LIMBIC PROSPECTIVE LONGITUDINAL STUDY ASSESSMENT PROTOCOLS

I) INITIAL AND FOLLOW-UP COMPREHENSIVE EVALUATION

- *These variables are completed at Initial and Comprehensive Re-Evaluations, except as noted. Collection Schedule – baseline, 1-year-post-index mTBI, 3-year-post-index mTBI, 5-year-post-index mTBI, then every 5 years afterwards*

- *The self-report questionnaires may be completed prior to visit, reviewed by study staff for completeness and reviewed with subject at visit; alternatively, they may be collected remotely, such as over the telephone, if the participant is logistically unable to come in person to a post-baseline comprehensive visit to achieve partial data collection instead of entirely missed visit.*

A - CONCUSSION CLINICAL INVENTORY TOOL (Self-report and interview)

1- Lifetime mTBI Identification and Diagnosis Structured Interview [mTBI(s), number and severity cause (blast vs. other)]

- Potential Concussive Events (PCEs) Mapping: modification of The Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID) validated screening tool
- Concussion (mTBI) diagnostic structured interview of every PCE using validated VCU rCDI
- DoD injury report information (MACE, PDHA, PDHRA, ANAM): electronic records search.
- Final diagnostic determination that incorporates open-ended portions of interview and medical records to confirm or overturn the preliminary automated algorithm diagnosis from the VCU rCDI followed by rigorous expert central review and quality assurance process.
- Comprehensive lifetime mTBI history profile is generated from above process with date, context, mechanism, and severity (LOC/PTA status) of all historical mTBIs. The table below depicts this and can be created separately or combined for deployment and non-deployment time periods. Follow-up visits determine any additional new mTBIs.

mTBI History Profile

mTBI without PTA or LOC	mTBI with PTA but no LOC	mTBI with LOC (& PTA)
None	None	None
Single	Single	Single
Multiple, total #	Multiple, total #	Multiple, total #

2- Personal Fixed Factors

- Demographics, age, highest level of completed education using The CDC Behavioral Risk Factor Surveillance System (BRFSS) core battery, section 8.1-8.4, 8.6-8.8, 8.11-8.12, 8.24-8.25
- Past health using selected items from TBIMS Pre-injury History Questionnaire (TBIMS PIHQ). [Baseline only]
- Genotyping: at baseline only, blood will be collected to assay for multiple genetic variants that have been reproducibly associated with chronic effects of neurotrauma including: *APOE, DRD2, COMT, MAO-A, BDNF, DAT1.* Genotyping at other alleles will be carried out as

more information becomes available regarding their association with neurodegenerative disorders after TBI, per Biomarkers Core.

3- Environmental Factors

- Military history including service years/duration, branch, rank, and times/locations of all combat deployments using the DCoE/DVBIC 15 yr. study General Assessment Form.
- Combat exposure; Deployment Risk and Resiliency Inventory, Version 2, Section D; Combat Experiences (DRRI-2-D) [Repeated after Baseline only for participants who have been redeployed after baseline data collection.]
- Social support; DRRI-2-Section O, Post-deployment Social Support Scale (DRRI-2-O): A shortened version with only relevant items will be used for longitudinal evaluations.
- Subconcussive Brain Insult Exposures:
    - Contact Sports History Questionnaire (CSHQ): Self-report measure of organized sports participant history focusing on football, hockey, and boxing as a gauge of exposure to subconcussive athletic head impacts
    - Military Training Head Jolt Exposure Questionnaire (MTHJEQ): Brief self-report measure of military career exposure to activities associated with repetitive subconcussive forces to the head; also queries neurotoxin exposure and PTSD history. Developed by CENC investigators specifically for this study.
    - Blast Exposure Threshold Survey (BETS): brief self-report questionnaire developed by the JPC-5 Exposures Standards Working Group to standardize the calculation of lifetime exposure of military personnel to blast overpressure

