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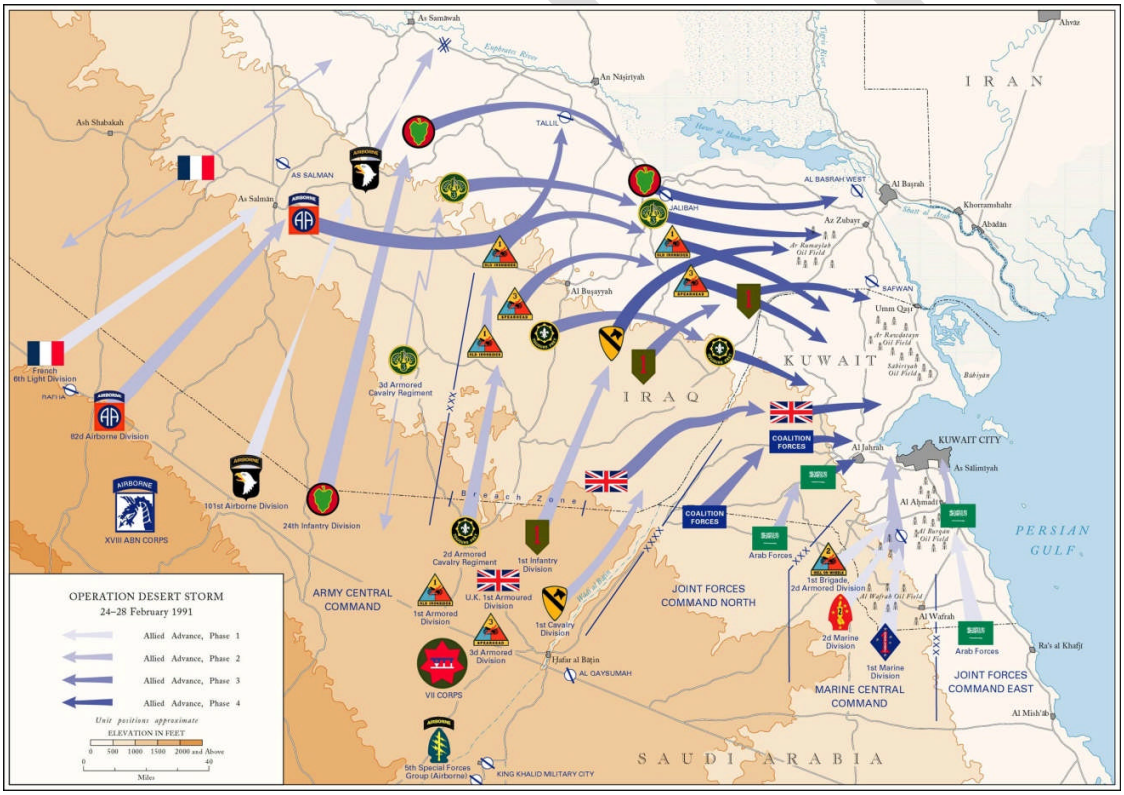
GULF WAR RESEARCH STRATEGIC PLAN

2012-2016



Highlighted text in this pre-decisional draft refers to areas of responsibility outside ORD. These are draft thoughts about goals requiring further discussion.

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1.0 EXECUTIVE SUMMARY

After Iraq's occupation of Kuwait in August 1990, the United States deployed military personnel to Southwest Asia in support of Operations Desert Shield and Desert Storm. At the conclusion of the first year of operations on July 31, 1991, the United States had deployed 696,841 military personnel from all five services and National Guard to the Kuwaiti Theater of Operations (KTO).

During and after their return from the KTO, a significant proportion of Gulf War Veterans reported a range of chronic symptoms and health problems at rates that exceeded the rates for non-deployed era Veterans. These symptoms included: persistent headaches, joint and muscle pain, fatigue and sleep disturbances, attention and memory (cognitive) problems, gastrointestinal symptoms, and skin abnormalities. While some of the ill Veterans meet case definition(s) for other chronic multisymptom illnesses such as chronic fatigue syndrome or fibromyalgia, the majority have defied exact diagnosis.

Recent studies by the Department of Veterans Affairs (VA) and others indicate that as many as 250,000 Gulf War veterans are affected. VA, the Department of Defense (DoD), and the Department of Health and Human Services (HHS) have funded 370 research projects related to the consequence of military service in the Gulf War. These studies have yielded substantial insight into the health problems of Gulf War Veterans, including physiological differences between Veterans with multisymptom illness and Veterans of the same era who were not deployed. However, neither diagnostic biomarkers nor effective treatments have been identified to date. The VA and CDMRP Gulf War Illness Research programs continue to solicit proposals aimed at identifying new treatments for ill Gulf War Veterans.

