# Quarterly Technical Progress Report Format
# Front Cover

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| Award Number: | W81XWH-19-2-0067 |
| Log Number: | PT180027 |
| Project Title: | Long-Term Impact of Military-Relevant Brain Injury Consortium |
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| Report Date: | April 29, 2020 |
| Report Period: | 01/01/2020 - 03/31/2020 |

**Email the report and any other attachments to the Grants Officer's Representative (GOR) and Grants Specialist at the email addresses specified in the award document. Name the file with the award number, followed by "QtrlyTechProgReport Month Year."**

**If you have questions, contact the GOR.**

**1. Accomplishments:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

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

## CORES

**Coordinating Center**:

1. Transition and Expand CENC to LIMBIC:

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

2. Add three new additional Prospective Study Enrollement Sites:

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

3. Conduct Call Center operations:

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

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

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

5. Conduct Consumer Advisory Board Meetings:

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

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

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

## **Neuroimaging Core**:

1. **Regulatory:**

a. IRB protocol development, submission, and continuing review. (Locally and in conjunction with Coordinating Center at VCU).
b. HRPO approval and continuing review

2. **Training:**

a. Hire and maintain all research consortium staff.

3. **Quality Assurance**:

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

4. **Clinical Reads**:

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

5. **Data Analysis**:

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

6. **Data Dissemination**:

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

7. **Data Organization, Archive and Storage**:

a. Organize, transfer, archive, and securely store neuroimaging data.

## Biomarkers Core:

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

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

3. Task: HRPO approval and continuing review.

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

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

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

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

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

## Data and Biostatistics Core:

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

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

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

4. Task: Translate knowledge and disseminate knowledge products

# STUDIES

## Prospective Longitudinal Study:

1. Task: Implement Study.

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

**Retrospective Data Base Study**:

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

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

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

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

## Phenotypes Study:

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

2. Task: Update data repository annually with latest VA data and merge with relevant DOD datasets and add additional DoD data to enhance acute TBI identification. Once assembled, perform quality checks and continue maintenance throughout study.
   Milestones**:** Compile VA data for Post-9/11 Veteran Cohort from existing data repository and obtain DoD data for Post 9/11 Veterans via DoDTR and DaVINCI.

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

## Health Economics Study:

1. Task: Obtain DoD and VA authorizations.

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

3. Task: Assemble a matching cohort on age of Vs without TBI. Once assembled, perform quality checks and continue maintenance throughout study.
   Milestone: Create a joint VA/DoD database within VINCI, matching on real SSN, for all veterans using VA and diagnosed with TBI either in DoD, VA or both since 2004 (matching cohort on age of veterans TBI (-) for comparisons) to include demographics, military characteristics, military exposures identified in MHS to potential concussive event mechanisms, TBI severity when diagnosed by DoD, trauma and non-trauma comorbidities identified by DoD, MHS health services utilization and costs, military readiness, disability, days of work duty limitations and time in service, date of military separation, first date of VA eligibility, VA service connected disability rating and payments, VA comorbidities, VA health services utilization and survival.

## Novel Neuroimaging Study:

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

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

2. Task: Critically examine and compare strengths and limitations of commonly used imaging analysis pipelines.
Milestone: Using data collected as part of CENC, results of comparisons of data analysis pipelines will be submitted as one or more manuscripts for publication.

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

4. Task: Create and refine novel, automated pipelines to address aspects of imaging analysis which are currently absent or incomplete.
Milestone: Further refine CENC pipelines including an automated analysis pipeline for detection and analysis of white matter hyperintensities as well as pipelines for volumetric, diffusion and functional connectivity, separately as well as in combination.

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

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

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

**Biomarkers Discovery Study**:

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

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

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

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

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

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

Milestones: (1) Carry out blood and saliva biomarker assays from all subjects with baseline specimens in the biorepository. (2) Carry out candidate biomarker correlations with TBI status (repetitive versus mTBI with LOC

versus blast versus no TBI), predeployment/pre-injury biomarker levels, neurobehavioral symptoms, advanced imaging, neuropsychological testing, serial biomarker levels among small cohort with incident neurodegenerative disorder (e.g. dementia), (3) Develop panel of prognostic biomarkers for each phenotype of chronic neurotrauma (e.g. dementia, headache, PTSD, sleep disorder).

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

## CORES

### Coordinating Center:

1. Transition and Expand CENC to LIMBIC:

a. We are still working on the establishment of Data Sharing Agreement with DHA for access and use of MHS data at VCU CC and appropriate sites.
b. Continued to work with all of the VA sites in order to get JIT approvals finished. The last site to gain JIT approval was San Diego due to waiting for their IRB approval.
c. All sub-award personnel, clinicians and associate researchers have been hired, trained and either certified or in the certification process.

2. Add three new additional Prospective Study Enrollment Sites:

a. Continuing to onboard the 3 new Prospective Longitudinal Study enrollment sites (Salisbury/San Diego/Fort Gordon).
b. Assisting with the training and certifying of all new staff.
c. Assisted all sites with regulatory approvals to include IRB and HRPO. The only site still working on IRB approval is Fort Gordon.

3. Conduct Call Center operations:

a. We are in the process of hiring a new Call Center supervisor.
b. Conducted liaison between enrollment sites.
c. Conducting all necessary follow-up calls to include BTACTs and Annual Telephone Assessments for Prospective Longitudinal Study (see table below for projected call volume).
d. Came up with a work from home plan due to the COVID-19 response. All Call Center personnel are able to conduct their job remotely and the call center is working at a 100%.

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

a. Established Site Metrics.
b. Established recruitment and retention goals as well as the overall plan.
c. Monitoring and reporting site performance
d. We have established and will maintain regular communication through meetings, teleconferences, e-mails, site visits and other methods to maintain consortium function.
e. Collected required information, prepare and submit Quarterly, Annual and Final Reports.

