AWARD NUMBER:  W81XWH-08-2-0178

TITLE:  Epidemiological Study of Mild Traumatic Brain Injury Sequelae Caused by Blast Exposure During Operations Iraqi Freedom and Enduring Freedom

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Preliminary Results: Accomplishments include initial and ongoing IRB review & approval of all initial submissions, protocol amendments, recruitment advertisements, serious adverse events reporting, and completion of enrollment. We continue to submit to both McGuire and WRAMC IRBs. During Year-5, we completed enrollment, intensified data analysis efforts, and continued to work on follow-up evaluation data collection. Research assistant positions were reduced from 2 full-time employees to 1 part-time employee by the end of year 4. Data management and analyses have been continued to be refined through meetings, reviews, quality checks, and consultations. At closure of enrollment, two hundred and thirty-eight (238) participants passed eligibility pre-screen and consented for study procedures. Of these, twenty-two (22) participants either did not meet final eligibility or failed to complete Phase 1 (baseline) evaluations resulting in the final enrollment sample size of two hundred and sixteen (216). The overwhelming majority of these participants meet criteria for post-concussion syndrome (PCS). Conclusions to Date: Enrollment is completed. Study personnel continue to work on Phase 3 (longitudinal) follow-up data collection. The emphasis of the investigator work effort has shifted to data analysis and dissemination of findings. From the analyses to date we have achieved 2 publications, and have 2 other manuscripts under review, and have multiple pending manuscripts in varying stages of completion. Final conclusions regarding the primary study aims and hypotheses await further analyses and thus are pending at this time.
I. INTRODUCTION:

Blast related Traumatic Brain Injury (TBI) is an important source of morbidity in Operations Iraq Freedom and Enduring Freedom (OIF/OEF). Mild TBI (MTBI) may go unrecognized and persist as post-concussion syndrome (PCS). Given that available information is largely anecdotal, the identification, characterization, and prediction of individuals who have PCS with persisting effects from blast-related MTBI are the focus of this series of epidemiological investigations. Multiple hypotheses are being tested including:

- a significant proportion (>18%) of service members experiencing blast events during OIF/OEF sustain a MTBI that leads to persisting symptoms consistent with PCS;
- multiple predictive factors for developing PCS can be identified;
- returnees with PCS will display objective impairments on neuropsychological testing, computerized posturography and/or quantitative electroencephalography; and,
- those with PCS will demonstrate improvement over time but will continue to display significant long-term disability.

A cross-sectional sample of 747 OIF/OEF returnees, who experienced a blast event on tour within the past two years, will undergo three phases of evaluations as follows:

- Phase-I: will determine the sample prevalence of PCS after blast related MTBI, characterize the constellation of related symptoms and problems, and allow predictive modeling.
- Phase-II: will utilize a case-control design to evaluate objective abnormalities among the subjects with PCS after MTBI.
- Phase-III is a longitudinal design using repeated measures for analysis of outcomes over time (baseline, 6 months, and one year).

II. BODY OF REPORT: Accomplishments relative to our Statement-of-Work (SOW):

A. SOW Task 1 - Objective: prepare and initiate the overarching research study plan.

1. Obtain IRB approval for project [Research Assistants, Mr. Heimiller, Dr. Walker]:

   Previously Accomplished. We have continued to receive continuing review approvals at all applicable IRBs.

2. Establish Military site screening/recruitment options [Dr. Walker & Research Assistants]:

   Previously established. During Year-5, an additional 8 subjects were enrolled from MCB Camp Lejeune before closing the study for new enrollments. In total, 91 subjects recruited from MCB CL consented for a combined 121 enrollments from Military base sites.

3. Establish availability and content of acute injury (war-zone) variables. [Dr. Walker]

   Previously accomplished.

4. Finalize Data collection forms including TELEforms. [Drs. McKinney, Cifu, Manning Franke & Walker]

   Previously accomplished.

5. Complete set-up of data management software system. [Mr. Bush]

   Previously accomplished.
6. Establish logistics (when, where, workspace) for study screening and recruitment of military personnel at Central Virginia PDHA clinic sites. [Dr. Cifu, Dr. Walker, Dr. Manning Franke & Research Assistants]

Previously accomplished. Volume of eligible subjects identified at Kenner Army Health PDHRA clinics was far below anticipated.

