Quarterly Technical Progress Report Format
Front Cover

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Project Title:	Long-Term Impact of Military-Relevant Brain Injury Consortium
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Email the report and any other attachments to the Grants Officer's Representative (GOR) and Grants Specialist at the email addresses specified in the award document. Name the file with the award number, followed by "QtrlyTechProgReport Month Year."

If you have questions, contact the GOR.

1. Accomplishments: The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer 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:

1. Transition and Expand CENC to LIMBIC:

a. Submission of IRB approved master protocol.
b. Delivery of expanded Consortium SOP.
c. Submission of timeline for onboarding performance sites.
d. Establishment of Data Sharing Agreement with DHA for access and use of MHS data at VCU CC and appropriate sites.
e. HRPO approval of master protocol.
f. IRB/HRPO/JIT approvals for all performance sites and consortium Cores.
g. Hiring, training and certification of subaward personnel, particularly subaward clinicians and associate researchers.

2. Add three new additional Prospective Study Enrollement Sites:

a. Onboard 3 new enrollment sites (Salisbury/San Diego/Fort Gordon).
b. Assist with hiring, training and certifying staff.
c. Assist with regulatory approvals to include IRB and HRPO.

3. Conduct Call Center operations:

a. Assist with hiring, training and certifying staff.
b. Conduct liaison between enrollment sites.
c. Conduct all necessary follow-up calls to include BTACTs and Annual Telephone Assessments for Prospective Longitudinal Study (see table below for projected call volume).

4. Set and publish all Performance Site Metrics to include (recruiting/retention/reporting/data collecting/FITBIR reporting):

a. Establish Site Metrics.
b. Establish recruitment and retention goals as well as the overall plan.
c. Monitor and report site performance
d. Maintain and establish regular communication through meetings, teleconferences, e-mails, site visits and other methods to maintain consortium function.
e. Collect required information, prepare and submit Quarterly, Annual and Final Reports.

5. Conduct Consumer Advisory Board Meetings:

a. Select Board Members and attain GSC approval of the selectees.
b. Publish the LIMBIC CAB Charter.
c. Publish the LIMBIC CAB Meeting Schedule
d. Conduct the meetings, provide appropriate feedback to Consortium Leadership and implement approved feedback
6. Management of Fiscal Resources:

a. Establish appropriate approved sub contractual arrangements.
b. Establish CRADA and other agreements as required, provide copies to the GOR, and update as necessary.
c. Monitor overall and individual site finances.
d. Develop strong working relationship with both the DoD and VA Contract Personnel to ensure 100% financial regulatory compliance.
e. Provide Quarterly and Annual Financial Reports to be included in the Consortium's Quarterly and Annual Reports.

7. Attend Semi-Annual GSC meetings with DoD and VA sponsors.
a. Coordinate with CDMRP Science Officer to make tentative schedule for semi-annual GSC Meetings.
b. Coordinate with all performance site PIs to ensure that their schedules permit attendance at meetings.
c. Provide CDMRP Science Officer with all required meeting materials in accordance with approved schedule.

Neuroimaging Core:

Major Tasks as outlined in the SOW are as follows and fall into the following categories:

Regulatory:
1. IRB protocol development, submission, and continuing review (locally and in conjunction with Coordinating Center at VCU)
2. HRPO approval and continuing review
3. Attendance at biannual GSC meetings

Training:
4. Hire and maintain all research consortium staff

Quality Assurance:
5. Oversee image acquisition for accuracy and consistency across sites through standardized protocols, MR and human phantom testing
6. Review MRI sequence parameters adherence and bi-monthly testing with research phantoms; Annual and pre/post-upgrade human phantom testing.
7. Perform qualitative and quantitative QA review of imaging data
8. Review quantitative testing for T1-weighted, diffusion, and functional connectivity QA, and qualitative data

Clinical Reads:
9. Review imaging data for clinical and incidental findings, and code imaging data according to the Inter-agency CDE for Imaging
10. Ongoing review and CDE coding of newly acquired conventional sequence data by neuroradiologists

Data Analysis:
11. Pre-process and analyze volumetric, diffusion, perfusion, and functional connectivity data, using pipelines for longitudinal analysis
12. Quarterly update of analyzed, summary imaging data provided to Data Core
13. With other Prospective Longitudinal Study investigators, examine imaging data in relation to demographic, injury, and biomarker data

Data Dissemination:
14. Share data with external investigators; Biannual submission to FITBIR (March and September)

Data Organization, Archive, Storage:
15. Organize, transfer, archive, and securely store neuroimaging data

Biomarkers Core:

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

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

3. Task: HRPO approval and continuing review.

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

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

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

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

8. Task: Provide biospecimens for approved LIMBIC-CENC biomarker projects.

Data and Biostatistics Core:

1. Task: To manage data capture (primarily through Medidata Rave), and efficiently and securely store all clinical data, and biospecimen and neuroimaging data for Prospective Longitudinal Study (Months 1-60). [In progress]

2. Task: To QA and QC all clinical data and work with Neuroimaging and Biorepository Cores to QA neuroimaging and biospecimen data (Months 1-60). [In progress]

3. Task: To disseminate requested data to investigators, provide analytical support for manuscripts, presentations, and other dissemination products, and submit data to FITBIR (Months 1-60). [In progress]

4. Task: Translate knowledge and disseminate knowledge products

STUDIES

Prospective Longitudinal Study:

1. Task: Implement Study.

   a. Milestones:
      (1) Hire and maintain all research study staff.
      (2) IRB protocol development, submission, and continuing review.
      (3) HRPO approval and continuing review.
      (4) Onboard 3 new enrollment sites.
      (5) Develop site-wide recruitment and retention plan.
      (6) Implement recruitment and retention plan.

Retrospective Data Base Study:

1. Task: Planning and regulatory review, data updating, and variable creation.

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

3. Task: 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.

4. Task: 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.

Phenotypes Study:

1. Task: Complete Regulatory Requirements.
   Milestones: Submission of University of Utah IRB, VA Research & Development and HRPO protocols and Approval of Protocols.

2. Task: 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.

   Milestones**:** Compile VA data for Post-9/11 Veteran Cohort from existing data repository and obtain DoD data for Post 9/11 Veterans via DoDTR and DaVINCI.

3. Task: Convene stakeholder panel of VA and DoD operational partners.
   Milestones: Identify VA, DoD and Servicemember/Veteran Stakeholders and convene first meeting.

Health Economics Study:

1. Task: Obtain DoD and VA authorizations.

2. Task: 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.

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

Novel Neuroimaging Study:

1. Task: 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.

2. Task: 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.

3. Task: 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).

4. Task: 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 hyperintensities as well as pipelines for volumetric, diffusion and functional connectivity, separately as well as in combination.

5. Task: 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.

6. Task: 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.

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

Biomarkers Discovery Study:

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

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

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

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

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

6. Task: 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.

Milestones:

(1) Carry out blood and saliva biomarker assays from all subjects with baseline specimens in the biorepository.

(2) Carry out candidate biomarker correlations with TBI status (repetitive versus mTBI with LOC versus blast versus no TBI), predeployment/pre-injury biomarker levels, neurobehavioral symptoms, advanced imaging,

neuropsychological testing, serial biomarker levels among small cohort with incident neurodegenerative disorder (e.g. dementia),

(3) Develop panel of prognostic biomarkers for each phenotype of chronic neurotrauma (e.g. dementia, headache, PTSD, sleep disorder).

What was accomplished under these goals?
For this quarterly reporting period only 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.

CORES

Coordinating Center:

1. Transition and Expand CENC to LIMBIC:

a. We continue to work on the establishment of Data Sharing Agreement with DHA for access and use of MHS data at VCU CC and appropriate sites.
b. All sub-award personnel, clinicians and associate researchers have been hired, trained and either certified or in the certification process.

2. Add three new additional Prospective Study Enrollment Sites:

a. Continuing to onboard the 3 new Prospective Longitudinal Study enrollment sites (Salisbury/San Diego/Fort Gordon). All three sites are now ready to start enrolling new participants. However, San Diego is still temporarily prohibited from conducting in-person research due to COVID-19.
b. Assisting with the training and certifying of all new staff. This will be an ongoing process due to normal departures of site staff personnel.
c. Assisted all sites with regulatory approvals to include IRB and HRPO Continuing Reviews. All three sites have all needed regulatory approvals.

3. Conduct Call Center operations:

a. We hired, trained and certified our third caller. All she is waiting for now is her WOC to be approved so that she can be added to the Richmond Site Study Team. This will complete all of the personnel actions needed due to hiring a new manager from within and also hiring one of our callers to be a Research Coordinator within the Coordinating Center. We were able to maintain call volume during this time due to most sites not enrolling new participants and we now stand ready to assume increased volume.
b. Continued to conduct liaison between enrollment sites.
c. Conducting all necessary follow-up calls to include BTACTs and Annual Telephone Assessments for Prospective Longitudinal Study.
d. All Call Center personnel are able to conduct their job remotely and the call center is working at a 100%.
e. Worked with the DBC in order to refine the Call Center Application. The automation of Call Center procedures also allows to conduct detailed analytics so that we can help sites make adjustments in order to improve call completion rates.

