Research Advisory Committee on Gulf War Veterans' Illnesses
Findings and Recommendations
Regarding the University of Texas Southwestern Gulf War Illness Research Program

April 18, 2008

The Research Advisory Committee on Gulf War Veterans' Illnesses was charged by Congress to review all federally-funded Gulf War research programs that address the health of Gulf War veterans. The Gulf War Illness and Chemical Exposure Research Program at the University of Texas Southwestern (UTSW) is projected to receive a total of $75 million in federal funding over a five year period, the single largest allocation of federal Gulf War research funds ever committed. The Committee was briefed on general plans for the UTSW program in 2006 and on additional program details at a public meeting in Dallas in July, 2007. Chairman Binns subsequently asked several members of the Committee with expertise in different aspects of the program to undertake further fact-finding to gain a more detailed understanding of the planned UTSW research and identify specific issues for review by the full Committee. The Committee held extended discussions of the UTSW program during its public meeting on April 8, 2008, and adopted the following findings and recommendations.

A. General Findings and Recommendations

The University of Texas Southwestern (UTSW) Gulf War Illness and Chemical Exposure Research Program is the prime contractor for the major Department of Veterans Affairs Gulf War illnesses research program. The legislative history related to the funding of the program indicates that Congress directed the program to implement the recommendations of the Research Advisory Committee on Gulf War Veterans' Illnesses, particularly the recommendation in its 2004 Report to create a comprehensive research plan and program. The recommendation included detailed guidance including: adopting a strategic research program that identifies and addresses key research questions regarding the nature, causes, and treatments for Gulf War veterans' illnesses; working with leading inside and outside scientists to develop comprehensive research protocols most capable of addressing priority Gulf War illnesses (GWI) research questions; and establishing an effective management strategy to ensure that studies capable of addressing priority research questions are satisfactorily developed and completed.

The Committee is encouraged to see VA-funded Gulf War illnesses research under the direction of scientists committed to solving the problem. The UTSW GWI Research Program is focused on issues long-identified by the Committee as having high priority. It represents a multifaceted effort designed to identify objective markers of GWI and better understand effects of toxic exposures encountered during the Gulf War. UTSW has developed an overall research plan with specific research objectives and over forty individual research studies. An umbrella research contract and individual task orders for many of these research projects have been signed, and some are underway. The plan is based largely on previous UTSW research concepts.

The Committee appreciates the interest and cooperation UTSW has shown the Committee in conducting this review and is pleased to offer the following recommendations to further the mutual goal that the program succeed in improving the health of Gulf War veterans.

1. The Committee recommends that UTSW expand its overall research plan to draw on the full range of scientific knowledge relevant to GWI, utilizing a formal group of outside experts (the "expert panel"), including some Committee members, who are knowledgeable in GWI

research. This panel should identify key research issues and provide guidance on the types and characteristics of studies to be included in the plan, as envisioned in the 2004 Committee Report.

2. The Committee recommends that UTSW also utilize the expert panel as liason to the UTSW merit review group to advise on the degree to which proposed studies address key issues relevant to the health of Gulf War veterans.

3. The Committee welcomes UTSW's practice of seeking input from knowledgeable outside scientists regarding individual studies. The Committee recommends that UTSW continue to contract out studies or functions that outside research teams are best able to provide.

4. The Committee notes with approval that UTSW envisions adding other research components to its program in the future, which include components to support clinical translation of its research results and the conduct of a genome study. The Committee recommends that UTSW formalize a clinical translation component at this time. The lead principal investigator of this component should ensure that potential applications of UTSW research to treatments and diagnostic tests are considered at every stage of the program.

5. The Committee recommends that UTSW also substantially expand the planned genetics/genomics component of the program and implement it now (as described below). In addition, the UTSW program should formally address other physiologic and pathophysiological processes potentially associated with Gulf War illness, including associations between Gulf War illness and central neuroinflammatory processes, immunological measures, and overlaps between systems (e.g., neuroimmune/autonomic processes potentially affected by toxic exposures).

