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 Enrollment 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. (Months 1-12)

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. (Months 6-30)

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. (Months 24-50)

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. (Months 24-60)

Phenotypes Study:

1. Task: Complete Regulatory Requirements.
   a. 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.
   a. 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.
   a. 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.
   a. 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.
    a. 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.
    a. 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.
    a. 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.
    a. 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.
    a. 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.
    a. 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.
7. 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.
    c. We replaced one of our long-time team members this past quarter, bringing the team back up to full strength. However, the Co-Director resigned which forced the consortium to adjust some of the duties within the Coordinating Center and the Data and Biostatistics core, mainly that of Regulatory Issues.

2. Add three new additional Prospective Study Enrollment Sites:

    a. Continued the onboarding process with the 3 new Prospective Longitudinal Study enrollment sites (Salisbury/San Diego/Fort Gordon). All three sites initiated enrollment of new participants. San Diego and Fort Gordon are still working out the kinks to get participants fully enrolled and turned into the Graduated to Follow Up stage but Salisbury has already fully mastered the process. In fact, they were not only our highest performing new site in March but our overall highest performing site out of all 11 sites.
    b. Continue to assist with the training of all new staff, especially as they begin to use all of the systems that we have trained them on months ago. This will be an ongoing process due to normal departures of site staff personnel as well as maternity leave.
    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 and she now has her WOC approved so that she can be added to the Richmond Site Study Team. This completed 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. Continue to work with the DBC in order to refine the Call Center Application.

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 in order to prepare and submit the first quarter Quarterly Report.

5. Conduct Consumer Advisory Board Meetings:

    a. Invited the CAB leaders to sit in during our Consortium-wide calls on the 3rd Monday of every month in order to gain a better and more up-to-date understanding of our progress and issues.
    b. We conducted a CAB meeting on February 2, 2021. We provided a brief consortium update as well as Dr. Seel provided a presentation on the Dementia Prognostic Tool Indicator, gaining a lot of valuable feedback.

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 on time.

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 by IRB 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 for this year during this review period, 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. HRPO has also determined the Core activities to constitute NHSR. We received notice of approval on 21 JAN 2021: Log E01140.7a.

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.'

   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 finalized all 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 have trained a new neuroradiologist who will be involved in the clinical reads and CDE codings under LIMBIC (i.e., Dr. Robert Shih).

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). We are awaiting formal VA approval to release the data in FITBIR to the public.

c. Scheduled LIMBIC upload of imaging data to FITBIR was completed in March, according to schedule.

d. 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). This has required working with site personnel to verify final subject list and transfer data that was not previously stored by the Neuroimaging Core.

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

f. 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.

g. 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 sufficient for the project. Continuing to receive, log, store, and distribute samples.
b. Quest lab continues to perform NED screen (IGF-1, testosterone, TSH) as requested.
c. Continue to receive shipments from LIMBIC sites, as VA sites resumes new enrollments post-COVID and from new sites added.
d. The 3 new sites, VA San Diego Health Care System, San Diego, CA, Salisbury VA Health Care System, Salisbury, NC, and Eisenhower Army Medical Center, Fort Gordon, GA, are up and running.
e. As of, 3-36-2021, BR has collated/stored processed/aliquoted biospecimens (DNA/buffy coat, plasma, serum, saliva, RNA (PaxGene) from 1951 (10 new this quarter) PLS (447) follow-up, (7 new this quarter) subjects, as well as samples from 163 previous CENC studies (2005 aliquots) and (300 aliquots) for current total 26,058 aliquots of in the biorepository available for analysis and 4202 (152 this quarter) shipped out.
f. Received 1 new shipment of 140 aliquots from Portland (new site) this quarter. Some samples are from new participants and some from follow-ups.

2. Task 2: IRB protocol development, submission, and continuing review. (Locally and in conjunction with Coordinating Center at VCU).
   a. Regulatory approvals and required submissions complete and up to date.
   b. Most current CR approved by USUHS IRB this quarter on 3-16-2021.
   c. CR submitted HRPO 3/18/2021 for second level approval, approval pending.
   d. No modifications this quarter.

3. Task 3: Task 3: Share data with external investigators through biannual submission to FITBIR (March and September) by VCU. NED and APOE data entered into FITBIR in March 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. No genotyping carried out this quarter. Waiting for a few more enrollments to meet the batch goal (100per batch) for cost-effective analysis in prospective study. As soon at the batch number is met, samples will be shipped to NIH for genotyping as planned.

5. Task 5: Carry out service operations (neuroendocrine screen through CLIA-certified lab).
   a. NED screening through Quest of samples of new enrollments in LIMBIC prospective study.
   b. Collaborating with Bill Walker for evaluation of NED screen in Longitudinal sample; manuscript finalized and has been submitted to Journal of Neurotrauma and in revision stage in response to the editors. Abstract of analysis results submitted 2021 MHSRS.

6. Task 6: Manage biospecimen sharing with LIMBIC-CENC and external investigators.
   a. 3 collaborative projects under way (MTA's with 3 sites and shipping completed):
      (1) Roskamp Institute, Fiona Crawford, "Identifying APOE Related Lipid Biomarkers for Diagnosing Chronic Neurocognitive Deficits in TBI patients".
      (2) Tampa VA, Drs. Patel/Nakase-Richardson, "Noncoding RNA in traumatic brain injury".
      (3) Roskamp Institute, Fiona Crawford for lipidomic analysis ongoing
   b. MSD, Chris Campbell, "Ultrasensitive Blood Tests for Investigating Pathogenesis of Chronic TBI symptoms" (145 samples from Nick Davenport CENC Study 49).
   c. 1 Request under review: MSD, Chris Campbell, "Ultrasensitive Blood Tests for Investigating Pathogenesis
   d. of Chronic TBI symptoms" (additional 500 samples from PLS requested) – Validation phase of MSD project underway with additional samples from PLS requested based on discovery set results.
   e. New CRADA still 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.
   1. Prepared for and will attend the GSC meeting on April 20th.

