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

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13. SUPPLEMENTARY NOTES

14. ABSTRACT:

Preliminary Results: We accomplished Institutional Review Board (IRB) full approval of our initial submission, protocol amendment, and subject recruitment advertisements both locally (McGuire VAMC) and at Army Headquarters (USAMRMC). A subsequent request for an additional Walter Reed Army Medical Center IRB approval by our Military partner study site (Kenner Health Clinic, Fort Lee, VA) is currently under review. Three full-time research assistants and a part-time Data Manager have been recruited and trained. Study procedures, recruitment, data management, and analyses have been refined through meetings, reviews, consultations, and mock study form completions. Subject recruitment and protocol implementation commenced at the VAMC site in December 2008. Through July 31, 2009, thirty-two (32) subjects have been accrued through Polytrauma Network Site Clinic screening, and on-site enrollment at Fort Lee, Virginia. While data analysis is premature, most appear to meet symptom criteria for PCS.
Conclusions to Date: Enrollment has commenced for this study of blast-related MTBI among OIF/OEF returnees. Early results suggest that recruiting OIF/OEF veterans with blast-related PCS is feasible. The accumulating sample should also be suitable for intervention trials under development. To ensure a sample representative of the target population, we are addressing the regulatory requirements for enrollment at our Military partner site, and mailing outreach recruitment letters to all local veterans with OIF/OEF service.

15. SUBJECT TERMS
Mild traumatic brain injury, blast exposure, head injury, post-traumatic stress disorder, post-concussion syndrome, military personnel, functional outcomes

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TABLE OF CONTENTS:

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. <u>Obtain IRB approval for project</u> [Ms. Nichols]:

Approval from the primary institutional review board, the McGuire IRB was obtained on August 15, 2008. Secondary IRB approval from USAMRMC (Fort Detrick IRB) was received on September 27, 2008. Virginia Commonwealth University IRB approval was received on March 5, 2009.

2. <u>Establish Military site screening/recruitment options</u> [Ms. Nichols & Dr. Walker]:

In addition to the three IRBs (MIRB, VCU/IRB, Fort Detrick) that were already reviewing this project, the Fort Lee base commander required an additional review by the Walter Reed AMC IRB. This process was/is quite complicated because any changes requested by WRAMC-IRB had to then be reviewed by the above three boards. Full WRAMC/IRB approval was received on June10, 2009. The CDMRP research team began the

recruitment and screening process at Kenner Army Health Clinic at Fort Lee on 6/19/2009. Through August, 2009, two (2) subjects were screened and two (2) subjects have been recruited from the Kenner Army Health Clinic site. Additionally, the connections and process were established to add an additional military recruitment site, at US Marine Corps Base, Quantico, Virginia, and work is underway on the associated regulatory processes.

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

After discussions with collaborators and colleagues within DVBIC and VAMC, we determined that acute injury documentation was not reliably available post-acutely, necessitating that our measures will rely entirely on self-report. Thus we spent much time refining our injury situation and experience questionnaires to be as thorough and specific as possible. Additionally, we chose to add several structured interviews to help cross-validate some of our key diagnostic screening questionnaires – see new SOW task added.

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

Accomplished.

5. Complete set-up of data management software system. [Dr. McKinney]

Accomplished.

6. Establish logistics (when, where, workspace) for study screening and recruitment of military personnel at Central Virginia PDHA clinic sites. [Dr. Cifu & Ms Nichols]

Accomplished for Kenner Army Health Clinic at Fort Lee where we have access and space to bring a several member research team to work with large group appointments. We also produced a digital video that describes the study and the nature of participation to potential subjects. Once approved by the respective IRBs, we will begin to use this as a supplementary recruitment tool, especially when our research team is unable to be physically present at Kenner PDHA (Post Deployment Health Assessments) clinic appointments and when there are large numbers of troops to be screened for potential recruitment, as it will ensure consistency in content delivery. Similar processes and logistics are being defined for future recruitment efforts at Marines Corps Base Quantico. While not a PDHA clinic, study personnel did participate in a Welcome Home Event on June 13, 2009 at the Richmond International Raceway where the team provided basic information on the study and had a means to follow up with interested parties to provide additional information via the informed consent process.

