Quarterly Technical Progress Report Format
Front Cover

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:	July 29, 2020
Report Period:	04/01/2020 - 06/30/2020

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:

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

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

Training:
4. Hire and maintain all research consortium staff

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

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

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

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

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

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.
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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 continue to work on the establishment of Data Sharing Agreement with DHA for access and use of MHS data at VCU CC and appropriate sites.
b. Continue to work with Fort Belvoir, Minneapolis and COL Radcliffe to complete the PI/Key Personnel changes,
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. Two of the three sites have received IRB and HRPO approvals and the only site still working on IRB approval is Fort Gordon.

3. Conduct Call Center operations:

a. We hired a new Call Center supervisor. However, the person we hired was one of our three callers so now we are in the process of hiring a new caller.
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%.
e. Worked with the DBC in order to launch the new Call Center Application, completely automating all call center procedures.
f. Completed the entry of back-logged interviews into Medidata that were not entered by the previous contractor.

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

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

5. Conduct Consumer Advisory Board Meetings:

a. Gained approval for the initial 10 member board and will work on additional guidance from the GSC.
b. Scheduled the first meeting for 14 August where we will finish and approve LIMBIC-CENC CAB Charter and also finalize the 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. Scheduled the Semi-Annual GSC meeting with our DoD and VA sponsors.

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

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

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

Neuroimaging Core:

1. **Regulatory**:

a. **IRB protocol development, submission, and continuing review:** During a past performance period (Q1 2020), the Neuroimaging Core protocol was submitted to the University of Utah/ VA Salt Lake City Healthcare System IRB; we received formal determination from the IRB that activities conducted under the Neuroimaging Core were not considered human subjects research and did not require further oversight by the IRB (03 Dec 2019). Since no continuing review is necessary, this is considered complete. We will continue to undergo annual RR&D committee approval at the VA.

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. Until we receive formal determination by HRPO for LIMBIC, we will consider this in process.

c. **Attendance at biannual GSC meetings:** No GSC meetings were scheduled during this performance period. We therefore consider this item up to date.

2. **Training:**

a. **Hire and maintain all research consortium staff:** As in the prior performance period, we have continued our training of a few additional staff members, including Hannah Lindsey, Emily Dennis, Paula Johnson, Josephine Dimanche and Elizabeth Hovenden, who are assisting with various aspects of clinical reads, data tracking and quality assurance, and imaging analysis. All staff members have WOC appointments at the VA, and are current on all required CITI training for University of Utah, SLC VA, and Office of the Undersecretary of the Department of Defense.We have continued training the neuroradiologists involved in the Common Data Element coding on new procedures in the Medidata system. Formal site training and annual/site qualification visits will occur via videoconference in July and August due to COVID-19 restrictions. These meetings involve all project staff involved in imaging data collection including both PI and project staff as well as MRI staff at each site.

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

3. **Quality Assurance**:

a. Note that the transfer of additional neuroimaging data to the Neuroimaging Core is pending IRB approval and lifting of COVID-19 restrictions that prohibit data collection. 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 have scheduled site visits with the majority of existing sites 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. We are sending weekly reminders regarding scheduling this meeting to sites that have not identified a date where all personnel are available.

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 have reviewed 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 reviewed the consolidation of the CDE data transferred from the older CENC system into the newer one which will be used in LIMBIC and reconciling and monitoring CDE codings. Reading of scans collected during January 2019-September 2019 was prioritized, and we have been working on completion of reads for outstanding scans acquired 2013-2018 and post September 2019. For scans collected 2013-2018, we have been working with the Data Core as well as individual sites to verify that data was/was not collected. We noted that some of the previously completed forms were missing fields, so we have been reviewing all data and adding new information, as required.

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 (including recent version of software that was released during the period of performance), though we have instituted some additional longitudinal pipelines, which are in process.

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

c. With regard to specific data requests, Neuroimaging Core investigators have been meeting regularly with investigators from the Biomarker Core (Drs. Kenney/Gill/Werner) as well as individual investigators (e.g., Dr. Richardson) to assist in data dissemination for approved requests. We have also consulted with several investigators both inside and outside the consortium to provide information and preview/advise on requests (e.g., Drs. Peter Fino, Benjamin Dunkley, Emily Dennis, Cooper Hodges, etc.).

