Quarterly Technical Progress Report Format
Front Cover

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

If you have questions, contact the GOR.

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

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

CORES

Coordinating Center:

1. Transition and Expand CENC to LIMBIC:

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

2. Add three new additional Prospective Study Enrollement Sites:

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

3. Conduct Call Center operations:

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

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

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

5. Conduct Consumer Advisory Board Meetings:

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

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

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 LIMBI-CENCC 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]

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. The IRB approved master protocol was submitted.
b. The expanded Consortium SOP was delivered.
c. Submitted the timeline for onboarding performance sites.
d. 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.
e. IRB/HRPO/JIT approvals for all performance sites and consortium cores are either submitted, pending approval or approved.
g. All subaward personnel, clinicians and associate researchers have been hired, trained and either certified or in the certification process.

2. Add three new additional Prospective Study Enrollement Sites:

a. Currently onboarding 3 new enrollment sites (Salisbury/San Diego/Fort Gordon).
b. Assisted with hiring and training of all new staff who are still in the certifying process.
c. Assisted all sites with regulatory approvals to include IRB and HRPO.

3. Conduct Call Center operations:

a. Hired, trained and certified the Call Center 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. 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. Selected Board Members and will attain GSC approval of the selectees at the GSC meeting in February.
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.

Neuroimaging Core:

1. **Regulatory**:

a. *IRB protocol development, submission, and continuing review. (Locally and in conjunction with Coordinating Center at VCU).* 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 the Coordinating Center at VCU on the day that we received IRB determination that the Neuroimaging Core activities did not constitute human subjects research. In the past, the CENC Neuroimaging Core activities were also determined to not constitute human subjects research. Until we receive formal determination by HRPO for LIMBIC, we will consider this in process.

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 are 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.

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.

4. **Clinical Reads**:

a. In conjunction with the Data Core (VCU and UU), we have assisted in the creation of Medidata forms for the collection and entry of data related to the clinical reads and CDE coding. 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.

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 via phone) attended FITBIR training in Bethesda (6-7 JAN 2020). During the course of the meeting, we discovered a few procedural steps that would facilitate upload of the imaging data to FITBIR.

b. Mr. Abildskov, who will have primary responsibility for the upload of imaging data (dicom) to FIRBIR received all necessary access to FITBIR. Permissions and account requests for several other Neuroimaging Core investigators (Wilde, Tate, Hunsaker, Dennis), and staff (including Velez, Lindsey, Dimanche) have been submitted and are pending.

c. We have begun identifying and preparing data for our first submission to FITBIR in March.

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 ongoing Prospective Longitudinal Study:

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	20 (total 1602)	0 (total to date 1308)
DNA	0 (1191)	0 (0)
Stock DNA	0 (196)	0 (0)

Plasma	308 (10,131)	0 (584)
Saliva	49 (1639)	0 (194)
Serum	249 (9826)	0 (0)
Whole Blood (PaxGene)	48 (1748)	0 (0)
Grand Total:	**674 (26,333)**	**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. Submit the Continuing Review to the USU IRB as due by April 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

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 implementation of new Medidata Rave url, with all current CRFs and migrated all previously collected data.
(2) Completed training workshops with all 11 enrollment sites to provide instruction on changes in new url.
(3) Set up HIPAA and other regulatory-compliant infrastructure and IT systems and provided IT-specific assistance to sites for regulatory approvals.
(4) Completed QC of all TBI diagnoses and clinical data, identified discrepancies, and made revisions.
(5) Completed scoring for previously unscored BTACT data for all the data collected through March 2019; implemented procedure for real time scoring.
(6) Built a MRI completion report in Medidata to ensure all the MRIs are received by Neuroimaging core and associated central read is completed.
(7) Deployed BTACT and Annual Telephone Visit case report forms in Medidata to capture telephonic visit data.
(8) Deployed central read forms in Medidata and migrated previously collected data.
(9) Created and deployed internal side of LIMBIC-CENC website to facilitate Prospective Longitudinal Study and Consortium operations.
(10) Created and deployed portal where participant name and phone numbers are collected and the Call Center can access information for telephone visits.
(11) Created and deployed Call Center Application to track all telephone visits attempts and dispositions.

(12) Created regulatory-compliant SFTP server for sites to submit raw files including: EEG, ERP, hearing test, eye tracking data, neuropsychological source documents, and certification videos and documents.
(13) Made changes in Medidata to accommodate data collected remotely for non-returning follow-up visits.
(14) Configured all the iPads to securely export the NIH Toolbox data to LIMBIC-CENC server.