4 - Moderating Factors

- Effort & Exaggeration; Medical Symptom Validity Test (MSVT)
- Self-efficacy; The General Self Efficacy (GSE) Scale
- Resiliency; The TBI-QOL resilience module:
- PTSD; see below
- Alcohol use; Alcohol Use Disorders Test-Consumption (AUDIT-C)
- Illicit substances use/misuse; Drug Abuse Screening Test 10 item version (DAST-10)

5 – Post-concussion Symptoms

- Neurobehavioral Symptom Inventory (NSI)

6 – Neuro-Sensory and Pain Symptoms

- Hearing: Hearing Handicap Inventory for Adults, Screening version (HHIA-S)
- Tinnitus: Tinnitus Functional Index (TFI)
- Dizziness: Dizziness Handicap Inventory, Screening version (DHI-S)
- Headache: Headache Impact Test Short Form (HIT-6)
- Body Pain: NIH Toolbox (PROMIS version) Pain Intensity, and TBIQol Pain Interference module, short-form

7 – Comorbidities and Mental Health

- Sleep disorders:
    - The Pittsburgh Sleep Quality Index (PSQI):
    - The STOP BANG
- Depression (PHQ-9); Patient Health Questionnaire Depression Scale (PHQ-9)
- PTSD:
    - PTSD Checklist for DSMV (PCL-5):
    - Clinician-Administered PTSD Scale for DSM5 (CAPS-5)
- Fatigue: TBIQoL module, short-form
- Anger: TBIQoL module, short-form
- Anxiety: TBIQoL module, short-form
- General Co-Morbidities: The CDC Behavioral Risk Factor Surveillance System (BRFSS)

8 - Participation, Activity, and Global Outcome Rating Scales

- Global Outcome
    - Extended Glasgow Outcome Scale – Extended (GOS-E)
- Participation
    - TBI-QOL module
    - Select items from The Community Reintegration of Injured Service Members (CRIS)
- Employment
    - Modified Abbreviated Employment Module
- Life Satisfaction
    - Satisfaction With Life Scale (SWLS)

9 - Dementia Assessment Tool

- Clinical Dementia Rating (CDR) Structured Interviews and mental status examination

B) CONCUSSION CLINICAL ASSESSMENT TOOL (Examination and Testing)

10 - Physiological

- Biometrics:
    - BMI (height and weight)
    - BP, HR, RR
- Brain Electrophysiology
    - Clinical Seizures:
        - *All Sites*: At baseline assessment and at all follow-up points, all participants complete the "Epilepsy Screening Questionnaire" (ESQ).
        - *All sites*: at baseline and comprehensive follow-up points study staff use medical record review to complete an Epilepsy Documentation Form (EDM).
        - *EEG sites only:* At baseline and at comprehensive follow-up points, participants undergo wakeful EEG testing per the standard paradigm used in the VA Epilepsy Centers of Excellence (CoE) clinical protocol.

    EEG sites only:

- Quantitative EEG (QEEG); 10 minutes of resting EEG collected for QEEG brain network analyses across frequency spectrums.
- Event Related Potentials (ERPs): Computerized behavioral tasks performed during EEG recording to generate ERPs to assess Electrophysiology of Cognition. Tasks include auditory and visual modalities of 'oddball task' and a semantic priming task.

- Advanced Brain Imaging for functional connectivity and cerebral blood flow (see module 'C' further below)