5. Conduct Consumer Advisory Board Meetings:

a. Initially selected 9 Board Members and attempted to gain GSC approval of the selectees at the GSC meeting in February. We've been asked to look at adding one more member as well as providing the entire CV for each member rather than a synopsis. Please see Appendix 1 for the new 10 member approval request along with their complete CVs.

b. After gaining approval of board members, we will publish the LIMBIC CAB Charter.

c. After gaining approval of board members, we will publish the LIMBIC CAB Meeting Schedule

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 and are waiting on the Walter Reed IRB to approve Fort Belvoir and Fort Gordon's IRB/HRPO request.

7. Attended the Semi-Annual GSC meeting with our DoD and VA sponsors.

a. Coordinated with CDMRP Science Officer to make tentative schedule for semi-annual GSC Meetings.

b. Coordinated with all performance site PIs to ensure that their schedules permit attendance at meetings.

c. Provided CDMRP Science Officer with all required meeting materials in accordance with approved schedule.

d. We also provided answers to all of the questions and concerns raised from the meeting (See Appendix #2).

8. We hosted a tele-conference kick-off meeting with Dr. Rachel Ramoni and Dr. Stuart Hoffman from the VA. The meeting was a great success and several ideas about follow-on research and Knowledge Translation were discussed.

9. The Coordinating Center sent three representatives to participate in the Brain Injury Awareness Day on Capitol Hill for the 3rd year in a row.

## **Neuroimaging Core**:

1. **Regulatory**:

a. *IRB protocol development, submission, and continuing review. (Locally and in conjunction with Coordinating Center at VCU).* During the last performance period, the Neuroimaging Core protocol was submitted to the University of Utah/ VA Salt Lake City Healthcare System IRB; we received formal determination from the IRB that activities conducted under the Neuroimaging Core were not considered human subjects research and did not require further oversight by the IRB (03 Dec 2019). Since no continuing review is necessary, this is considered complete. We will continue to undergo RR&D committee approval at the VA.

b. *HRPO approval and continuing review*: We notified Justin Alicea at VCU on the day that we received IRB determination that the Neuroimaging Core activities did not constitute human subjects research. In the past, the CENC Neuroimaging Core activities were also determined by HRPO to not constitute human subjects research. Justin is awaiting verification that no additional review by HRPO is required (as of the drafting of this report). Until we receive formal determination by HRPO for LIMBIC, we will consider this in process.

c. *Attendance at biannual GSC meetings:* Dr. Wilde attended the first biannual GSC meeting on 11 FEB 2020 to report on the activities of the Neuroimaging Core. Drs. Wilde and Tate also presented at the virtual LIMBIC kick off meeting held 11 March 2020. We therefore consider this item up to date.

2. **Training**:

a. *Hire and maintain all research staff*: The Neuroimaging Core has been somewhat consolidated in Salt Lake City, Utah. As a result of the relocation of several key investigators. In the final year of CENC, Dr. Wilde (previously at Baylor College of Medicine and Michael E. DeBakey VA Medical Center) relocated to the University of Utah/ VA Salt Lake City Health Care System. Additionally, Dr. Tate relocated from the University

of Missouri – St. Louis to the University of Utah/ VA Salt Lake City Health Care System. Finally, Dr. Erin Bigler assumed an emeritus status at Brigham Young University and also obtained adjunct status at the University of Utah. Staff from Dr. Wilde, Tate and Bigler who were previously involved in the project are now all co-located in the same lab. Since many of the staff members now working on the LIMBIC Neuroimaging Core previously held similar duties under CENC (including Tracy Abildskov, Naomi Hunsaker, Carmen Velez, Benjamin Wade), the transition has been relatively smooth. We have hired and are in the process of training a few additional staff members, including Hannah Lindsey, Paula Johnson, Joey Dimanche and Elizabeth Hovenden.

b. We have begun training the neuroradiologists involved in the Common Data Element coding on some new procedures in the Medidata system.

c. We have been updating the Standard Operating Procedure manual and training materials, particularly with regard to clarification of the phantom 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. The transfer of additional neuroimaging data to the Neuroimaging Core is pending IRB approval at several sites. For those sites that have received approval, we have performed quality control review of data which has been transferred. We will review data quality at additional sites as approval is granted.

b. We were in the process of scheduling site visits with each existing and new site to 1) perform initial or refresher training with each site and review “course correction” items to facilitate data collection, organization and transfer, 2) to review the acquisition protocols on the scanner, 3) to collect human phantom and phantom object data, 4) review the process for QA data collection and transfer. These have now required conversion to teleconference meetings given the COVID-19 social distancing and travel restrictions. We are in the process of providing each site with a list of instructions to enhance their compliance with imaging protocols and procedures.

c. We have been using tools that allow semi-automated monitoring of parameters of quality assurance. In addition, we perform visual inspection of the data to determine reliability. We note that all sites have paused acquisition of imaging data due to COVID-19 social distancing, infection control, and stay at home orders, but we are continuing to review previously acquired data.

4. **Clinical Reads**:

a. Because coding provides context for future data collection on subjects that are followed over time, we have also been reviewing the consolidation of the CDE data transferred from the older CENC system into the newer one which will be used in LIMBIC and reconciling and monitoring CDE codings. Reading of sans collected during January 2019-September 2019 was prioritized. These have been completed and entered for all site except Portland. We are also working back through scans collected prior to this time to ensure accuracy and completion. 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. We are in the process of training the existing neuroradiologists (Drs. Gerry York, Tim Duncan and Aaron Betts) on the new Medidata system and training 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, though we have instituted some additional longitudinal pipelines, which are in process.

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

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 this was completed during the performance period.

c. We explained that there was an inconsistency in the naming of the imaging data that was collected between 2013-2018, which would potentially create significant confusion for investigators both within and outside of the LIMBIC team; in brief, the file names did not match the labeling convention of the clinical and other data for various visits. In an effort to make the data as consistent and easy to use as possible, we have elected to rename the file names of those data, which requires changing the name in all associated imaging files (millions of data files). This is in process and is expected to be completed during the next quarter.

d. We are preparing to submit previously collected imaging data for other CENC studies that were not part of the Prospective Longitudinal Study. We also anticipate that these will be completed during the next quarter.

e. We are preparing imaging data to share with Dr. Kimbra Kenney to complete an analysis previously approved.