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

(1) Awaiting data submissions for LIMBIC study.

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) Developed an internal process for tracking and responding to incoming data requests.
(2) Created a flow chart to illustrate the data request process for investigators.
(3) Completed data request flow chart with clearly defined roles and responsibilities for the two site team.
(4) Created a listserv for investigators to invite collaborators from enrollment sites and LIMBIC-CENC cores.

e. Data Request Processing:

(1) We responded to and completed 4 data requests. Each data request included an average of more than 100 variables across domains and measures. Extracted data are then validated through rigorous testing before submitting to investigator.
(2) LIMBIC-CENC Biostatistics group is actively conducting advanced analyses for 3 investigator-initiated projects.
(3) We are processing on an additional 7 data requests which are in different stages of submission, review and revision by investigators.

f. Data Dictionary:

(1) Developed data dictionary with user friendly and menu driven interface that enables investigators to select desired variables, which has been tested and is improved iteratively with investigator feedback.
(2) Organized by study domains, measures, and variables and their labels. There are 7 main domains with 30 associated measures and more than to 2,000 associated variables.
(3) Made revisions to data dictionary that lists and describes all the variables available to select for Prospective Longitudinal Study.

g. FITBIR Data Submission Preparation:

(1) Attended biweekly meetings with FITBIR Ops.
(2) Completed in-person training with CDMRP and Neuroimaging Core.
(3) Worked with FITBIR Ops to finalize the last 3 (new) form structures.
(4) Set up FITBIR account access for LIMBIC-CENC Data and Biostatistics Core personnel for data submission and all Prospective Longitudinal Study site personnel for GUID creation.

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 (4 data requests complete; 7 in progress).

- 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 initiated.

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

c. IRB protocol development, submission, and continuing review.
(1) All 8 of the existing sites (Richmond/Tampa/San Antonio/Houston/Boston/Minneapolis/Portland?Fort Belvoir have LIMBIC IRBs approved.
(2) The three new sites have their protocols at their IRB pending approval.

d. HRPO approval and continuing review.
(1) Portland has HRPO approval.
(2) HRPO requests have been submitted for the other 7 previous CENC sites.
(3) HRPO requests will be submitted for the three new sites once they receive IRB apprvals.

e. Develop site-wide recruitment and retention plan.
(1) Plans have been completed.
(2) Recruitment plans will be slightly adjusted due to delay in recruitment awaiting HRPO approval.

f. Recruitment and retention plan will be initiated once all approvals have been gained.

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, Clinical Administered PTSD Scale DSM-5 (CAPS-5), RightEye) finalized and readied to launch; TOPF determined redundant based on psychometric analysis so removed along with SVV; All primary IRB approvals obtained.
(2) New data capture system launched
(3) Quarterly FITBIR uploads completed and issues resolved with prior CENC data under RTI.
(4) QA ongoing; one highlight was extensive QA and digitalization of phone assessment data collected and stored as free text data by RTI.
(5) First version of enhanced investigator-driven data dictionary developed and launched.
(6) New scientific analysis requests received and processed with analytic/dissemination work ongoing

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.

i. Wrapped up CENC dissemination activities:

(1) Dismuke-Greer, CE. *Health Services Utilization, Healthcare Costs, and Diagnoses by Mild Traumatic Brain Injury Exposure: A Chronic Effects of Neurotrauma Consortium Study*. Submitted to Arch Phys Med Rehabil.

Aim: Compare Veterans Administration (VA) health services utilization and costs by mild (m)TBI group (Blast-Related (BR) mTBI vs. non-Blast-Related (NBR) mTBI vs. no mTBI).

Findings: Vs with BR mTBI had greater combat and detonation exposures, greater prevalence of select diagnoses (headache, PTSD, anxiety), and higher health services utilization and costs, relative to NBR and no mTBI.

Meaning: Because we have not yet observed outcomes differences in our prospective data, the higher VAMC resource use and comorbid diagnoses in those with blast-related mTBI versus non-blast mTBI may reflect differences in demand for services.

(2) Kenney, K. *Exosomal MicroRNAs in Chronic Mild Traumatic Brain Injury: Preliminary Results from a Chronic Effects of Neurotrauma Consortium (CENC) Biomarker Discovery Project*. Submitted Sep 2019 to 5th Annual NABIS Conference on Brain Injury (ABI2020), Feb 26-29, 2020, New Orleans, LA.