11 – <u>Human Performance</u>

- Neuro-Cognition comprehensive multi-modal battery
  - NIH Toolbox Cognition Battery
  - Wechsler Adult Intelligence Scale 4th version (WAIS-IV)
  - Trail Making Test (TMT) Part A& B :
  - California Verbal Learning Test (CVLT-II)
  - Brief Visuospatial Memory Test-Revised (BVMT-R
  - Delis-Kaplan Executive Function System (D-KEFS) Verbal Fluency Test (VFT).
  - Brief Test of Adult Cognition by Telephone (BTACT)
  - Brief Mental Status Examination (CDR)
- Motor/Movement Performance Tests
  - Fine motor: Grooved Pegboard
  - Gait: NIH Toolbox 4-Meter Walk Gait Speed Test
  - Motor Examination Index from Unified Parkinson's Disease Rating Scale (UPDRS)
  - Computerized oculomotor (eye tracking) test
- Sensory Systems Performance Tests:
  - Smell: BRIEF Smell Identification Test (BSIT)
  - Hearing
    - Audiometry testing for hearing thresholds
    - SCAN-3. This test is comprised of a battery of tests to detect auditory processing disorders in adolescents and adults. Results can help identify the presence of a temporal processing problem, can test the ability to listen with background noise, and provides a dichotic listening task.
  - Visual Acuity of each eye using a standard Snellen eye chart.
- Postural Stability as Motor-Sensory (Vestibular, Visual, & Proprioception) Integration Performance Test:
  - *CDP sites* - Computerized Dynamic Posturography (CDP)
  - *Sites not doing CDP*– Balance Error Scoring System (BESS)

C) CONCUSSION NEUROIMAGING TOOL

12 – <u>Advanced Brain Imaging (Structural & Physiological)</u>

- *Mock Scanner Training*. To mitigate fear, enhance comfort, and reduce motion artifact, participants expressing apprehension or anxiety about scanning will be invited to undergo mock scanner training with guided imagery and relaxation techniques to become desensitized to scanning environment.

- *Urine (women of child-bearing age only)*: depending on local MRI policies procedures, sites may obtain specimen solely for pregnancy testing in premenopausal females to confirm nongravid status. Specimens are tested locally and destroyed after testing.
- *Neuroimaging Data Acquisition*. Volumetrics, FLAIR white matter hyper intensity analysis, DTI/DKI, fcMRI, and ASL done at comprehensive evaluation time points. The specific protocol sequence that each participant will undergo is as follows:
    - Localizer: Calibration/Reference Scan
    - Sagittal 3D T1 MPRAGE/IR-SPGR
    - Axial 3D T2* GRE/SWAN/SWI
    - Axial DTI
    - Axial Resting State fMRI - Subjects should have eyes OPEN.
    - Axial 3D T2-FLAIR (CUBE/SPACE/VISTA)
    - Sagittal 3D T2 (CUBE/SPACE/VISTA)
    - Axial ASL
    - HDFT protocol (SAMMC and MEDVAMC only)
    - *All scans are performed in straight orthogonal planes*
- *Primary Imaging Variables.* Numerous variables are generated from acquisition and analysis and will be readily available for specific exploratory analysis at little additional effort. However, to reduce the number of variables and analyses for the primary aims of the grant, the following measures will be used
    - Volumetrics (volume in cubic millimeters): Total frontal gray matter and white matter (GM, WM), total temporal GM/WM, total parietal GM/WM, right and left cingulate GM/WM, right and left hippocampus and amygdala, right and left caudate, right and left thalamus, right and left cerebellum GM/WM, total GM, total WM, ventricle-to-brain-ratio.
    - DTI tractography (fractional anisotropy [FA] and mean diffusivity [MD]: right and left cingulum bundles, fornix, total corpus callosum, uncinate fasciculus, ventral striatum, anterior thalamic radiation.
    - FLAIR white matter hyperintensity analysis: total lesion volume and count, anterior cerebral middle cerebral, posterior cerebral, and vertebral basilar system (feeding brainstem and cerebellum) vascular territories
    - ASL cerebral blood flow (CBF) in the same vascular territories as detailed above as well as whole brain GM and WM CBF, and CBF of the thalamus and posterior cingulate
    - fcMRI connectivity changes in seedpoints involving anterior cingulate cortex, lateral prefrontal cortex, default mode network, posterior cingulate cortex, and hippocampus.
    - Common Data Elements: presence or absence of potentially clinically-relevant pathology.