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.

7. **Data Organization, Archive and Storage**:

a. The server housing the neuroimaging data is operational and all active sites and personnel that have requested access have accounts.

## Biomarkers Core:

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

a. The LIMBIC-CENC Biomarker Core has the following aliquots from the Prospective Longitudinal Study as of 19 MAR 2020:

| **S01C - Material Types Received this quarter** | | **Total this quarter and (overall total)** |
|---|---|---|
| **Material Type** | **0.5 mL Vials received this q and (total in storage)** | **Vials Shipped Out** |
| Buffy Coat | 22 (total 1622) | 0 (total to date 1308) |
| DNA | 0 (1191) | 0 (0) |
| Stock DNA | 0 (196) | 0 (0) |
| Plasma | 239 (10,370) | 0 (584) |
| Saliva | 40 (1,679) | 0 (194) |
| Serum | 206 (10,032) | 0 (0) |
| Whole Blood (PaxGene) | 39 (1787) | 0 (0) |
| **Grand Total:** | **546 (26,877)** | **0 (2086)** |

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

a. The mod was submitted at the beginning of December and we are waiting for review by IRB at USU.

3. Task: HRPO approval and continuing review.

a. CENC Biorepository originally approved by USUHS IRB 4/28/2014 with HRPO second level approval 8/28/2014. It has received CR renewal approval letters annually from April 2015 to March 2020. Modification to change PI from Dr. Cox to Dr. Werner approved 1-2020. Modification to increase CENC participants from whom samples can be received longitudinally from 2,500 to 3,500 approved 1-2020. CR approved 3-30-2020.

## **Data and Biostatistics Core**:

1. **Major Activities**:

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

2. **Specific Objectives**:

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

(1) Completed training component of Medidata enablement and began mentorship phase, during when the team independently works on tasks and seek support from Medidata when needed.

(2) Migrated all previously collected participant information into new Contact Information Management System.

(3) Implemented a soft launch of Call Center Application.

(4) Began and made significant progress toward building system for regular, automated download of clinical data from Medidata to LIMBIC-CENC database on server.

(5) Created drafts of automated dashboard reports to track enrollments, recruitment, and receipt of biospecimen and MRIs.

(6) Created drafts of Biomarkers Core reports and dashboards to track biofluid availability.

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

(1) 1st level of QA/QC of clinical data has been developed and continues to be implemented

(2) Plan for 2nd level QA/QC of clinical data continues to be developed

(3) Plan for QA/QC of neuroimaging and bospecimen data has been developed and was implemented

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

d. Data Request Infrastructure:

(1) We have done some adaptation to the data request process to accommodate new information in the prior quarter

e. Data Request Processing:

(1) We completed and disseminated analytic data sets for **three** previously approved data requests for investigators at Tampa, Richmond, and Salt Lake City.
(2) We are processing data for four additional data requests for investigators at Richmond, Houston.
(3) LIMBIC-CENC Biostatistics group is actively conducting advanced analyses for 1 investigator-initiated projects and awaiting VINCI data for another approved project.
(4) LIMBIC-CENC Biostatistics group began exploring ideas for phenotype analyses to present to the study PI and investigators.
(5) The Data Core processed three new data requests that have not yet been approved but which were in different stages of submission, review and revision by investigators.

f. Data Dictionary:

(1) Worked on development of search function for data dictionary.

g. FITBIR Data Submission Preparation:

(1) Attended biweekly meetings with FITBIR Ops.
(2) Completed in-person training with CDMRP and Neuroimaging Core.
(3) Finalized the last 3 (new) form structures with FITBIR Ops.
(4) Completed March Submission
(5) Pulled data for Q2 for data Q and QC for September FITBIR Submission.

h. Knowledge Translation:

(1) Contacted core and study investigators to obtain complete set of 2019 publications and presentations; conducted Pubmed search to assure complete set.
(2) Continued updating KTC website including publication lists and products.
(3) Prepared and participated in GSC semi-annual meeting and LIMBIC-CENC Kick Off event.
(4) In response to GSC feedback, developed formal presentation for LIMBIC-CENC Kick Off event with plans, goals and tasks. Discussion focused on making implementation science a larger part of KT effort
(5) Had follow-up meeting with Dr. Stu Hoffman to discuss clinical products and types of potential implementation science projects.

3. **Key Outcomes**:

- Data entry, storage and Quality Assurance/Quality Control Processes ready for live data submission by sites once IRB/R&D/HRPO approvals complete.
- Processes for data requests are tested and working with continual quality improvement processes in place.
- Data is being distributed to investigators (3 data requests complete; 4 in progress in Q2).
- Basic FITBIR infrastructure is prepared for March LIMBIC FITBIR submission.

## STUDIES

### Prospective Longitudinal Study:

1. Task: Implement Study.

a. Onboard 3 new recruitment sites.
(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 almost all instruments.

b. Personnel at existing locations have been hired to fill vacancies.

c. IRB protocol development, submission, and continuing review.

(1) All 8 of the previous CENC sites (Richmond/Tampa / San Antonio / Houston / Boston / Minneapolis / Portland / Fort Belvoir plus the new site at Salisbury have LIMBIC PLS local IRB approval.
(2) San Diego has verbal local IRB approval, simply awaiting documentation. Ft. Gordon is making minor revisions at the request of the Walter Reed IRB.

d. HRPO approval and continuing review.
(1) Portland, Tampa, Richmond and Boston have HRPO approval.
(2) HRPO requests have been submitted for the other 4 previous CENC sites as well as one new site (Salisbury) and the LIMBIC-CENC Data and Biostatistics Core.
(3) HRPO requests will be submitted for the other two new sites once they receive IRB approvals.

e. Develop site-wide recruitment and retention plan.
(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.
(1) Retention plan has been initiated and implemented.
(2) Recruitment and new enrollments were initiated at Portland site where HRPO approval was gained ahead of all other sites. Unfortunately, new enrollments were subsequently suspended at all sites including Portland due to COVID-19 crisis restrictions on face to face clinical research activities.