Aim: Measure and compare plasma exosomal miRNA (exomiR) across mTBI groups and assess relationships between differentially expressed miRNA and NSI symptom burden.

Findings: Exosomal miRNA differed across mTBI groups, with incrementally more dysregulation from non-TBI, to 1-2 mTBI, to >2 mTBI (repetitive mTBI). The differences found were closely associated with inflammatory regulation and neuronal repair processes. A correlation between miRNA and clinical symptoms was also observed.

Meaning: Exosomal miRNA expression analysis may provide novel insights into the underlying pathobiology of chronic symptom persistence in Vs and SMs with remote mTBI, especially if repetitive.

(3) Walker WC, Khokar B. *Influence of demographic and comborbid factors on Pain Interference in Veterans and Servicemember with mild TBI.* Manuscript in preparation; tentative journal Military Medicine.

Aim: examine the associations between pain interference (with daily life) and factors including type/number of mTBIs, demographics, and common co-morbid conditions.

Findings: In adjusted analysis, high pain interference was associated with repetitive mTBI history and Arthritis, but more strongly with PTSD and Anxiety.

Meaning: In Vs and SMs with TBI, those with repetitive mTBI are at higher risk for pain-related disability. Treatment programs for Vs and SMs with mTBI and pain-related disability should be holistic to address mental health conditions.

(4) Garcia A (Tampa). *Association between STOPBANG Risk and Sleep Quality in an mTBI Sample: A Chronic Effects of Neurotrauma Consortium Study*. Submitted Dec 2019 to Sleep 2020 June 13-17, 2020, Philadelphia, PA.

Aim: Assess the relationship a sleep apnea screening tool (STOPBANG) has with self-reported sleep measures (PSQI) in Vs and SMs with mTBI across different scoring methods.

Findings: The relationship between sleep apnea screening and perceived sleep quality was altered by mTBI history. Having the triad ‘Snoring, Tired and Hypertension’ correlated most strongly with sleep quality in those without mTBI but the relationship was attenuated in those with mTBI.

Meaning: Sleep apnea and positive mTBI history both contribute to poor perceived sleep quality. Sleep apnea is a treatable comorbidity, and should be screened for regardless of mTBI history.

(5) Garcia A (Tampa). *Obstructive Sleep Apnea Risk is Associated with Cognitive Impairment After Controlling for mild TBI history: A Chronic Effects of Neurotrauma Consortium Study*. Manuscript submitted to J Neurotrauma.

Aim: Examine the risk of OSA and the association between OSA risk and cognitive performance.

Findings: Independent of TBI status and demographic variables, increased OSA risk was significantly associated with worse performance on measures of complex processing speed and executive functioning (WAIS IV Coding, Trailmaking Test B) and greater symptom burden. T

Meaning: OSA may contribute to cognitive performance following mild TBI. As a modifiable condition, OSA is a target for intervention to improve clinical and cognitive outcomes after injury.

j. LIMBIC Scientific Analysis Underway:

(1) Miles, SR. *Sleep Disturbances after mTBI Increase Anger in Veterans with PTSD Symptoms: A CENC Study.*

Aim: Examine the relationships between sleep disturbance (STOP-Bang [OSA-Risk], Pittsburg Sleep Quality Index), PTSD symptoms, and anger in Veterans with mTBI. Hypothesis: PTSD symptoms are associated with anger and to a higher degree when sleep is disturbed.

(2) Levin, H. *White Matter Hyperintensities and Mild TBI in Post 9-11Veterans and Service Members*.

Aim: Evaluate whether sustaining one or more mTBIs is associated with a number of WMHs that is greater than expected for age.

(3) Ageymang, A. *Validity of BTACT in a combat veteran and military sample from the CENC multicenter study*

Aims: Assess several aspects of the BTACT validity within the CENC/LIMBIC cohort including internal consistency, external validity vis a vis original MIDUS validation sample, concurrent and divergent validity vis a vis in-person comprehensive neuropsychological battery, and ecological validity vis a vis quality of cognitive functioning.