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

Please see the table below for study staff name, role, and effort. Mr. Heimiller and Ms. Nichols helped write/prepare the original application, and have been continually involved in this project from its inception. Dr. McDonald, research psychologist joined us in August, 2008, and contributed to various aspects of the project. After award and funding were received, these individuals continued in part-time paid roles. Ms. Tiffany Clory, Ms. April Dean, and Ms. Tammy Searles were hired between November, 2008 and June, 2009 as full time research assistants.

CDMRP/Walker: Study Staff Summary

NAME & ROLE	MONTH/YEAR HIRED	% EFFORT
William C. Walker, MD, Principal Investigator	**September, 2008**	**20 (see: VCU sub-award)**
Michelle Nichols, MSN, RN, Co-Investigator and Clinical Research Coordinator	**September, 2008**	**20**
Jerome Heimiller, RPH, MPA, Administrative Assistant	**September, 2008**	**(up to) 10**
Tiffany Clory, BS, Research Assistant	**November, 2008**	**100**
April Dean, BS, Research Assistant	**January, 2009**	**100**
Tammy Searles, RN, Lead Research Assistant	**June, 2009**	**100**
Scott McDonald, PhD., Research Psychologist	**September, 2008**	**(up to) 10**

***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. <u>Consent & Enroll 747 Subjects Total</u>. [Ms. Nichols, Dr. Walker, Ms Searles]

Through August, 2009, three hundred sixty one (361) potential subjects have been screened, and thirty-four (34) subjects have been enrolled. Enrollment started slowly due to the lag time between selection and meeting USAMRAA pre-funding requirements, and the period devoted to recruiting/appointing our three full-time study staff (Clory, Dean and Searles). As noted previously, the requirement for an additional army IRB review delayed enrollment at Kenner Health Clinic. We found that many of the patients screened at VAMC Polytrauma Network Clinic who screened positive for blast exposure during OIF/OEF deployment were not eligible because the exposure was more than 2 years prior. We expanded our Richmond (McGuire) VAMC recruitment through outreach letters to registered patients and created a poster (see APPENDIX #1) to be displayed to enhance subject recruitment efforts. Through August 31, 2009, we have mailed out 3,632 recruitment letters to subjects/patients who were registered at the Richmond VA Medical Center, and had served in OIF or OEF. And as noted previously, we also opted to pursue an additional military recruitment site (Quantico, Virginia US Marine Base).

2. <u>For each subject above, complete standardized current state questionnaires for qualitative and quantitative measurement of: Post-concussion syndrome (PCS)</u>

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 will be utilized to standardize this diagnostic assessment. [Oversight: Ms. Nichols, Dr Walker and Dr Cifu. Scheduling: Ms Searles. Monitoring and facilitation of subject form completion: Ms Searles, Research Assistants, Ms.Cohen]:

Accomplished on the 34 subjects enrolled through August 31, 2009.

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: Ms. Nichols, Dr Walker and Dr Cifu. Scheduling: Ms Searles. Monitoring and facilitation of subject form completion: Ms. Searles, Research Assistants, Ms. Cohen]

Accomplished on the 34 subjects enrolled thru August 31, 2009.

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 the 34 subjects enrolled through August 31, 2009.

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 McKinney]

Accomplished on the 34 subjects enrolled through August 31, 2009.

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

Performed on the first subject; 37 subject accrual is pending. Additionally, to ensure accuracy of data collection while training newly hired study personnel, Phase-I data audits were performed through August 2009 on the first 29 subjects enrolled. In May 2009, this study was also audited by the VA Research Compliance Officer, as part of their Standard Operating Procedures and it was found at that time to be 100% compliant.