S01C - Total Shipments per site

Center	Total Shipments
San Antonio	29
Richmond	48
Tampa	35
Houston	26
Portland	20
Boston	13
Minneapolis VAHCS	15
Fort Belvoir	10
S01C - Total Blood Draws Rec'd (440 new)	**1951**
Number from 1yr. Follow-up visits (17 new)	**447**

S01C - Total Material Types Received

Material Type	Vials Currently In Inventory	Vials Shipped Out
Buffy Coat	1698	1308
DNA	1191	0
Stock DNA	196	0
Plasma	9205	2550
Saliva	1741	194
Serum	10178	150
Whole Blood (PaxGene)	1849	0
Grand Total:	**26058**	**4052**

Specimen Request	Total
S01C-Buffy Coat 1st request	214
S01C-Buffy Coat 2nd request	268
S01C-Buffy Coat 3rd request	282
S01C-Buffy Coat 4th request	241
S01C-Buffy Coat 5th request	279
S01C- Plasma Request	2690
S01C- Saliva Request	194
SO1C- Serum Request	150

Currently there are only 99 Genetic Consented Baseline Samples IDs that have not had DNA Extractions.

Data and Biostatistics Core:

1. **Major Activities**:

- Data capture, storage and QC
- Developing and implementing data capture and collection training and workshops for 11 enrollment sites
- IT Systems and Infrastructure
- Data Requests
- Data Request Infrastructure
- Data Dictionary
- FITBIR data submission preparation
- Knowledge Translation

2. **Specific Objectives**:

a. Developing IT Systems and Infrastructure.

1) Updated and maintained content of the public and private sides of the LIMBIC-CENC website
2) Provided ongoing Medidata and Study Portal user-end support
3) Completed Medidata mentorship phase, such that the team now works independently on tasks and seeks support from Medidata when needed
4) Completed the first independent migration successfully in Medidata.
5) Maintained and made improvements to Call Center Application, including adding new features requested by Call Center staff
6) Finalized implementation of the new Neuroimaging Quarterly Self-Audit Report module in the Study Portal and disseminated login information to all enrollment site and the neuroimaging core staff
7) Updated/optimized system for regular, automated download of clinical data from Medidata to LIMBIC-CENC database on server
8) Implemented dynamic (i.e., updated in near real time as data is captured in Medidata) automated dashboard reports to track enrollments, recruitment, graduated to follow-up and receipt of biospecimen and MRIs.
9) Implemented dynamic Biomarkers Core reports to track biofluid availability.
10) Initiated April 2021 version of Data at a Glance
11) Developed and implemented 1st version of Publication Committee Request Form, which optimizes the previous system that used emails and will facilitate tracking of dissemination products.
12) Implemented a regulatory tracking module to track all the regulatory information and documents for the consortium.

b. Data Management

3. Data Collection
   I. Continued managing data capture (primarily through Medidata), and efficiently and securely stored all clinical data, and biospecimen and neuroimaging data for Prospective Longitudinal Study
   II. Successfully completed 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.
   III. Successfully added three new CRFs for LIMBIC-CENC: BETS, CDR, and COVID-19 questionnaire
   IV. Successfully implemented secondary data capture system through REDCap to facilitate remote data collection for baseline visits and automated transfer of data into Medidata.

4. Clinical Data Quality Assurance and Quality Check (QA/QC)
   I. Continued monthly QA and QC of clinical data in Medidata

II. Pulled together review materials for the TBI Diagnosis Committee for all potential problematic cases
III. Assisted Call Center to ensure all BTACT and annual telephone visits are completed in a timely manner
IV. Managed and coordinated NIH Toolbox, EEG, CDP, Righteye and other raw file uploads in SFTP server
V. Completed quarterly QC of NIH Toolbox data
VI. Monthly Site Metrics Reports detailing sites' performance in timeliness, accuracy, and completeness of data entry continue to be generated
VII. The QC team has developed 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 are 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. Neuroimaging Core
   I. Assisted in inventory and reconciliation of scans across neuroimaging core databases
   II. Regularly QA/QC clinical read forms in Medidata

6. Biomarkers Core
   I. Assisted in reconciliation of biospecimen sample received by the biomarkers core
   II. Ongoing transfer of consent permissions (per subject) and future research use to the biomarkers core.

   a. Trainings and Certification
      (1) Continued hosting monthly Q&A sessions with all 11 PLS sites providing guidance and resources for data collection and query management
      (2) Hosted ad-hoc workshops to train site staff on administering CRFs, Study Portal modules, and other data capture systems.
      (3) Created and disseminated technical memos
      (4) Certified new site staff on administering PCE Mapping and RCDI interviews
      (5) Certified new PIs on RCDI discrepancy review and indexing participants

   b. Data Requests

      (1) Provided guidance to investigators on submitting research requests and availability of study data
      (2) Disseminated requested data to investigators and provided analytical support for manuscripts, presentations, and other dissemination products
      (3) 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. Finalized implementation of online query tool (Data Cube) to allow investigators to determine available sample size(s) to inform data requests.

   c. Data Request Processing:
      (1) Completed and disseminated analytic data sets for three previously approved data requests. Two data sets were released to LIMBIC-CENC Biostatistics group for statistical analysis and one data asset released to investigator at California.
      (2) Provided additional variables to previously disseminated analytic data sets for two data requests for investigators at Tampa and Salt Lake City.
      (3) Central Biostatistics is actively conducting advanced analyses for 4 investigators and one for already initiated projects and performing analysis on VINCI data for another approved project.
      (4) Central Biostatistics group began exploring ideas for phenotype analyses to present to the study PI and investigators

   d. Data Dictionary:

(1) Structural changes has been completed and it's currently in the final stages of validation and implementation.
(2) The new version when released will include elements from CRFs and will also match data elements/variables in the analytical data sets.
(3) This structural change will ease the process of locating specific Form(s) or variables within data dictionary and their corresponding data.