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 (which was completed during the prior performance period) and the submission of data collected 2013-2018 during the current 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 was completed during this quarter and the revised data was submitted to FITBIR.

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

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

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.

g. We have submitted a manuscript on the relation between hippocampal and amygdala subfields and symptoms of PTSD and mood disorders (lead author: Benjamin Wade). Members of the Imaging Core have also participated in manuscripts associated with the larger consortium (lead authors: Amanda Garcia, Maya O'Neill)

h. Members of the Core have been engaged in conversations related to data sharing and collaboration with other larger consortia groups, including TRACK-TBI, MVP and ENIGMA. Dr. Wilde participated in a grant application to co-lead the Imaging Core on a TRACK-TBI related study (with Dr. Mukherjee) and Drs. Wilde, Tate and Dennis participated (as co-PIs) on an R61/R33 application related to ENIGMA that will leverage LIMBIC data and methods. Drs. Wilde and Tate participated in an application with other LIMBIC investigators (Pugh, Kenney, Gill) to examine post-traumatic epilepsy which leverages LIMBIC-based data. Drs. Wilde and Dennis also participated in an application with other LIMBIC investigators (PI: Davenport) to examine late changes in Veterans with TBI who develop AD.

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. Data has been reorganized and accuracy/consistency between the PACS and the ftp server has been examined.

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	0 (total 1622)	0 (total to date 1308)
DNA	0 (1191)	0 (1197)
Stock DNA	0 (196)	0 (432)
Plasma	0 (10,240)	189 (773)
Saliva	0 (1,689)	0 (194)
Serum	0 (10,085)	0 (0)
Whole Blood (PaxGene)	0 (1797)	0 (0)
Grand Total:	**546 (26,820)**	**189(3094)**

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

a. The mod was approved at CR 3-30-2020.

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) Developed ~200 different automated edit checks in Medidata for approximately 44 CRFs (about 50% of all PLS CRFs) to improve data entry, facilitate data QA, and optimize overall data capture.
(2) Finalized two new CRFs for LIMBIC-CENC: BETS and CDR
(3) Began developing secondary data capture system through REDCap to facilitate remote data collection and automated transfer of data into Medidata.

b. Developing IT Systems and Infrastructure.

(1) Continued Medidata mentorship phase, during when the team independently works on tasks and seek support from Medidata when needed.
(2) Launched Call Center Application and Contact Information Management System, completed trainings with all PLS site staff and Call Center staff, and completed periodic upgrades to optimize both systems.
(3) Completed and deployed system for regular, automated download of clinical data from Medidata to LIMBIC-CENC database on server
(4) Began developing dynamic (i.e., updated proximal to real time as data is collected) automated dashboard reports to track enrollments, recruitment, and receipt of biospecimen and MRIs.
(5) Finalized Biomarkers Core reports to track biofluid availability.

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

(1) 1st level of QA/QC of clinical data has been developed and continues to be implemented monthly
(2) Monthly Site Metrics Reports detailing sites' performance in timeliness, accuracy, and completeness of data entry continue to be generated and distributed

(3) Plan for 2nd level QA/QC of clinical data completed for primary outcomes (cognitive variables) and is nearing completion for variables to be included in the phenotype analyses. Data to be included in the next (July) detailed 2nd level data for phenotype analyses includes measures such as: depression, anxiety, PTSD, Substance Use Disorder, tinnitus, vestibular, blurred vision, blindness, pituitary, seizure, cognitive, stroke, headache, pain, obesity, OSA, insomnia.

(4) The QA/QC team are developing an interactive platform for on demand review of data where users can interact with data, download a partial or entire report, look for historical data/report at a fraction of time. These reports will be published in a secure reporting server and are only accessible, at all times, to authorized staff. We are currently working on administrative and VA regulatory hurdles to accomplish this task.