7. Hire and train study coordinator and other TBH study personnel. [Hiring: Mr. Heimiller, Dr. Walker. Training: Drs. Nelson, Walker & McDonald]:

Previously accomplished. During this reporting year, the remaining Research Assistant, transitioned to part-time status after enrollment was closed May 01, 2013. To facilitate end of study analyses and dissemination efforts, Dr Walker increased his % effort on the project this year. Otherwise, there have been no subaward (VCU) staff changes since our last annual report.

B. SOW Task 2 - Objective: Determine the prevalence of PCS after blast related MTBI in OIF/OEF to better define the scope of residual injury and determine early factors predictive of PCS after blast injury to aid the development of better secondary prevention and treatment strategies. Timeline for all subtasks: Gradually accrue over 4 years 747 subjects total (50 subjects by end Year 1, 325 subjects by end Year 2, 600 subjects by end Year 3, 747 subjects by end Year 4) into Phase-I. Responsible personnel: listed below for each subtask [ ].

1. Consent & Enroll 747 Subjects Total. [Dr. Walker, Dr. Manning Franke, Research Assistants]

Before closing enrollment, we have mailed out an additional 2,603 recruitment letters during Year-5 for a total of 14,987 recruitment letters mailed to subjects/patients who were registered at the Richmond VA Medical Center, and had served in OIF or OEF. During Year-5, an additional 275 potential subjects were screened in person and/or through medical record review for eligibility for a grand total of 3,210 screened (1296 at RVAMC, 1780 at Fort Lee, 34 at Quantico, and 100 at Camp Lejeune). During Year-5 an additional 22 subjects consented before enrollment closure resulting in a final total of 238 subjects who met preliminary eligibility criteria and consented for enrollment. After 22 subjects were either determined to be ineligible or dropped out prior to completing Phase 1, the final sample size was n=216. Please see “Appendix #1” for a demographic breakdown of the final study sample. We have previously reported on the reasons for the slower than anticipated enrollment rate and our extensive efforts to overcome this. It should be noted that our final number of enrollees with symptoms consistent with PCS is actually higher than target. For study Aims 2 and 3, power analysis had determined a minimal sample size of 138 and 142 cases of PCS respectively and we exceeded that with 198 cases of PCS for Phase 1 and over 90% of these completing Phase 2. We far exceeded the power calculation minimal needed sample size for Aim 4 (44 cases of PCS needed; achieved over 100 completing). The shortfall in enrollment was limited to “controls” (asymptomatic persons with blast exposure, only 18 achieved). Despite this, we believe the number of controls is large enough to achieve statistical power for the bulk of our study aims. Additionally we will reexamine the symptom threshold for categorizing subjects as with versus without PCS.

Due to slower than anticipated subject enrollment(s), Dr. Walker requested, and USAMRAA/CDMRP have approved an additional one-year, cost neutral study extension in order to complete pending longitudinal follow-up evaluations and continue work on data analysis and dissemination of findings.

2. For each subject above, complete standardized current state questionnaires for qualitative and quantitative measurement of: Post-concussion syndrome (PCS) using the Rivermead Post-Concussion Symptoms Checklist (RPQ) (King, 1995), Combat Stress using the PTSD Checklist Military Version (PCL-M) (Weathers et al, 1991), pain using both the McGill Pain Questionnaire
short form (MPQ-SF) (Melzak, 1987) and the 11 point Numerical Scale (Jensen MP et al, 1989), and affective disorder using the Center for Epidemiological Studies Depression Scale (CES-D) (Radloff, 1977). The ICD-10 criteria for PCS will be used to categorize the cases with PCS for the prevalence numerator, subjects with PCS after OIF/OEF blast exposure Injury (Boake, 2005; WHO, 1992; WHO, 1993). The International Classification of Diseases is published by the World Health Organization (WHO). The ICD-10 criteria for PCS are 1) a history of MTBI and 2) a minimum of 3 of following symptoms (present to a moderate degree compared to pre-morbid): headache, dizziness, fatigue, irritability, insomnia, poor concentration, memory problems, or intolerance of stress, emotion, or alcohol. The RPQ is being utilized to standardize this diagnostic assessment. [Oversight: Research Coordinator, Dr Walker and Dr Cifu. Scheduling: Research Assistants. Monitoring and facilitation of subject form completion: Research Assistants]

Accomplished on an additional 9 subjects, resulting in a total 216 subjects completing Phase 1.

