OFFICE OF RESEARCH AND DEVELOPMENT

PROGRAM ANNOUNCEMENT

REQUEST FOR APPLICATIONS IN COMBAT CASUALTY NEUROTRAUMA

1. Purpose:

The Department of Veterans Affairs (VA) Office of Research and Development (ORD) offers this program announcement to stimulate research in the area of neurotrauma. Due to the ongoing conflicts in Afghanistan and Iraq, Traumatic Brain Injury (TBI) and Spinal Cord Injury (SCI) accounts for almost 25% of combat casualties.

2. Background:

Improvised explosive devices, blast (high pressure waves), landmines, and explosive fragments account for the majority of combat injuries in Afghanistan and Iraq. Although Kevlar helmets and advances in body armor have saved the lives of many soldiers, they do not protect against blasts and impacts to the head, face and cervical spinal cord.

In order to advance treatment and rehabilitation following TBI and cervical SCI, fundamental information about the post-acute and long-term processes is essential. Blast injuries often result in multiple traumas, including injuries to internal organs, limb loss, sensory loss, and psychological disorders. The term “polytrauma” has been coined to describe the co-occurring injuries. While this solicitation focuses on TBI, cervical SCI and their associated sequelae, studies that address co-occurring conditions as they relate to the treatment of these conditions are encouraged.

VA’s Office of Research and Development is taking the lead to ensure that soldiers in harm’s way achieve maximal recovery from combat casualty neurotrauma.

*Traumatic Brain Injury:*
Kevlar helmets have done much to protect the head but leave the forehead unprotected. The left and right frontal lobes, located behind the forehead control intellectual abilities such as the ability to plan and organize. This area of the brain also controls personality, behavior, and emotional control.

Concussion or mild TBI is the most common form of combat-related injury. Mild TBI can occur even in those not directly hit by the blast, without obvious external injuries, without loss of consciousness and without visible findings from acute Magnetic Resonance Imaging. Problems with memory, lack of concentration, increased anxiety and irritability are common hallmarks of mild TBI. Although evidence suggests that the majority of OIF/OEF soldiers who suffer mild TBI will recover over time, early diagnoses and treatment are critical so that aberrant behaviors due to TBI are not misinterpreted and soldiers are spared the risk of second impact syndrome. Appropriate recognition of TBI will facilitate quick return to pre-injury activity levels, including return to duty status.
In addition to mild TBI, soldiers close to the blasts are experiencing severe diffuse and contrecoup injuries. Soldiers with a moderate to severe TBI often show the similar symptoms as mild TBI yet also report: worsening headaches; repeated vomiting or nausea; seizures; inability to awaken from sleep; slurred speech; weakness, numbness and loss of coordination. Unlike mild TBI, these problems and others can persist long-term or result in permanent difficulties with memory, reasoning, emotion and expression making it impossible to return to duty, hold steady employment or regain pre-injury quality of life.

Penetrating focal injuries from mortar rounds or other forms of heavy artillery resulting in severe brain injury are not as prevalent. However, focal destruction of brain tissue is the most life-threatening, intractable type of brain injury causing permanent damage to the affected area and the functions it controls.

Multidisciplinary approaches must be investigated to ensure maximum recovery and assist those with substantial lifelong consequences.

**Spinal Cord Injury:**
Current designs in military protective gear and advanced evacuation procedures have resulted in both a decrease in the percentage of spinal cord injured soldiers and an increase in the number of those that ultimately survive. Blast force and shrapnel injuries are most common. For those that survive, the cervical spinal cord, the unprotected and most mobile portion of the spinal cord, is the most common site of injury.

Soldiers with cervical SCI face short- and long-term consequences of losing motor and sensory function below the level of injury, coupled with a loss of autonomic regulation. Every organ system may be affected by cervical spinal cord injury. Alterations in the gastrointestinal, renal, skin and musculoskeletal organs are common, and respiratory problems are the overwhelming cause of morbidity and mortality. In addition, patients may experience chronic pain at or below the level of injury and, less frequently, above it.