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

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

(1) Data Request Infrastructure

i. Updated data request procedure to clarify timelines

ii. Began developing query tool to allow investigators to determine available sample size(s) to inform data requests

(2) Data Request Processing:

i. Core data team completed and disseminated analytic data sets for four previously approved data requests for investigators at Houston, Tampa, Richmond, and Boston and Portland.

ii. We provided additional variables to previously disseminated analytic data sets for two data requests for investigators at Tampa and Salt Lake City.

iii. We are processing data for two additional data requests for investigators at Houston and Salt Lake City.

iv. LIMBIC-CENC Biostatistics group completed analyses for 1 investigator-initiated project.

v. LIMBIC-CENC Biostatistics group is actively conducting advanced analyses for 4 investigator - initiated projects and awaiting VINCI data for another approved project.

vi. LIMBIC-CENC Biostatistics group began exploring ideas for phenotype analyses to present to the study PI and investigators.

(3). Data Dictionary:

i. Worked on development of search function for data dictionary.
The revised and enhanced version of data dictionary is currently under development and will be released in the fourth quarter. A global search function is introduced in this version that enables investigators to search for desired variables of interest and then add those variables to the final list. In addition, the new version will include the PCE & TBI variables that are currently provided to investigators as separate documents to main data dictionary.

(4). FITBIR Data Submission Preparation:

i. Attended biweekly meetings with FITBIR Operations

ii. In month of June, 92 Forms were resubmitted (i.e., data up to December 2018) as a part of Fitbir study closeout

iii. Began preparing data (i.e., completed QA for October 1, 2019-March 31 2020 data) 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. 1. Task: Implement Study.

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

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

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

(1) Seven of the eight previous CENC sites (Richmond/Tampa / Houston / Boston / Portland / Minneapolis / Fort Belvoir) plus two of the new sites (Salisbury / San Diego) have LIMBIC PLS local IRB approval.
(2) San Antonio and Ft. Gordon are still awaiting local IRB approval.

d. HRPO approval and continuing review.
(1) Portland, Tampa, Richmond, Boston, Houston, Minneapolis, Fort Belvoir, Salisbury and San Diego have HRPO approval.
(2) HRPO requests will be submitted for the other two new sites once they receive IRB approvals.

e. Develop site-wide recruitment and retention plan.—Task 1e is completed.
(1) Plans have been completed.
(2) As per recommendations from the GSC meeting in March 2020, we reviewed the retention plan used by the NIDILRR funded TBI Model Systems (TBI-MS) Program. All methods being used in TBI-MS are already in place for the LIMBIC PLS unless there is a privacy restriction against it by the Veterans Affairs of Dept. of Defense. The LIMBIC PLS also already uses additional methods above and beyond those being used in TBIMS.

f. Recruitment and retention plan will be initiated once all approvals have been gained – partially completed with delay in recruitment due to COVID-19 pandemic.
(1) Retention plan has been initiated and implemented.
(2) Recruitment and new enrollments were initiated at Portland site where HRPO approval was gained ahead of all other sites. Unfortunately, new recruitment and enrollments remain suspended at all sites 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. – ongoing

(1) Revised protocol and MOP with new measures (Clinical Dementia Rating (CDR) scale, RightEye computerized eye-tracker, and AudioStar Audiometer) launched and CDR training completed. Contract established with Audiology subject matter expert (SME), Dr. James Hall, to revise SOP and supervise QA for audiometer data collection with new equipment (Audostar).

(2) Continued entry of all new data collected for longitudinal follow-up assessments.

(3) Continued preparing data for FITBIR uploads.

(4) QA/QC for data quality ongoing; highlights included:

a. Continued fully developed QA procedures including system queries and launching of additional QC activities and processes as part of revised Data Quality plan

b. Continued auditing of neuropsych testing and TBI diagnosis ratings

c. Vetting and categorizing of more records of free text entries for medications and characterization of blast-related mTBI sub-type (pure blast vs mixed blunt-blast).

(5) Continued development of the second version of enhanced investigator-driven data dictionary.

(6) New scientific analysis requests received and processed with analytic/dissemination work ongoing. (See Current Data Requests section of Appendix #5 for full listing of recent requests)

(7) This quarter, 153 new Telephone Follow-Ups were completed and 56 In Person Follow-Ups were completed for an accumulated total of 525 Annual Telephone Follow-Ups and 181 In Person Follow-Ups in the first three 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. – ongoing

(1) Continued updating website dashboard and developing new knowledge translation center end-products.

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

i. Scientific dissemination activities. – ongoing

(1) See Appendix #1 (Current CENC Publication tracker) for complete listing of publications for all analytic projects utilizing datasets from the LIMBIC-CENC Prospective Longitudinal Study.