3. For each subject, collect blast injury and individual characteristics data including: dazed, memory gap (injury, pre-injury, and post-injury), lost consciousness, stress, pain, helmet wearing, shrapnel injury, tympanic membrane rupture, hearing loss, type of blast, immediate blast effects, number of blast exposures, demographic, education level, psychiatric history, medical history, and time since injury. These variables will be collected using a series of questionnaires including: Full Blast Questionnaire (modified version of Walter Reed Blast Inventory (Scherer et al, 2007), see Protocol), a Health History Questionnaire (see Protocol), the recalled immediate psychological stress of the blast event using the Impact of Events Scale (IES) (Horowitz et al, 1979), the recalled physical pain level of the blast event using the 11 point Numerical Scale and the Alcohol Use Disorders Test-Consumption (AUDIT-C), a brief screening tool for heavy drinking and/or active alcohol abuse/dependency (Bradley et.al., 2007).

[Oversight: Dr Walker and Dr Cifu. Scheduling: Research Assistants. Monitoring and facilitation of subject form completion: Research Assistants]

Accomplished on an additional 9 subjects, resulting in a total 216 subjects completing Phase 1.

4. For each subject, the study biostatistician will designate a group assignment (with PCS versus without PCS) using a predetermined threshold of MTBI symptom severity (ICD-10 diagnostic criteria applied to the RPQ data) in order to derive prevalence of PCS and to select subjects for Task 3 [Dr. McKinney]

Accomplished on 216 subjects with 9 additional this report year.

5. Study biostatistician will provide interval (monthly) updates of the ratio of PCS to no PCS group membership to the PI for the purpose of monitoring accrual targets and trends, but will otherwise will not reveal assignment to either subject or study staff (double blind). [Dr Ketchum]

Accomplished on 216 subjects with 9 additional this report year.

6. Perform data audits after first subject completed Phase 1 and on 5% of accrual target (37 subjects) on a monthly basis. [Dr. McKinney]

To date, we have been 100% compliant with subject consent requirements.

7. Using a case-control design (PCS versus no PCS) and adjusting for PTSD, several statistical analyses will be performed including two-way analysis of variance (ANOVA) (to compare quantitative variables), chi-square tests (to compare proportions of qualitative variables, and a multiple logistic regression model (to determine the predictive nature of these variables as a group). PTSD will be measured as a continuous variable using the PTSD Checklist – Military Version (PCL-M) total score. These analyses will determine factors associated with (or
predictive of) developing PCS after blast related MTBI. [Statistics: Dr. Ketchum. Interpretation: all key investigators]

Pending final data analyses.

C. Task 3 - Objective: Identify and describe objective cognitive performance and neurophysical impairments in returnees with PCS after blast-related MTBI incurred during OIF/OEF (Study Phase 2). Timeline: Gradual accrual into Phase 2 of minimum of 284 total subjects over 4 years (30 subjects by end Year 1, 125 subjects by end Year 2, 225 subjects by end Year 3, 284 subjects by end Year 4). Responsible personnel: listed below for each subtask [].

1. At least monthly, groups of subjects who completed Phase-I (Task 2 above), will be assigned to enter Phase-II evaluations as follows: With PCS (all), Without PCS (equal number to “With PCS” who are selected using described randomization scheme). [Research Assistants & Dr. Walker]

Accomplished on 216 subjects with 9 additional this report year.

2. Study biostatistician will provide the study coordinator with a list (at least monthly) of de-identified subjects who are assigned for Phase-I evaluations, but will NOT reveal group assignment (With PCS versus Without PCS) to study staff or subject (i.e. to minimize bias of objective evaluations during Phase 2, double blinding of group assignment will be maintained). [Dr. Ketchum]

Accomplished on 216 subjects with 9 additional this report year.