Alterations in respiratory mechanics, and the development of alveolar hypoventilation, pneumonia, aspiration of gastric contents, pulmonary embolism, pulmonary edema, and sleep apnea are a few of the common respiratory complications associated with cervical SCI. Ultimately, dysfunction depends on the level and extent of injury. Lesions above $C_3$ paralyze all respiratory muscles. When SCI involves $C_3$ to $C_5$ lesions, profound respiratory muscle dysfunction occurs leaving the patient unable to generate a cough or clear secretions. Because of this, neuroprotective strategies that rescue even one or two segments may be of significant functional benefit to veterans with SCI.

3. Sample Research Issues in TBI:

   a. Development of innovative, animal and *in vitro* models for blast-force-associated mild to severe brain injury;
b. Relationships between the neurobiology and neuropsychology of acute and chronic TBI;

c. Primary and secondary therapeutic interventions following diffuse, contrecoup or penetrating TBI;

d. Neuroprotection of TBI and effectiveness of interventions;

e. Innovative approaches to late sequelae of TBI, such as post-traumatic epilepsy (including primary prevention strategies);

f. Innovative approaches to short- and long-term consequences of TBI that affect relationships, employment and ultimately reintegration -examples include cognitive deficits, mood impairment; self-awareness and planning;

g. Impact of rehabilitation strategies on neural plasticity following TBI, using imaging, neurobiological, and cognitive approaches;

h. Development of efficient diagnostic criteria and treatment milestones for detecting mild TBI using MRI, DTI, PET or other diagnostic tools;

i. Outcomes and cost effectiveness of clinical and rehabilitation interventions for TBI and its sequelae;

j. Identification of factors influencing metabolic and body composition changes after TBI, such as pituitary dysfunction and alterations in mobility and lifestyle and development of interventions;

k. Comparison of intervention strategies for caregiving and family coping, such as education, support groups, and therapy;

l. Identification and testing for early detection of TBI (methods that can be used in the field are encouraged);

m. Identification of biomarkers for early detection of TBI and to follow the course of treatment;

n. Examination of the continuity of care while transitioning from Department of Defense Military Treatment Facilities to the Polytrauma Centers and from the Polytrauma Centers into VA’s inpatient or outpatient health care system;

o. Examination of continuing service use patterns and barriers to accessing the continuum of available care;
p. Development of accurate and efficient screening instruments for TBI sequelae from associated conditions co-occurring from blast trauma, e.g., post-traumatic stress disorder, sensory disorders for the purpose of developing effective plans of care;

q. Treatment trials to enhance cognition and attention and to treat emotional, behavioral, and psychomotor conditions related to TBI;

r. Identification of issues related to community reintegration and intervention strategies to address them;

s. Comparisons of pathophysiology and/or treatment of TBI that results from blast injury with that which results from direct contact injury to the head;

t. Vocational Rehabilitation training for persons mild to severe TBI.

4. Sample Research Issues in Cervical SCI:

a. Development of innovative, humane animal and in vitro models for blast-force-associated cervical SCI;

b. Comparisons of pathophysiology of cervical SCI with lower (thoracic and lumbar) SCI;

c. Studies on neuroprotection in SCI;

d. Comparisons of cervical SCI with lower (thoracic or lumbar) SCI in terms of effects of upper motor neurons;

e. Innovative approaches to treatment of sequelae associated with cervical SCI (including primary prevention strategies);

f. Impact of unique rehabilitation strategies for cervical SCI with incorporation of effectiveness measures such as imaging, biomarkers and functional recovery;

g. Development of efficient diagnostic criteria for field assessment of cervical spinal cord versus column injury;

h. Identification of short- and long-term consequences and comparison of treatment paradigms associated and coping mechanisms of losing motor function, losing sensory function, and autonomic dysregulation;