g. Collect data and conduct analyses in to explore neurologic outcomes and comorbidities, develop predictive models, discover potentially treatable factors, and improve EOD algorithm:
(1) Revised protocol and MOP with new measures (Clinical Dementia Rating (CDR) scale, RightEye computerized eye-tracker, and AudioStar Audiometer) finalized and readied to launch; TOPF determined redundant based on psychometric analysis so removed along with SVV; All primary IRB approvals obtained. Decision was made to continue the MINI PTSD interview instead of replacing with the CAPS 5 due to concerns over participant burden and potential negative impact on retention. Instructions were added to the MINI to improve understanding of the Criterion A lead in question.
(2) Back entry of all data collected during Medidata transition period entered into new data capture system.
(3) The next FITBIR uploads due were prepared and additional issues identified and resolved regarding prior CENC data under RTI.
(4) QA ongoing; highlights included:
a. completion of detailed plan and schedule
b. in-depth review and adjudication by Dr. Walker of all TBI diagnosis ratings from the EDC transition period
c. vetting and categorizing of free text medication entries.
(5) Began developing the second version of enhanced investigator-driven data dictionary.
(6) New scientific analysis requests received and processed with analytic/dissemination work ongoing. (See Appendix #5 for full listing)
(7) This quarter, 209 new Telephone Follow-Ups were completed and 46 In Person Follow-Ups were completed for an accumulated total of 450 Annual Telephone Follow-Ups and 108 In Person Follow-Ups in the first two quarters of LIMBIC-CENC.

h. Describe multicenter cohort and over time (VCU LIMBIC) for administrative purposes including federal oversight and requests as well as potential data requests from external researchers.

(1) New Website launched with metrics and descriptors of cohort as well as enhance knowledge translation center and products.

(2) Two different versions of dashboard content developed for public and private sides of the Website. Additional metrics planned for the private side.

(3) To provide more detail on blast injury mechanism, new variables were created for subtype of blast-related mTBI, specifically pure blast (i.e. primary blast) versus mixed blast-blunt (i.e. includes secondary/tertiary blast-effect mechanism).

(4) To make the longitudinal in-person assessment schedule easier to understand, new figures were created showing graphic representation of the study time-line with respect to the dates of index injury and the initial (enrollment/baseline) assessment. (See Appendix #2 for figures)

i. Wrapped up CENC dissemination activities:

(1) Projects reported last quarter have had manuscripts submitted for publication and/or have been presented at scientific meetings. See master tracking spreadsheet for all analytic projects utilizing datasets from the LIMBIC-CENC Prospective Longitudinal Study.

(2) In general, analyses from CENC 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 preliminary data suggests 3 or more mTBIs may have late neurologic effects (lower postural stability, neurodegeneration byproducts in blood).

(3) Newly submitted manuscripts:

**Accepted Manuscript:**

Dismuke-Greer CE, Fakhry SM, Horner MD, Pogoda TK, Pugh MJ, Gebregziabher M, Hall CL, Taber D, Spain DA. *Ethnicity/race and service-connected disability disparities in civilian traumatic brain injury mechanism of injury and VHA health services costs in military veterans: Evidence from a Level 1 Trauma Center and VA Medical Center.* Trauma. 2020 Apr 6:1460408620914436.

**Submitted Abstracts:**

J. Kent Werner; Josephine Pucci; Pashtun Shahim, Jessica Gill, Risa Nakase-Richardson; Kimbra Kenney. Poor Sleep *Quality Correlates with Plasma Biomarkers of Neurodegeneration, Neurobehavioral Symptoms, and* Executive *Function but not Declarative Memory in Chronic Mild Traumatic Brain Injury*

Vivian deGuedes; Chen Lai, Christina Devoto, Bao-Xi Qu, William C Walker, Elisabeth Wilde, Ramon Diaz-Arrastia, Kimbra Kenne, Jessica Gill. *Exosomal Proteins and MicroRNAs as Prognostic Biomarkers of Persistent Affective Symptoms in Veterans with History of Mild TBI; Preliminary Results from a CENC Biomarker Discovery Project*

Edwards K;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*

Sara MIthani; Chen Lai, Christina Devoto, Vivian A Guedes, Bao-Xi Qu MD , William C Walker, Elisabeth Wilde, Ramon Diaz-Arrastia, Jessica Gill RN, Kimbra Kenney MD. *Exosomal MicroRNA in Blast-Exposed Veterans with Mild Traumatic Brain Injury; Preliminary Results from a CENC Biomarker Discovery Project*

Bilal Khokhar; Megan Lindberg; William Walker*. Post-mTBI pain interference in a US military population: a Chronic Effects of Neurotrauma Consortium study*

Victoria C. Merritt; Sarah M. Jurick, McKenna S. Sakamotoa, Laura D. Crocke, Molly J. Sullan, Samantha N. Hoffman, Delaney K. Daveya, & Amy J. Jak. *Post-Concussive Symptom Endorsement and Symptom Attribution Following Remote Mild Traumatic Brain Injury in Combat-Exposed Veterans*

Jared A. Rowland; Sarah L. Martindale, Ph.D., Robert D. Shura, Psy.D, Anna Ord, Psy.D., Sagar Lad, Psy.D., Katherine H. Taber, Ph.D. *Trajectories of Recovery in the Chronic Phase of Mild Traumatic Brain Injury Acquired During a Combat Deployment*

. j. LIMBIC Scientific Analysis Underway: See Data analysis tracker spreadsheet in Appendix.

k. Other Prospective Study Collaborations and Spin Off Studies:

(1) FITBIR: Accelerating Synthesis of TBI Research Using Novel Methods" (FAST RUN Methods). This project will utilize FITBIR data to examine key outcomes related to TBI and psychological health including PTSD, depression, suicide, and substance use as well as employment, functioning, and quality of

life. It will also use advanced software and analysis techniques to facilitate future utilization of FITBIR among other stakeholders, and to accelerate synthesis of existing FITBIR data by creating model methodologic products including data management, harmonization, and merging syntax, that can be applied to future expanded analyses including more variables of interest and more datasets as they are contributed to FITBIR.