e. FITBIR Data Submission Preparation:
(1) Worked with FITBIR Operations Team to create BETS and CDR form structures
(2) Validated collected data against the newly created form structures
(3) Attended biweekly meetings with FITBIR Operations
(4) Completed March 2021 submission; 94 Forms were resubmitted (i.e., data up to September 2020) as a part of FITBIR study closeout. The new process of automating and streamlining FITBIR submission has drastically reduced data and forms preparations. Data core team continues to look for more report automation technology and processes.
(5) Continued working with sites to ensure conversion of all pseudo GUIDs to GUIDs

f. Knowledge Translation:
(1) Updated Website with Core Online Products (On-going)
I. Developed template for new organization of Service member, Veterans page for knowledge translation products.
II. Began programming changes for this page
i. Updated lay abstracts and postcards for LIMBIC-CENC registry studies; doing quality control on biomarker/imaging abstracts
ii. Awaiting new organization of Service member, Veterans page prior to moving existing materials on website and uploading the new materials

(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. Initial programming completed for Dementia Risk Survey and Personalized Report on Website Test Symptom.
II. My Dementia Risk Profile' and 'Veteran Dementia Risk Fact Sheet' was vetted in LIMBIC-CENC Consumer Advisory Board meeting on 2/2/2021; all feedback was documented and changes that were easy to implement were incorporated on the prognostic tool and fact sheets.
III. Conducted significant user acceptance testing to ensure that all survey item responses accurately increased or decreased the dementia risk dial, and triggered the correct personalized recommendations. Programming changes made following three rounds of testing.
IV. Finalized review of the Veteran and Clinician Dementia Risk Fact Sheets.
V. Deployed My Dementia Risk Profile and the Dementia Risk Fact Sheets on the LIMBIC-CENC website.

(4) Created LIMBIC-CENC Searchable Journal Database:
I. Updated search criteria with LIMBIC-CENC research faculty members and ran a literature search of peer-reviewed publications thru 2-28-2021, which identified 126 new publications to add to the system.
i. Set-up structured abstract sections and labeled research categories for all 126 new publications.
ii. Uploaded the 126 articles into the database.

II. Added ‘and’ ‘or’ selection feature to ‘Advanced search’ that programs ‘and’ or ‘or’ between each search phrase.
III. Added RAND Maturity category on the Structured Abstract page of all studies.

(5) LIMBIC-CENC/Biogen Dementia Awareness, Education and Prevention Campaign: Met with Biogen regarding the proposal and provided answers to outstanding questions.

(6) *Brain Injury* Special Issue:
I. Switched proposed contract from Journal of Neurotrauma to Brain Injury to produce 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. Authors regularly report progress on special issue articles.
III. Will include consumer pages, a podcast for each article, and two webinars.

2. **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; 1 in under review).
- Basic FITBIR infrastructure is prepared for September LIMBIC-CENC FITBIR submission.

STUDIES

Prospective Longitudinal Study:

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: Previously completed, but ongoing for continuing review. All PLS sites, including the new LIMBIC sites, have gained initial HRPO approval and all have maintained their active approval status under continuing review processes.

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 – With easing of COVID restrictions to variable degree and timing across PLS sites, this is now fully completed for ten of the eleven PLS sites. The exception, Boston site, remains barred by their local facility from conducting in-person research for this study.
   (1) Retention plan has been initiated and implemented.
   (2) Recruitment and new enrollments were initiated: This quarter, 55 new participants were consented and 53 completed all the required baseline/enrollment assessments to be graduated to follow-up, for cumulative totals of 72 consents and 70 graduated to follow-up in the first six quarters of LIMBIC-CENC.

g. Conduct follow-up Assessments to include phone assessments. – ongoing
   (1) This quarter, 191 new Brief Annual Follow-Up evaluations were completed and 48 new comprehensive Follow-Up evaluations were completed for an accumulated total of 1176 Brief Annual and 335 Comprehensive Follow-Ups in the first six 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.
      I. For public site, see: https://www.limbic-cenc.org/index.php/knowledge-translation-center/data-at-a-glance/
      II. For private side; additional metrics are being added at the following URL: https://www.limbic-cenc.org/index.php/study-operations/dashboard/
      III. This quarter, finished developing and the DBC deployed 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 continued to be curtailed by COVID-19 pandemic. As mentioned earlier, the ban on in-person research was lifted at ten of our sites by the end of this reporting quarter. Nevertheless, many participants remain unwilling or unable to come on-site due to COVID concerns or COVID related lifestyle changes such as need to monitor children doing remote schooling. Because we worked proactively and quickly to set up and deploy new processes, we are able to collect some additional neuropsychological data during our back-up remote comprehensive visits. For all of our new data collected, we continued the following activities:
   (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.

2. During last quarter, <u>datasets were released for the following newly approved data analysis projects</u>:

Principal Investigator	**Title of Analysis Project**
Bailie, Jason	The Impact of Blast Exposure on Recovery Trajectory from Mild Traumatic Brain Injury
Bailie, Jason	Military Occupational Specialties and Blast Exposure Risk Related to Health Outcomes
Walker, William	Characterizing cognitive and functional profiles by dementia medical record code status within the CENC multicenter cohort

3. 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.

4. Last quarter, the following manuscripts were disseminated as <u>new electronic publications in scientific journals</u>:

Citation	Key Points		
	Question	Findings	Meaning
O'Neil ME, Klyce DW, Pogoda TK, Eggleston BE, Cameron DC, Wilde EA, Walker WC, Cifu DX, Carlson KF. Associations Among PTSD and Postconcussive Symptoms in the Long-Term Impact of Military-Relevant Brain Injury Consortium-Chronic Effects of Neurotrauma Consortium Prospective, Longitudinal Study Cohort. J Head Trauma Rehabil. 2021 Feb 22. Online ahead of print. PMID: 33656490.	How do mTBI-related symptoms measured by the Neurobehavioral Symptom Inventory (NSI) correlate with mTBI history and PTSD status?	NSI symptoms highly correlated with PTSD symptoms in both mTBI positive and negative. Symptoms clustered similarly (somatosensory, affective, cognitive, and vestibular) regardless of mTBI or PTSD status.	NSI symptom clusters are broadly valid for future research and may serve as useful clinical constructs for evaluation and treatment.
Miles, S. R., Silva, M. A., Neumann, D., Dillahunt-Aspillaga, C., Corrigan, J. D., Tang, X., Eapen, B. C., & Nakase-Richardson, R. (2021). Demographic and mental health predictors of arrests up to 10 years post-traumatic brain injury: A Veterans Affairs TBI Model Systems study. J Head Trauma Rehabil. 2021 Jan 27. Online ahead of print. PMID: 33528175.	What factors are associated with prior arrests and felony incarceration among combat-exposed Veterans and Service Members (Vs/SMs)?	In the LIMBIC-CENC PLS, 35% of Vs/SMs had prior arrest and 3% had prior felony incarceration. The incarcerated group was younger, less educated, and had less social support, greater PTSD symptoms and had higher proportions of men, never being married, and hazardous alcohol use. The same pattern of differences was observed for the arrest-only group compared to the no arrest group. Non-correlates included mTBI history.	Among combat-exposed Vs/SMs, the correlates of legal involvement span demographic and psychological dimensions. Some are modifiable, including social support, PTSD symptoms, and alcohol use. Addressing these risk factors may lower the risk of future criminal justice involvement.