4. Set and publish all Performance Site Metrics to include (recruiting/retention/reporting/data collecting/FITBIR reporting):

a. Established Site Metrics.
b. Established recruitment and retention goals as well as the overall plan.
c. Monitoring and reporting site performance

d. We have established and will maintain regular communication through meetings, teleconferences, e-mails, site visits and other methods to maintain consortium function.
e. Collected required information, prepare and submit Quarterly, Annual and Final Reports.

5. Conduct Consumer Advisory Board Meetings:

a. Gained approval for the initial 10 member board and will work on additional guidance from the GSC.
b. The next meeting is scheduled for February 2nd where we will provide a brief consortium update as well as Dr. Seel providing a presentation on the Prognostic Tool Indicator.

6. Management of Fiscal Resources:
a. We established appropriate approved sub contractual arrangements.
b. We are still attempting to establish CRADA and other agreements as required.

7. Scheduled the Semi-Annual GSC meeting with our DoD and VA sponsors.
a. Coordinated with CDMRP Science Officer for the second semi-annual GSC Meeting.
b. Coordinated with all performance site PIs to ensure that their presentations were turned in.
c. Conducted the Virtual GSC Meeting on October 9th.
d. Provided the CDMRP Science Officer with answers to the follow up questions.

8. We have continued to host calls ranging from individual site calls to Consortium-Wide Calls.

Neuroimaging Core:
1. **Regulatory**:

a. During a past performance period (Q1 2020), the Neuroimaging Core protocol was submitted to the University of Utah/ VA Salt Lake City Healthcare System IRB; we 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). Since no continuing review is necessary, this is considered complete. We will continue to undergo annual RR&D committee approval at the VA. Our RR&D renewal was submitted and approved, and this is also considered up to date.

b. We notified the Coordinating Center at VCU on the day that we received IRB determination for LIMBIC that the Neuroimaging Core activities did not constitute human subjects research according to our UU/VA IRB. In the past, the CENC Neuroimaging Core activities were also determined by HRPO to not constitute human subjects research. Documents for HRPO review have been submitted. Until we receive formal determination by HRPO for LIMBIC, we will consider this in process.

c. Dr. Wilde participated in the GSC meeting on 9 October 2020 during this performance period. We therefore consider this item up to date.

2. **Training:**

a. **Hire and maintain all research consortium staff:**
(1) As in the prior performance period, we have continued supervision of staff members, including Hannah Lindsey, Emily Dennis, Paula Johnson, Josephine Dimanche and Elizabeth Hovenden, who are assisting with various aspects of clinical reads, data tracking and quality assurance, and imaging analysis. 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.

(2) We have continued training the neuroradiologists involved in the Common Data Element coding on new procedures in the Medidata system.
(3) We have further updated the Standard Operating Procedure manual and training materials, particularly with regard to site-specific imaging parameters and quarterly self-assessment report procedures.

The manual also now reflects more accurately personnel and contact information for the Neuroimaging Core investigators.

(4) Additional site training meetings to review the new quarterly site assessment procedures and completion of data in Medidata are underway via videoconference with personnel from each site. These meetings involve project staff involved in imaging data collection, usually including the PI and project staff as well as MRI staff at each site.'

(5) Dr. Taylor (MR physicist) transitioned from VCU to MD Anderson in Houston, Texas in June 2020 and continued to work with the Neuroimaging Core through July 2020. Dr. Robert Welsh at the University of Utah joined the Neuroimaging Core in October 2020. He and Dr. Wilde meet weekly to review procedures related to quality assurance, sequence parameter and protocol design for new/upgrade sites, and to discuss data analysis.

b. **Training materials development**: We have further updated the Standard Operating Procedure manual and training materials, particularly with regard to clarification of the phantom procedures, new site auditing procedures, and naming conventions for the imaging data. The manual also now reflects more accurately personnel and contact information for the Neuroimaging Core investigators.

3. **Quality Assurance**:

a. Note that the transfer of additional neuroimaging data to the Neuroimaging Core is pending resuming data collection following the lifting of COVID-19 restrictions that had prohibited data collection. For those sites that have received approval, we are in the process of receiving and performing quality control review of phantom object and human volunteer data which has been collected. We will review data quality at additional sites as approval is granted.

b. As before the COVID-19 restrictions, we are using tools that allow semi-automated monitoring of parameters of quality assurance. In addition, we perform visual inspection of the data to determine reliability.

4. **Clinical Reads**:

a. Because coding provides context for future data collection on subjects that are followed over time, we have continued work on reviewing 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. Reading of scans collected during January 2019-September 2019 was prioritized, and we have been finalizing reads for outstanding scans acquired 2013-2018 and post September 2019. 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.

b. In a past project period, we had completed training for the existing neuroradiologists (Drs. Gerry York, Tim Duncan and Aaron Betts) on the new Medidata system. We are in the process of training a new neuroradiologist who will be involved in the clinical reads and CDE codings under LIMBIC (i.e., Dr. Robert Shih) now that imaging data collection is scheduled to resume.

5. **Data Analysis**:

a. The preprocessing of imaging data maintained by the Neuroimaging Core is largely up-to-date for the standard pipelines (including recent version of software that was released during the period of performance), though we have instituted some additional longitudinal pipelines, which are in process.

b. We have been meeting regularly with the VCU and Utah Data Core team, as needed, to assist in reviewing and reconciling data needed to complete data requests from CENC and LIMBIC investigators.

c. With regard to specific data requests, Neuroimaging Core investigators have been meeting regularly with investigators from the Biomarker Core (Drs. Kenney/Gill/Werner) as well as individual investigators (e.g., Dr. Richardson) to assist in data dissemination for approved requests. We have also consulted with several

investigators both inside and outside the consortium to provide information and preview/advise on requests (e.g., Drs. Peter Fino, Benjamin Dunkley, Emily Dennis, Cooper Hodges, and others).

6. **Data Dissemination**:

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

b. The Imaging Core prioritized the submission of data collected January 2019-September 2019 to FITBIR) and the submission of data collected 2013-2018 (which were completed during prior performance periods).

c. We are preparing to submit previously collected imaging data for non-Prospective Longitudinal Study studies that would be very beneficial to the current project since it was collected at sites that have since been incorporated into the PLS. In addition to the anatomic data, we are preparing to submit data on advanced modalities including diffusion and resting state data as well as MTI/MEG (Salisbury), and McDESPOT (San Diego). This has required working with site personnel to verify final subject list and transfer data that was not previously stored by the Neuroimaging Core.

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

e. 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 1) Drs. Stone, Tustison and Avants, 2) Dr. Newsome, 3) Cooper Hodges, 4) Risa Richardson and Amanda Garcia, 5) Peter Fino.

f. Members of the Core have been engaged in conversations related to data sharing and collaboration with other larger consortia groups, including TRACK-TBI, MVP and ENIGMA. Dr. Wilde and Core investigators are participating in a grant application to MTEC with other LIMBIC consortium personnel. Drs. Wilde, Tate and Dennis were awarded (as co-PIs) an R61/R33 application related to ENIGMA that will leverage LIMBIC data and methods. Drs. Tate and Wilde participated in an application with other LIMBIC investigators (Pugh, Kenney, Gill) to examine post-traumatic epilepsy which leverages LIMBIC-based data; this was also selected for funding.

7. **Data Organization, Archive and Storage**: The server housing the neuroimaging data is operational and all active sites and personnel that have requested access have accounts. Data has been reorganized and accuracy/consistency between the PACS and the ftp server has been examined.

Biomarkers Core:

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

a. Biorepository director and staff remain consistent. Continuing to receive and distribute samples.

b. Renewed Contract with CLIA-certified lab (Quest) for NED screen (IGF-1, testosterone, TSH)

c. 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.

d. As of 16 DEC 2020, BR has collated/stored processed/aliquoted biospecimens (DNA/buffy coat, plasma, serum, saliva, RNA (PaxGene) from 1,941 (494 new) Study 1 (440 F/U) (17 new) subjects, as well as samples from 143 Study 49 (2005 aliquots) & 20 Study 20 subjects (300 aliquots) for current total **26,068** aliquots of in the biorepository available for analysis and 4,052 shipped out.

e. Received shipments from LIMBIC sites through 12/16/2020, primarily from follow-up visits.

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

a. Local regulatory approvals complete.

b. 12-9-2019 Mod 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.

c. HRPO approval 10-16-2020

d. New CR will be due in Feb. 2021.

3. Task 3: Task 3: Share data with external investigators through biannual submission to FITBIR (March and September) by VCU.

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

4. Task 4: Carry out genotyping assays of common genetic variants associated with the chronic effects of neurotrauma.

a. • No genotyping carried out because we have not had enough new enrollments in LIMBIC prospective study in Yr. 1.