**Retrospective Data Base Study**:

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

a. We have made excellent progress in the second quarter of this project. We continue to have regular, recurring team meetings between all the investigators and research staff on this project.

b. In the past quarter we finalized our ICD-10 diagnostic codes for TBI. We merged the new data through fiscal year 2018 (new TBI cases since 2015 and expanding the 2% random sample) with the old dataset. We are now in the process of running the outcomes and comorbidity codes (dementia, physical and psychiatric comorbidities, etc.) in the updated dataset.

c. During the data updating, we investigated incident dementia in older veterans with TBI exposure by race. Using a sample of nearly 1 million veterans with data from 2000-2015, we excluded all people with prevalent dementia. Compared to those without TBI, Hispanic Veterans with TBI were almost two times more likely (HR: 1.74, 95% CI: 1.51-2.01), Black Veterans with TBI were over two times more likely (HR=2.15, 95% CI: 2.02-2.30), and White Veterans with TBI were nearly three times more likely to develop dementia (HR=2.71, 95% CI: 2.64-2.77). A significant interaction between TBI and race for developing dementia was observed ($p<0.001$). A manuscript detailing these exciting results was just accepted for publication in Neurology.

**Phenotypes Study:**

1. Task: Complete Regulatory Requirements.

a. Regulatory and Data Acquisition activities complete except HRPO. The package is ready to submit once we have the signed VA R&D letter. It was expected long ago and is likely delayed due to COVID.

b. Data Acquisition: We have the VA cohort already included in the Characterizing Health Outcomes in Post-9/11 Era Veterans Cohort. We will transfer to the Phenotype Study VINCI folder once we have completed the R&D and HRPO approval processes.

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

a. We identified the following Veteran Stakeholders: VA PM&R, VA National Center on Homelessness among Veterans (NCHAV), VA Mental Health and Suicide Prevention, two Veterans with TBI, one caregiver of Veterans with TBI, one Active Duty Service member – working on identifying one to three additional active duty service members or recent retirees.

**Health Economics Study:**

1. Task: Obtain DoD and VA authorizations.

a. Received approvals by the Stanford IRB and VA Palo R&D committees.

b. JIT was submitted and cleared. The official funding letter is pending.

c. Stanford IRB and VA Palo Alto R&D approvals have been sent to Mary Jo Pugh at Utah to add Dr. Dismuke-Greer to the VINCI DART for Dr. Dismuke-Greer to begin to work with the Utah team on data cleaning, merging and analysis.

2. 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. Real SSNS and associated Longitudinal study IDs have been obtained from Portland, Tampa and Boston.
b. Added Richmond VA (Drs. Walker and Karmarkar) and Houston VA (Hector Garza) to study DART and received approvals. Mr. Garza will upload SSNs to the VINCI project folder.
c. Received approval on a modified IRB that added Houston VA and Richmond VA as sites. Submitted an IRB amendment to add Utah VA. We're awaiting approval.
d. Coordinating with Salisbury VA to obtain real SSNs.
e. Will be meeting with study PIs at San Antonio, Richmond and Minneapolis in April to obtain real SSNs.
f. Drafted DUA between VA Palo Alto and VCU DBC. Review is pending.

**Novel Neuroimaging Study**:

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

a. We have performed initial analyses of the CENC data to examine the COMBAT method of data harmonization to overcome site differences. This resulted in substantial reduction of variability across sites, but we are awaiting additional data to examine how this affects additional relationships with other clinical and outcome data.

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 have discussed collaboration with this group and with others in the InTBIR and ENIGMA communities.

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.

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

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

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

a. The WMH pipeline has been updated and we are in the process of applying this to a larger set of data collected under CENC. Pending receipt of additional clinical and outcome data, we will perform analysis examining the relation of these variables.

5. Task: Incorporate elements of advanced statistical analysis (e.g., Bayesian analysis, machine learning) to utilize multi-modality imaging data in conjunction with other injury, demographic and outcome data to develop subgroups/phenotypes and identify related variables in those at highest risk for poor outcome.

a. 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. These analyses suggest that repeated exposures and blast exposure influence the imaging findings for both the volumetric and diffusion data.

b. We have performed some initial analyses examining the use of advanced statistical analysis in existing CENC data, particularly with regard to the relation between imaging metrics in the hippocampus and amygdala and measures of PTSD and mood. These interim results using a limited data set suggest that PTSD has a significant impact on imaging findings in these subcortical structures over and beyond TBI.

c. We have been meeting with the Data Core and Biostatistics group 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. Members of the Neuroimaging Core attended in person FITBIR training in Bethesda 6-7 JAN 2020. We have identified the data that requires upload for the scheduled March submission and are organizing and preparing this data for upload.

b. We have submitted the imaging data for the scheduled March submission. Please see the Neuroimaging Core report for additional information.

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

d. Neuroimaging Core investigators heavily lead and support the ENIMA Military Working Group; we are also involved in communication with TRACK-TBI, TED, and InTBIR.

**Biomarkers Discovery Study**:

1. Manuscript "Exosomal NFL: a prognostic biomarker for remote symptoms after mild traumatic brain injury?" was accepted by Neurology 12/2/2019; proofs have not yet been received.

2. Manuscript of miRNA analysis results, "Exosomal MicroRNAs in Veterans with Mild Traumatic Brain Injury: Preliminary Results from a Chronic Effects of Neurotrauma Consortium (CENC) Biomarker Discovery Project" was submitted to Journal of Neurotrauma 11/2019 and revisions requested from initial review are currently under review 3-30-2020.

