Research Advisory Committee on Gulf War Veterans' Illnesses
Comments and Recommendations
Regarding New VA Gulf War Illness Research Program
November 17, 2009

In recent months VA has begun the development of a major new Gulf War Illness (GWI) research program to succeed the VA-funded Gulf War illness research program at the University of Texas Southwestern (UTSW). The Committee has had the opportunity to review three Research Funding Announcements (RFA's) issued as part of this new program. After discussion at its November 3, 2009 meeting, the Committee adopted the following comments and recommendations regarding the new program. Many of these comments have previously been offered informally by Committee members to the VA Office of Research and Development (ORD) regarding earlier/draft versions of the RFA's; comments which were subsequently addressed in the current RFA's are so noted below. At its November 3 meeting, an informal discussion between Committee members and ORD representatives took place regarding the possible content and structure of the balance of the program. The Committee looks forward to the opportunity to provide more detailed recommendations as the program takes shape and expressed the hope that the new program will make effective use of results obtained in the UTSW program.

A. Fundamental Recommendations Regarding a VA Gulf War Illness Research Program

The Committee emphasizes the lessons learned from previous VA Gulf War Illness research programs at the cost of so many years and so many millions of dollars.
The Committee strongly reiterates the general recommendations made in its 2004 Report regarding VA-managed GWI research and its April 2008 recommendations regarding the VA-funded University of Texas Southwestern GWI program as follows.

1. Begin with a comprehensive research plan that addresses priority research topics identified in Research Advisory Committee (RAC) reports. The plan should include information on the objectives and hypotheses of the program and of each study, the design of each study, and how individual studies and components relate to one another.

2. Utilize a formal expert panel of scientists from inside and outside VA knowledgeable in GWI and related fields to develop the plan, including some RAC members.

3. Place responsibility for reviewing proposals and approving what studies to fund in the hands of the same or similar scientists taking into account the relevance to the plan as well as the scientific merit of the proposals.

4. Manage the program as a coherent whole, under the direction of people committed to solving the problem with expertise directly relevant to GWI.

B. The Committee makes the following general comments and recommendations regarding the new VA GWI Research Funding Announcements (RFA's) issued in October 2009 related to Biological Laboratory Research and Clinical Science Research.

1. The RFA's should challenge researchers to design proposals that will further the goal of improving the health and lives of veterans who have Gulf War Illness.

2. Both RFA's addressed physiological mechanisms underlying Gulf War Illness (GWI), a step in the right direction for furthering the understanding of GWI mechanisms and targets for future treatments. The Committee was pleased that proposed research topics were drawn from the recommendations of the Committee's 2008 report.

3. An additional topic for research should be sophisticated models for Gulf War illness case definitions, to avoid confusion that GWI is the same as fibromyalgia or chronic fatigue syndrome.

4. Inadequate time was given for Committee members to offer comments and for prospective researchers to prepare their proposals.

5. The merit review board should be comprised of experts familiar with GWI research including experts outside VA, and the decision regarding what projects to fund should rest with a similar body, working from a comprehensive plan, rather than left to the unilateral discretion of ORD staff.

6. VA is repeating the mistakes of earlier GWI research efforts by issuing RFA's without first creating a comprehensive research plan and management structure utilizing outside experts.

7. The background section of the RFA's was not acceptable because it suggested that GWI is not a major problem and unduly emphasized concomitant psychiatric conditions. Thus this section would discourage the right prospective researchers from committing themselves to work in this area. (partially addressed in final RFA)

a. The text stated that chronic multisymptom illness in GW veterans merely "exceeded" that in the non-deployed. It should state that the excess rate is 25% (according to VA's recently published study of the "Health of US Veterans of 1991 Gulf War" by Han Kang, et al) to more clearly convey the size of this problem. (addressed)

b. The cited figure of 3,400 veterans found by VA to have a service-connected disability is incorrect. The actual figure as of Feb. 2008 according to the VBA GWVIS report is 208,000 (33% of 631,477). (addressed following Nov. 3 meeting)

c. The paragraph about "depressive and anxious reactions" should be deleted. While all chronic illnesses can of course lead to depression, including this paragraph as the only discussion of Gulf War veterans' health problems in a one-page "background," when in fact the rate of psychiatric problems is lower than in other wars and far lower

than the 40% number mentioned, gives the reader the impression that the main problem in Gulf War veterans is psychiatric. (partially addressed)

C. Specific Recommendations Regarding the Clinical Science RFA

1. Committee members questioned whether the annual funding cap of $250,000 is too low for some complex and costly imaging studies and that only studies with smaller numbers of subjects would be possible within this budgetary constraint. (addressed)

2. As many Gulf War veterans have stopped receiving medical care at their local VA, a question arose whether enough Gulf War veterans could be recruited to participate in all of these planned studies. Will the VA provide funded investigators with Gulf War registry participants contact information to recruit for these studies, if requested? (addressed at meeting)

3. Committee members also urged that Gulf War brain bank resources be shared with potential investigators in order to get the most talented VA investigators working collaboratively to identify any subtle neuropathology that may underlie Gulf War illness.