5. Task 5: Carry out service operations (neuroendocrine screen through CLIA-certified lab).

a. No NED screening through Quest because of not enough new enrollments in LIMBIC prospective study in Year 1.

b. Collaborating with Bill Walker for evaluation of NED screen in Longitudinal sample; manuscript finalized and will submit to a special LIMBIC publication.

6. Task 6: Manage biospecimen sharing with LIMBIC-CENC and external investigators.

a. 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 lifted and samples shipped June 29 and received by Roskamp Inst. on June 30.

b. MTA for project with Dr. Nakase-Richardson, and her team at the Tampa VA approved Oct. 7, 2020. Research project titled: “"Noncoding RNA in traumatic brain injury", and specimens for sub-analysis being selected per approved Research proposal.

c. New CRADA in the works among USUHS, Geneva, Eisenhower (EAMC), and FBCH, requested by FBCH.

7. Task 7: Provide biospecimens for approved LIMBIC-CENC biomarker projects.

a. Samples shared with Roskamp Institute, Fiona Crawford for lipidomic analysis (in process).

8. Task 8: Attend biannual GSC meetings.

a. Attended and presented at the GSC meeting on October 9th.

Center	Total Shipments
San Antonio	29
Richmond	48
Tampa	35
Houston	26
Portland	19
Boston	13
Minneapolis VAHCS	15
Fort Belvoir	10
S01C - Total Blood Draws Rec'd (440 new)	**1941**
Number from 1yr. Follow-up visits (17 new)	**440**

S01C - Total Material Types Received

Material Type	Vials Currently In Inventory	Vials Shipped Out
Buffy Coat	1678	1308
DNA	1191	0
Stock DNA	196	0
Plasma	9145	2550
Saliva	1731	194
Serum	10288	0
Whole Blood (PaxGene)	1839	0
Grand Total:	**26068**	**4052**

Data and Biostatistics Core:

1. **Major Activities**:

- Data capture, storage and QC
- IT Systems and Infrastructure
- Data Requests
- Data Request Infrastructure
- Data Dictionary
- FITBIR data submission preparation
- Knowledge Translation

2. **Specific Objectives**:

a. To manage data capture (primarily through Medidata Rave), and efficiently and securely store all clinical data, and biospecimen and neuroimaging data for Prospective Longitudinal Study Developing IT Systems and Infrastructure.

(1) Successfully completed test migration of newly developed ~200 different automated edit checks in Medidata for approximately 44 CRFs (about 50% of all PLS CRFs) to improve data entry, facilitate data QA, and optimize overall data capture.
(2) Successfully completed test migration of three new CRFs for LIMBIC-CENC: BETS, CDR, and COVID-19 questionnaire
(3) Successfully implemented secondary data capture system through REDCap to facilitate remote data collection and automated transfer of data into Medidata.
(4) Developed materials for amendment packet

b. Developing IT Systems and Infrastructure.

(1) Continued Medidata mentorship phase, during when the team independently works on tasks and seek support from Medidata when needed.
(2) Updated and made improvements to Call Center Application (i.e., more flexible scheduling functionality for Call Center staff).
(3) Added one new module to Study Portal--Reports and Tracking (which transformed two formerly paper and pencil forms to electronic versions—a) Neuroimaging Quarterly Self-Audit Report and b) Pre-screening Summary Log.
(4) Updated/optimized system for regular, automated download of clinical data from Medidata to LIMBIC-CENC database on server
(5)Implemented draft versions of dynamic (i.e., updated in near real time as data is captured in Medidata) automated dashboard reports to track enrollments, recruitment, and receipt of biospecimen and MRIs.
(6)Implemented draft online versions of Biomarkers Core reports to track biofluid availability.
(7) Implemented December 2020 version of Data at a Glance
(8) Developed and implemented 1st version of Publication Committee Request Form, which moves the optimizes the previous system that used emails and will facilitate tracking of dissemination products.

c. To QA and QC all clinical data and work with Neuroimaging and Biorepository Cores to QA neuroimaging and biospecimen data.

(1) 1st level of QA/QC of clinical data has been developed and continues to be implemented monthly
(2) Monthly Site Metrics Reports detailing sites' performance in timeliness, accuracy, and completeness of data entry continue to be generated and distributed
(3) 2nd level QA/QC of clinical data continues regularly.
(4) The QA/QC team are developing an interactive platform for on demand review of data where users can interact with data, download a partial or entire report, look for historical data/report at a fraction of time. These reports will be published in a secure reporting server and are only accessible, at all times, to authorized staff. We are currently working on administrative and VA regulatory hurdles to accomplish this task.

(5) Regularly implemented QA/QC of neuroimaging and biospecimen data

d. To disseminate requested data to investigators, provide analytical support for manuscripts, presentations, and other dissemination products, and submit data to FITBIR.

(1) Data Request Infrastructure:
i. Updated data request procedure to facilitate the process by breaking it down to a two-step process: Preliminary and Full Application
ii. Implemented first draft of online query tool (Data Cube) to allow investigators to determine available sample size(s) to inform data requests.

(2) Data Request Processing:
i. Core data team completed and disseminated analytic data sets for three previously approved data requests for investigators at Florida, Portland, and Salt Lake City.
ii. We provided additional variables to previously disseminated analytic data sets for two data requests
for investigators at Tampa and Salt Lake City.
iii. We are processing data for three additional data requests for investigators at Virginia and California.
iv. LIMBIC-CENC Biostatistics group completed analyses for 1 investigator-initiated project.
v. LIMBIC-CENC Biostatistics group is actively conducting advanced analyses for 2 investigators – initiated projects and performing analysis on VINCI data for another approved project.
vi. LIMBIC-CENC Biostatistics group began exploring ideas for phenotype analyses to present to the study PI and investigators.

(3). Data Dictionary:
i. Completed and added search function to data dictionary. A global search function is introduced in this version that enables investigators to search for desired variables of interest and then add those variables to the final list. In addition, the new version will include the PCE & TBI variables that are currently provided to investigators as separate documents to main data dictionary.
ii. Data dictionary is currently going under structural changes. The new version that will be released next quarter includes elements from CRFs and will also match data elements/variables in the snapshot data sets. This structural change will ease the process of locating specific Form(s) or variables within data dictionary and their corresponding data.

(4). FITBIR Data Submission Preparation:
i) Attended biweekly meetings with FITBIR Operations
ii) Completed in-person training with CDMRP and Neuroimaging Core
iii) 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.
iv) In month of June, 92 Forms were resubmitted (i.e., data up to December 2018) as a part of Fitbir study closeout.
v) data up to December 2018 went live on July 1st 2020
vi) In month of September, 92 Forms were resubmitted (i.e., data between Jan 2019 – Sep 2019) as part of Fitbir Study closeout and approved for the data to go live
vii) in month of September, 92 Forms were submitted (i.e., data between Oct 2019 – Mar 2020) as part of Limbic study. Study close out is pending.
viii) Started developing new FITBIR data preparation and processing that further automate the submission of 92 Forms. The new process will take effect in the first quarter of 2021 and be implemented and used for March 2021 data submission.
ix) Continued working with sites to ensure conversion of all pseudoGUIDs to GUIDs

h. Knowledge Translation:
(1) Updated Website with Core Online Products (On-going)
i. 5 plain language abstracts and key points for published research articles
ii. Began search and update of peer-reviewed publications thru 12-31-2020 for website

(2) Created Prospective Longitudinal Study Data Visualization Dashboard: Update "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.

(3) Developed Prognostic Dementia Risk Tool Prototype for Service members, Veterans and their Clinicians:

i. Programming started on Dementia Risk Survey
ii. Template selected for personalized 'My Dementia Risk Profile'; will be vetted by the LIMBIC-CENC Consumer Advisory Board on 2/2/2021
iii. Created draft Veteran Fact Sheet on Dementia Risk Factors

(4) Created LIMBIC-CENC Searchable Journal Database:

i. Begin determining RAND research readiness ratings for studies in database
ii. Tweaked 'Advanced search' features to allow more targeted filters of publications

(5) LIMBIC-CENC/Biogen Dementia Awareness, Education and Prevention Campaign: Remain in communication with Biogen for funded campaign to fully inform Servicemembers, Veterans, families, clinicians and advocates about dementia prevention and treatment strategies, and Biogen's medications and research studies; timing of funding will be tied to medication FDA approval.

(6)Journal of Neurotrauma Special Issue:

i. DXC negotiated special issue on "Practical Approaches to Assessing and Mitigating the Risk of Cognitive Decline after Concussion: Findings from the Long-term Impact of Military-relevant Brain Injury Consortium (LIMBIC)"
ii. Special issue will include 10 articles, consumer pages, a podcast for each article, and two webinars

3. **Key Outcomes**:

• Data entry, storage and Quality Assurance/Quality Control Processes ready for live data submission by sites once IRB/R&D/HRPO approvals complete.
• Processes for data requests are tested and working with continual quality improvement processes in place.
• Data is being distributed to investigators (3 data requests completed; 3 in progress in Q4; 1 in under review).
• Basic FITBIR infrastructure is prepared for March LIMBIC FITBIR submission.