3. Submitted manuscript to Human Brain Mapping as co-author on ENIGMA manuscript reviewing TBI biomarkers, "ENIGMA Brain Injury: Framework, Challenges, and Opportunities" in 12/2019. Under review 3-2020

4. Submitted manuscript to special military edition of Brain Imaging and Behavior as co-author on ENIGMA manuscript reviewing military TBI, "Coordinating Global Multi-Site Studies of Military TBI: Potential, Challenges, and Harmonization Guidelines" in 12/2019. Under review 3-2020

5. Preparing 2 additional manuscripts of miRNA analyses, 1 analyzing miRNA and PTSD/depression symptoms and the second miRNA in blast TBI for submission in next quarter. In preparation 3-2020 with plans to submit in first and last week of April, 2020.

6. Preparing manuscript of NFL, sleep, cognitive analysis by LCDR Werner, presented at MHSRS 2019. In preparation 3-2020 with plans to submit the first week of April, 2020.

7. Continued analysis of candidate biomarkers of samples from Nick Davenport's Study 49 cohort collaboratively with industry partner, MSD.

8. MTA for Research committee approved and signed (collaborative project submitted by Roskamp Institute, Fiona Crawford and colleagues) for lipidomic analysis of samples studied with proteomic analysis by CENC biomarker discovery project. March 2020. Unable to access samples to distribute until Covid-19 restrictions lifted.

9. MTA for approved project with Dr. Nakase-Richardson and her team in process.

10. Collaborating with Bill Walker for evaluation of NED screen in Longitudinal sample.

**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**

**PROTOCOL (1 of 9 total):**

Protocol [HRPO Assigned Number]: E01140.2i

Title: Data and Biostatistics Core

Target required for clinical significance: 4000

Target approved for clinical significance: 4000

**SUBMITTED TO AND APPROVED BY:**

- The Salt Lake City, Utah arm of the DBC received local IRB determination that the Data and Biostatistics Core does not constitute human subjects research on February 21, 2020. On March 31, 2020 the USAMRDC HRPO concurred with the local IRB determination that research does not involve human subjects and waived oversight. HRPO Log E01140.2i.
- The Richmond, Virginia arm of the DBC received local IRB approval through an amendment to the VCU protocol submission HM20002321 on February 26, 2020. Submitted to the USAMRDC HRPO for initial determination on March 18, 2020.

**STATUS:**

**(i)** Number of subjects recruited/original planned target: N/A
Number of subjects screened/original planned target: N/A
Number of patients enrolled/original planned target: N/A
Number of patients completed/original planned target: N/A

**(ii)** Report amendments submitted to the IRB and USAMRMC HRPO for review:

(iii) **Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation:**

**PROTOCOL (2 of 9 total):**

Protocol [HRPO Assigned Number]:

Title: Neuroimaging Core

Target required for clinical significance: N/A

Target approved for clinical significance: N/A

**SUBMITTED TO AND APPROVED BY:**

- The IRB determined that the activities of this project do not constitute human subjects research.

**STATUS:**

**(i)** Number of subjects recruited/original planned target: N/A
Number of subjects screened/original planned target: N/A
Number of patients enrolled/original planned target: N/A
Number of patients completed/original planned target: N/A

**(ii)** Report amendments submitted to the IRB and USAMRMC HRPO for review:

(iii) **Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation:**

**PROTOCOL (3 of 9 total):**

Protocol [HRPO Assigned Number]:

Title: Biomarkers Core

Target required for clinical significance: N/A

Target approved for clinical significance: N/A

**SUBMITTED TO AND APPROVED BY:**

- The LIMBIC-CENC Biomarkers Core originally approved by USUHS IRB 4/28/2014 with HRPO second level approval 8/28/2014. It has received CR renewal approval letters annually from April 2015 to April 2019.

**STATUS:**

**(i)** Number of subjects recruited/original planned target: N/A
Number of subjects screened/original planned target: N/A
Number of patients enrolled/original planned target: N/A
Number of patients completed/original planned target: N/A

**(ii)** Report amendments submitted to the IRB and USAMRMC HRPO for review:

- Active protocol with modification submitted in 12/2019 as described below to change PI from Dr. Cox to LCDR Werner and pending at the time of this report. Mod also contains acknowledgement of renewed funding, updated specimen request form (under new funding), and increase of CENC participants from whom samples can be received longitudinally, from 2,500 to 3,500 (3,000 Longitudinal Study and 500 other CENC study participants).

(iii) **Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation:**

**PROTOCOL (4 of 9 total):**

Protocol [HRPO Assigned Number]: E01140.2

Title: Prospective Longitudinal Study

Target required for clinical significance: 3000

Target approved for clinical significance: 3000

**SUBMITTED TO AND APPROVED BY:**

- Hunter Holmes McGuire VA- IRB Submission 02038 was approved at Continuing Review on April 3, 2019 by McGuire VA IRB. HRPO Log E01140.2d was approved by the USAMRDC HRPO on March 31, 2020.
- Michael E. Debakey VA - IRB Submission H-34199 was approved at Continuing Review on February 4, 2020 by Baylor College of Medicine and Affiliated Hospitals IRB. HRPO Log E01140.2e was submitted to the USAMRDC HRPO for approval on January 14, 2020.
- James A. Haley Veteran's Hospital- IRB Submission Pro00017385 was approved at Continuing Review on July 2, 2019 by University of South Florida Institutional Review Board. HRPO Log E01140.2b was approved by the USAMRDC HRPO on March 31, 2020.
- South Texas Veterans Health Care System –Protocol HSC 20140416H was approved at Continuing Review on August 26, 2020 by UT Health San Antonio IRB. HRPO Log E01140 was submitted to the USAMRDC HRPO for approval on January 15, 2020.
- Virginia Commonwealth University- IRB submission HM20002321 was approved at Continuing Review on January 21, 2020.
- Fort Belvoir Community Hospital – IRB Submission Log Number PT120517 was approved at Continuing Review by the Walter Reed National Military Medical Center IRB on May 21, 2019. HRPO Log E01140 was submitted to the USAMRDC HRPO for approval on January 22, 2020.
- Portland VA Healthcare System and Oregon Health & Science University – IRB Submission #16174_m3930 was approved at Continuing Review on September 16, 2019. HRPO Log E01140.2a was approved on January 9, 2020.
- Boston VA Healthcare System – IRB Submission #3043 was approved at Continuing Review on August 19, 2019. HRPO Log E01140.2f was approved by the USAMRDC HRPO on April 1, 2020.
- Minneapolis VAMC – IRB Submission #4670 was approved on September 13, 2019. HRPO Log E01140 was submitted to the USAMRDC HRPO for approval on January 21, 2020.