5. Last quarter, the following manuscripts were disseminated as <u>new print publications in scientific journals</u>:

Citation	Key Points		
	Question	Findings	Meaning
Yee, J., Marchany, K., Greenan, M. A., Walker, W. C., & Pogoda, T. K. (2021). Potential concussive event narratives of post-9/11 combat veterans: Chronic Effects of Neurotrauma Consortium study. Military	What ways did current and former Post-9/11 combat-deployed U.S. military SMs experience	Among Boston-site participants, 51% of worst deployment-incurred PCEs were blast-related. Qualitative analysis of semi-structured interview found these leading	First-hand accounts of PCEs offer a richness in description and intensity not often captured in quantitatively-oriented head injury research.

Medicine, Volume 186, Issue Supplement_1, January-February 2021, Pages 559–566.	potential concussive events (PCEs)?	themes: driving over IEDs, knocked off feet by blast and hitting head on another object or surface, and experiencing headache or disorientation even without physical impact to head.	Capturing this qualitative data should lead to better understanding their relation to any acute and long-term effects.

6. During the last quarter, the following manuscripts were <u>submitted for publication in scientific journals</u>:

Authors/Title	Key Points		
	Question	Findings	Meaning
Franke LM, Perera R, Aygemang A, Marqhardt C, Teich C, Sponheim SR, Duncan CC, Walker WC. Assessing auditory brain potentials as potential markers of risk for late-life cognitive decline after mTBI: A LIMBIC-CENC study. Submitted to Clin Neurophysiol.	What is the relationship between mTBI history, auditory Evoked Response Potential (ERP) metrics, and common comorbidities?	Auditory brain function differed between the positive and negative mTBI groups, especially for repetitive injury, which implicated more basic, early auditory processing than did any mTBI exposure. Symptoms of internalizing psychopathology (depression and anxiety) and hearing loss are implicated in mTBI's diminished brain responses to behaviorally relevant and novel stimuli.	A mid-life neurologic vulnerability conferred by mTBI, particularly repetitive mTBI, may be detectable using auditory brain potentials, and so auditory ERPs are a target for study of dementia risk in this population.

7. **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.

8. 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). Also, many comorbidities and psychological factors have been identified as associated with poorer outcomes; addressing those that are modifiable through clinical care and further research may improve outcomes.

9. 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.

<u>Retrospective Data Base Study</u>:

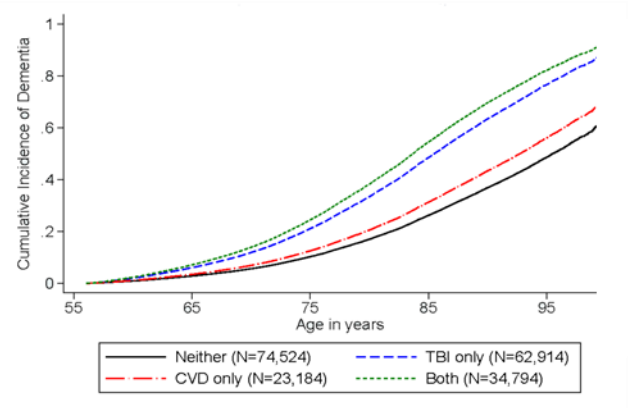
1. <u>Task 1</u>: Planning and regulatory review, data updating, and variable creation.

a. Our project continues to move forward and report great progress in Year 2, Quarter 2. 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. In the past quarter we finalized an analysis examining cardiovascular disease and its relationship to TBI/dementia (part of Task 2). The manuscript is nearing completion and will be submitted for the LIMBIC Special Issue. We also began an analysis exploring dementia risk factors after TBI (Task 3.

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. TBI, Cardiovascular Disease (CVD), and Risk of Dementia: While both CVD and TBI are important risk factors for dementia, little is known about their inter-related effects on this risk. Our objective was to investigate the role of CVD and TBI on risk of dementia by studying a large, diverse, nationally representative cohort of older Veterans. We studied 195,416 Veterans age 55+ diagnosed with TBI within the Veterans Health Administration in the US (October 1, 2001 to September 30, 2019) and a comparison sample of Veterans without TBI matched on age, sex, and race. Veterans had ≥ 1 follow-up visit and were without prevalent dementia. We defined CVD as coronary artery disease, heart failure, atrial fibrillation, and stroke/transient ischemic attack.

      At baseline, Veterans had a mean age of 67 (SD 9.3 years), were 6% female and 80% white. During follow-up (mean 6.6 years), 12.0%, of Veterans with TBI only received dementia diagnosis (HR: 2.13 95% CI 2.05-2.21), 10.3% with CVD only developed dementia (HR 1.20 95% CI 1.14-1.26), compared to 6.5% with neither exposure. Among Veterans with both TBI and CVD, 18.4% received a dementia diagnosis (HR 2.39, 95% CI 2.30-2.49).



   b. TBI and CVD independently increase risk for dementia among older US Veterans; together they had an additive effect with risk highest for Veterans who have both exposures, suggesting that careful prevention/management of CVD in older Veterans with TBI is needed.

Phenotypes Study:

1. Task: Complete Regulatory Requirements.

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

   b. Data Acquisition:
      - Preliminary Stakeholder Panel meeting November 2020; Updated panel meeting scheduled. Includes Veterans, Active-Duty clinicians and line personnel. Dr. Dismuke will lead this effort.