STUDIES

Prospective Longitudinal Study:

1. 1. Task: Implement Study.

a. Onboard 3 new recruitment sites. – Task 1a previously completed.
(1) San Diego-Camp Pendleton / Fort Gordon / Salisbury sites have been added.
(2) Coordinators have been hired.
(3) Equipment has been purchased and delivered.
(4) Training and certifications have been completed for all instruments.

b. Personnel at existing locations have been hired to fill vacancies. --Task 1b completed, but will need to be maintained with filling of future vacancies created by any departures of current personnel.

c. IRB protocol development, submission, and continuing review: Previously completed, but ongoing for continuing review. All PLS sites, including the three new LIMBIC sites, have gained initial local IRB approval and all sites have maintained their active approval status under continuing review processes.

d. HRPO approval and continuing review: All PLS sites, including the new LIMBIC sites, now have gained initial HRPO approval. Maintenance of continuing review approvals will be an ongoing task.

e. Develop site-wide recruitment and retention plan.—Task 1e is completed.

(1) Plans have been completed.

(2) As per recommendations from the GSC meeting in March 2020, we reviewed the retention plan used by the NIDILRR funded TBI Model Systems (TBI-MS) Program. All methods being used in TBI-MS are already in place for the LIMBIC PLS unless there is a privacy restriction against it by the Veterans Affairs of Dept. of Defense. The LIMBIC PLS also already uses additional methods above and beyond those being used in TBIMS.

f. Recruitment and retention plan will be initiated once all approvals have been gained – partially completed with delay in recruitment due to COVID-19 pandemic.

(1) Retention plan has been initiated and implemented.

(2) Recruitment and new enrollments were initiated: This quarter, 7 new participants were consented and 5 completed all the required baseline/enrollment assessments to be graduated to follow-up, for cumulative totals of 21 consents and 18 graduated to follow-up in the first five quarters of LIMBIC-CENC.

g. Conduct follow-up Assessments to include phone assessments. – ongoing

(1) This quarter, 143 new Brief Annual Follow-Up evaluations were completed and 27 new comprehensive Follow-Up evaluations were completed for an accumulated total of 968 Brief Annual and 303 Comprehensive Follow-Ups in the first five quarters of LIMBIC-CENC.

h. Report descriptive data – ongoing

(1) Continued updating website dashboards. Two different versions of dashboard content have been developed and deployed for public and private sides of the Website.

a. For public site, see: https://www.limbic-cenc.org/index.php/knowledge-translation-center/data-at-a-glance/

b. For private side; additional metrics are being added at the following URL: https://www.limbic-cenc.org/index.php/study-operations/dashboard/

(2) Began developing Data Cubes for researchers to explore data for hypothesis generation and better prepare for data analysis requests. https://www.limbic-cenc.org/index.php/for-scientists-and-clinicians/data-cube/

i. Acquire, safely store and analyze eye tracking data, Balance Master data, Neuropsychological data, biospecimens and imaging data – ongoing. All of these specialized data require in-person visits to acquire, so this aspect has continue to be curtailed by COVID-19 pandemic. As an alternative strategy, we developed and launched telehealth versions of some of the neuropsychological tests for remote longitudinal visits (not feasible for all neuropsychological tests). For all of our data, collected we continued the following acitivies:

(1) Continued new data collection and entry for longitudinal follow-up assessments.

(2) Continued QA/QC activities including preparing data for FITBIR uploads.

j. Analysis & Publication of Cross-sectional Data and Longitudinal Data – ongoing; details for last quarter below.

(1) During last quarter, datasets were released for the following newly approved data analysis projects:

Principal Investigator	**Title of Analysis Project**
O'Neil, Maya; Walker, William	Influence of prior mild TBI and PTSD on Cognition in the LIMBIC-CENC multicenter cohort (a family of 4 separate analysis projects)
Miles, Shannon	Sociodemographic and Mental Health Predictors of Arrests in Veterans and Service Members with Mild Traumatic Brain Injury: A CENC-LIMBIC Study
Walker, William	Is physical exercise and activity related to cognition and well-being after mTBI? A LIMBIC-CENC Multicenter Study
Dismuke, Libby	CENC-LIMBIC Longitudinal Variables to merge with VINCI health economics study data

(2) Work continued on multiple other analysis projects. **See Appendix #1**; LIMBIC-CENC PLS sheet of the **LIMBIC-CENC Analysis Tracker** for full list of ongoing scientific analysis projects.

(3) Last quarter, the following manuscripts were disseminated as new electronic publications in scientific journals:

Citation	Key Points		
	Question	Findings	Meaning
Werner, J. K., Shahim, P., Pucci, J. U., Lai, C., Raiculescu, S., Gill, J. M., Nakase-Richardson, R., Diaz-Arrastia, R., & Kenney, K. Sleep. 2020 Dec 6;zsaa272. doi: 10.1093/sleep/zsaa272. Online ahead of print. PMID: 33280032	Do poor sleepers with mild TBI (mTBI) have worse cognition and/or elevated biomarkers of neurodegeneration?	Poor sleepers with mTBI had elevated plasma Neurofilament light (NfL) chain and lower executive function scores by verbal fluency and stop-go tests compared to good sleepers with TBI. These findings were not observed in controls.	These findings suggest a link exists between poor sleep, cognition, and biomarkers of neurodegeneration in the military mTBI population, supporting further research with potential for therapeutic implications.
Khokhar, B. R., Lindberg, M. A., & Walker, W. C. (2020). Post-mTBI pain interference in a U.S. military population: A Chronic Effects of Neurotrauma Consortium study. Military Medicine, usaa249. Advance online publication. https://doi.org/10.1093/milmed/usaa249	Among service members and combat veterans with mTBI, how common is pain interference (functional limitations from chronic pain) and what are the potential risk factors?	Over 76% of our sample reported moderate to high pain interference. PTSD, anxiety, depression, and $\geq$ 3 lifetime mTBIs were each associated with greater degrees of pain-related functional limitations.	These findings highlight the complexity and overlap of comorbid symptoms. Service members and veterans with lingering effects of mTBI may require a more comprehensive and holistic approach during treatment.

(4) Last quarter, the following manuscripts were disseminated as new print publications in scientific journals:

Citation	Key Points		
	Question	Findings	Meaning
Bigler, E. D., Skiles, M., Wade, B. S., Abildskov, T. J., Tustison, N. J., Scheibel, R. S., Newsome, M. R., Mayer, A. R., Stone, J. R., Taylor, B. A., Tate, D. F., Walker, W. C., Levin, H. S., & Wilde, E. A. (2020). FreeSurfer 5.3 versus 6.0: Are volumes comparable? A Chronic Effects of Neurotrauma Consortium study. Brain Imaging and Behavior. 2020 Oct;14(5):1318-1327. doi:10.1007/s11682-018-9994-x	How does the new version of FreeSurfer, a widely-used method to automate neuroimaging analyses, compare with the previous version in volumetric output across various regions of interest (ROI) of the brain?	Cross-validation error was significantly higher using segmentations from FreeSurfer version 5.3 versus version 6.0. The relative importance of ROIs used to predict age with random forest also differed between versions. However, fitted regression lines and their slopes were similar between the two versions.	While absolute volumes are not interchangeable between version 5.3 and 6.0, ROI correlational analyses appear to yield similar results, suggesting the interchangeability of ROI volume for correlational studies. These findings aid the assimilation of quantitative neuroimaging literature across time eras.
Devoto, C., Lai, C., Qu, B., Guedes, V. A., Leete, J., Wilde, E., Walker, W.	Is exosomal microRNA, a	Presence of and number of remote Mild	Exosomal microRNA may serve as