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. McKinney. Interpretation: all key investigators]

Pending complete enrollment and data collection.

***C. Task 3* - Objective: Identify and describe objective cognitive performance and neuro-physical 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). [Ms. Nichols & Dr. Walker]**

   Accomplished on the 34 subjects enrolled through August 31, 2009.

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. McKinney]**

   Accomplished on the 34 subjects enrolled through August 31, 2009.

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 asses 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, & Arithmetic (processing speed, attention, and working memory),(McKay, Casey, Wertheimer, & Fichtenberg, 2007) Delis-Kaplan Executive Function System (D-KEFS) Category Fluency (Animals And Boys' Names) (Harrison, Buxton, Husain, & Wise, 2000):Controlled Oral Word Association Test single letter and category items (COWAT, verbal fluency),(Iverson, Franzen, & Lovell, 1999) Benton Visual Memory Test-Revised (BVMT-R) (visual perception and memory).(Morey, Cilo, Berry, & Cusick, 2003) [Test scheduling: M. Nichols, MSN, RN and T. Searles RN Neuropsychological testing: Ms. Cohen, Drs Pickett & McDonald. QEEG testing: Dr McDonald, M. Nichols, MSN, RN, and trained research assistants with consultation with Dr. McDonald: T. Searles RN, M. Nichols, MSN, RN, trained research assistants]

Accomplished on the 24 subjects who were assigned to 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. McKinney. Interpretation: all key investigators]**

   Pending complete enrollment and data collection.

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. McKinney. Interpretation: all key investigators]**

   Pending complete enrollment and data collection.

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. McDonald]**

   Dr. McDonald, Dr. Walker, and other members of the research team had several meetings with radiology staff and other key personnel to develop a pilot DTI protocol.

The protocol "*Diffusion Tensor Imaging and Post-Concussion Syndrome: A Feasibility Study*" (PI: Walker) was written and received IRB approval on 4/24/2009. The Richmond VAMC has purchased a 3.0 Tesla MRI scanner that will be used in this study, and we are awaiting final calibrations. We expect to start enrolling DTI-pilot study subjects in October 2009.

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. **Pending IRB and DoD Administrative approvals, 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). [M. Nichols, MSN, RN, Dr. McDonald, Dr. Cifu, Dr. McKinney, and Dr. Walker]**

   The MINI and CAPS have been obtained and the TBI interview has been developed. Optical scanner sheets have been designed to improve data transfer accuracy and efficiency. A MINI training workshop will be conducted onsite 10/9/2009 by Juris Janavs, MD, one of the authors of the MINI and an interview trainer. CAPS interview training resources have been acquired and staff training will commence in 10/2009. IRB Amendment 2, which will add these measures to the study, was submitted to the McGuire IRB in August 2009 and will be forwarded to USAMRMC, and the IRBs at VCU and WRAMC upon local approval.

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

   Phase-II activity (see D1 above). Not applicable to Year-One progress report.

3. **Analyze findings and implications for the primary analyses described in Tasks 2 and 3. [Dr. McKinney, Dr Walker, and all investigators]**

   Phase-II analytical activity (see D1 above). Not applicable to Year-One progress report.

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, 2225 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: Ms Nichols and Ms. Searles. Telephonic or in-person data collection: Ms Searles, Research Assistants, Ms. Cohen.]

Completed Phase-III (6 month) evaluations, on four (4) subjects through August 31, 2009.

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 enrollment and 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 McKinney, Interpretation: All key investigators]**

   Pending complete enrollment and 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]**

   Not applicable to year-one progress report**.**

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].**

   Not applicable to year-one progress report. However Dr Walker presented the study objectives and design in oral and poster presentation format at the 2009 Military Health Research Forum in Kansas City on Sept 1st and 2nd of this reporting year (see below).

III. KEY RESEARCH ACCOMPLISHMENTS: .

- 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 years two, three, and four. For year-one accomplishments to date, please see "II" above (pages 4-11).