- All data except DODTR obtained; working on this with LCDR Werner, our DoD sponsor and DHA and have completed USU IRB statement of findings. We are on the final steps for obtaining the DSAA approval for the DoDTR data.
- We received 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. These data were used to identify the deployed and non-deployed cohorts.
- We are awaiting National Death Index data for this DoD only, DoD+VA data cohort.
- We are identifying ICD-9 and ICD-10 based diagnoses through FY20 in DoD health system data
- We have received notification that we will eventually be able to obtain military treatment facility cost data via DaVINCI. This is a special permission for this study only.

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 have updated data through FY20 and are developing code for conditions, procedures, etc. for the FY20 data.
   b. We are meeting with a broad group (biomarker core, neuroimaging core, prospective longitudinal study investigators) to develop papers identified by the investigators using previously developed data.

3. Task: Convene stakeholder panel of VA and DoD operational partners: 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 have a stakeholder meeting with active-duty Active duty service members and Veterans in May, 2021. Dr. Dismuke will lead this effort going forward.

4. Task: Use phenotypes and mTBI to develop risk scores for military outcomes, neurosensory/neurodegenerative disease, and adverse outcomes by deployment.
   - Milestones: Develop risk scores for military outcomes, neurosensory/neurodegenerative disease, and adverse outcomes by deployment (months 24-48)

   We are preparing for phenotype analysis by conducting traditional biostatistics analyses.

   a. We are continuing to work on the special issue paper describing phenotypes of cognitive dysfunction associated with TBI.
   b. We completed a homelessness paper developed in partnership with the National Center on Homelessness in Veterans and submitted it to the American Journal of Public Health. Our goal was to determine if homelessness was more common among Veterans who had TBI diagnoses documented in DoD care. We also examined the impact of race/ethnicity, other comorbidity and relative socioeconomic disadvantage using the area deprivation index (ADI).

      We conducted multivariable Cox proportional hazards models to model time to homelessness and time to criminal justice involvement, both within 2 years of separation from the military. All statistical analyses were conducted in SAS, assumed a 2-sided alpha of 0.05, and controlled for the aforementioned measures of demographics, military history, clinical status, and socioeconomic disadvantage. Finally, we calculated mean incidence (1 minus survival from Cox proportional hazard models) of homelessness and criminal justice involvement as a function of combinations of three risk factors (SMI, SUD, and PTSD) shown to be related to both outcomes, stratified by ADI quartile.

      Of the 418,624 post-9/11 veterans who entered VA healthcare within a year of leaving active duty 4.64% (n=19,436) experienced homelessness and 0.77% (n=3,221) experienced criminal justice involvement within two year of military separation. Among transitioning service members who became homeless within 2 years of military separation 6% met criteria for TBI, 31% met criteria for serious

mental illness (depression, bipolar, schizophrenia), 46% substance use disorder (SUD), 15% PTSD, 6% personality disorder, and 1% conduct disturbance.

The most robust risk factors were: SUD (Hazard Ratio (HR)=2.08, 95% CI [2.01, 2.14], p<.0001), being Black (HR=2.24, CI [2.16, 2.31], p<.0001), SMI (HR=1.93, CI [1.85, 1.998], p<.0001), personality disorder (HR=1.71, CI [1.60, 1.82] , p<.0001), and younger age (HR=.026, CI [0.21, 0.32], p<.0001) specifically 50+ years old compared to below 30 years old. Other variables with significant association (p<.001) included: Hispanic ethnicity, being Native American or Pacific Islander, male sex, having served in the Army, having been enlisted, deployment during military service, TBI, conduct disturbance, and residing in the highest ADI quartile.

Among service members who has justice involvement within 2 years of separation from the military, 11% met criteria for TBI, 34% met criteria for SMI, 62% SUD, 21% PTSD, 6% personality disorder, and 2% conduct disturbance. The most robust risk factors were: SUD (HR=3.53, CI [3.27, 3.81], p<.001), being unmarried (HR=1.84, CI [1.70, 1.99], p<.001), SMI (HR=1.96, CI [1.80, 2.15], male sex (HR=.34, CI [.29, .40], p<.001), and history of military deployment (HR=1.85, CI [1.66, 2.06], p<.001). Other variables with significant association (p<.001) included: younger age, having served in the Army, having been enlisted, **TBI,** and personality disorder.

While TBI was not a strong predictor of homelessness it was a stronger predictor of criminal justice involvement than PTSD. Race/ethnicity was not a strong predictor of criminal justice involvement, but Blacks and Native American/Pacific Islanders had the highest hazard ratio compared to whites for homelessness.

Table 2. Cox Proportional Hazards Models of Homelessness and Criminal Justice Involvement within 2 years of Military Separation

	Homelessness				**Criminal Justice Involvement**			
Parameter	Hazard Ratio	95% Wald Confidence Limits		p-value	Hazard Ratio	95% Wald Confidence Limits		p-value
Age at VA Entry								
30-39	1.01	0.98	1.05	0.558	0.84	0.76	0.92	<.001
40-49	0.43	0.40	0.46	<.001	0.41	0.34	0.50	<.001
50+	0.26	0.21	0.32	<.001	0.12	0.04	0.32	<.001
Female	0.92	0.89	0.96	<.001	0.34	0.29	0.40	<.001
Race/Ethnicity								
Asian	1.00	0.90	1.11	0.934	0.69	0.51	0.93	0.016
Black	2.24	2.16	2.31	<.001	1.11	1.01	1.23	0.038
Hispanic	1.34	1.28	1.40	<.001	1.11	1.00	1.24	0.058
Native American/Pacific Islander	1.54	1.41	1.69	<.001	1.23	0.98	1.53	0.073
Unknown	0.65	0.59	0.71	<.001	0.58	0.46	0.72	<.001
Marital Status								
Unmarried	1.56	1.51	1.61	<.001	1.84	1.70	1.99	<.001
Unknown Marriage Status	0.50	0.42	0.60	<.001	0.85	0.58	1.25	0.414
Branch of Service								
Air Force	0.52	0.49	0.55	<.001	0.43	0.37	0.51	<.001
Marines	0.67	0.64	0.69	<.001	0.84	0.77	0.92	<.001
Navy/Coast Guard	0.71	0.68	0.74	<.001	0.52	0.46	0.59	<.001
Other	0.24	0.10	0.58	0.001	0.44	0.06	3.13	0.411
Highest Rank								
Officer	0.42	0.38	0.47	<.001	0.51	0.39	0.66	<.001