C., Diaz-Arrastia, R., Kenney, K., & Gill, J. (2020). Exosomal microRNAs in military personnel with mild traumatic brain injury: Preliminary results from the Chronic Effects of Neurotrauma Consortium Biomarker Discovery project. Journal of Neurotrauma. doi:10.1089/neu.2019.6933	mediator of intercellular communication, involved with chronic TBI symptom persistence?	TBIs were associated with distinct exosomal microRNA profiles. Expression of certain microRNAs were also associated with neurobehavioral symtoms.	biomarker of past mTBI and its late effects. Analysis of exosomal miRNA expression may provide novel insights into the underlying pathobiology of chronic TBI symptom persistence.
Dismuke-Greer, C., Hirsch, S., Carlson, K., Pogoda, T., Nakase-Richardson, R., Bhatnagar, S., Eapen, B., Troyanskaya, M., Miles, S., Nolen, T., & Walker, W. C. (2020). Health services utilization, health care costs, and diagnoses by mild traumatic brain injury exposure: A Chronic Effects of Neurotrauma Consortium study. Archives of Physical Medicine and Rehabilitation. doi:10.1016/j.apmr.2020.06.008	Are Veterans' long-term comorbidities and/or VA health services utilization/costs related to their mild TBI (mTBI) history?	In this LIMBIC-CENC multicenter study from the CENC early Snaphot sample, covariate adjusted regression analysis showed that co-morbidities, health services use and costs were all highest for blast-related mTBI, followed by non-blast mTBI , and lowest with negative TBI histories.	Veterans with mTBI, especially those with blast-related mTBI, are receiving some degree of the additional health care services intended by VHA. The nature of the relationship between mTBI history, comorbidities and health care utilization/costs needs further study within the growing LIMBIC study cohort.
Garcia, A., Reljic, T., Pogoda, T. K., Kenney, K., Agyemang, A., Troyanskaya, M., Belanger, H. G., Wilde, E. A., Walker, W. C., & Nakase-Richardson, R. (2020). Obstructive sleep apnea risk is associated with cognitive impairment after controlling for mild traumatic brain injury history: A Chronic Effects of Neurotrauma Consortium study. Journal of Neurotrauma, 10.1089/neu.2019.6916. https://doi.org/10.1089/neu.2019.6916	How common is obstructive sleep apnea (OSA) in the previously deployed military population with mild TBI (mTBI) and what is it's relation to cognition?	64% of mTBI participants were at risk for OSA (versus 50% for TBI negative). Multi-variable analysis adjusting for demographics and TBI history showed those at OSA risk on the STOP-BANG had poorer scores on trail-making B and WAIS-IV coding and reported greater cognitive difficulties.	Because OSA risk is associated with cognitive functioning, early identification and treatment of OSA may improve outcomes after mTBI. Further study of OSA in LIMBIC and other TBI populations is indicated.

(5) During the last quarter, the following manuscripts were submitted for publication in scientific journals:

Authors/Title	Key Points		
	Question	Findings	Meaning
O'Neil, M. E., Klyce, D. W., Pogoda, T. K., Eggleston, B. E., Cameron, D. C., Wilde, E. A., Walker, W. C., Cifu, D. X., & Carlson, K. F. Associations among PTSD and post-concussive symptoms in the Long-term Impact of Military-relevant Brain Injury Consortium – Chronic Effects of Neurotrauma Consortium (LIMBIC-CENC) Prospective, Longitudinal Study cohort.	How do mild traumatic brain injury (mTBI)-related symptoms measured by the Neurobehavioral Symptom Inventory (NSI) correlate with	Symptoms measured by NSI were highly correlated with PTSD symptoms in those with or without mTBI history. There were similar clusters of symptoms (somatosensory, affective, cognitive, and vestibular) regardless	These findings suggest that the NSI symptom clusters are broadly valid for future research and may serve as useful clinical constructs for evaluation and treatment.

	mTBI history and PTSD status?	of mTBI and PTSD status.	
Guedes, V. A., Lai, C., Devoto, C., Edwards, K., Qu, B., Rush, H., Mithani, S., Acott, J. D., Martin, C., Wilde, E. A., Walker, W. C., Diaz-Arrastia, R., Gill, J. M., & Kenney, K. Exosomal MiRNAs and proteins are linked to chronic post-traumatic stress disorder symptoms in service members and veterans with mild traumatic brain injury.	Are there links between exosomal proteins and miRNAs measured in the peripheral blood and persistent PTSD symptoms in a military cohort with remote mTBI(s)?	Exosomal and plasma NfL, a neuronal protein marker of axonal injury and degeneration, are elevated in individuals with more severe PTSD symptoms. Furthermore, NfL elevations are associated with severity of PTSD symptoms. Specific miRNAs linked to PTSD symptom severity include hsa-miR-139-5p, hsa-miR-103a-3p, hsa-miR-33a-5p, hsa-miR-520f-3p, which have been linked to neurodegenerative diseases.	Our results suggest a possible role for axonal degeneration and neurodegenerative changes in the development of chronic PTSD symptoms years after mTBI.
Wade, B. S. C., Tate, D. F., Velez, C., Dennis, E. L., Goodrich-Hunsaker, N. J., Walker, W. C., Kennedy, E., Hinds, S., Taylor, B. A., Bigler, E. D., Abildskov, T. J., Newsome, M. R., York, G. E., Betts, A., Duncan, T., Kenney, K., Pugh, M. J., Cifu, D. X., & Wilde, E. A. Mapping post-traumatic stress disorder and depressive symptoms to hippocampal subfields and amygdala nuclei in service members and veterans with mild traumatic brain injury.	Do symptom dimensions of depression and PTSD uniquely relate to subregional volumes of the hippocampus and amygdala in Service Members and Veterans with mTBI?	Overall, latent symptom dimensions of PTSD and depression were more robustly associated with regional volumes than PCL-5 and PHQ-9 total scores. PTSD arousal/reactivity symptoms were more broadly related to subregional volumes of both structures than depression and this pattern did not depend on a history of mTBI.	The effects of PTSD and depression on limbic structures may be separable and thus may help inform treatment targets for future therapeutic intervention strategies.

(6) **See Appendix #2** (Current CENC Publication tracker) for a complete accumulated listing of scientific journal publications for all analytic projects utilizing datasets from the LIMBIC-CENC Prospective Longitudinal Study along with their Key Points. Additional knowledge translation products including lay abstracts are available on our website.

(7) In general, analyses from CENC Snapshot dataset #1 indicated that 1-2 prior mTBIs is a risk factor for symptom burden but not for objective neurologic findings (neurocognitive testing, imaging, neurosensory testing). Some early analyses suggest that 3 or more mTBIs may have late neurologic effects (lower postural stability, neurodegeneration byproducts in blood). One of the new electronic publications listed in in the first bullet, Werner et al, Sleep, was highlighted in a recent edition of Neurology Advisor (https://www.neurologyadvisor.com/topics/traumatic-brain-injury/sleep-quality-and-cognitive-function-in-patients-with-mild-traumatic-brain-injury/).

(8) Other Prospective Study Collaborations and Spin Off Studies. – ongoing. During the last quarter, the PLS leadership continued to spend extensive time and efforts working on collaborations with other scientists and organizations. See Appendix #3 (LIMBIC-CENC Collaborations tracker) for a listing and status update on these collaborations. Colonel Hines also provides additional descriptive information elsewhere in this quarterly report.

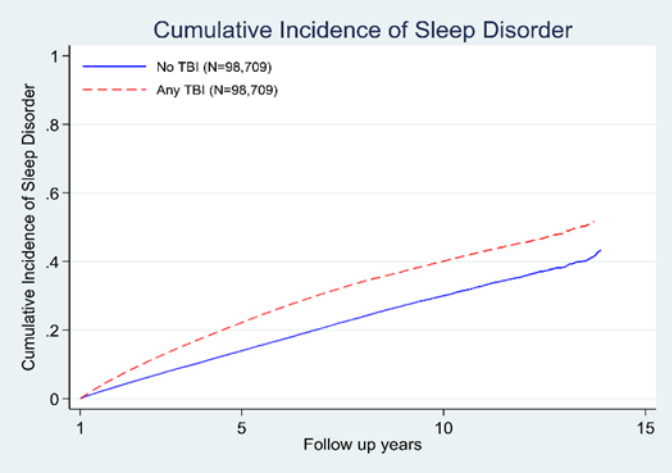
Retrospective Data Base Study:

1. Task 1: Planning and regulatory review, data updating, and variable creation.

a. We continued to make great progress in Year 2, Quarter 1 of this project. We have regular, recurring team meetings between all the investigators and research staff on this project. In-process analyses have regular working group meetings to discuss analytic techniques, plan further analyses, and discuss data interpretation.

2. 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.

a. In a manuscript recently accepted for publication in Neurology, we investigated the association between TBI and incident sleep disorders in veterans. The study included 182,247 veterans with TBI and 182,247 age-matched veterans without TBI (aged 48.6±19.8y). 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. 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.



b. In a new project we are examining the role of cardiovascular disease (CVD) in the relationship between TBI and dementia. Finding a strong connection may be evidence that dementia after TBI may be more mechanistically related to vascular dementia than Alzheimer's dementia. Specifically, we are looking to see if CVD diagnoses (coronary artery disease, TIA/stroke, heart failure, or atrial fibrillation) or CVD risk factors (smoking, obesity, hypertension, hypercholesterolemia, diabetes) increase the risk of dementia after TBI. Currently, we are finalizing definitions for CVD diagnoses, risk factors, and comorbidities, including mental health comorbidities. In this analysis, we will be examining Veterans aged 55 and older without dementia at baseline who have at least year of follow-up data. Our dataset has 97,708 Veterans with TBI history that meet these criteria. We will match those Veterans with TBI to Veterans without TBI and examine the contributions of CVD to dementia risk.