6. The Committee recommends that UTSW incorporate the overall research plan, and the structures and studies developed to execute the plan, into a program document comparable to the format utilized for a major National Institutes of Health research center. This program document would 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. It would also describe the program's management structure, including provisions to ensure the program is managed as a coherent whole.

7. The Committee applauds UTSW's commitment to managing the program on an industrial model, reviewing all components at the end of pilot and successive phases in light of new developments, and eliminating, modifying, or adding studies as indicated. The Committee also notes with approval that UTSW has charged all lead principal investigators on the program management team with the ongoing responsibility of reviewing existing and emerging external research relevant to their areas of study, particularly research that may contribute to identifying diagnostic tests and treatments. The Committee recommends that formal procedures to carry out these commitments be detailed in the program document.

8. The Committee notes that, at the onset of the program, UTSW and VA discussed a clinical/research collaboration, and that UTSW developed plans for a Gulf War Illness Treatment Clinic at the Dallas VA Medical Center committing the first $3 million of its research funding to an advanced neuroimaging center there. The Committee recommends that VA and UTSW undertake a clinical/research collaboration to develop a model for evaluating and treating ill Gulf War veterans within VA facilities, which might logically

include clinical research utilizing the 3T MRI system provided to the Dallas VA Medical Center with UTSW research program funding.

9. The Committee notes that VA has no mechanism for providing funding to non-VA organizations as grants and that UTSW and VA have had to develop contract formats for this complex program from scratch. The Committee appreciates both parties' efforts to arrive at constructive solutions and recommends that VA Central Office provide guidance to the Dallas VA Contracting Office and its VISN leadership to support the UTSW program's ability to operate with the flexibility and speed necessary to make the program successful.

10. The Committee recognizes that the hopes of 175,000 Gulf War veterans who suffer from chronic multisymptom illness rest on this program. It is not an ordinary research project where an investigator is funded to pursue a particular thesis, while other investigators are also funded to pursue alternative theses. The Committee recognizes the considerable effort that has been invested to date by UTSW and VA, and that some of these recommendations envision reconsideration of decisions already made. The Committee encourages UTSW and VA to identify constructive solutions for implementing these recommendations in order to optimize this vital program for success.

B. Gulf War Illness Case Definition

The method or methods by which Gulf War illness cases are identified is a crucial consideration in all phases of the UTSW program. The UTSW program currently focuses on cases identified using criteria for the three "Haley syndromes," previously defined at UTSW using a unique factor analysis strategy. For the current study, UTSW plans to also develop a "new" case definition by using the same factor analysis technique, applied to data collected for the UTSW national survey. The program will also classify GWI cases using approximations of definitions previously developed by other research teams, including the CDC/Fukuda "chronic multisymptom illness" definition and the Kansas GWI case definition. UTSW intends to optimize the way that GWI cases are defined, assessing the relative utility of the differently identified case definitions by comparing their associations with risk factors and clinical measures assessed in the survey, serum studies, and clinical studies. The Committee recommends:

1. That UTSW plans for developing a "new" Gulf War illness case definition utilizing symptom data collected in the national survey be modified as follows. The revised approach should use a rational method, other than factor analysis, to identify a case definition based on the pattern of symptoms that best characterizes the chronic ill health of Gulf War veterans since the Gulf War. At minimum, this approach should identify the pattern of symptom expression that most clearly distinguishes the chronic symptoms affecting Gulf War veterans from ambient symptoms affecting individuals who did not serve in the Gulf War. The case definition should also be "portable", that is, straightforward enough so as to be usable in other research and clinical settings. Additional efforts to identify clinically meaningful illness subgroups would also be highly valuable.

2. That UTSW administer symptom questionnaires to clinical study participants to clearly identify those who, at the time of intake, meet defining criteria for the newly-identified GWI case definition, the CDC CMI case definition, and the Kansas GWI case definition. This will allow all clinical measures to be evaluated in relation to differently defined illness outcomes,

allow comparisons between those case definitions and the Haley syndromes, and allow findings from the UTSW program to be compared to those from previous clinical studies.