Warrant Officer	0.34	0.26	0.44	<.001	0.72	0.44	1.18	0.197
Deployment During Service	1.18	1.14	1.22	<.001	1.85	1.66	2.06	<.001
TBI in DOD	1.16	1.09	1.23	<.001	1.58	1.40	1.78	<.001
Severe Mental Illness in DOD	1.93	1.85	2.00	<.001	1.96	1.80	2.15	<.001
Substance Abuse in DOD	2.08	2.01	2.14	<.001	3.53	3.27	3.81	<.001
PTSD in DOD	1.13	1.08	1.18	<.001	1.20	1.09	1.33	<.001
Physical Conditions in DOD								
1 Diagnosis	1.09	1.05	1.12	<.001	0.98	0.90	1.07	0.668
2-3 Diagnoses	0.97	0.93	1.01	0.122	0.85	0.75	0.95	0.004
4+ Diagnoses	0.52	0.48	0.56	<.001	0.47	0.37	0.58	<.001
Personality Disorder in DOD	1.71	1.60	1.82	<.001	1.43	1.23	1.67	<.001
Disturbance Conduct in DOD	1.25	1.10	1.43	<.001	1.39	1.07	1.82	0.015
Area Deprivation Index (ADI)								
Quartile 2 (26-50)	0.86	0.82	0.90	<.001	1.03	0.93	1.15	0.583
Quartile 3 (51-75)	0.94	0.90	0.98	0.008	1.05	0.94	1.17	0.376
Quartile 4 (76-100)	1.17	1.12	1.23	<.001	1.13	1.01	1.27	0.030
Unknown ADI Quartile	0.80	0.75	0.84	<.001	0.47	0.38	0.57	<.001

c. LTC Stewart (co-I of phenotype study) will lead papers describing risk of TBI for the adverse outcome of marital status change after TBI and emergence of cardiovascular disease. Preliminary data in our cohort of 2270396, found prevalence for the following conditions:

Conditions	N=2,270,396 N (%)
Acute Coronary Artery Disease	28,818 (1.27%)
Previous Coronary Artery Disease	6,889 (0.30%)
Cardiac Arrest	646 (0.03%)
Stroke	21,109 (0.93%)
Peripheral Artery Disease	21,269 (0.94%)

In the next quarter we will finalize the analyses and begin manuscript development.

d. We are working on a cross LIMBIC collaboration with Dr. Pogoda to examine long-term outcomes (service-connected disability, central nervous system (CNS) polypharmacy) and health care utilization (DoD and VA inpatient, outpatient utilization) among those who have TBI screening

1) TBI screen + Mild TBI based on Comprehensive TBI evaluation (CTBIE)
2) TBI Screen+ No other evidence of TBI based on CTBIE
3) TBI screen+ CTBIE not completed, no other evidence of TBI
4) TBI screen- CTBIE not completed, no other evidence of TBI

These analyses will help describe the impact of subconcussive events without loss of consciousness compared to mTBI.

e. Dr. Sayko Adams is working with the LIMBIC phenotype team to develop a manuscript to describe predictors of substance use disorder (SUD) phenotype (developed in the CENC study) 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, and results of this study will inform our long-term phenotyping effort.

f. We are working on a cross LIMBIC collaboration with Dr. Werner to develop a paper on sleep disorders using linked DoD and VA data. Other collaborator include Dr. Anne Germaine and other interested LIMBIC-CENC researchers.

Health Economics Study:

1. Task: Obtain DoD and VA authorizations: Sought guidance from the local VA's privacy officers about modifying the IRB protocol and DUA between the VA Palo Alto and VCU to include DoD EDIPI (Electronic Data Interchange Personal Identifier) by study ID to obtain biomarkers.

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. Tricare Cost Data. We have added DoD Tricare Cost data to our administrative data cohort.
   b. Merging longitudinal data with VINCI DATA. We have merged data from the longitudinal study on combat and training exposures as well as potential concussive events and TBIs for analysis of the association of combat and training exposures with 1) VA utilization and costs as well as 2) DoD utilization and Tricare costs. After we received the updated cohort dataset from VCU, we performed the following analysis 1) pulled VA inpatient, outpatient, pharmacy costs and utilization of health service in both individual collapsed and annual levels, 2) pulled non-VA inpatient, outpatient costs and utilization of health service in both individual collapsed and annual levels, 3) pulled the number of Elixhauser Comorbidity and Index, including inpatient and both inpatient and outpatient ICD codes, 4) pulled high risk conditions including dementia and PTSD, 5) merged datasets and total costs and health care utilization, and, 6) transferred and cleaned datasets to STATA.

3. Task: Assemble a matching cohort on age of Vs without TBI. Once assembled, perform quality checks and continue maintenance throughout study.
   a. TBI + Dementia for Special Brain Injury Issue. Veterans with a diagnosis of TBI were age-matched with a cohort without TBI diagnosis from inpatient and outpatient patient treatment file (PTF) between January 1, 2000 and December 31, 2015. The data was pulled from VA Informatics and Computing Infrastructure (VINCI). TBI diagnosis came from the standard surveillance case definitions used by the Armed Forces Health Surveillance Branch (AFHSB) Veterans were followed for any dementia diagnosis after TBI exposure until September 30, 2020. A clinical diagnosis of dementia was based on the FY21 VHA Dementia ICD codes list) applied to the PTF files.
   b. The VA's Vital Status Files (VSF) and Health Economics Resource Center (HERC) files were linked to PTF files using a scrambled social security number to calculate annual survival and identify VHA annual costs from FY2000-2020 (FY2020 was the last year available for annual cost by Veteran). All costs were adjusted for 2020 inflation. Demographics and co-morbidities were obtained from inpatient and outpatient PTF, mini vital, and OMOP files.
   c. To estimate the covariate-adjusted likelihood of dementia with a TBI diagnosis, logit models were used. To estimate the covariate-adjusted association of TBI diagnosis status with dementia, a Cox Proportional Hazards Survival model (time to dementia) was used. To estimate the covariate-adjusted association of TBI/dementia diagnosis status with all-cause mortality, a Cox Proportional Hazards Survival model was used. For estimation of the inpatient, outpatient, pharmacy, and community care cost categories for different TBI and dementia statuses, a generalized linear model (GLM) with gaussian family and identity link were used. To estimate the covariate-adjusted association of TBI and dementia status with annual total VHA plus community care, a generalized estimating equations (XTGEE) was used. For the adjusted model we tested two models:

      (1) **Model 1:** Adjusting for age, gender, race/ethnicity, marital status, insurance,urban/rurality, service-connected disability, number of Elixhauser conditions, OEFOIF, and death.

