a national level.

Funding Support: N/A

Name: Moore, Carol
Project Role: Supervisory Clinical Research Coord.
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project: Supervisory Clinical Research Coord.
Funding Support: N/A

Name: Muth, Conner
Project Role: Call Center Assistant
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 12
Contribution to Project: Call Center Assistant
Funding Support: N/A

Name: Nagasugi, Lauren
Project Role: Research Assistant
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:

assist with a host of study management activities including auditing data to maintain data quality, assisting with training Clinical Site personnel on neuropsychological testing and scoring, and with implementing consortium- and study-wide conference calls.

Funding Support: N/A

Name: Nguyen, Huong
Project Role: Data Scientist
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:

Data scientist- FITBIR submissions, data QC, analytical support

Funding Support: N/A

Name: O'Neal, Beth

Project Role: Research Coordinator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change contribution Contribution to Project:

completed multiple assessment trainings/certifications and has taken on operations management for the project at this site.

Funding Support: N/A

Name: Padilla, Silvia
Project Role: Research Analyst
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project: Research and assist with phenotype study
Funding Support: N/A

Name: Parnian, Roxana
Project Role: Project Manager
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:

coordinate data collection and cleaning procedures for the Data and Biostatistics Core (DBC). She will also serve as dedicated FITBIR liaison for LIMBIC.

Funding Support: N/A

Name: Peltz, Carrie
Project Role: Project Coordinator
Researcher Identifier (e.g. ORCID ID): 0000-0003-3807-8682
Nearest person month worked: No Change
Contribution to Project:

coordinates the project, sets up meetings, assists with manuscripts, presentations, and reporting, and manages regulatory documents.

Funding Support: N/A

Name: Presson, Angela
Project Role: Biostatistician
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project: Biostatistician on central biostats team
Funding Support: N/A

Name: Pugh, Mary Jo
Project Role: Multiple Principal Investigator
Researcher Identifier (e.g. ORCID ID): 0000-0003-3807-8682
Nearest person month worked:
Contribution to Project: Data & Biostatistics
Funding Support: N/A

Name: Pugh, Mary Jo
Project Role: Multiple Principal Investigator
Researcher Identifier (e.g. ORCID ID): 0000-0003-3807-8682
Nearest person month worked:
Contribution to Project: Phenotypes
Funding Support: N/A

Name: Qu, Bao-Xi
Project Role: Research Assistant Professor
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project: Assist Dr. Kenney

Funding Support: N/A

Name: Seel, Ronald
Project Role: Knowledge Translation Director
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:

Director of Knowledge Translation. In this role Dr. Seel will oversee the development of publications, presentations, website content, and other initiatives for disseminating LIMBIC research findings.

Funding Support: N/A

Name: Shaik, Refah
Project Role: Data Analyst
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:

Data analyst for DBC, FITBIR submissions, Data QA/QC Analytical Support

Funding Support: N/A

Name: Sickinger, Christine
Project Role: Fiscal Coordinator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:

assist Ms. McCarthy in the procurement of materials and supplies, publications, postage, shipping, duplication, retention items, and retention events. Ms. Sickinger will also provide travel coordination and reimbursement processing support for the GSC meetings, DoD/VA sponsored meetings, scientific/technical meetings, site visits, imaging core site visits, and the longitudinal study participanttravel.

Funding Support: N/A

Name: Sickinger, James
Project Role: Coordinating Center Co-Director
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:

serves as Coordinating Center Co-Director. LTC Sickinger served for 23 years in the US Army, is a combat decorated veteran, and served in a variety of leadership and command roles requiring logistical administrative, process management, recruiting and quality control expertise. LTC Sickinger will serve as Director of the Coordinating Center, managing the day-to-day activities of the consortium, including Core Facilities and the 6 Studies they support. In addition, he will review, enhance, and refine all LIMBIC
human study recruitment and retention efforts on a national level.