Phenotypes Study:

1. Task: Complete Regulatory Requirements.

a. a. Regulatory and Data Acquisition activities for VHA and DoD data for those in VA care complete. complete.

b. Data Acquisition: We have identified ICD-9 and ICD-10 based diagnoses through FY19 in VA health system data. We have requested DoD data through DaVINCI, and have received DoD data for individuals who have received any contact with VA. We are working with the DaVINCI team to obtain DoD data for individuals without VA contact. We have been successfully able to accomplish this for a different (but much smaller cohort) study.

c. In December we submitted the DSAA to DHA to obtain the DoD Trauma Registry in addition to the TBI Neuro module that recently became available. The new data source required a new application.

d. We submitted an amendment to include VA/DOD Identity Repository (VADIR) data, which provides information on deployment dates, number of deployments and locations of deployments for our cohort. The existing variable identifying those deployed based on the OEF/OIF roster needs updating, and this data source provides a more comprehensive description of deployment history. The amendment was approved in December, and the data request was submitted in late December.

2. Task: 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.

a. We are meeting with a broad group (biomarker core, neuroimaging core, prospective longitudinal study investigators) to develop papers identified by the investigators. These include

1. LTC Stewart will lead papers describing risk of TBI for the adverse outcome of marital status change after TBI and emergence of cardiovascular disease,
2. Dr Pogoda proposed analysis for identifying association between service-connected disability across different levels of TBI severity (none, mild, moderate/severe), higher DoD inpatient, outpatient, and medication regimens based on the cohort who has data in the Comprehensive TBI Evaluation data which has more clear information on TBI Severity.
3. Dr. Rachel Sayko Adams will describe predictors of substance use disorder (SUD) phenotype across deployed Veterans with different levels of TBI severity. We will describe the breakdown of different types of SUD (e.g., opioid use disorder, alcohol use disorder, cannabis use disorder, etc.), the types of SUD treatment received, and predictors of overdose, suicidal ideation/attempt, homelessness, all-cause mortality, and "deaths of despair." We are currently compiling data to address these aims.
4. We are also compiling data to address an analysis that will be led by Dr. Terri Pogoda to examine substance use disorders and related outcomes (overdose, suicidal ideation/attempt, homelessness, all-cause mortality, and "deaths of despair") for individuals with VA screening data that indicates no TBI exposure vs. TBI exposure without chronic symptoms. For instance a) those who report a head injury but no loss/alteration of conscious/post-traumatic amnesia (LOC/AOC/PTA), b) those with head injury with report of LOC/AOC/PTA but no initial post-concussion symptoms, c) those with head injury with report of LOC/AOC/PTA and initial post-concussion symptoms, but no current symptoms (classified currently as historically resolved).
5. Dr. Werner suggested a paper on sleep disorders using linked DoD and VA data.
6. We are compiling information on individuals with diagnoses of dementia that have been identified by our prior work as having high reliability and validity— Alzheimer's dementia (AD: ICD 9 331.0; ICD10: G309) and frontotemporal dementia (FTD: ICD-9 331.1; ICD10 G3101 G3109) and for the Journal of Neurotrauma special issue.

b. Using the data for all Post-9/11 era Veterans in VA care two or more years between FY2002 and FY2018 (N=1,794,598) we found very few cases of individuals with FTD and AD, but any cases in this young cohort is concerning. The majority for both conditions were diagnosed under under the age of 65, and over half were diagnosed under the age of 55 suggesting early onset dementia.

AD in VA		FTD in VA	
Dx in Both DoD+VA:	120	Dx in Both DoD+VA:	73
Dx in DoD	681	Dx in DoD	188
Dx in VA	326	Dx in VA	268
Total	1,127	Total	529
Prevalence	0.09%	Prevalence	0.03%
Median Age:	55	Median Age.	52
Percent ≥ 65 years:	20.23%	Percent ≥ 65 years:	11.72%

c. Basic descriptive data (chi square analysis) found that women are significantly less likely to have FTD diagnoses, Whites are significantly more likely to have both AD and FTD diagnoses, and Veterans who served in the Air Force are significantly more likely to be diagnosed with both AD and FTD diagnoses than expected by chance. Among individuals with either AD or FTD, prevalence of other diagnosed epilepsy and other neurological conditions were significantly higher than expected by chance.

d. Other neurological conditions defined by the Elixhauser algorithm include Parkinson's disease, multiple sclerosis, other demyelinating diseases of central nervous system, Huntingtons and other choreas, spinocerebellar disease, anterior horn and motor neuron disease, encephalopathy not classified elsewhere, aphasia, anoxic brain damage, and cerebral degeneration unspecified.

	AD n=1127 %	FTD n=529 %	Cohort N=1,794,598 %
Gender: Women	15.97	11.72	16.86
Race/Ethicity			
White	61.85	71.27	57.57
Black	18.37	12.48	18.42
Hispanic	11.27	8.70	10.05
Asian	1.51	1.89	2.40
Native American Pacific Islander	1.77	1.51	1.84
Unknown	5.24	4.16	9.53
Branch of Service			
Army	51.82	51.04	51.14
Navy/Coast Guard	16.95	17.01	18.10
Air Force	22.63	19.85	15.06
Marines	7.01	10.78	15.46
Epilepsy	17.04	23.82	2.23
Other Neurological Conditions			

e. We are working with data scientists to develop machine learning and logistic regression models to identify DoD (and VA) risk factors for these dementia diagnoses with an emphasis on.

3. Task: Convene stakeholder panel of VA and DoD operational partners.

a. We identified the following Veteran Stakeholders: VA PM&R, VA National Center on Homelessness among Veterans (NCHAV), VA Mental Health and Suicide Prevention, two Veterans with TBI, one caregiver of Veterans with TBI, two Active-Duty Service members and one recent retiree. Dr. Dismuke is also recruiting

additional active duty/Veteran and caregiver members. We held a stakeholder meeting with active-duty personnel in November 2020. .

Health Economics Study:

1. Task: Obtain DoD and VA authorizations.

   a. We submitted modification to the IRB protocol and DART to include the newly hired analyst and received approvals.

2. Task: 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.
   a. DUA between VA Palo Alto and VCU DBC was executed.
   b. Study DART was amended to include DUA between VA Palo Alto and VCU DBC and we received DART approval.

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

a. We hired an analyst with MD and PhD degrees. We received the cohort subjects' ID and SSN (TBI subjects) from VCU for the Health Economics Study. We uploaded the cohort to the VINCI firewall area, and we are performing quality checks to evaluate the availability of subjects' information in CDW and our research study projects.

b. For the Health Economics Longitudinal Study, the Veterans Heath Administration (VHA) Health Economics Resource Center (HERC), Center for Innovation to Implementation (Ci2i), Veterans Affairs Palo Alto Health Care System (VAPAHCS) transferred all the health related VA/DoD information for the LIMBIC study (up to November/December of 2020) to the Data and Biostatistics Core (DBC) at Virginia Commonwealth University (VCU). We have received Social Security Numbers (SSN) and their study IDs for 1556 subjects (both TBI and non TBI) from the VA study sites: Richmond, Tampa, Houston, San Antonio, Minnesota, Portland and Boston. The Subject SSN and ID are stored within the VINCI folder in our research project study. We identified the health care related information of 1542 subjects (SCRSSN) in the CDW (14 subjects do not have health records in VA health system). Using SAS grid, we created a macro to de-identify (removing the PHI) the available/requested tables in CDW. We de-identified and created total of 189 tables in 13 folders (25.91 GB) from VA/DoD database within VINCI and transferred them to the DBC at VCU web portal (https://www.limbic- cenc.org, LIMBIC-CENC). The transmitted data included the subject ID that can be matched with the Longitudinal Study data. We removed all the de-identified tables from all VAPAHCS's and VINCI servers to comply with VA data security policies. The transferred tables stored in the VCU web portal as following:

1 - BCMA (8 tables, 58.44 MB)
2 - COVID (14 tables, 3.06 MB)
3 - DaVINCI (33 tables, 2.56 GB)
4 - Fee (7 tables, 1.11 GB)
5 - HERC (7 tables, 46.56 MB + (Duplicated files in CSV=7 tables, 37.88 MB))
6 - MEDSAS (8 tables, 58.44 MB)
    A - INC (12 tables, 2.25 MB)
    B - INP (16 tables, 22.5 MB)
    C - OUTPAT (2 tables, 404.19 MB)
7 - NOSOS (2 tables, 24.5 MB)
8 - OMOP (14 tables, 973.44 MB) +
    A - DIM_Other (23 tables, 19.1 GB)
9 - OUTPAT (16 tables, 1.32 GB)
10 - PATSUB (7 tables, 9.94 MB)
11 - PSSG Geocoded (11 tables, 4.38 MB)
12 - RXOUT (4 tables, 257.25 MB)
13 - SSTAFF (3 tables, 3.94 MB)

14 - VETSNET (1 table, 1.5 MB)
15 - VITAL Status (1 table, 704 KB)

c. We also stripped real SSN and other patient identifiers from all Veterans in the longitudinal VINCI data for the following files: INP_PB, INP_PM, INPEXC_SM, INPEXC_XB, INPNVA_NB, INPNVA_NM, INPPCE, OUTP_SE. These files represent all inpatient stays inside and outside VA including long term care and bed stays. They also include all outpatient care within VA and provider claims associated with inpatient care inside and outside the VA. These files were uploaded to VCU servers for statisticians involved in the Dementia Study to search for dementia related diagnosis codes.