      (2) **Model2:** we added the PTSD, alcohol abuse, drug abuse, psychoses, depression comorbidities to the first model.

We used panel datasets for GLM and XTGEE estimation and added years to adjusted models. All costs were converted to 2020-dollar values using the US Department of Labor Consumer Price Index (CPI) Inflation calculator. All analyses were performed using STATA version 15.0 in VINCI. Statistical significance was determined at $P<0.05$.

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 have begun work on a funded NIH R61/R33 grant application to explore this in LIMBIC-CENC and other data. Our team is working with other investigators to develop a decentralized COMBAT algorithm that can be applied in LIMBIC and other "big data" analyses.

    c. We have continued collaboration with VA, University of Utah, Psychology Software Tools Phantometrics Division, University of Pittsburgh and NYU to advance work on the phantom developed under CENC. We are actively performing phantom testing and meet on a weekly basis to review results. This is an additional approach to reducing variability and enhancing accuracy.

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 extending those results. We also submitted an NIH R01 grant application to explore additional analysis pipelines which scored well and was resubmitted during the current cycle.

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

    a. We are in the process of creating a limited data set which can be used for this objective and creating a set of parameters which can be manipulated for testing. We have identified cases that would excluded from these analysis based on suboptimal quality (typically motion artifact).

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 in the LIMBIC-CENC data. We have executed data sharing agreements between NICoE and University of Utah as well as between NICoE and University of Virginia and hope to receive data in the next reporting period.

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 was submitted during this reporting period and is under review.

    b. We have been meeting regularly 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.

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 submitted imaging data to FITBIR for the scheduled March 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. We meet biweekly with the Biomarkers Core and have several investigations underway with regard to the analysis of structural and functional imaging with primary fluid biomarkers; we submitted one conference abstract to NNS and are preparing several manuscripts. 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. Project 1, Task 1: Progress this quarter: Obtaining pre-injury serum samples from DoD serum biorepository to assess pre-injury biomarkers levels.

2. Project 1, Task 2: Accomplishments this quarter: 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 database locked and analyses underway collaboratively with imaging. Grant submitted collaboratively with Kevin Wang, PhD at Gainesville, FL VA for VA biomarker project of sweat biomarkers in LIMBIC participants with VA prime and USUHS Biorepository as a sub-contract.

    Preparing/submitted the following manuscripts/abstracts by analysis:
    (1) Brain Injury Special Issue: blast miRNA & cognition manuscript- in prep
    (2) Brain Injury Special Issue: Sleep cognition biomarker manuscript
    (3) Behavioral symptoms miRNA analysis- Abstract submitted to MHSRS; Manuscript in prep for submission to Sci Reports this week
    (4) Sleep micro-RNA: manuscript under review Sleep Medicine and abstract submitted to MHSRS
    (5) Inflammatory biomarkers, sleep, & cognition: manuscript in prep
    (6) MSD p-tau species- Abstract submitted to MHSRS
    (7) DTI-NfL- Abstract submitted to Neurotrauma
    (8) NED screening in PLS- manuscript under revision at Neurotrauma and manuscript submitted to MHSRS

3. Project 1, Task 3: Accomplishments: 6 analyses ongoing:
    (1) Brain aging (collaborative with Imaging core)

(2) Cohort analysis- 7 proteins & outcomes
(3) DTI-NfL, collaboratively with Neuroimaging
(4) Volumtrics-NfL, collaboratively with Neuroimaging
(5) Big Data, collaboratively with Neuroimaging
(6) rsfMRI- sleep dysfunction, collaboratively with Neuroimaging

4. Project 1, Task 4: Accomplishments: Collaborating with Roskamp Institute for lipidomic analysis on Biomarker Discovery set. Roskamp running assays on protein biomarkers of chronic TBI.

5. Project 1, Task 5: Accomplishments: Collaborating with Imaging and Informatics as above. Project is currently underway.

6. Project 1, Task 6: Accomplishments: Correlations of candidate prognostic biomarker correlations with symptoms and outcomes underway. Correlations for Year 3 of SOW
   - Milestone: Carry out blood and saliva biomarker assays from all subjects with baseline specimens in the biorepository.
   - Milestone: Carry out candidate biomarker correlations with TBI status (repetitive versus mTBI with LOC versus blast versus no TBI), pre-deployment/pre-injury biomarker levels, neurobehavioral symptoms, advanced imaging, neuropsychological testing, serial biomarker levels among small cohort with incident neurodegenerative disorder (e.g. dementia).
   - Milestone: Develop panel of prognostic biomarkers for each phenotype of chronic neurotrauma (e.g. dementia, headache, PTSD, sleep disorder)

7. Project 2, GWAS: Accomplishments: Waiting for sufficient number of DNA samples for analysis and availability of Broad to analyze samples as they are currently unable to test any non-COVID samples.

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 #6 (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 training and certifying new study site personnel.
3. Continue to work with sites to gain IRB and HRPO Continuing Review approvals.
4. Plan our third CAB meeting.
5. Continue to interface with other researchers, entities, and consortiums.
6. Work to improve communications with our Sponsors and Program Officers.

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.
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. Local regulatory approvals updated as needed.
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.
7. Present at the next GSC Meeting on April 20th.

Data and Biostatistics Core:

1. Convene and complete 1st TBI Diagnosis Committee Meeting.
2. Update dashboards as needed.
3. Update Data Cube as needed.
4. Complete changes to Data Dictionary and deploy online.