Funding Support: N/A

Name: Suarez, Javier
Project Role: Biospecimen Repository Technician
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project: responsible for the day-to-day operations of Biorepository
Funding Support: N/A

Name: Tangog, Ekaterina
Project Role: Research Assistant
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:

maintaining the biospecimen biorepository, under the direction of the Biorepository laboratory

Funding Support: N/A

Name: Tate, David
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID): 0000-0003-0213-1920
Nearest person month worked: No Change
Contribution to Project:

maintaining the biospecimen biorepository, under the direction of the Biorepository laboratory

Funding Support: N/A

Name: Taylor, Brian
Project Role: Physicist
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:

Responsible for monitoring quality assurance measurements and subject quality. He will also provide expertise on image acquisitions/ processing and how to tie it into the analysis of the data.

Funding Support: N/A

Name: Thompson, Katherine
Project Role: Research Coordinator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:

Assist Coordinating Center Managers in coordinating the clinical aspects of the project

Funding Support: N/A

Name: Velez, Carmen
Project Role: Graduate Student Assistant
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:

Assist Coordinating Center Managers in coordinating the clinical aspects of the project

Funding Support: N/A

Name: Wade, Benjamin
Project Role: Biostatistician
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:

Work with Research Assistant at Palo Alto, Carla Garcia to submit LIMBIC Health Economics protocol and CENC Health Economics Amendment to Stanford IRB and VA Palo Alto Health Care System R&D committees. Also prepared Quad Chart and PI Assurance. Neuroimaging Core

Funding Support: N/A

Name: Walker, William
Project Role: Principal Investigator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:

PI for the consortium, contributing to data management, analysis, and translation. Dr. Walker will help to develop and oversee the outcome measures and the protocol for the Prospective Longitudinal Study, as well as ensure that all testing is administered consistently

at each of the study sites.
Funding Support: N/A

Name: Werner, Kent
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 1
Contribution to Project:
Co-I: DoD TBI clinical expert for interpretation of data/analyses
Funding Support: N/A

Name: Wilde, Elisabeth
Project Role: Principal Investigator
Researcher Identifier (e.g. ORCID ID): 0000-0002-9839-4428
Nearest person month worked: No Change
Contribution to Project:
Oversight of project, including training, quality control, FITBIR submission - Neuroimaging Core
Funding Support: N/A

Name: Williams, Rose
Project Role: Research Assistant
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:
assist with a host of study management activities including auditing data to maintain data quality, and with implementing consortium- and study-wide conference calls.
Funding Support: N/A

Name: Wood, Ginger
Project Role: Fiscal Coordinator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: No Change
Contribution to Project:
assist Ms. McCarthy in the set-up of the contractual arrangements with Consortium partners and the coordination of internal VCU processes by completing internal paperwork, monitoring the status of fiscal operations, and organizing documentation for her review and approval. She will process the complex procurements for Medidata and the website services, and monitor the invoicing of these procurements. Ms. Wood will also process the extensive monthly reconciliation of all LIMBIC expenditures and assist in the preparation of financial statements and progress reports.
Funding Support: N/A

Name: Yaffee, Kristine
Project Role: Principal Investigator
Researcher Identifier (e.g. ORCID ID): 0000-0003-0919-3825
Nearest person month worked: No Change
Contribution to Project:
project leadership and oversees all research. She will be involved in data analysis, interpretation and manuscript preparation.
Funding Support: N/A

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

We had the following PI changes during this period of performance:

- COL Kristofer Radcliffe assumed the role of Consortium Co-Director upon the retirement of COL Sidney Hinds.
- Dr. Hee Chin Chae resumed the duty of Site PI at our Fort Belvoir Prospective Longitudinal enrollment site when Dr. Melissa Guerra moved to San Antonio, TX.
- Dr. Nick Davenport switched roles to PI from co-PI with Dr. Scott Sponheim at our Minneapolis Prospective Longitudinal enrollment site.

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ers.amedd.army.mil*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

9. 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.*