In 2010, an Institute of Medicine (IOM) report, *Gulf War and Health, Vol. 8*, reviewed the literature and accepted that this multisymptom illness is a diagnostic entity, which it found to be associated with Gulf War service [41]. It further found that the symptoms "cannot be ascribed to any known psychological disorder." Rather, "it is likely that Gulf War illness results from an interplay of genetic and environmental factors."

The IOM report concluded with a call for "a renewed research effort with substantial commitment to well-organized efforts to better identify and treat multisymptom illness in Gulf War veterans . . . to alleviate their suffering as rapidly and completely as possible." [41]

In the preface to the report, the chairman of the IOM committee, Dr. Stephen Hauser, a former president of the American Neurological Association, emphasized the need "to speed the development of effective treatments, cures, and, it is hoped, preventions." He stressed that the committee regarded this goal as achievable: "We believe that, through a concerted national effort and rigorous scientific input, answers can likely be found." [41]

The *Gulf War Research Strategic Plan 2012-2016* is VA's response to this challenge. **Its overall goals are 1) to improve the health and well-being of Gulf War veterans, and 2) to utilize emerging knowledge to prevent similar war-related illnesses in the future.** As recommended by the IOM, the Plan has two branches: 1) to monitor the health of Gulf War veterans and 2) to identify diagnostic biomarkers and treatments for Gulf War Veterans' illnesses.

Recognizing the need, articulated by the IOM, to accomplish this mission *rapidly*, the Plan establishes a program to identify biomarkers and treatments within the time frame of the Plan -- five years. VA's ability to turn RFA's quickly and to establish other research projects through executive action gives it the

flexibility to move at this accelerated pace. In view of the magnitude of the need and the opportunity for success, VA is committed to this timetable.

The Plan has six major sections:

1. Executive Summary
2. Introduction and Background
3. Evolution of the Gulf War Strategic Plan
4. Summary of Federal Funding of Gulf War Research 1994-2010
5. Gulf War Research Strategic Objectives 2012-2016
6. Conclusions

The eight strategic goals that the *Gulf War Research Strategic Plan 2012-2016* advances are presented in detail in Section 5 of the Plan:

5.1. Symptomatic and Specific Treatments

5.2. Databases and Continued Surveillance

5.3. Research to establish new Gulf War Case Definitions

5.4. Genetics/Genomics/Systems Biology

5.5. Biomarkers

5.6. Animal Models

5.7. Coordination and Communication with Federal Partners, Researchers, and the Private Sector

5.8. Translation of Research into Practice

Since the overall goals of the Strategic Plan are improved health and prevention, the first specific goal presented focuses on symptomatic and specific treatments. The Strategic Plan then presents scientific approaches that will yield improvements in treatment, health and prevention. These sections are followed by approaches to enhance coordination and communication between partners and researchers. The Strategic Plan then ends with approaches to translate research into practice to yield improved treatments, health and prevention.

Although progress has been made in Gulf War Research, much work remains to be done. This *Gulf War Research Strategic Plan 2012-2016* has been formulated to accelerate this progress. The Plan will be reviewed annually by the Gulf War Steering Committee and the Research Advisory Committee on Gulf War Veterans Illnesses, and updated as needed.

2.0 INTRODUCTION AND BACKGROUND

2.1 The 1990-1991 Gulf War and the Nation's Response to the Need for Research

After Iraq's occupation of Kuwait in August 1990, the United States deployed military personnel to Southwest Asia in support of Operations Desert Shield and Desert Storm. At the conclusion of the first year of operations on July 31, 1991, the United States had deployed 696,841 military personnel from all five services and National Guard to the Kuwaiti Theater of Operations (KTO).

During and after their return from the KTO, a significant proportion of Gulf War Veterans reported a range of chronic symptoms and health problems at rates that exceeded the rates for non-deployed era Veterans. These symptoms included: persistent headaches, joint and muscle pain, fatigue and sleep disturbances, attention and memory (cognitive) problems, gastrointestinal symptoms , and skin abnormalities. While some of the ill Veterans meet case definition(s) for other chronic multisymptom illnesses such as chronic fatigue syndrome or fibromyalgia, the majority have defied exact diagnosis.