(2) In general, analyses from CENC Snapshot dataset #1 indicated that 1-2 prior mTBIs is a risk factor for symptom burden but not for objective neurologic findings (neurocognitive testing, imaging, neurosensory testing). Some preliminary data suggests 3 or more mTBIs may have late neurologic effects (lower postural stability, neurodegeneration byproducts in blood). A few are still under review or accepted pending approval of minor revisions. One recent publication was selected by the journal Neurology, “Exosomal MiRNAs and Proteins are Linked to Chronic Post-Traumatic Stress Disorder Symptoms in Service Members and Veterans with mild Traumatic Brain Injury” (first author Vivian A. Guedes), for their press release program, with coauthor Dr. Kimbra Kenny hosting a podcast describing the study’s findings and their impact.

(3) Multiple analyses under LIMBIC utilizing the larger n=1550 dataset are underway with some nearing manuscript submission.

. j. LIMBIC Scientific Analysis Underway. – ongoing. Refer again to Appendix #5 for details.

k. Other Prospective Study Collaborations and Spin Off Studies. – ongoing.

(1) See Appendix #2 for update on organizational collaboration efforts.

(2) New related grant submissions this quarter:

a. Supplement to an existing K01 award (AA025692; entitled “Overlap in genetic and learning-based mechanisms for alcohol use disorder and posttraumatic stress disorder”).

The goal of this Competitive Revision Supplement is to expand the scope of the K01 to examine the impact of the COVID-19 pandemic on alcohol phenotypes (e.g., consumption, binge drinking, problems, AUD symptoms), PTSD, and risky behaviors. It aims to 1) Assess the immediate, and trajectory of, impact of COVID-19 on alcohol use phenotypes and 2) Examine the time-varying aspects of alcohol use phenotypes, PTSD, and risky behaviors using EMA. The proposed study will recruit and enroll 250 participants from the LIMBIC-CENC PLS. PI: Christina Sheerin, Ph.D.

(3) New awards under LIMBIC

a. FITBIR: Accelerating Synthesis of TBI Research Using Novel Methods” (FAST RUN Methods).

Dept. of Defense Defense Health Program, Congressionally Directed Medical Research Programs, Joint Program Committee-6/Combat Casualty Care Research Program, Psychological Health and Traumatic Brain Injury Research Program, Federal Interagency Traumatic Brain Injury Research Analysis Award, Funding Opportunity Number: W81XWH-19-PHTBIRP-FITBIRA. FITBIR: Accelerating Synthesis of TBI Research Using Novel Methods" (FAST RUN Methods). Maya O'Neil PI. This project will utilize FITBIR data to examine key outcomes related to TBI and psychological health and will create model methodologic products that can be applied to future expanded analyses including more variables of interest and more datasets as they are contributed to FITBIR. Awarded 2020. Performance Period: Oct 01, 2020 – Apr 01, 2022.

(4) Previously reported awards under LIMBIC with work underway and ongoing

a. Amma Agyemang, PhD (PI). NIH Diversity Supplement grant. The mediational role of sleep quality in the relationship between chronic mTBI and cognitive functioning.

Laila Abdullah, PhD (PI). VA RR&D. Identifying APOE Related Lipid Biomarkers for Diagnosing Chronic Neurocognitive Deficits in TBI Patients.

Retrospective Data Base Study:

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

a. In the past quarter we finalized our dataset with data through 2019, which now contains more than 2 million veterans. We completed programming the ICD-10 diagnostic codes for TBI. We merged the new data through fiscal year 2019 (new TBI cases since 2015 and expanding the 2% random sample) with the old dataset. We are now in the process of defining comorbidities (medical and psychiatric) and outcomes (dementia, Parkinson's disease, etc.) using ICD9, ICD10, and pharmacy data in the complete dataset.

b. We have instituted regular working group meetings for in-process analyses. We are currently planning two analyses: one examining cardiovascular risk factors after TBI, and one looking at resilience after TBI.