(4) Walker WC. *Neuroendocrine abnormalities: Prevalence, relation to symptoms, relation to TBI history.*

Aims: Determine prevalence of hypothalamic-pituitary-adrenal (HPA) axis dysfunction (testosterone level, IGF-1 level, and TSH levels outside of reference range) and association with mTBI history. Among participants with mTBI, determine if HPA axis dysfunction is associated with select clinical symptoms and/or select areas of cognitive performance.

(5) Pickett, T. *Characteristics of Mild TBI and non-TBI participants in military epidemiology research; comparison of CENC-LIMBIC multicenter study and DVBIC 15 year study*.

Aim: Describe and compare the demographic characteristics and overlapping injury, comorbidity, symptom profile and functional status measures between the CENC-LIMBIC multicenter study and the DVVBIC 15 year study among participants with positive mild TBI histories and negative TBI histories (controls).

k. Other Prospective Study Collaborations and Spin Off Studies:

(1) Abdullah, L (Tampa VAMC). *Identifying APOE Related Lipid Biomarkers for Diagnosing Chronic Neurocognitive Deficits in TBI Patients*. Funding: VA RR&D. Status: Funding approved. Key collaborator(s): Roskamp Institute.

Objectives: develop a biomarker panel that can predict a possible risk of AD subsequent to mTBI by evaluating inter- and intra-subject variations of plasma lipids and bioactive lipid metabolites and its relation to TBI diagnosis as well as cognitive decline after TBI.

Methods Synopsis & Relation to CENC-LIMBIC multicenter longitudinal study: The study will enroll 42 CENC participants at Tampa site; 21 control subjects and 21 mild TBI subjects. Additional blood samples will be collected at several timepoints over a short-term period to assess the effects of intra

and inter-subject variations on lipid measurements. After a participant is consented and enrolled in this study, blood samples will be collected once per month for three months, for a total of 3 blood draws of approximately 30ml of blood.

(2) Walker, WC. *Optimizing Heart Rate Variability (HRV) to Improve Sleep and Performance after Concussion in Combat Veterans in a Chronic Effects of Neurotrauma Consortium Cohort*. Submitted for CDMRP CTA funding. Funding status: pending review/decision. Key collaborator(s): Columbia, SC VAMC and Univ of South Carolina.

Objectives: Short-term: Assess the treatment effect of HRV biofeedback to reduce functional vulnerabilities and enhance human performance in c-Vs and SMs with chronic mTBI. Long-term: Improve the health and lives of c-Vs and SMs by enabling clinicians to provide an efficacious, self-activating treatment for persistent symptoms and performance deficits after combat- and blast-related mTBI that is scalable and sustainable.

Methods Synopsis & Relation to CENC-LIMBIC multicenter longitudinal study: Phase II/III, randomized, clinical trial with 2 parallel groups of equal size comparing the efficacy of in-person HRV-B training versus directed in-person education program in c-V/SMs with chronic mTBI and disturbed sleep. The study procedures will occur in Richmond and leverage the CENC cohort for recruitment. Power analyses support enrolling 116 participants. After baseline testing, participants will have 6 sessions (once per week) of in-person training with outcome assessments at baseline, week 7 (end of treatment) and week 11 (1-month post-treatment).

(3) Carlson, K (Portland VAMC). *Effects of Opioid and Other Psychotropic Drug Exposures on Long-term Outcomes of TBI: Developing Measurement Best Practices.* VA R&D, SPiRE. Funding status: approved.

Objectives: Develop best practices for epidemiologic and clinical research, and serve as the foundation for a new research program, that evaluates the impact of opioids and other psychotropic medications on the long-term neurological outcomes of Veterans with TBI history.

Methods Synopsis & Relation to CENC-LIMBIC multicenter longitudinal study: This 2-year project will generate the methods and preliminary data needed for subsequent research focused on opioids and neurological health among Veterans with TBI. It will use VA administrative data, and state prescription drug monitoring program (PDMP) data, to develop reproducible and scalable approaches to valid TBI and medication measurement. The investigator team includes several CENC-LIMBIC investigators and the findings of the project are anticipated to facilitate more comprehensive and accurate data capture of opiate and psychotropic medication usage in the multicenter longitudinal study cohort as well as other clinical studies in this population.

(4) Pugh, MJ. Dept. of Defense, Epilepsy Research Program, Idea Development Award (ERP-IDA). *The Epidemiology of Epilepsy and Traumatic Brain Injury: Severity, Mechanism, and Outcomes". Supporting Agency*: Sponsor/Award W81XWH-16-2-0046.