Novel Neuroimaging Study:

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

a. In a prior reporting period, we 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 are also including additional data to examine how this affects additional relationships with other clinical and outcome data. We have continued work on an initial manuscript on the results obtained to date.

b. 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 are continuing discussion of collaboration with this group and with others in the InTBIR and ENIGMA communities; we submitted an NIH R61/R33 grant application to explore this in the LIMBIC and other data, and this grant was successfully funded. Our team in working with other investigators to develop a decentralized COMBAT algorithm that can be applied in LIMBIC and other "big data" analyses.

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

a. 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 are also working with Drs. Stone, Tustison and Avants to utilize their SyMLR method, and are in the process of reviewing those results. We also submitted an NIH R01 grant application to explore additional analysis pipelines which scored well and will be resubmitted during the next cycle.

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

a. We are in the process of formulating a limited data set which can be used for this objective and creating a set of parameters which can be manipulated for testing.

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

a. 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.

5. Task: 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.

a. 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.

b. 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 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.

6. Task: Assess merits and challenges of existing methods of "individualized" data analysis.

a. Work on this aim is scheduled for a later stage in the project.

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

a. We are in the process of preparing the imaging data for the scheduled September submission. Please see the Neuroimaging Core report for additional information.

b. 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.

c. Neuroimaging Core investigators heavily 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.

Biomarkers Discovery Study:

1. Task 1: Obtain pre-deployment biospecimens from the DoD biorepository to assess pre-injury levels of candidate biomarkers in the CENC longitudinal cohort.
a. Full Regulatory approvals obtained (NIH exempt under Common Rule and HRPO second level approval received 12-2-2020). Obtaining pre-injury serum samples from DoD serum biorepository.

2. Task 2: Carry out biomarker discovery project (N = 2000) of Prospective Longitudinal Study participants, expanding initial project CENC study 1 initial participants.
a. Completed assays of 4 proteins (t-tau, NfL, GFAP & UCH-L1) on 1,200 Prospective Study participants. Completed inflammation panel (IL-6, IL-10, TNF-α) and now cleaning and preparing to lock database.
b. Published 3 manuscripts (NfL- Neurology; MiRNA- J Neurotrauma; Neurodegeneration biomarkers and poor sleep after mTBI- Sleep) and 1 author reply (NfL- Neurology). 1 manuscript revision under review (Exosomal MiRNA and Psych symptoms- Translation Psychiatry) and 3 manuscripts under prep (miRNA and sleep; miRNA and blast; Poor sleep and inflammatory biomarkers); Produced 1 podcast of Neurology NfL manuscript with AAN. Published Chapter on TBI Biomarkers in Brain Injury Medicine, Board Review, 7-19-2020. Submitted 10 abstracts for national/international conferences (3 accepted as oral presentations at MHSRS, 1 presented at ANA, 1 presented at European Sleep Research Society, 2 accepted as poster presentations at the SfN global connectome, and 3 submitted to Sleep 2021).
3. 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.
a. 6 manuscripts under prep (NED in mTBI, Exosome methods paper, miRNA and blast TBI, miRNA and poor sleep, Poor sleep and Inflammatory biomarkers, CENC Study 49 TBI Biomarkers with Nick Davenport). 3 manuscripts under review/revision (Biomarkers of TBI, poor sleep & cognition- Sleep; MiRNA & PTSD symptoms- Translational Psychiatry).

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

5. Task 5: Correlate candidate biomarker levels from pre-deployment and post-TBI specimens, as well as with outcome measures (neurobehavioral, imaging, neurocognitive testing).
a. Collaborating with Imaging and Informatics for Biomarker-Imaging analyses (Random Forest Biomarkers, DTI-NfL). Project is currently underway.

6. 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.
a. Correlations of candidate prognostic biomarker correlations with symptoms and outcomes underway.

Describe the Regulatory Protocol and Activity Status (if applicable).
Describe the Protocol and Activity Status for sections a-c, as applicable, using the format described for each section. If there is nothing significant to report during this reporting period, state "Nothing to Report."

(a) *Human Use Regulatory Protocols*

TOTAL PROTOCOLS: *State the total number of human use protocols required to complete this project (e.g., 5 human subject research protocols will be required to complete the Statement of Work."). If not applicable, write "No human subjects research will be performed to complete the Statement of Work."*

PROTOCOL(S): *List the identifier and title for all human use protocols needed to complete the project. Include information about the approved target number for clinical significance, type of submission, type of approval with associated dates, and performance status.*

The following format shall be used:

Protocol (of total):

Protocol [HRPO Assigned Number]:

Title:

Target required for clinical significance:

Target approved for clinical significance:

Submitted to and Approved by:

Provide bullet point list of protocol development, submission, amendments, and approvals (include IRB in addition to HRPO).

Status:

Report (i) progress on subject recruitment, screening, enrollment, completion, and numbers of each compared to original planned target(s), e.g., number of subjects enrolled versus total number proposed; (ii) amendments submitted to the IRB and USAMRMC HRPO for review; and (iii) any adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation.

TOTAL PROTOCOLS: 9 For all Regulatory reporting, please see Appendix #3 (Regulatory Tracking Spreadsheet).

What do you plan to do during the next reporting period to accomplish the goals and objectives?

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

CORES

Coordinating Center:

1. Continue to closely monitor all sites.
2. Continue certifying new study site personnel.
3. Continue to work with sites to gain IRB and HRPO Continuing Review approvals.
4. Hold our second CAB meeting.
5. Continue to interface with other researchers, entities, and consortiums.

Neuroimaging Core:

1. Conduct virtual refresher training at all project sites to review new Medidata form and procedures related to quarterly site assessment.
2. Assist in ensuring consistency as sites resume collection of neuroimaging data.
3. Prepare next installment of imaging data to FITBIR (by 31 MAR 2021)
4. Complete training of new neuroradiologist and MR physicist.
5. Continue monitoring quality assurance for neuroimaging data, as above.
6. Continue to perform analysis of imaging data on standard pipelines.
7. Continue work on pending and new analyses.

Biomarkers Core:

1. Continue to receive and distribute biospecimens.
2. Collate/store processed/aliquoted biospecimens (DNA/buffy coat, plasma, serum, saliva, RNA (PaxGene) from LIMBIC new and follow-up subjects.
3. Make samples in the biorepository available for analysis and sharing.
4. CR to be submitted to WRNMMC IRB first part of Feb.2021.
5. Continue to finalize new CRADA among USUHS, Geneva, Eisenhower (EAMC), and FBCH, requested by FBCH.
6. Continue collaborating with Bill Walker for evaluation of NED screen in Longitudinal sample; manuscript finalized and will submit to a special LIMBIC publication.

Data and Biostatistics Core:

1. Complete Medidata Migration.
2. Convene and complete 1st TBI Diagnosis Committee Meeting.
3. Finalize dashboards.
4. Finalize Data Cube.
5. Complete changes to Data Dictionary.
6. Implement electronic versions of internal reports (recruitment, visit completion, upcoming visit reports, retention, call center).
7. Finalize Dementia Prognostic Tool with Knowledge Translation Center.
8. Finalize and deploy Publication Committee Request Form.

STUDIES

Prospective Longitudinal Study:

1. Continue collecting data via the Remote Data Collection method since In-Person Follow-Up visits are not currently allowed at any of the enrollment sites.

2. Continue to prepare for enrollment initiation at 7 of the original sites (Richmond, Houston, Tampa, Fort Belvoir, Minneapolis, Portland and Boston) and 2 of the new sites (San Diego and Salisbury).
3. Continue training and certifying of personnel at the three new sites (Salisbury, San Diego and Fort Gordon) with a goal of being ready to initiate enrollments prior to the lifting of the pause on face-to-face participant research.
4. Continue to work on the regulatory issues at the San Antonio and the Fort Gordon sites.
5. Carry on with all study procedure and administrative activities including telephonic longitudinal visits, data collection and quality assurance.
6. Continue work on scientific analyses, dissemination, and knowledge translation.

Retrospective Data Base Study:

1. Continue 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.

Phenotypes Study:

1. Obtain data from DoDTR and Joint Trauma System TBI Neuro Module Data requests and obtain DoD health system data for those who do not enter VA.
2. Process DoDTR and DoD Health System data for individuals not in VA care once data are available
3. Develop new variables using VA and DoD health system data based on new data requests by investigators based on staffing availability.
4. Develop manuscript for Neurotrauma Special Issue
5. Continue SUD disorder outcomes papers.
6. Assist Dr. Dismuke as needed.

Health Economics Study:

1. Stanford IRB and VA Palo Alto R&D approvals have been sent to Mary Jo Pugh at Utah to add Dr. Dismuke-Greer to the VINCI DART for Dr. Dismuke-Greer to begin to work with the Utah team on data cleaning, merging and analysis.
2. Continue obtaining real SSNs of study subjects to provide to VINCI to obtain VA and DoD data (Da VINCI) on these subjects.