On August 31, 1993, pursuant to Public Law 102-585, President Clinton named the Secretary of Veterans Affairs to coordinate research on the health consequences of service in the Gulf War. VA initially carried out its coordinating role through the auspices of the Persian Gulf Interagency Research Coordinating Council (PGIRCC). On January 21, 1994, the Secretaries of Defense, Health and Human Services, and VA announced the establishment of the Persian Gulf Veterans Coordinating Board (PGVCB) to coordinate efforts to resolve the health concerns of Gulf War Veterans. PGVCB developed three mission objectives, and assigned each to a separate working group: the Clinical Working Group, the Research Working Group, and the Disability and Benefits Working Group. The Research Working Group (RWG) subsumed PGIRCC responsibilities.

In 1995, the PGVCB developed a contextual framework for evaluating research related to military service in the 1990-1991 Gulf War. To that end, the PGVCB identified 19 major epidemiological research questions and subsequently added two additional questions in 1996. This framework was published as the "Working Plan for Research on Persian Gulf War Veterans' Illnesses" and has served as the guiding principles for Gulf War Research up to the present day. To date, VA, the Department of Defense (DoD), and the Department of Health and Human Services (HHS) have funded 370 research projects pertaining to the health consequences of military service in the 1990-1991 Gulf War, as reported annually to Congress.

These studies have yielded substantial insight into the health problems of Gulf War veterans, including physiological differences between veterans with multisymptom illness and veterans of the same era who were not deployed. However, neither diagnostic biomarkers nor effective treatments have been identified. Studies by the Department of Veterans Affairs (VA) and others indicate that as many as 250,000 Gulf War veterans are affected.

In 2010, an Institute of Medicine (IOM) report, Gulf War and Health, Vol. 8, reviewed this literature and accepted that this multisymptom illness is a diagnostic entity, which it found to be associated with Gulf War service[41]. It further found that the symptoms "cannot be ascribed to any known psychological disorder." Rather, "it is likely that Gulf War illness results from an interplay of genetic and environmental factors."

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In the preface to the report, the chairman of the IOM committee, Dr. Stephen Hauser, a former president of the American Neurological Association, emphasized the need "to speed the development of effective treatments, cures, and, it is hoped, preventions." He stressed that the committee regarded this goal as achievable: "We believe that, through a concerted national effort and rigorous scientific input, answers can likely be found." [41]

2.2 Gulf War Research Strategic Plan 2012-2016

The *Gulf War Research Strategic Plan 2012-2016* is the most recent and substantial revision of the original "Working Plan" put forth in 1995-96. It is VA's response to the need and opportunity identified by the 2010 IOM report.

The *Gulf War Research Strategic Plan 2012-2016* will be reviewed annually by the Gulf War Steering Committee and the Research Advisory Committee on Gulf War Veterans' Illnesses to determine if modifications are needed.

2.3 VA Research and Development Strategic Plan: 2009-2014

The *Gulf War Research Strategic Plan 2012-2016* complements the existing *VA Research and Development Strategic Plan: 2009-2014*, which is the strategic plan for all research in the VA Office of Research and Development (ORD) [57]. This larger strategic plan also articulates the need for continuing targeted Gulf War Research. For example, the "Deployment-related exposure to hazardous environmental agents" is listed as one of the 10 priority areas for VA's ORD. In addition, the *VA Research and Development Strategic Plan: 2009-2014* notes and cites several examples of the need for Gulf War-related research, such as:

- Research in Amyotrophic lateral sclerosis (ALS) related to environmental exposure (Objective 1.3,
- Identification of biomarkers for different stages of illness and recovery (Objective 1.9),
- Illnesses related to service in the 1990-1991 Gulf War (Objective 2.20), and
- A communication portal to improve communication among VA researchers (Objective 4.8).

The *VA Research and Development Strategic Plan: 2009-2014* sets four over-arching goals that apply to all VA Research, including Gulf War Research. These are:

- Advance knowledge toward improving each Veteran's health and well-being, relying on a spectrum of research including basic, translational, clinical, health services, and rehabilitative science.
- Apply advances in scientific knowledge to create, test, compare, and implement new treatments, technologies, education modules, and models of care so that Veterans receive the most effective individualized care solutions.
- Attract, train, and retain the highest-caliber investigators and staff, and nurture their continuous development as leaders in their fields.

- Assure a state-of-the-art research enterprise with a culture of professionalism, collaboration, accountability and the highest regard for research volunteers' safety and privacy.

3.0 EVOLUTION OF THE GULF WAR RESEARCH STRATEGIC PLAN

During deployment to the Gulf, and as Service members began returning from the Gulf, it became apparent that some Service members and Veterans were showing symptoms that were difficult to explain using current diagnostic criteria for illnesses. In January 1994, the Secretaries of DoD, HHS and VA announced the establishment of the Persian Gulf Veterans Coordinating Board (PGVCB) to coordinate efforts to resolve the health concerns of Gulf War Veterans.