IV. REPORTABLE OUTCOMES:

- Oral Symposium presentation, Military Health Research Forum, Kansas City, MI, Sept 1, 2009 (see APPENDIX # 2)

- Poster presentation, Military Health Research Forum, Kansas City, MI, Sept 2, 2009 (see APPENDIX # 3).

V. CONCLUS ION:

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

VI. REFERENCES:

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VII. APPENDICES:

APPENDIX # 1: Subject Recruitment Poster
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HAVE YOU SERVED IN

Operation Iraqi Freedom or

Operation Enduring Freedom

AND BEEN

Exposed to a Blast?

If so, you may be eligible to participate in a clinical research study to better understand the causes of mild traumatic brain injury after a blast exposure. This study includes up to four study visits and participants will receive study-related evaluations.

To qualify, you must:

Be between the ages of 18 and 65

Be a military or veteran beneficiary

Have been exposed to a blast in the past 2 years

If you or someone you know is interested in participating, please contact:

Principal Investigator
William Walker, MD
804-675-5117

Co-Investigator
Michelle Nichols, MSN, RN
804-675-5625

Principal Investigator: Williams Walker, MD
Sponsors: Congressionally Directed Medical Research Programs/ Department of Defense
Defense and Veterans Brain Injury Center (DVBIC)
McGuire VA Medical Center, Richmond, VA

APPENDIX # 2: Oral Symposium presentation, Military Health Research Forum, Kansas City, MI, Sept 1, 2009

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Epidemiological Study of Mild Traumatic Brain Injury Sequelae caused by Blast Exposure during Operations Iraq Freedom and Enduring Freedom

William C. Walker, MD
Professor, VCU Dept PM&R,
and
Principal Investigator, CDMRP PT074224
Hunter Holmes McGuire VAMC
Richmond, Virginia

Hypotheses:
(1) **a significant proportion** (>18%) of service members **experiencing blast events** during OIF/OEF sustain a MTBI that leads to **persisting symptoms** consistent with PCS.

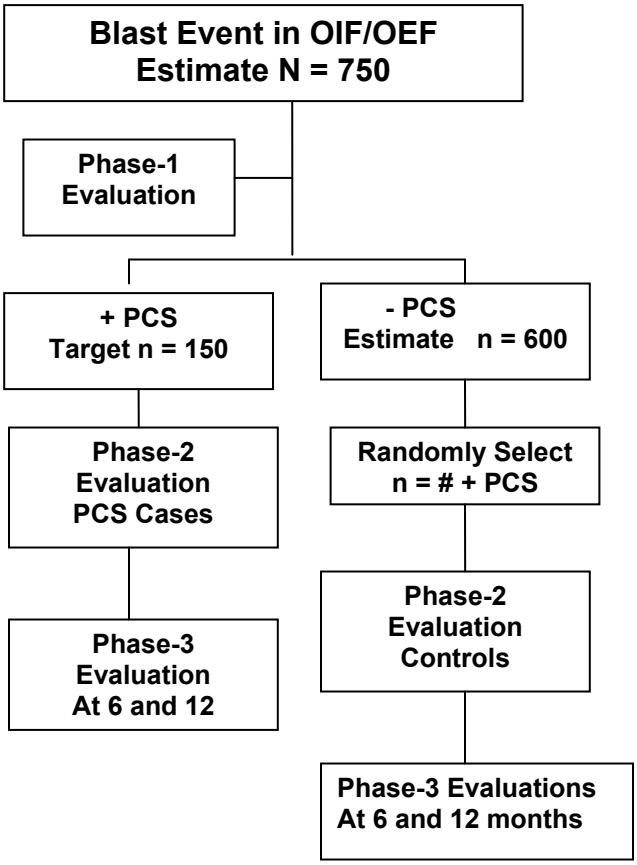
(2) Multiple **predictive factors** for **developing PCS** can be identified.