3. For each Phase-II subject, conduct objective evaluations and collect data including full neuropsychological batteries (cognitive performance and fine motor assessment), quantitative electroencephalography (neurophysiologic cognitive assessment), and computerized posturography (balance impairment assessment). CPT will consist of The Sensory Organization Test (SOT), a composite index that defines abnormalities across somatosensory, visual, and vestibular systems. QEEG recordings will consist of baseline 10 minute eyes closed and a 10 minute eyes open resting period. There are multiple normative databases for comparison of individual electrocortical activity. The “life-span” database included with the Neuroguide® EEG analysis software consists of 625 records from normal individuals ranging in age from 2 months to 89 years. Neuroguide® also includes a discriminant function analysis to calculate the probability that a person has sustained a TBI based on their eyes closed resting baseline recording alone. In the initial validation study, a sensitivity of 95.45% and a specificity of 97.44% were reported for classification accuracy in comparison to normals. This discriminant function was developed based on the work of Thatcher and others with the Defense and Veterans Head Injury Program (DVHIP) in the 1990’s and used a sample of veterans from what have become the lead Polytrauma centers within the Veterans Affairs health care system (Palo Alto, CA, Minneapolis, MN, Richmond, VA, and Tampa, FL). Thus, it is an appropriate comparison group for our purposes. The neuropsychological battery will consist of the following standardized, validated, tests of proven reliability: Wechsler Test of Adult Reading (WTAR, pre-morbid IQ estimate),(Mathias, Bowden, Bigler, & Rosenfeld, 2007) Conners Continuous Performance Test-II (CCPT-II, sustained attention),(Conners, 2000) Paced Auditory Serial Addition Test (PASAT, processing speed),(Vanderploeg, Curtiss, & Belanger, 2005) Halsted-Reitan Trail Making Test A & B (TMT, visual scanning and executive function),(Lange, Iverson, Zakrzewski, Ethel-King, & Franzen, 2005) Stroop classic test (target processing speed and divided attention),(Soeda et al., 2005) Grooved Pegboard to assess fine motor speed and dexterity (Hanna-Pladdy, Mendoza, Apostolos, & Heilman, 2002), Test of Memory Malingering (TOMM) (Tombaugh, 1997) California Verbal Learning Test-II (CVLT-II) (learning and working memory),(Vanderploeg et al., 2005) Wechsler Adult Intelligence Scale III (WAIS-III) items: Digit Symbol Coding, Digit Span, Letter-Number Sequencing, Symbol Search, &

During year-5, accomplished on an additional 11 subjects for a final total of 176 subjects completing Phase-II.

4. Use this data to perform and fit several two-way ANOVA models with main effects for PCS (present/absent) and cognitive or neurological impairment (present/absent). A separate model will be fit for each response variable. [Statistics: Dr. Ketchum. Interpretation: all key investigators]

These analyses will be completed next year.

5. Determine the sensitivity and specificity for detecting neurophysiologic abnormalities after MTBI from blast injury during OIF/OEF using QEEG with the goal of assessing the accuracy of detection of mild TBI using a purely neuro-physical method of measurement. [Statistics: Dr. Ketchum. Interpretation: all key investigators]

These analyses will be completed next year.

6. Determine the feasibility of a functional magnetic resonance and diffusion tensor imaging pilot descriptive study (anatomic/physiologic assessment) in a subset of cases and controls. [Dr. Walker]

Due to an ongoing, local shortage of radiology personnel, we canceled plans for this imaging pilot.

D. Task 4 - Objective: Assess the sensitivity and specificity within this sample of select key diagnostic questionnaires used in Phase 1 relative to “gold standard” structured interviews.

1. Structured interviews will be added to Phase-II measures for: Major Mental Health disorders (Major Depressive Disorder, Bipolar Disorder, Panic Disorder w/ w/o Agoraphobia Social Anxiety Disorder, Specific Phobia, Obsessive-Compulsive Disorder, Generalized Anxiety Disorder, and Psychotic Disorders) using the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998); PTSD using the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995); mild blast related TBI using an instrument newly developed for this study loosely based on existing interviews used in acute rehabilitation settings (e.g., Gioia et al., 2008). [Dr. McDonald, Dr. Cifu, Dr. Ketchum, and Dr. Walker]

Previously accomplished.

2. Collect these interview measures in the subsequent approximately 200 subjects entering Phase 2. [Dr. McDonald, Dr. Walker, Trained Research Assistants]

Phase-II activity (see D1 above). Structured interviews completed on an additional 11 subjects this reporting year for a final total of 106 subjects (note that this figure was misreported in earlier reports because Mr Heimiller did not account for the subjects who withdrew or were withdrawn after Phase 1 was completed.).

3. Analyze findings and implications for the primary analyses described in Tasks
Phase-II analytical activity (see D1 above). These analyses were begun and are partially completed.

**E. Task 5:** Determine the trajectory of symptoms and social/vocational functioning in PCS after blast related MTBI (Study Phase-III). Timeline: Gradual accrual into Phase 2 of 225 total subjects over 4 years (25 subjects by end Year 1, 125 subjects by end Year 2, 225 subjects by end Year 3). Responsible personnel: listed below for each subtask.