Novel Neuroimaging Study:

1. If allowed given the COVID travel and infection control restrictions and stay at home orders, 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. Complete manuscript and review of SYMLR analysis.
6. Continue to work with other consortia and military-relevant groups (e.g., ENIGMA, InTBIR, TED, TRACK-TBI) to collaborate on data aggregation and analysis.

Biomarkers Discovery Study:

1. Merge clinical and laboratory data
2. Obtain pre-injury samples

3. Examine relationships of 4-plex data and 3-plex data and TBI exposures, resulting in manuscript(s) to be submitted by 4/2021, including the Neurotrauma special issue
4. Develop a manuscript to link protein changes to chronic symptoms related to TBI, to be submitted by 5/2021

2. Products: List any products resulting from the project during the reporting period. If there are no products to report for the current quarter, state "Nothing to report."

Examples of products include:

- *publications, conference papers, and presentations;*
- *website(s) or other Internet site(s);*
- *technologies or techniques;*
- *inventions, patent applications, and/or licenses; and*
- *other products, such as data or databases, biospecimen collections, germplasm, audio or video products, software, models, educational aids or curricula, instruments or equipment, data and research material, clinical or educational interventions, or new business creation.*

Please see Appendix #2 (Publications Tracker) and all of the publications and presentations for this quarter are attached to end of this report.

3. Participants & Other Collaborating Organizations

What individuals have worked on the project?
Provide the following information for: (1) Project Directors (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).

Provide the name and identify the role the person played in the project. Indicate the nearest whole person month (Calendar, Academic, Summer) that the individual worked on the project. Show the most senior role in which the person worked on the project for any significant length of time. For example, if an undergraduate student graduated, entered graduate school, and continued to work on the project, show that person as a graduate student, preferably explaining the change in involvement.

Describe how this person contributed to the project. If information is unchanged from a previous submission, provide the name only and indicate "no change."

See Appendix #4 for Personnel Effort and Quarterly Financials.

4. Changes/Problems: The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer 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:

a. Actual Problems or delays and actions to resolve them

Provide a description of current problems or issues that may impede performance or progress of this project along with proposed corrective action. Also 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.

For an award that includes the recruitment of human subjects for clinical research or a clinical trial, discuss any problems or barriers encountered, if applicable, and what has been done to mitigate those issues. Discussion may highlight enrollment problems, retention problems, and actions taken to increase enrollment and/or improve retention.

1. The COVID-19 pandemic is having a significant impact on our consortium, especially so in the Prospective Longitudinal Study. Just as the original 8 sites were receiving HRPO approvals, all enrollment locations started shutting down in-person research. Portland was able to enroll 6 new participants prior to the shutdown but none of the other locations were able to initiate enrollment operations. However, all of the locations are able to continue collecting data during this time frame due to a remote data collection system that we had previously set up to handle participants that were not able to return for in-person visits for some reason. Last quarter, some of our sites received permission to restart in-person research activities for this study. Unfortunately, new recruitment and enrollments remain suspended at several sites and for those that are restarted, potential participants remain reticent to come in for their enrollment visits due to the new surge in COVID-19 cases throughout the U.S. Sites that have been permitted to restart face-to-face have all enacted mitigation strategies that reduce COVID transmission risk, but complicate the assessments (e.g. social distancing and masking interfering with communication and not allowing hands-on assessments, cleaning and disinfection procedures that lengthen the evaluation). As the pandemic continues to cause the PLS sites disruptions with in-person research, concern is mounting that we will have difficulty reaching our end-goal of 3000 participants. As of today, we are able to shift the year one projections into years 2-5 but that will be difficult to manage if we remain significantly curtailed for another 6 months. Our longitudinal assessments have remained operational with good retention, however we have been unable to collect the portions of data that require in-person visit (e.g. blood, MRI). As a corrective action, we developed and launched procedures for collecting additional data remotely for the comprehensive longitudinal assessments including additional questionnaires (by mail or home internet), video enabled interviews and neuropsychological tests.

2. The other studies and cores have adapted to new work arrangements and most if not all of the actions listed in our Statement of Work are still able to be completed but with some delay.

3. With the exception of being able to collect phantom and participant imaging data because of the COVID-19 restrictions, the Neuroimaging Core is generally able to progress in our work as planned. Our neuroradiologists have been very busy with COVID-19-reated clinical work, and this resulted in a slight delay in completing the clinical reads by March 31. However, we anticipate that this will be complete in the coming weeks and that the delay is not sufficient to warrant bringing on additional neuroradiologists.

4. Biomarker's Core: Current research restrictions due to the COVID-19 pandemic resulted in the halting of new enrollments and shipments which imposed unexpected delays in workflow. Shipments have begun again but with the surges in COVID, enrollments and shipments are tenuous at this time.

a. Duration of shutdown: CENC/LIMBIC Biorepository was not closed due to COVID but sites were closed or restricted so no shipments of specimens were going into the Biorepository. The Biorepository personnel could not assemble or ship new lab kits to enrolling sites as they normally would have from 3/16/2020 until 8/15/2020. The Biorepository personnel also could not ship specimens to approved projects during that same period. The NIH lab was completely shut down for 6 weeks, 3/13/2020 through 5/1/2020. Enrolling sites that usually ship samples to the Biorepository were unable to ship

samples. Sites that had requested samples from the Biorepository before the shutdown were also closed for various periods of time. No new requests for samples could be filled.

b. % capacity for study activities at each site The Biorepository at USUHS was at 10% (emergency maintenance only) from March until August, 2020 and is now at 100%. The Biomarker Core NIH laboratory was at 0% for 6 weeks and is now at 100%.

c. Description of what study activities were impacted/restricted: Lab personnel were not allowed to be in the NIH lab to accept new samples and unable to ship requested samples for 5 months (March to August, 2020). Quest Diagnostics could not perform analyses contracted for with the Biorepository or the NIH lab since they were receiving no samples.

5. Discovery Project: activities were impacted by the shutdown, as well. No lab analyses could be done while the NIH lab was closed to personnel for 6 weeks. No shipments from Quest Diagnostics for analyses Dr. Gill was overseeing.

a. Steps taken to safely reopen: CENC/LIMBIC Biorepository lab personnel implemented the CDC Stop the Spread guidelines by wearing masks, PPE, hand sanitizer stations throughout the lab, and socially distancing 6 ft. apart.

6. The Novel Neuroimaging Study has generally been able to progress through its work as planned. With the exception of a delay in collecting phantom and participant imaging data because of the COVID-19 restrictions.

7. Because of the nature of the Neuroimaging Core, our work and the existing infrastructure we had developed, the Neuroimaging Core team was minimally affected both by the COVID-19 shut down and by the current working environment. Obviously, some members were affected to varying degrees by individual challenges related to their personal situations (e.g., loss of childcare and having children at home, etc.), but these were largely accommodated by shifting work schedules, etc.). Drs. Wilde and Tate were generally able to communicate with members of the team on a daily or near-daily basis. There were five major areas that were or have been impacted by the pandemic.

a. Early in the course of the pandemic, and to a more limited degree now, the neuroradiologists involved in the clinical reading/coding experienced increased clinical demands related to the pandemic (leaving less time for research), which slowed clinical reads.

b. Neuroimaging Core personnel had planned to travel to each site for annual site training meetings and to collect human phantom data on each scanner used in the project. Travel restrictions imposed nationwide, by the VA, and by academic institutions has prohibited.

8. The Phenotype study is working with DaVINCI to obtain DoD data for individuals who are not VA patients. The guidance suggests this is possible, but the Data Steward at VINCI says this isn't possible. Dr. Pugh is working with Dr. Duvall to resolve this issue.

b. Anticipated Problems/Issues

Provide a description of anticipated problems or issues that have a potential to impede performance or progress. Also provide course of actions planned to mitigate problems or to take should the problem materialize.

1. The recruiting goals for the Prospective Longitudinal Study have been delayed by five quarters at this time and it appears that this will continue for at least one more quarter if not more. We had room to shift these recruitment goals to the back end of the Period of Performance at this time but given the ongoing restrictions and barriers from COVID19, we are uncertain if we will reach our original goal of 3,000 enrollments. Our longitudinal assessments remain operational with good retention, however we have been unable to collect the portions of data that require in-person visit (e.g. blood, MRI).

2. Due to the Covid-19 pandemic, the Retrospective Study has experienced some minor delays in their dataset creation, merging, and early analyses due to staff working from home. The VA servers they use for their projects are running slowly due to the increased access from home computers. They estimate that they may incur a 3-4 month delay due to the pandemic and shelter-in-place orders if not lifted soon.

3. Rates of enrollment and follow-up activity have been variable depending on COVID restrictions and return to work modifications/precautions and amount of participant in-person contact allowed at the individual sites. Because of the lack of enrollment of new participants in LIMBIC Prospective study, the GWAS sub-study may be delayed until sufficient LIMBIC participants have been enrolled for our power analysis.

5. Special Reporting Requirements:

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

See Appendix #5 for Quad Charts.