C. Sampling Strategy

The serum/DNA collection and clinical evaluation phases of the UTSW program are of primary importance for addressing priority questions related to Gulf War illness. The current plan calls for serum, blood, and DNA to be collected from all survey participants who meet Haley and Kansas GWI case definitions, identified special populations, and subgroups of nonsyndromic survey participants, totaling about 2,000 samples. The sampling plan for the clinical study calls for the clinical tests (neuroimaging, neuropsychological, and biomarker studies) to initially be piloted in targeted samples that include Navy Seabees previously evaluated at UTSW and twin pairs who differ by deployment and/or health characteristics. The main population-based sample to be evaluated clinically at UTSW, under the current plan, will include a total of 80 subjects (20 veterans with each of the three Haley syndromes and 20 controls).

Identified sample sizes for both the serum collection and clinical phases of the UTSW program were based on calculations that determined that these samples would provide adequate power for testing several prominent hypotheses in cases identified using the Haley syndrome definitions. But the program will assess a broad range of health outcomes in cases and controls identified by different definitions, as well as in multiple exposure and genetic subgroups. Effect sizes for many of the outcomes of interest are unknown, limiting the utility of *a priori* sample size estimates. A substantially larger clinical sample is desirable to maximize prospects for successfully identifying significant distinctions between the subgroups of interest. Given the number of hypotheses to be tested, the larger sample sizes will also provide greater confidence and scientific credibility for any findings that emerge. The Committee recommends:

1. That UTSW collect serum and DNA samples from all consenting survey participants (approximately 10,000 veterans), to permit a broader range of comparisons between sick and healthy veterans, as well as different exposure subgroups.

2. That UTSW substantially expand the number of subjects to be evaluated clinically. Calculated estimates of the precise sample size needed to address study questions of interest require data from the survey, the genetics/genomics study, and the pilot phase of the clinical study. The clinical sample should be sufficiently large, however, to accommodate clinical comparisons between veterans who are GWI cases/noncases (using more than one definition), exposed/not exposed veterans (for various exposures), and veterans with/without genetic or genomic distinctions. Back-of-the envelope estimates, based on effect sizes expected for neuroimaging and neurocognitive studies, suggest that a clinical sample in the neighborhood of 400 subjects would be required.

D. Serum/DNA Bank

The serum/DNA collection represents an extremely valuable resource, and should be used for a broader assessment of genomic and genetic differences between sick and healthy veterans. This technology has great potential for providing information leading to diagnostic tests and treatments. The Committee recommends:

1. That UTSW add a large scale, unbiased genetic/genomics study as a major program arm now, utilizing the expanded number of serum samples recommended above.

2. That identified experts, with appropriate expertise in the design and execution of genomic and genetic studies, be contracted to develop the plan for experimental design, data collection, statistical data analysis, and the details required to structure the experiments and sampling to achieve the appropriate deliverables.

3. That RNA be collected from a substantial fraction of survey participants using appropriate specialized techniques, as determined by the plan described above.

4. That the study be pursued expeditiously so that results are available to inform the selection of the optimal neuroimaging evaluations to be included in the full clinical study and the selection of veteran subgroups to be included in the clinical sample, particularly in the event that the twins pilot study does not provide information adequate for optimally narrowing the neuroimaging battery.

5. That costs of this study be paid for through savings achieved through elimination of other studies in the program, as recommended below.

E. Neuroimaging and Neuropsychological Projects

The UTSW program includes a broad range of innovative and sophisticated neuroimaging projects. Since these projects consume a substantial amount of program funding, the Committee is pleased to note that the UTSW plan incorporates a series of pilot studies to determine which studies are most likely to yield results that can contribute to understanding, diagnosing, and treating Gulf War illness. To further refine this arm, the Committee recommends:

1. That UTSW prioritize the neuroimaging studies from the onset, and consider eliminating those with lowest priority.

2. That UTSW further refine its planned protocols based on results from pilot studies conducted in a subgroup of Seabees evaluated in previous UTSW research, and an appropriately sized twin sample. Use of twin pairs, preferably monozygotic twins discordant for case status and/or exposure history, will minimize effects of inter-individual variability in brain anatomy and mental processing, of particular concern in relation to approaches such as MRS, which provide relatively poor spatial resolution.