1. On over 232 returnees (consecutive Phase-I enrollments described in Task 1 & 2), collect follow-up longitudinal data (6 months, and one year) on phase-I current-state measures, AND collect complete longitudinal outcome data (6 months and one year) using standardized and validated TBI specific outcome measures including: Extended Glasgow Outcome Scale (GOS-E) (Wilson et al, 1998) (global outcome), Mayo-Portland Adaptability Inventory-4 (MPAI-4) (Malec, 2004) (ability, participation, adjustment), and the Satisfaction With Life Scale (SWLS) (Diener et al, 1985) (quality of life). [scheduling: Research Assistants. Telephonic or in-person data collection: Research Assistants]

Completed Phase-III (6 month) evaluations on **an additional 32 subjects** during Year-5 for a total of 146 completed 6-month evaluations through Sept 30, 2013. Completed Phase-III (12 month) evaluations on **an additional 32 subjects** during Year-5 for a total 138 completed 12-month evaluations through Sept 30, 2013. Completion of Phase-III evaluations has been hindered by subject relocation and or redeployment and is below our expectations. Thus, we previously instituted additional strategies to optimize our Phase-III retention rate. These additional strategies have facilitated improvement of the collection of final outcome data. We continue to monitor progress on this and track those participants who are deployed at the time of study visits. Since instituting a mailer version of data collection earlier this year, we have succeeded in obtaining mailed form collection on 3 of the Phase III evaluations. These represent “saves” of data that was potentially unobtainable via phone or in-person collection.

2. **Describe the trajectory of symptoms and social/vocational functioning among returnees with PCS after blast-related MTBI. [Analysis by all key investigators]**

Pending complete longitudinal data collection.

3. **Conduct statistical analysis using repeated measures mixed-models for analysis of outcomes over time (baseline, 6 months, and one year). [Statistics: Dr Ketchum, Interpretation: All key investigators]**

Pending complete longitudinal data collection.

**F. Task 6 – Objective: Disseminate Findings:**

1. **Disseminate results via publication in peer reviewed journals. [All key investigators coordinated/led by Dr. Walker]**

Publications to date (accomplished this reporting year in **bold**):


- Walker, W., Nichols, M., McDonald, S., Ketchum, J., & Cifu, D. The identification of transient altered consciousness induced by military related blast exposure and

- Franke LM, Czarnota, J.N, Ketchum JM, Walker WC. Factor Analysis of the Rivermead Postconcussion Questionnaire following blast exposure within a military sample with blast exposure and compared to a civilian sample. Submitted to: *J Head Trauma Rehabil.*


2. **Present at professional meetings to reach the variety of practitioners treating TBI and blast injured patients** [All key investigators coordinated/led by Dr. Walker].

National Presentations to date: (no new presentations this reporting year):


**III. KEY RESEARCH ACCOMPLISHMENTS:**

- See previous task (Task 6) for publications and presentations accomplished to date.

- Developed structured interview for the post-acute detection/diagnosis of mild TBI. Such an instrument did not previously exist in the published literature.

- Additional “key” research accomplishments are expected in year five. For year-four accomplishments, please see “II” above (pages 4-13).

**IV. REPORTABLE OUTCOMES:** Outcomes await data analysis and study closure.
V. CONCLUSION:

When completed, this study will aid in developing targeted secondary prevention strategies by identifying factors that predispose service-members to PCS after blast-related MTBI. Characterization of the impairments and problems related to PCS will aid health care planning and development of targeted medical and rehabilitative treatment strategies.

VI. REFERENCES:


VII. APPENDICES:

**APPENDIX # 1:**

*Subject Demographics through Year-V*

CDMRP W81XWH-08-2-0178 Demographic Summary Sheet

N = 216 (as of 5/31/2013)

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<table>
<thead>
<tr>
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Some College 35.2  
College Graduate 11.6  
Post-Graduate Degree 1.4

Prior Deployment Status

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<tr>
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</table>

1 Other Race includes: 1 Black/White, 6 Hispanic, 3 Latino, 1 Latino/White, 1 Native American, 1 Native American/Black, 1 White/Asian.

**VIII. SUPPORTING DATA:** Please see table and figures above. No additional supporting data at this time (Year-V).