A critical unresolved issue was whether deployed Service members were experiencing these symptoms at a higher rate than comparable non-Gulf War Service members and Veterans. In addition, many Service members and Veterans were questioning whether the illnesses that are common and diagnosable were etiologically linked to their service in the Gulf War. It became apparent to both DoD and VA that scientific and medical research would be required to address this complex issue. The question then had to be answered: "What research needs to be undertaken?" (1995-6). The PGVCB established three primary mission objectives to achieve through interagency coordination:

- Ensure all Veterans receive the complete range of healthcare services necessary to evaluate and treat Gulf War-related health problems;
- Develop a research program that produces a complete and accurate understanding of Gulf War-related health problems; and
- Develop clear, consistent guidelines for evaluating disabilities related to Persian Gulf service.

Three broad research goals were presented in the original 1995-6 Working Plan:

- Establish the nature and prevalence of symptoms, diagnosable illnesses, and unexplained conditions among Persian Gulf Veterans in comparison to appropriate control groups;
- Identify the possible risk factors for any illnesses, beyond those expected to occur, among Persian Gulf Veterans;
- Identify appropriate diagnostic tools, treatment methods, and prevention strategies for any excess illness conditions found among Persian Gulf Veterans.

The plan also identified a number of areas for which significant gaps in knowledge existed at that time:

- Information on the prevalence of symptoms, illnesses, and/or diseases within other coalition forces;
- Information on the prevalence of symptoms, illnesses, and/or diseases within indigenous populations within the Persian Gulf area including Saudi Arabia and Kuwait;
- Information on the prevalence of adverse reproductive outcomes among Persian Gulf Veterans and their spouses;
- Simple and sensitive tests for *Leishmania tropica* infection that could lead to quantification of the prevalence of *L. tropica* infection among Persian Gulf Veterans; and
- Information on the long-term, cause-specific mortality among Persian Gulf Veterans.

In the revised 1996 Working Plan, 21 epidemiological research questions were formulated. These research questions have served as the guiding principles for federally-funded Gulf War Research up to

the present day. The strategic elements described below in Section 5.0 have been formulated to accelerate progress in improving the health and well-being of Gulf War Veterans.

4.0 SUMMARY OF GULF WAR RESEARCH RESULTS AND PAST FEDERAL RESEARCH SUPPORT

The most recent evaluation of the results of Gulf War Research was published in the 2010 IOM report entitled *Gulf War and Health: Volume 8: Update of Health Effects of Serving in the Gulf War*. [41] The IOM is generally regarded as the "Gold Standard" with respect to evaluating the results of research programs that are published in the peer-reviewed literature, including publications resulting from federally-funded research programs across agencies. The VA first contracted with the IOM to review Gulf War research and produce such reports in 2000.

These IOM assessments are used by the VA and other federal agencies to help determine and reassess the extent to which the collective findings of completed Gulf War Illnesses research projects have in fact addressed key Gulf War Research questions, and whether research questions being investigated remain relevant. The IOM report of 2010 is an independent, thorough and comprehensive analysis of past Gulf War Research results across the VA and all federal agencies [41].

In addition, the most recent report of the Research Advisory Committee for Gulf War Veterans' Illnesses (RACGWVI), *Gulf War Illness and the Health of Gulf War Veterans* represents a second independent opinion on the results of Gulf War Research. This report was also comprehensive and provided additional specific research recommendations [64].

By carefully comparing the RACGWVI and IOM reports, as well as other information, the present *Gulf War Research Strategic Plan 2012-2016* identifies the areas of research that appear most likely to succeed in providing new information that will help Gulf War Veterans. Such a careful prioritization, based on the best knowledge available at this time, is essential when research funding has finite limits.

For the findings that have emerged from past research, readers are referred to these reports. The findings most relevant to future research are summarized in Section 5 below. Additional information is available in the Annual Reports to Congress on Federally Funded Research on Gulf War Veterans' Illnesses prepared by the interagency Deployment Health Working Group [14-21].