Objectives: The major goals of this project are to understand the development of epilepsy among Veterans with mild TBI; specifically the epidemiology of epilepsy and TBI in Iraq and Afghanistan war Veterans using available data from the Departments of Defense (DoD) and Veterans Affairs (VA), and primary data collection.

Methods Synopsis & Relation to CENC-LIMBIC multicenter longitudinal study: CENC investigators are on the project. Survey respondents are referred to CENC multicenter longitudinal study for

recruitment and CENC participants are recruited into the survey study; co-enrollees are asked to share their CENC data.

Retrospective Data Base Study:

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

a. We have made excellent progress in the first quarter of this project. We submitted and received all the required regulatory approvals. The LIMBIC Epidemiology Study was approved through UCSF IRB on 25-OCT-2019, the SF VA Medical Center on 8-NOV-2019 and approved through HRPO on 31-DEC-2019.

b. We set up regular, recurring team meetings between all the investigators and research staff on this project. We are in the process of updating our data repository through 2018 (the most recently available data from the VA). We are adding all new TBI cases since 2015 as well as expanding our 2% random sample through 2018. We are updating all diagnosis codes in the study (TBI, dementia, medical and psychiatric comorbidities, etc.) from ICD-9 to ICD-10.

c. While the data updating is ongoing, we have been preparing for our first analysis. Some pilot work from our group investigated incident dementia with TBI exposure by race. Using a sample of nearly 1 million veterans with data from 2001-2015, 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 ($p<0.001$).

Phenotypes Study:

1. Task: Complete Regulatory Requirements.

a. University of Utah IRB and VA Salt Lake City Research and Development Committee submissions are submitted and awaiting approval.

b. DoDTR and DSAA request forms complete pending IRB, R&D and HRPO approvals.

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

a. We identified the following stakeholders: VA PM&R / VA National Center on Homelessness among Veterans (NCHAV) / VA Mental Health and Suicide Prevention.

Health Economics Study:

1. Task: Obtain DoD and VA authorizations.

a. Both the protocol and amendment are currently under review by the Stanford IRB and VA Palo Alto Health Care System R&D committees. The Stanford IRB requested clarification on subjects vs medical records and we have responded.

b. Both the Quad Chart and the PI assurance have been prepared for the JIT approval.

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: 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.

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.
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 currently under review.
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.
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.
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.
6. Preparing manuscript of NFL, sleep, cognitive analysis by LCDR Werner, presented at MHSRS 2019.
7. Preparing MTA for Research committee approved collaborative project submitted by Roskamp Institute (Fiona Crawford and colleagues) for lipidomic analysis of samples studied with proteomic analysis by CENC biomarker discovery project.

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]:

Title: Data and Biostatistics Core

Target required for clinical significance: N/A

Target approved for clinical significance: N/A

SUBMITTED TO AND APPROVED BY:

- An amendment to the existing IRB approval was submitted on 28 Oct 2019. Still pending approval.

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]:

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 was submitted to the USAMRDC HRPO for approval on January 17, 2020.
- Michael E. Debakey VA - IRB Submission H-34199 was approved at Continuing Review on March 15, 2019 by Baylor College of Medicine and Affiliated Hospitals IRB. HRPO Log E01140 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 was submitted to the USAMRDC HRPO for approval on January 14, 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 October 23, 2014.
- 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 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 was submitted to the USAMRDC HRPO for approval on January 14, 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 – Submitted to Salisbury VAMC IRB for initial approval January 2020, awaiting determination.
- San Diego VAMC & Camp Pendleton - Submitted to local IRB for initial approval January 2020, awaiting determination.
- Ft. Gordon – Submitted to Dwight D. Eisenhower Army Medical Center IRB for initial approval January 2020, awaiting determination.

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]:

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"

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. Prepare for and participate in our first LIMBIC-CENC Government Steering Committee meeting in February.
5. Participate in the Brain Injury Awareness Day on Capitol Hill in March.
6. Plan, prepare and execute LIMBIC-CENC Kick Off event at the Hunter Holmes McGuire VAMC with Dr. Rachel Ramoni in attendance.
7. Continue to interface with other researchers, entities, and consortiums.