5. Update electronic versions of internal reports (recruitment, visit completion, upcoming visit reports, retention, call center) as needed.
6. Update Dementia Prognostic Tool with Knowledge Translation Center based on feedback.
7. Update Publication Committee Request Form as needed.
8. Develop self-serve module for data downloads.

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. Complete and submit the cardiovascular manuscript for the LIMBIC Special Issue.
2. Continue our new analysis exploring dementia risk factors after TBI and begin drafting the manuscript.
3. Engage new investigators and begin working to understand the relationship between TBI, mental health, and long-term outcomes.
4. We will continue regular group meetings between investigators and regular reporting on LIMBIC consortium calls and at the Government Steering Committee meetings.

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. Continue to conduct analyses of combat and training exposures with Service-Connected Disability, health services utilization and costs using the merged Longitudinal Study and VA data. Teams will be created for manuscripts to create models, estimate models and report results for 1) VA utilization and costs 2) DoD utilization and Tricare costs.
2. We hope to receive the MTF cost data for the Phenotype study to complete the cost data acquisition to begin analyses of costs and utilization by Phenotypes identified by the Phenotype team.
3. We will begin work on acquiring VA disability costs for veterans with TBI.
4. We will work on improving our cost comparison dashboard across VA, DoD and private sector.

Novel Neuroimaging Study:

1. If allowed given the COVID travel and infection control restrictions and stay at home orders, resume phantom testing with the diffusion phantom to collect additional 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 SiMLR 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. Continue analysis of full, locked dataset collaboratively with imaging core
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. Continue developing a manuscript to link protein changes to chronic symptoms related to TBI, to be submitted by 5/2021.
5. Extract DNA as available and coordinate with Broad timing of GWAS samples

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.*

1. Please see LIMBIC PLS Appendix #2 (Publications Tracker) and all of the publications and presentations for this quarter are attached to end of this report. It includes those utilizing PLS data as well as other LIMBIC-CENC publications and presentation.

2. Leng Y, Byers AL, Barnes DE, Peltz C, Li Y, Yaffe K. Traumatic Brain Injury and Incidence Risk of Sleep Disorders in Nearly 200,000 US Veterans. Neurology, March 30, 2021; 96(13):e1792-e1799.

3. Tate DF, Dennis EL, Adams JT, Adamson MM, Belanger HG, Bigler ED, Bouchard HC, Clark AL, Delano-Wood LM, Disner SG, Goodrich-Hunsaker NJ, Hayes JP, Hinds SR, Hodges CB, Hovenden ES, Irimia AI, Kenney K, Lindsey HM, Morey R, Newsom MR, Scheibel RS, Shenton ME, Sullivan DR, Troyanskaya M, Wade B, Thompson PM, Wilde EA. Coordinating Global Multi-Site Studies of Military TBI: Potential, Challenges, and Harmonization Guidelines. Brain Imaging and Behavior (Military Special Issue) 2021 Jan 7. doi: 10.1007/s11682-020-00423-2. Online ahead of print. PMID: 33409819

4. Mithani SM, Leete J, Pucci JU, Guedes V, Kenney K, Werner JK, Gill JM. Sleep Quality Affects Plasma Exosomal MicroRNA Expression Profiles in Military Personnel with Traumatic Brain Injury. Abstract accepted as poster presentation at the 2021 Sleep conference, June 2021.

5. Pucci JU, Mithani S, Leete J, Lai C, Kenney K, Gill JM, Werner JK. Poor sleep quality in traumatic brain injury patients is associated with elevated inflammatory biomarkers. Abstract accepted as poster presentation at the 2021 Sleep conference, June 2021.

6. Garcia A, Wilde EA, Tate D, Reljic T, Kenney K, Troyanskaya M, Agyemang A, POgoda T, Walker W, Richardson R. Obstructive Sleep Apnea Risk is Associated with Number of White Matter Hyperintensities, But Mild TBI Exposure is Not: A CENC-LIMBIC Study. Abstract accepted as oral presentation at the 2021 Sleep conference, June 2021.

7. Edwards KA, Campbell C, Kendrick N, Kenney K, Diaz-Arrastia R, Davenport N, Gill JM, Debad J. Ultrasensitive Blood Test for Hyperphosphorylated Tau is Associated with Blast Exposures in Military Veterans with Chronic Traumatic Brain Injury. Abstract submitted to the 2021 MHSRS, AUG, 2021.

8. Mithani SM, Leete J, Pucci JU, Guedes V, Kenney K, Werner JK, Gill JM. Exosomal MicroRNA is Associated with Sleep Quality in Military Personnel with Traumatic Brain Injury. Abstract submitted to the 2021 MHSRS, AUG, 2021.

9. R, Werner JK, Gill JM, Kenney K. Extracellular Vesicle Proteins and MicroRNAs as Biomarkers of Persistent PTSD Symptoms in Veterans with History of Mild TBI. Abstract submitted to the 2021 MHSRS, AUG, 2021.

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 continued to have an impact on our consortium, especially so in the Prospective Longitudinal Study (PLS). As a corrective action, PLS leadership proactively developed and implemented an array of procedural changes that have successfully limited the impact. These included collecting additional data remotely for the comprehensive longitudinal assessments including additional questionnaires (by mail or home internet), video enabled interviews and neuropsychological tests. These are described in greater detail earlier in the report Fortunately, the national roll-out of vaccinations and lower case counts in the U.S. population, regulatory restrictions on clinical research began easing in early 2021. During the last quarter, ten of the eleven PLS gained local approvals for restarting in-person research activities including new enrollments for the LIMBIC-CENC PLS. All of the locations are able to continue collecting data during this time frame due to a remote data collection system. 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 hesitancy for on-site visits among our current and potential future participants, 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 and first part of year 2 projections into years 3-5 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 at some sites we are still unable to collect some portions of data even with in-person visit due to hands-on restrictions (e.g. blood).

2. 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.

a. 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 (PLS) have been delayed by six quarters at this time and it appears that pandemic-related headwinds, although to a much lesser degree, will continue for at least one more quarter as the country continues its vaccination efforts. Our longitudinal assessments remain operational with good retention rates, however at some sites we

have been unable to collect some portions of data even with in-person visit due to local restrictions (e.g. blood).

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.