- Salisbury VAMC – IRB Submission 19-019 was approved by the W.G. (Bill) Hefner IRB on February 10, 2020. HRPO Log E01140.2j was submitted to the USAMRDC HRPO for approval on March 26, 2020.
- San Diego VAMC & Camp Pendleton – IRB Submission H200001 was approved by the VA San Diego HCS IRB on March 31, 2020. HRPO Log E011402.k was submitted to USAMRDC HRPO for approval April 20, 2020.
- Ft. Gordon – Submitted to Dwight D. Eisenhower Army Medical Center IRB for initial approval January 2020 and the submission is still currently under review.

**STATUS:**

**(i)** Number of subjects recruited/original planned target:
Number of subjects screened/original planned target:
Number of patients enrolled/original planned target:
Number of patients completed/original planned target:

**(ii)** Report amendments submitted to the IRB and USAMRMC HRPO for review:

**(iii)** Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation:

**PROTOCOL (5 of 9 total):**

Protocol [HRPO Assigned Number]: HRPO Log Numbers E01140.1a (UCSF) and E01140.1b (SFVAMC)

Title: Retrospective Data Base Study

Target required for clinical significance: N/A

Target approved for clinical significance: N/A

**SUBMITTED TO AND APPROVED BY:**

- The subject protocol was approved by the UCSF Institutional Review Board (IRB) on 25 October 2019.

**STATUS:**

**(i)** Number of subjects recruited/original planned target: N/A
Number of subjects screened/original planned target: N/A
Number of patients enrolled/original planned target: N/A
Number of patients completed/original planned target: N/A

**(ii)** Report amendments submitted to the IRB and USAMRMC HRPO for review:

**(iii)** Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation:

**PROTOCOL (6 of 9 total):**

Protocol [HRPO Assigned Number]:

Title: Phenotypes Study

Target required for clinical significance: N/A

Target approved for clinical significance: N/A

**SUBMITTED TO AND APPROVED BY:**

- Protocol submitted to University of Utah IRB (IRB of record for VA Salt Lake City) and the VA Research and Development program. Approvals in progress.

**STATUS:**

**(i)** Number of subjects recruited/original planned target: N/A
Number of subjects screened/original planned target: N/A
Number of patients enrolled/original planned target: N/A
Number of patients completed/original planned target: N/A

**(ii)** Report amendments submitted to the IRB and USAMRMC HRPO for review:

(iii) **Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation:**

**PROTOCOL (7 of 9 total):**

Protocol [HRPO Assigned Number]: E01140.3

Title: Health Economics Study

Target required for clinical significance: N/A

Target approved for clinical significance: N/A

**SUBMITTED TO AND APPROVED BY:**

- IRB #54604 "VA-DOD Long-Term Impact of Military-Relevant Brain Injury Consortium: Economic Study"
- RDIS # DISNEW_0001 "Long-Term Impact of Military-Relevant Brain Injury Consortium (LIMBIC): Economic Study"
- Approved by HRPO on April 23, 2020 (HRPO log # E01140.3a).

**STATUS:**

**(i)** Number of subjects recruited/original planned target: N/A
Number of subjects screened/original planned target: N/A
Number of patients enrolled/original planned target: N/A
Number of patients completed/original planned target: N/A

**(ii)** Report amendments submitted to the IRB and USAMRMC HRPO for review:

(iii) **Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation:**

**PROTOCOL (8 of 9 total):**

Protocol [HRPO Assigned Number]:

Title: Novel Neuroimaging Study

Target required for clinical significance: N/A

Target approved for clinical significance: N/A

**SUBMITTED TO AND APPROVED BY:**

- Consistent with the Neuroimaging Core, we anticipate that the IRB will determine that the activities of this project do not constitute human subjects research, though this is pending.

**STATUS:**

**(i)** Number of subjects recruited/original planned target: N/A
Number of subjects screened/original planned target: N/A
Number of patients enrolled/original planned target: N/A
Number of patients completed/original planned target: N/A

**(ii)** Report amendments submitted to the IRB and USAMRMC HRPO for review:

(iii) **Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation:**

**PROTOCOL (9 of 9 total):**

Protocol [HRPO Assigned Number]:

Title: Biomarkers Discovery Study

Target required for clinical significance: N/A

Target approved for clinical significance: N/A

**SUBMITTED TO AND APPROVED BY:**

**STATUS:**

**(i)** Number of subjects recruited/original planned target: N/A
Number of subjects screened/original planned target: N/A
Number of patients enrolled/original planned target: N/A
Number of patients completed/original planned target: N/A

**(ii)** Report amendments submitted to the IRB and USAMRMC HRPO for review:

(iii) **Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation:**

**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 onboarding new sites.
2. Continue certifying new study site personnel.
3. Continue to work with sites to gain all IRB and HRPO approvals.
4. Continue building the Consumer Advisory Board and hold our first meeting in order to approve Charter and Meeting Schedule.
5. Continue to interface with other researchers, entities, and consortiums.

**Neuroimaging Core**:

1.Conduct virtual refresher training at 4-6 project sites to 1) review study procedures and course correct (minor) issues from prior cycle that will facilitate data organization and consistency, 2) obtain annual human phantom and phantom object data, 3) review scanner protocols on site.
2. Prepare next installment of imaging data to FITBIR (by 30 SEP 2019)
3. Complete training of neuroradiologists on new Medidata system
4. Complete reconciliation entries of existing CDE data into new Medidata system
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 analyses.

**Biomarkers Core**:

1. Continue to receive, store and distribute samples from Longitudinal study participants as research committee approves
2. Finalize Quest contract renewal and add 3 new enrolling sites and continue support NED screening tests
3. Carry out DNA extractions and APOE genotyping on baseline specimens with permission for genetic testing in batches of 100
4. Submit the Continuing Review to the USU IRB as due by April 2020.
5. Continue monthly conference calls with the LIMBIC consortium.