(3) Returnees with PCS will display **objective impairments** on neuropsychological testing, computerized posturography and/or quantitative electroencephalography.
(4) Those with PCS will demonstrate **improvement over time** but will continue to display **significant long-term disability**.

Design/Objectives:

- Phase 1: Cross Sectional
  - determine the sample **prevalence of PCS** after blast related MTBI, **characterize** the constellation of related symptoms and problems, and allow predictive modeling.
- Phase 2: Case Control
  - evaluate **objective abnormalities** among the subjects with PCS after MTBI.
- Phase 3: Longitudinal -repeated measures
  - analysis of **functional outcomes** over time (baseline, 6 months, one year).

Subject Flow



Subject Selection

- Inclusion Criteria:
  - Male or Female (age 18 or older)
  - Military or Veteran Healthcare Beneficiaries
  - Blast Event * within past 2 years during OIF/OEF deployment

- Exclusion Criteria:
  - TBI with a primary etiology other than blast
  - Severe TBI

*event defined as any of the following symptoms or experiences occurring during or shortly after the blast or explosion: dazed, confused, saw stars, headache, dizziness, irritability, memory gap (not remembering injury or injury period), hearing loss, abdominal pain, shortness of breath, struck by debris, knocked over or down, knocked into or against something, helmet damaged, evacuated

Main Outcome Measures:

- Rivermead Post-concussive Symptom Questionnaire
- Extended Glasgow Outcome Scale
- Mayo-Portland Adaptability Inventory-4: Participation Index
- Satisfaction with Life Scale

- Neuropsychological Testing: Battery chosen to tap relevant cognitive domains and effort

- Quantitative Electroencephalography
- Computerized Posturography: Sensory Organization Test

Preliminary Findings:

- Study procedures were refined through meetings, reviews, consultations, and mock study form completions.
- Full local and military IRB approval obtained.
- Dedicated study staff recruited, hired, & trained.
- Subject recruitment and protocol implementation commenced at the McGuire VAMC site in December 2008.
- Subject recruitment and protocol implementation commenced at Kenner Health Clinic, Fort Lee, VA in June 2009.
- Current Enrollment (as of 9/1/09) = 34 participants

Conclusion:

- Enrollment has commenced for this study of blast-related MTBI among OIF/OEF returnees. Early findings suggest that recruiting veterans and returning service-members with PCS is feasible.
- The accumulating sample should also be suitable for intervention trials under development.
- To ensure a sample representative of the target population, we are: addressing the regulatory requirements for enrollment at an additional Military partner site, and mailing outreach recruitment letters to all local veterans with OIF/OEF service.

Impact Statement:

- Identifying factors that predispose service-members to PCS after blast-related MTBI will aid in developing targeted secondary prevention strategies.
- Characterization of the impairments and problems related to PCS will aid health care planning and developing targeted medical and rehabilitative treatment strategies.

Credits:

- Funding by CDMRP, Grant W81XWH-08-2-0178
- Hunter Holmes McGuire VAMC (primary site)
- McGuire Research Institute (award recipient)
- Virginia Commonwealth University (major collaborator)
- Kenner Health Clinic, Fort Lee, VA (active duty recruitment site)
- Co-PI: David X. Cifu, MD
- Fort Lee PI: Ruth Crampton, MS, FNP-BC
- Co-investigators:
    - Michelle Nichols, MSN, RN
    - Scott McDonald, PhD
    - Jessica McKinney Kethcum, PhD
    - Shane McNamee, MD
    - Jeffery Ericksen, MD
    - TrevenPickett, PsyD

***APPENDIX # 3*: Poster presentation, Military Health Research Forum, Kansas City, MI, Sept 2, 2009**

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Epidemiological Study of Mild Traumatic Brain Injury Sequelae Caused By Blast Exposure During Operations Iraq Freedom and Enduring Freedom

William C. Walker MD; David X. Cifu, MD; Michelle Nichols MSN,RN; Scott McDonald PhD; Ruth Crampton, MS, FNP-BC
Hunter Holmes McGuire VA Medical Center, Virginia Commonwealth University, Defense & Veterans Brain Injury Center – Richmond, VA

Background:

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.