Neuroimaging Core:

1.Conduct in person 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 and submit next installment of imaging data to FITBIR (by 31 MAR 2019)
3. Complete training of Neuroimaging Core personnel.
4. Complete training of neuroradiologists on new Medidata system
5. Reconcile entries of existing CDE data into new Medidata system
6. Continue monitoring quality assurance for neuroimaging data, as above.
7. Continue to perform analysis of imaging data on standard pipelines.
8. Following receipt of data, continue work on pending analyses.
9. Publish CAB Meeting Calendar, conduct the first meeting and publish the charter.

Biomarkers Core:

1. Receive approval for modification to change PI from Dr. Cox to Dr. Kent Werner because Dr. Cox is retiring at the end of January. The mod was submitted at the beginning of December and we are waiting for review by IRB at USU.
2. Continue to receive, store and distribute samples from Longitudinal study participants as research committee approves
3. Renew Quest contract and add 3 new enrolling sites and continue support NED screening tests
4. Carry out DNA extractions and APOE genotyping on baseline specimens with permission for genetic testing in batches of 100
5. Submit the Continuing Review to the USU IRB as due by April 2020.
6. Continue monthly conference calls with the LIMBIC consortium

Data and Biostatistics Core:

1. Complete Medidata enablement.
2. Migrate all previously collected participant information into new Contact Information Management System.
3. Automate and streamline semi-annual data submission to FITBIR in order to better complete bi-annual FITBIR submissions.
4. Create and implement system for regular, automated download of clinical data from Medidata to LIMBIC-CENC database.
5. Build and implement automated dashboard reports to track enrollments, recruitment, and receipt of biospecimen and MRIs.
6. Implement comprehensive study QAQC monthly report and meeting.
7. Redesign and deploy Web friendly data dictionary with global search functionality

STUDIES

Prospective Longitudinal Study:

1. Restart enrollments at all 8 CENC sites NLT Feb 2020.
2. Start enrollments at the 3 new sites NLT Mar 2020.
3. Carry on with all study procedure and administrative activities including longitudinal visits and data collection and quality assurance.
4. Continue work on scientific analyses, dissemination, and knowledge translation.
5. Conduct next quarterly FITBIR upload.

Retrospective Data Base Study:

1. Continue the dataset updating with new TBI cases and ICD-10 codes for relevant variables.
2. Once the dataset is finalized, we will begin to examine interactions between mTBI, mental health, and long-term outcomes.
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. Obtain VA and DoD Health system data via DaVINCI once regulatory requirements complete.

Health Economics Study:

1. Once the LIMBIC protocol has been approved we will request to be added to the Utah VA DART in VINCI to work with Dr. Pugh (PI Phenotype study) to begin cleaning and merging data for analysis.
2. Once the Longitudinal Study amendment has been approved we will work with Dr. Walker and sites to obtain real SSNs of study subjects to provide to VINCI to obtain VA and DoD data (Da VINCI) data on these subjects.

Novel Neuroimaging Study:

1. Conduct phantom testing at initial onsite training visits with the diffusion phantom to collect data for data harmonization.
2. Participate in further discussion with colleagues who are developing additional harmonization methods.
3. Complete analysis of 1-2 additional pipelines for diffusion imaging and begin analysis to directly compare results. 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. Pending receipt of requested data, we plan to perform additional analyses using qualitative comparative analysis and additional machine learning techniques.

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. Present miRNA and NFL-sleep data at 2020 NCA TBI symposium in Bethesda, MD in March 2020.

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: Guedes VA, Kenney K, Shahim P, Qu B-X, Lai C, Devoto C, Walker WC, Nolen T, Diaz-Arrastia R, Gill JM. Exosomal NFL, a prognostic biomarker for remote symptoms after mild traumatic brain injury? Neurology, in press, 12-2019.

2. 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 #1 for Personnel and Appendix #2 for 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 Consortium name change from CENC to LIMBIC-CENC caused some delay in gaining IRB approvals thus causing some further delay in gaining HRPO approval. We had expected to start enrollment for the Prospective Longitudinal Study at the eight existing sites in the first quarter and only one site at this point has HRPO approval and has started enrollment (Portland). However, we feel confident that we will be able to move those projected enrollments to year three without causing sites any difficulty since they were initially scheduled to start decreasing their enrollment at that time.

2. The delay in the Federal Government funding the VA has delayed the JIT process for all of our sites that are supposed to receive VA funding. Most of the sites are able to support themselves during this lull but at least one site, VA Salt Lake City, has not been able to initiate work as initially projected.

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.

None to report.

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 #3 for Quad Charts.