**Data and Biostatistics Core**:

1. Automate and streamline semi-annual data submission from Medidata and Amazon Web Services work space to FITBIR using SQL in order to better complete bi-annual FITBIR submissions.
2. Finalize and implement comprehensive study QA-QC monthly report and meeting.
3. Complete search function for excel-based data dictionary
4. Create and implement system for regular, automated download of clinical data from Medidata to LIMBIC-CENC database.
5. Collaborate between the two sites to assess the most feasible approach to redesign and deploy Web friendly data dictionary to the LIMBIC-CENC study website.
6. Reach out to investigators with open data requests/incomplete publications who were using RTI central data support to either close those data requests or move them forward with LIMBIC-CENC Central Data Support.
7. Continue developing new KT products, e.g., lay abstracts, clinical pearls, post cards
8. Develop a one-page overview for potential implementation science projects and funding requirements; discuss at next GSC meeting.
9. Contact and have initial meeting on harmonization of imaging methods paper

## 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 the 8 original sites (Richmond, Houston, Tampa, San Antonio, Fort Belvoir, Minneapolis, Portland and Boston).
3. Continue training, certifying and gaining regulatory approvals 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. Carry on with all study procedure and administrative activities including telephonic longitudinal visits, data collection and quality assurance.
5. Continue work on scientific analyses, dissemination, and knowledge translation.

**Retrospective Data Base Study**:

1. Further update the dataset by adding VA data through 2019 (which just recently became available).
2. We are preparing for an analysis examining cardiovascular risk factors and their affect on the relationship between TBI and dementia.
3. We will continue regular group meetings between investigators and regular reporting on LIMBIC consortium calls.

**Phenotypes Study:**

1. Complete regulatory requirements.
2. Begin DSAA for DoDTR Data requests once regulatory requirements complete.
3. Transfer Repository data to study file once VA R&D and HRPO approvals are complete.
4. Provide finder file for DaVINCI staff once VA R&D and HRPO approvals are complete. This will require significant coordination as this is much more complicated than anything DaVINCI has ever done. Data will not be available in the next quarter.

**Health Economics Study:**

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

**Novel Neuroimaging Study**:

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

**Biomarkers Discovery Study**:

1. Correlate all exosomal and plama biomarker results with Neuroimaging and neurocognitive outcomes in collaboration with Imaging core and prepare results for dissemination.
2. Complete analysis of saliva samples for protein, exosomal and microRNA biomarkers of chronic TBI from CENC study 1 subjects.
3. Submit 2 additional manuscripts regarding miRNA (blast and PTSD)
4. Obtain pre-deployment specimens from DoD biospecimen biorepository.
5. Measure pre and CENC baseline protein biomarker panel
6. Establish collaboration with Kevin Wang for complementary specimen analyses by his lab under external VA funding.
7. Complete Study 49 analyses and prepare manuscripts of results.

**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. Manuscript in press: Kornblith E, Peltz CB, Xia F, Plassman B, Novakovic-Apopain T, Yaffe K. Sex, Race, and Risk of Dementia Diagnosis after Traumatic Brain Injury among Older Veterans. Neurology, in press.

2. Dismuke-Greer CE, Fakhry S, Horner M, Pogoda T, Pugh MJ, Gebregziabher M, Hall C, Taber D. Ethnicity/Race and Service-Connected Disability Disparities in Civilian TBI Mechanism of Injury, Death, and VA Health Services Costs in Military Veterans: Evidence From A Level One Trauma Center. Published In ***Trauma.***

3. Bouldin ED, Swan AA, Norman RS, Tate DF, Tumminello C, Amuan ME, Eapen BC, Wang CP, Trevino A, Pugh MJ. Health phenotypes and neurobehavioral symptom severity among post-9/11 veterans with mild traumatic brain injury: A Chronic Effects of Neurotrauma Consortium Study. In press: *Journal of Head Trauma Rehabilitation.*

4. Correa DJ, Milano L, Kwon CS, Jetté N, Dlugos D, Harte-Hargrove L, Pugh MJ, Smith JK, Moshé SL. Quantitative readability analysis of websites providing information on traumatic brain injury and epilepsy: A need for clear communication. Epilepsia. 2020 Mar;61(3):528-538. doi: 10.1111/epi.16446. Epub 2020 Feb 24.

5. Created a new LIMBIC-CENC website: www.limbic-cenc.org

## 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 #3 for Personnel Effort and Quarterly Financials.

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

### a. Actual Problems or delays and actions to resolve them

*Provide a description of current problems or issues that may impede performance or progress of this project along with proposed corrective action. Also describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.*

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

1. The COVID-19 pandemic is having a significant impact on our consortium, especially so in the Prospective Longitudinal Study. Just as the original 8 sites were receiving HRPO approvals, all enrollment locations started shutting down in-person research. Portland was able to enroll 6 new participants prior to the shutdown but none of the other locations were able to initiate enrollment operations. However, all of the locations are able to continue collecting data during this time frame due to a remote data collection system that we had previously set up to handle participants that were not able to return for in-person visits for some reason.

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

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

4. There will be a delay in shipping and receiving samples while there is a social distancing requirement at the Biospecimen Repository due to the COVID-19 pandemic.

### b. Anticipated Problems/Issues

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

1. The recruiting goals for the Prospective Longitudinal Study have been delayed by one quarter at this time and it appears that this will continue for at least one more quarter if not more. We still have room to shift these recruitment goals to the back end of the Period of Performance at this time so we fully expect to meet our overall goals, just 1-2 quarters later than projected.

2. Due to the Covid-19 pandemic, the Retrospective Study has experienced some minor delays in their dataset creation, merging, and early analyses due to staff working from home. The VA servers they use for their projects are running slowly due to the increased access from home computers.

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| They estimate that they may incur a 3-4 month delay due to the pandemic and shelter-in-place orders if not lifted soon. |

## 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 #4 for Quad Charts.