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.

d. We also recently began investigating the association between TBI and incident sleep disorders in veterans. Development of sleep disorders was defined as any inpatient or outpatient diagnosis of sleep apnea, hypersomnia, insomnia or sleep-related movement disorders based on ICD-9 codes. The study included 182,247 veterans with TBI and 182,247 age-matched veterans without TBI (aged 48.6±19.8y). After an average follow-up of 3.4(0-14) years, 78,860 (21.6%) veterans developed sleep disorders. We will next add adjustment for demographics and comorbidities and look at risk of incident sleep disorders in veterans with and without TBI. Once the analyses are complete we will write up a manuscript detailing the findings.

Phenotypes Study:

1. Task: Complete Regulatory Requirements.

a. Regulatory and Data Acquisition activities complete.

b. Data Acquisition: We have identified ICD-9 and ICD-10 based diagnoses through FY19 in VA health system data. We have requested DoD data through DaVINCI, but are dealing with a hurdle regarding data for individuals who do not transition to VA. We are working with Dr. Duvall the director of DaVINCI to address this issue. Alternatively, we will submit a separate DSAA for these data. We can, however begin processing DoD data and conduct analyses for those in DoD and VA once those DoD data are received.

c. We are also in process of requesting the DoD Trauma Registry in addition to the TBI Neuro module that recently became available. The new data source required a new application.

d. We are meeting with a broad group (biomarker core, neuroimaging core, prospective longitudinal study investigators and Lisa Brenner's team in Denver) to develop a series of papers using different methods to assess/validate TBI severity based on ICD-9/ICD-10 code. Data sources for validation are the VA comprehensive TBI evaluation, DoD Trauma Registry, TBI/Neuro Module from the Joint Trauma System. These papers will be designed to identify "best practices" for using health system data to identify TBI severity. Dr. Cifu is evaluating the option of a special issue for this series of papers.

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, two Active Duty Service members and one recent retiree.

Health Economics Study:

1. Task: Obtain DoD and VA authorizations.

a. Received HSR&D pink sheet
b. Funds were stationed
c. Submitted HRPO submission forms
d. Amended IRB to add VA COVID-19 Shared Data Resource database and received IRB approval. Then amended DART to request data access to VA COVID-19 data and received DART approval.

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

a. DUA between VA Palo Alto and VCU DBC was executed.
b. Study DART was amended to include DUA between VA Palo Alto and VCU DBC and we received DART approval.
c. Mr. Hector Garza at the Houston VA uploaded SSNs to the VINCI project folder.
d. Real SSNs and associated Prospective Longitudinal study IDs have been obtained from Richmond, Houston, San Antonio, Minneapolis, Tampa, Portland, and Boston.
e. Real SSNs have been uploaded to VINCI. Currently waiting for all VA and DoD data including COVID-19 data.

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

a. DUA between VA Palo Alto and VCU DBC was executed.
b. Study DART was amended to include DUA between VA Palo Alto and VCU DBC and we received DART approval.
c. Mr. Hector Garza at the Houston VA uploaded SSNs to the VINCI project folder.
d. Real SSNs and associated Prospective Longitudinal study IDs have been obtained from Richmond, Houston, San Antonio, Minneapolis, Tampa, Portland, and Boston.
e. Real SSNs have been uploaded to VINCI. Currently waiting for all VA and DoD data including COVID-19 data.

Novel Neuroimaging Study:

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

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

b. We have identified another novel method of data harmonization using a technique developed by colleagues at Brigham and Women's Hospital (BWH) which is being applied in other consortia. We have discussed collaboration with this group and with others in the InTBIR and ENIGMA communities; we submitted a grant application to explore this in the LIMBIC data, and the reviews are pending.

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

a. In addition to the standard "Core" pipelines that we have been using as part of CENC, we have identified several additional pipelines for comparison of results. These data analyses are in process at the University of Utah. We have also worked with Drs. Stone, Tustison and Avants to utilize their SyMLR method, and are in the process of reviewing those results. We also submitted an NIH R61/R33 grant application to build a novel pipeline for both structural and functional imaging analysis; this is pending council meeting, but received a fundable score.

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

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

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

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

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

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

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

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

Biomarkers Discovery Study:

1. 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: Approved to receive up to serially collected samples from up to 3,500 CENC/LIMBIC participants

SUBMITTED TO AND APPROVED BY:

- 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.