Objectives:

Multiple hypotheses will be tested including:

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

Target Population:

Inclusion Criteria:

- Male or Female (age 18 or older)
- Military or Veteran Healthcare Beneficiaries
- Blast Event* within past 2 years during OIF/OEF deployment

Exclusion Criteria:

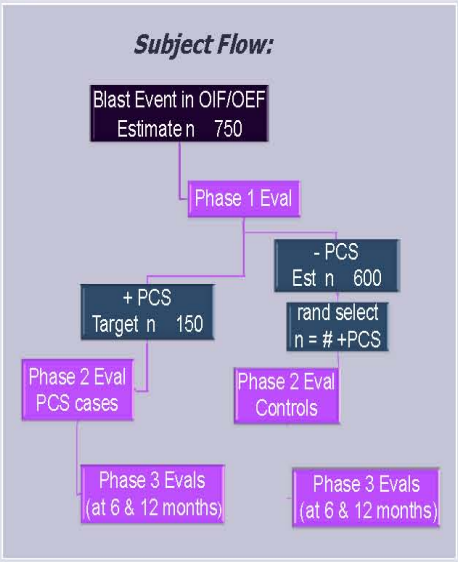
- TBI with a primary etiology other than blast
- Severe TBI

**Event defined as any of the following symptoms or experiences occurring during or shortly after the blast or explosion: dazed, confused, saw stars, headache, dizziness, irritability, memory gap (not remembering injury or injury period), hearing loss, abdominal pain, shortness of breath, struck by debris, knocked over or down, knocked into or against something, helmet damaged, evacuated.*

Methods/Design:

- Cross-Sectional: Phase 1 will determine the sample prevalence of PCS after blast related MTBI, characterize the constellation of related symptoms and problems, and allow predictive modeling.
- Case-Control: Phase 2 will evaluate objective abnormalities among the subjects with PCS after MTBI.
- Longitudinal, repeated measures: Phase 3 will assess functional outcomes over time (baseline, 6 months, and one year).

Subject Flow:



Main Outcomes Measures:

- Rivermead Postconcussive Symptom Questionnaire
- Extended Glasgow Outcome Scale
- Mayo-Portland Adaptability Inventory-4: Participation Index
- Satisfaction with Life Scale
- Neuropsychological Testing: Battery chosen to tap relevant cognitive domains and effort
- Quantitative Electroencephalography
- Computerized Posturography: The sensory organization test

Preliminary Findings:

- Study procedures, recruitment, data management, and analyses were refined through meetings, reviews, consultations, and mock study form completions.
- Full local and military IRB approval obtained.
- Dedicated study staff recruited, hired, & trained.
- Subject recruitment and protocol implementation commenced at the McGuire VAMC site in December 2008.
- Subject recruitment and protocol implementation commenced at Kenner Health Clinic, Fort Lee, VA in June 2009.
- Current enrollment is n = 32.

Conclusion:

- Enrollment has commenced for this study of blast-related MTBI among OIF/OEF returnees.
- Early results suggest that recruiting veterans and returning service-members with blast-related PCS is feasible.
- The accumulating sample should also be suitable for intervention trials under development.
- To ensure a sample representative of the target population, we are:
  1) addressing the regulatory requirements for enrollment at an additional Military partner site,
  2) mailing outreach recruitment letters to all local veterans with OIF/OEF service.

Impact Statement:

- Identifying factors that predispose service-members to PCS after blast-related MTBI will aid in developing targeted secondary prevention strategies.
- Characterization of the impairments and problems related to PCS will aid health care planning and developing targeted medical and rehabilitative treatment strategies.

Funding by CDMRP-PT074224, Grant W81XWH-08-2-0178

VI. SUPPORTING DATA:

Please see table and figures above. No additional supporting data at this time (Year-One).