i. Comparison of intervention strategies for caregiving and family coping following cervical SCI, such as education, support groups, and therapy;

j. Identification of biomarkers for early detection and progression of sequelae associated with cervical SCI;
k. Examination of the continuity of care while transitioning from Department of Defense Military Treatment Facilities to the SCI Centers and into VA’s inpatient or outpatient health care system;

l. Examination of continuing service use patterns and barriers to accessing the continuum of available care;

m. Development of accurate screening instruments for consequences of cervical SCI such as pain or depression and development of appropriate interventions;

n. Evaluation of current technology for utilization, reintegration and health outcomes for persons with cervical SCI;

o. Development of assistive technology that improves independence and quality of life for persons with cervical SCI beyond the expectations of currently available technologies;

p. Vocational Rehabilitation training for persons with cervical SCI.

5. Eligibility:

VA clinician and non-clinician scientists currently eligible to apply for research funding from any of the four ORD Services (Biomedical Laboratory, Clinical Sciences, Health Services, Rehabilitation Research and Development) may submit an application under this RFA. Principal Investigators with other VA funding, including Merit Review funded by any of the ORD Services, are eligible to apply to this program; funding under this RFA would be in addition to the “single Merit Review rule” in Biomedical and Clinical R&D Services. For further information about eligibility, please review VA Handbook1200.15.

6. Letter of Intent:

An approved Letter of Intent (LOI) is required to submit an application. LOIs will be reviewed for relevance to this specific RFA. Eligible applicants must submit a LOI in the following format:

a. VHA LOI Cover (VA Form 10-1313-13)  
   (available at http://www.va.gov/resdev/funding/process/forms.cfm)

b. LOI text. Succinctly address each of the following (limited to two pages):
   (1) Hypothesis(es)/Research Questions
   (2) Discrete Study Objectives
   (3) Description of Relevance to this RFA/
   (4) Identification of targeted Research Service
   (5) Overview of Design/Methods
   (6) Description of Intervention(s)/Treatment(s) - if applicable
   (7) Total Budget and Study Duration
(8) Statement of Disclosure – 1-2 sentence statement from the PI indicating that no financial or contractual relationship exists between any organization involved in the proposed study that could constitute a real or apparent conflict of interest (including all investigators and collaborators who plan to devote 5 percent or more effort to the proposed project). If such a relationship or contract does exist, full disclosure must be provided.

(9) Acknowledgment of the VA policy to include women and minorities in clinical research (if applicable).

LOI’s should be mailed to:

TBI Research Initiative (124S)
Office of Research and Development
810 Vermont Avenue, NW
Washington, DC 20420

7. Application Preparation and Submission.

Applicants will be notified by e-mail of the acceptance of the LOI. The applicant will submit a full research proposal to the ORD Service that has accepted the LOI. Please follow the submission and funding guidelines of the ORD Service to which the proposal will be submitted. Visit the following website for the latest submission deadlines, forms, and Handbooks for each of the four ORD Services:

http://www.va.gov/resdev/funding/process

8. Due Date:

The deadline for LOI submission is January 15, 2006 for those applicants who are addressing topics relevant to the Biomedical Laboratory and Clinical Sciences Research Services. LOIs will be accepted until February 15, 2006, which address topics relevant to Rehabilitation and Health Services Research and Development Services. Proposals are due on the next published proposal deadline for the specified service at http://www.va.gov/resdev/funding/process.

9. Inquiries:

Questions may be directed to: Health Services Research and Development: Martha Bryan, EdD (202) 254-0251, martha.bryan@va.gov; Rehabilitation Research and Development: Danielle Kerkovich, PhD (202) 254-0258 danielle.kerkovich@va.gov; Biomedical Laboratory and Clinical Science Research Services: Joseph Webster, PhD (202) 254-0273, joseph.webster@va.gov.

Joel Kupersmith, MD
Chief Research and Development Officer
REFERENCES