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 (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 March 27, 2020 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. This submission is still under review.
- Virginia Commonwealth University- IRB submission HM20002321 was approved at Continuing Review on January 21, 2020. Submitted USAMRDC HRPO on March 27, 2020 and is currently still under review.
- 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, 2020. USAMRDC HRPO Log E01140.2h granted approval on June 6, 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 July 13, 2020. HRPO Log E01140.2f was granted initial approval 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.
- SFVAMC R&D Committee approved this protocol on 7 November 2019.
- USAMRDC HRPO approved on 31 December 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:

- The Salt Lake City Phenotype study received VA R&D approval Mar 23, 2020 and a determination that the USAMRDC waived oversight. HRPO Log Number E01140.4a on May 13, 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 (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. Hold our first CAB 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 all 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 2020)
3. Complete training of neuroradiologists on new Medidata system
4. Continue monitoring quality assurance for neuroimaging data, as above.
5. Continue to perform analysis of imaging data on standard pipelines.
6. Continue work on pending and new analyses.

Biomarkers Core:

1. Continue to receive, store and distribute samples from Longitudinal study participants as research committee approves (on hold for COVID-19 staff restrictions this quarter but scheduled to resume in mid-July 2020)
2. Finalize Quest contract renewal and add 3 new enrolling sites and continue support NED screening tests. (Quest has the new contract in hand. HJF has signed.). Will update and disseminate MOP once Quest contract renewal executed and additional Quest account numbers established.
3. Continue to carry out DNA extractions and APOE genotyping on baseline specimens with permission for genetic testing in batches of 100, as participants have consented for DNA extraction and genetic testing.
4. Placed order for 3rd Biorepository freezer under Y1 funding.
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 7 of the original sites (Richmond, Houston, Tampa, Fort Belvoir, Minneapolis, Portland and Boston) and 2 of the new sites (San Diego and Salisbury).
3. Continue training and certifying of personnel at the three new sites (Salisbury, San Diego and Fort Gordon) with a goal of being ready to initiate enrollments prior to the lifting of the pause on face-to-face participant research.
4. Continue to work on the regulatory issues at the San Antonio and the Fort Gordon sites.
5. Carry on with all study procedure and administrative activities including telephonic longitudinal visits, data collection and quality assurance.
6. Continue work on scientific analyses, dissemination, and knowledge translation.

Retrospective Data Base Study:

1. In the next quarter we plan continue analysis for the sleep paper. We will also finalize definitions for important variables in our cardiovascular and resiliency analyses. Once that is complete, we will begin those analyses.
2. We will continue regular group meetings between investigators and regular reporting on LIMBIC consortium calls.

Phenotypes Study:

1. Complete DSAA for DoDTR and Joint Trauma System TBI Neuro Module Data requests.
2. Awaiting DoD health system data; Process those data once they are received from DaVINCI.
3. Clarify the ability to get non-VA patient DoD data from DaVINCI with Dr. Duvall; if not possible, initiate DSAA process with the Defense Health Agency.
4. Continue Best Practices for TBI severity identification work group.

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 manuscript and review of SYMLR analysis,
6. Continue to work with other consortia and military-relevant groups (e.g. ENIGMA, InTBIR, TED, TRACK-TBI) to collaborate on data aggregation and analysis.

Biomarkers Discovery Study:

1. Correlate all exosomal and plama biomarker results with Neuroimaging and neurocognitive outcomes in collaboration with Imaging Core and prepare results for dissemination. Our lab at NIH has entered Phase 2. With re-opening of biorepository, identified 1200 for analysis and in next quarter will pull baseline samples from longitudinal study participants and run 4-plex proteomics for correlation with symptoms, imaging and outcomes.
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. 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, Hirsch, S, Carlson, KF, Pogoda, TK, Nakase-Richardson R, Bhatnagar, S, Eapen, BC, Troyanskaya, M, Miles SR, Nolen, T, Walker, WC. Health Services Utilization, Healthcare Costs, and Diagnoses by Mild Traumatic Brain Injury Exposure: A 14-Year Longitudinal Chronic Effects of Neurotrauma Consortium Study. Accepted to Archives of Physical and Rehabilitation Medicine.

3. Dr. Dismuke-Greer presented, "A Prediction Model of Military Combat and Training Exposures on VA Service-Connected Disability: A CENC Study," at the VA HSR&D Cyberseminar series: Mild TBI Diagnosis and Management Strategies.