4. The RFA should seek proposals from additional areas that can contribute to improved diagnostic testing for GWI and/or improved understanding of its pathobiology. Particular areas of interest include research on objective indicators of biological processes or abnormalities in GWI associated with:
• Central nervous system structure and function
• Central neuroinflammatory processes
• Neuroendocrine measures
• Autonomic nervous system function
• Immune parameters
• Indicators of chronic infection
• Overlaps between systems
• Genetic, genomic, proteomic, or metabolomic characteristics
(partially addressed)

D. Specific Recommendations regarding Biological Laboratory RFA

1. Sensitive neurohistological approaches should be used to assess potential underlying neuropathology associated with combined chronic exposures to PB/DEET/pesticides and low-level sarin or its surrogates, and the results of the neuropathology studies should be used to inform target regions affected by the combined exposures (as previously recommended for the preclinical component of the UTSW program).

2. The emphasis on proinflammatory processes in the CNS is very encouraging but needs more focus and specifics. It should include suggested dosing models and time points for post exposure.

3. Altered signal transduction processes should be brought back into this RFA as it has contemporary relevance to protracted neurological disease states.

4. Regarding markers of past exposure, it would be helpful for researchers if preliminary animal and/or veteran data are presented to aid in their understanding and focus of what they should look for and where they should start their investigations.

5. The RFA should seek proposals from a variety of areas that can contribute to improved diagnostic testing for GWI and/or improved understanding of its pathobiology. Particular areas of interest include research on objective indicators of biological processes or abnormalities in GWI associated with:
• Central nervous system structure and function
• Central neuroinflammatory processes
• Neuroendocrine measures
• Autonomic nervous system function
• Immune parameters
• Indicators of chronic infection
• Overlaps between systems
• Genetic, genomic, proteomic, or metabolomic characteristics
(partially addressed)

E. The Committee makes the following comments and recommendations regarding the Clinical Science RFA for New Treatments issued earlier in 2009.

1. The RFA should challenge researchers to design proposals that will further the goal of improving the health and lives of veterans who have Gulf War Illness.

2. The focus on potential new treatments was an important step toward developing treatment options for ill Gulf War veterans. However, Committee members felt that the requirement to include chronic fatigue syndrome (CFS) and fibromyalgia (FM) patients in the treatment groups was not acceptable because it would likely make the studies more difficult and costly to do. Members also failed to see how this would contribute scientifically to the study of treatments for Gulf War illness. Including these additional treatment groups will likely result in fewer Gulf War veterans being included in these studies. (addressed)

3. It is unclear why alternate designs are not permissible, for example, allowing ill Gulf War veterans to serve as their own controls in cross-over trial designs. This method often provides stronger statistical power in that fewer study participants are needed and cases can serve as their own controls in the placebo arm of the treatment. This method also provides for significant cost savings over other treatment trial designs. (addressed)

4. The focus relating GWI to fibromyalgia and chronic fatigue syndrome implies that these illnesses are virtually interchangeable. Committee members agree that there are

overlaps between these conditions, and there are GW veterans with diagnoses of CFS and FM. However, this is a small group compared with the larger number of veterans with the chronic multisymptom illness commonly known as Gulf War illness. The Committee stated this conclusion in its 2008 report, and provided detailed information regarding identified similarities and differences between GWI, CFS, and FM. Although some therapies for FM and CFS may be useful for treating GWI, there could also be therapies that show efficacy for GWI that are not useful for CFS and FM, or have not been studied in these conditions. Exclusive focus on these two disorders may be detrimental to identifying beneficial treatments for GW illness and puts an unnecessary constraint on researchers. (addressed)

5. The RFA should elaborate to state that health outcomes of interest include effects of treatments on:
• Global health measures, functional status
• Symptom complexes (e.g. cognitive function, musculoskeletal/pain symptoms, gastrointestinal symptoms, fatigue, respiratory problems, skin abnormalities) individually and as they may interact with each other
• Measurable clinical outcomes, biomarkers
• GWI subgroups characterized by symptom or other clinical characteristics

6. This RFA provided no direction on other essential study parameters. There was no requirement, for example, related to defining Gulf War illness cases for these studies and no guidance on how this can or should be done. Would any sick Gulf War veteran be eligible to participate in these treatment trials regardless of the kind of illness or his/her symptoms?

7. There was no mention of how treatment efficacy would be measured in this RFA. How does the VA anticipate that treatment outcomes should be measured in these treatment trials?

8. VA-funded research on Gulf War illness should be complementary to research funded by DOD's CDMRP, and not duplicative. For example, DOD currently has two funding mechanisms to study treatments for GWI this year and the timeline of this new VA RFA is very similar to the DOD timeline. Therefore it will be very difficult for reviewers to know what is duplicative across agencies.

9. VA treatment research for Gulf War illness should be a multifaceted, coordinated effort that includes establishing "best practice" standards for treating Gulf War illness. This could best be accomplished by establishing a Center of Excellence specifically for GWI treatment that would include both a clinical and research component. This would be a similar model to the one discussed by the RAC and VA several years ago called the Gulf War Treatment Research Center (GWTRC) model and described in the 2004 Committee report at pp. 37-38.

This Center of Excellence could be funded to provide "expert" guidance to clinicians and researchers for treatment studies and outcomes research, serve as a clearinghouse for

all treatment-related information, and establish the "best practice" guidelines for treatment of ill Gulf War veterans.

This Center of Excellence could also identify potentially beneficial treatments through pilot studies in order to identify new treatments to disseminate VA-wide for larger cooperative treatment trials in promising areas. This more comprehensive approach to treatment research is paramount in importance given the large number of ill Gulf War veterans and the lack of information on beneficial treatments currently available to clinicians.