3. That the optimal battery of neuroimaging and neuropsychological tests to be utilized in the full population-based sample be determined based on findings from the pilot studies, utilizing data from the national survey and genomics study. The optimal battery should be limited to those tests that most clearly identify significant differences between GWI cases/noncases as determined by the several case definitions assessed, differences between the exposed/unexposed subgroups assessed, and differences between veteran subgroups with/without genetic or genomic distinctions. In addition, the final protocol for the imaging and neuropsychological studies should include those outcomes that are most reproducible and feasible.

F. Other Clinical Evaluations

The clinical phase of the UTSW program includes a variety of clinical measures, in addition to neuroimaging and neuropsychological testing. The UTSW plan includes numerous clinical testing protocols to evaluate previously-identified indicators of objective differences between GWI cases and controls, including PON1 and BChE tests, tests of autonomic function, and assessment of hypothalamic-pituitary-adrenal axis parameters. Because of the extensive nature of the data to be collected on this group, it is particularly important that all previously-identified objective findings in Gulf War veterans be assessed in the clinical study and, when possible, further characterized, and that priority objective findings associated with other multisymptom conditions also be assessed in the clinical study. The Committee applauds UTSW's continuing efforts to solicit suggestions for other useful tests. The Committee recommends:

1. That UTSW evaluate all previously-identified indicators of objective differences between Gulf War illness cases and controls. This evaluation should include consultation with investigators who identified these differences and other experts to determine optimal testing procedures to ensure that previously-identified findings are adequately retested and/or further characterized. In particular, tests should be added to assess the association of GWI with mycoplasma and leishmania infections, squalene antibodies, immune parameters, and coagulopathies.

2. That UTSW consult with researchers with expertise in other multisymptom conditions to identify clinical tests most likely to be informative in Gulf War illness. This might include, for example, evaluation of fibromyalgia tender points, indicators of central pain sensitivity, levels of neuropeptides and metabolites, measures of herpes virus and enteropathogen infections, and sleep studies.

3. That UTSW contract out specific clinical tests to laboratories most experienced in testing for the abnormalities targeted for evaluation.

G. Preclinical (Animal) Studies

The UTSW program includes diverse animal studies, conducted to shed light on pathophysiological processes resulting from Gulf War exposures. The program has adopted a uniform dosing protocol for chlorpyrifos pesticide, sarin nerve agent, and pyridostigmine, which will allow comparison of effects among studies. In order to maximize the utility of these studies in understanding Gulf War illness, it is important that outcomes assessed reflect problems seen in Gulf War veterans that can not be directly evaluated in humans and that exposure protocols optimally reflect Gulf War exposures. The Committee recommends:

1. That UTSW add a comprehensive neuropathological evaluation of exposed animals to the preclinical arm. This evaluation should include sensitive, state-of-the-art measures to evaluate neural degeneration, astrogliosis, and microglial activation to determine if the exposure models are associated with underlying neural damage that is not obvious by traditional histopathology. These studies should be conducted by an experienced outside contractor.

2. That UTSW eliminate the mouse neuroimaging studies. These studies could later be reconsidered if results from the human neuroimaging studies or animal neuropathology

studies suggest priority research questions that are best addressed by mouse imaging studies, despite spatial resolution and other limitations associated with these methods.

3. That UTSW establish criteria for assessing a "positive" outcome from the findings obtained in the first year's animal studies that is unified across all projects.

4. That the neurotoxin dosing protocol be expanded to include individual and combined effects of DEET and permethrin, and that delayed and persistent effects of exposures be assessed six months and 12 months after exposures.

5. That studies in the preclinical arm of the UTSW program be limited to those that specifically explore effects of Gulf War exposures in relation to abnormalities associated with Gulf War illness or other conditions that disproportionately affect Gulf War veterans, reflecting previous research in the field. This would require that some currently proposed studies, although of sound scientific design, be eliminated or substantially revised to reflect previous research findings. This includes studies focused on aging, Huntington's disease, developmental neurotoxicity, fear conditioning and PTSD, and vaccine effects previously shown not to be a concern.