4. Publication: 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 2020 May 27: 10.1212/WNL.0000000000009577 doi:

5. Publication: Kenney K, Guedes V, Gill JM. Authors reply: Exosomal NFL, a prognostic biomarker for remote symptoms after mild traumatic brain injury? Neurology 2020, on line June 29, 2020, //n.neurology.org/content/author-response-exosomal-neurofilament-light-prognostic-biomarker-remote-symptoms-after-mild.

6. Publication: Devoto C, Lai C, Qu B-X, Guedes V, Wilde E, Walker WC, Diaz-Arrastia R, Kenney K, Gill JM. Exosomal MicroRNAs in Veterans with Mild Traumatic Brain Injury: Preliminary Results from a Chronic Effects of Neurotrauma Consortium (CENC) Biomarker Discovery Project. J Neurotrauma 2020 May 27. doi: 10/1089/neu.2019.6933 online ahead of print.

7. Publication: Dennis E, Baron D, Bartnik-Olson B, Caeyenberghs K, Esopenko C, Hillary F, Kenney K, Koerte I, Lin A, Mayer A, Mondello S, Olsen A, Thompson P, Tate D, Wilde E. ENIGMA Brain Injury: Framework, Challenges, and Opportunities. Hum Brain Mapping 2020 Jun 1. doi: 10.1002/hbm.25046 online ahead of print. PMID: 32476212.

8. Publication: Peltz C, Kenney K, Gill J, Diaz-Arrastia R, Gardner RC, Yaffe K. Blood-based biomarkers of traumatic brain injury-associated cognitive impairment in older veterans. Neurology 2020 June 22: DOI: 10.1212/WNL.0000000000010087 online ahead of print.

9. 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”, Brain Imaging and Behavior 2020. Revisions under review 7-2020.

10. Submitted manuscript and under review: Guedes VA, Chen L, Devoto C, Qu B-X, Edwards K, Martin C, Mithani S, Rush H, Wilde E, Walker WC, Diaz-Arrastia R, Gill J, Kenney K. Exosomal MicroRNAs and Proteins are linked to Psychiatric Symptoms of PTSD and Depression in Veterans with mild Traumatic Brain Injuries. Translational Psychiatry. Under Review 6-2020.

11. Preparing manuscript of NfL, sleep, cognitive analysis for Sleep by LCDR Werner, presented at MHSRS 2019, IBIA in 2-2020 as oral presentation and Sleep 6-2020. Manuscript In final preparation to submit July, 2020.

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. However, if the pandemic continues to cause the PLS sites to not be able to conduct person-to-person research for another couple quarters, we might have difficulty reaching our end-goal of 3000 participants. As of today, we are able to shift the year one projections into years 2-5 but that will be difficult to manage if we are shut-down for another 6-9 months.

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

4. 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.

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

6. Biomarker Core and Study expects delays in shipping and receiving samples while social distancing requirement at some sites due to the COVID-19 pandemic although the Biorepository has just opened

for shipping and receiving samples in their new location. Project may go on hold if sites completely shut down due to the pandemic.

7. The Neuroimaging core experienced a delay in collecting phantom and participant imaging data due to COVID-19 restrictions. The Neuroimaging Core's team of neuroradiologists have been very busy with COVID-19-reated clinical work, and this resulted in a delay in completing the clinical reads. 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.

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

b. Anticipated Problems/Issues

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

1. The recruiting goals for the Prospective Longitudinal Study have been delayed by three quarters at this time and it appears that this will continue for at least one more quarter if not more. We had room to shift these recruitment goals to the back end of the Period of Performance at this time so we fully expect to meet our overall goals, just 1-2 quarters later than projected. However, if the sites are not allowed to start conducting in-person research within the next 6-9 months, we might run the risk of not being able to meet our goal of 3000 participants.

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

3. The Nueroimaging Core's Dr. Taylor (MR physicist) transitioned from VCU to MD Anderson in Houston, Texas in June 2020. He has continued to work with the Neuroimaging Core, with plans to assist until the end of July. However, VCU has indicated that contracting for his effort on the project at his new position will be difficult, and Dr. Cifu is looking at possible investigators that may be able to assume his responsibilities related to the Neuroimaging Core. A substitution will require some training and introduction to the project.

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.