D) CONCUSSION FLUID BIOMARKER TOOL

13 - <u>Biologic Fluids</u>

- Blood for Commercial Lab Neuroendocrine Panel
    - Blood (serum (red top tube) for insulin-like growth factor 1 (IGF-1), thyroid stimulating hormone (TSH) and testosterone) collected for neuroendocrine assays

- BioRepository (processed and frozen locally and shipped in batch to the Biorepository for long-term storage, future analyses and distribution to collaborators for research)
    - Blood: serum, plasma, buffy coat (baseline visit only) and PAXgene^{TM} RNA tubes, processed, aliquoted, frozen and stored for serum, plasma, buffy coat, RNA and DNA analyses (as individually consented/allowed by each participant in the tiered consent)
    - Saliva: for future analyses, including metabolic and neuroendocrine, as approved per the Research Committee
    - All baseline samples will have the 4-plex assay completed for: total tau, neurofilament light chain (Nfl), glial fibrillary protein (GFAP), ubiquitin carboxy-terminal hydrolase-l1 (UCLH1), Interleukin-6 (IL-6), IL-10 and TNF-alpha.
    - For samples selected for the development of novel assays ("Discovery cohorts"), this will include:
        - Exosomes isolation and characterization
        - Inflammatory cytokines (IL-6, IL-10, TNF-alpha)
        - Vascular endothelial growth factor (VEGF)
    - All samples with separate permission for DNA extraction and genetic testing will have global DNA sequencing completed

E) CONCUSSION HEALTH ECONOMICS IMPACT TOOL

14. <u>Health Care Utilization and Disability</u>

- Health Care Utilization Questionnaire developed from literature: Quantitative measures of self- and informant-reported usage of seven domains of medical (hospitalization, outpatient treatment and procedures, assistive devices, and medications) and nonmedical care (home health aides, respite care, and adult day care).
- Documented utilization and costs: The VA Informatics and Computing Infrastructure (VINCI) resource center, which facilitates access to data from the Veterans Information System Technology Architecture (VistA), and additional relevant data sets will be used to acquire all data relevant to the health economics analyses. Given the longitudinal design of this study, updated data will be requested and acquired on an annual basis for reach subject.
- Disability Economic Impact; EuroQol Group 5 dimension 5 level version quality of life questionnaire
- VA and DoD Compensation and Pension qualified for: VA records and self-report
- Other Disability Income: self-report of Social Security

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II) CONCUSSION BRIEF EVALUATION TOOL

- *Variables collected annually (and during COVID-19 for some comprehensive assessments) virtually, via telephone to briefly assesses the key outcomes in an efficient manner while minimizing costs and subject burden.*

1 – <u>Neuro-Cognition Performance Tests</u>

- Brief Test of Adult Cognition by Telephone (BTACT): The BTACT assesses dimensions central to adult cognitive functioning: episodic memory, working memory, reasoning, verbal fluency, and executive function without the need for an in-person assessment. This is the first instrument which integrates measures of processing speed, complex reaction time, and task switching and inhibitory control for use over the telephone.
- Digit Span Forward from WAIS-IV

2 – <u>Cognitive and Emotional Functioning Self-Report Scales</u>

- Cognitive Symptom Scales:
    - TBIQOL Applied Cognition modules
        - Applied Cognition - General Concerns module, short form
        - Applied Cognition - Executive Function module, short form
- Emotional-Behavioral Function Symptom Scales
    - Impulsive Control & Emotional Instability & Irritability & Aggression: TBI-QOL Emotional-Behavioral Dyscontrol module, short form
- Depression: eight-item Patient Health Questionnaire Depression Scale (PHQ-8)

3 – <u>Life Participation Scale</u>

- TBI-QOL Abilities to Participate in Social Roles and Activities, short form

4 – <u>Epilepsy Screening Tool</u>

- Epilepsy Screening Questionnaire (ESQ)