4.1 Summary of Federal Funding of Gulf War Research 1994-2010

Fiscal Year	VA*	UTSW Contract**	DoD*	HHS*	FY Total
1994	$ 1,157,879	$ 0	$ 6,492,882	$ 0	$ 7,650,761
1995	$ 2,334,083	$ 0	$ 10,973,000	$ 2,514,762	$ 15,821,845
1996	$ 3,853,095	$ 0	$ 11,905,214	$ 1,616,755	$ 17,375,064
1997	$ 2,834,790	$ 0	$ 28,880,536	$ 0	$ 31,715,326
1998	$ 4,722,820	$ 0	$ 13,213,232	$ 1,634,347	$ 19,570,399
1999	$ 9,006,155	$ 0	$ 22,674,338	$ 1,640,378	$ 33,320,871
2000	$ 12,020,519	$ 0	$ 23,847,679	$ 1,567,439	$ 37,435,637
2001	$ 8,576,675	$ 0	$ 31,587,006	$ 998,870	$ 41,162,551
2002	$ 4,512,676	$ 0	$ 18,827,819	$ 799,814	$ 24,140,309
2003	$ 5,746,467	$ 0	$ 16,419,497	$ 964,105	$ 23,130,069
2004	$ 7,644,560	$ 0	$ 11,096,063	$ 466,126	$ 19,206,749
2005	$ 9,484,679	$ 0	$ 10,091,848	$ 466,481	$ 20,043,008
2006	$ 13,013,552	$ 0	$ 10,128,261	$ 455,587	$ 23,597,400
2007	$ 7,059,061	$ 15,000,000	$ 3,417,570	$ 441,974	$ 25,918,605
2008	$ 6,934,214	$ 15,000,000	$ 11,672,967	$ 433,467	$ 34,040,648
2009	$ 9,628,318	$ 6,972,481	$ 10,380,423	$ 0	$ 26,981,222
2010§	$ 11,567,997	$ 2,288,755	$ 3,145,000	$ 0	$ 17,001,752
Total 1994-2010	$ 120,097,540	$ 39,261,236	$ 244,753,335	$ 14,000,105	$ 418,112,216

* Funds expended to support Gulf War research projects

** Funds obligated for reimbursement to UTSW at completion of contracted work on individual task orders

§ Current estimate of VA, DoD, and HHS funds allocated for GW research in FY2010. DoD estimate does not include CDMRP funds.

The VA estimate for FY2010 includes40% of MRI imaging equipment upgrade at San Francisco for Gulf War research.

This estimate does not include expenditures from the VA Medical Care appropriation of $3.7 million for the Veterans Equitable Resource Allocation (VERA) System to support funded Gulf War research projects. Historically, these costs have not been included in the FY expenditures reported above.

5.0 GULF WAR RESEARCH STRATEGIC OBJECTIVES 20112-2016

5.1 Symptomatic and Specific Treatments

5.1.1 Goal

Develop symptomatic and specific treatments for Gulf War Veterans' Illnesses. Even if the molecular mechanisms behind Gulf War Illnesses are not fully understood, it is possible to study and develop treatments that may improve a Veteran's medical condition. As the molecular mechanisms which may explain the causal relationship of toxic insults and observed symptoms are continuing to be discovered – using information revealed in genetic/genomic, biomarker and model organism research – systematic approaches to the development of specific or causative treatments for GWVI will be pursued. This will initially involve mechanistic proof-of-concept studies in both animals and humans and can be rapidly scaled up to larger programs using the cooperative studies clinical trials resources of the VA.

5.1.2 IOM Recommendations

The IOM noted that: "There is a dearth of organized clinical trials to examine potential treatments for the observed symptoms experienced by Gulf War Veterans. Aligned with the effort to improve care pathways for Gulf War illness sufferers, there should be a focused effort to consider the development of clinical trials informed by the best biological data related to the cause of Gulf War illness." [38]

Also in the IOM report briefing for the April 2010 report, it was recommended that there was a need to, "Expand the number of clinical trials to examine potential treatments for symptoms of Gulf War veterans and improve care pathways for Gulf War illness sufferers." [41]

5.1.3 RACGWVI Recommendations

"Gulf War illness is a serious condition that affects at least one fourth of the 697,000 U.S. Veterans who served in the 1990-1991 Gulf War. This complex of multiple concurrent symptoms typically includes persistent memory and concentration problems, chronic headaches, widespread pain, gastrointestinal problems, and other chronic abnormalities not explained by well-established diagnoses. No effective treatments have been identified for Gulf War illness and studies indicate that few Veterans have recovered over time." [64]

The 2008 RAC Report (Chapter 5, Research Priorities and Recommendations) states that "the highest priority should be given to research conducted to identify beneficial treatments for Gulf War Illness. The primary objective is the conduct of well-designed clinical trials of treatment that hold promise for providing substantial benefit for veterans with Gulf War illness or identifiable subgroups." [64]

Specific RAC recommendations stated that this research should include:

- "Studies that identify and systematically evaluate the effectiveness of currently available treatments used for Gulf War illness or conditions with similarities to Gulf War illness.

Preliminary research should include pilot studies and/or observational studies capable of identifying promising treatments suitable for evaluation in larger clinical trials.

- Research to identify specific pathophysiological mechanisms underlying Gulf War Illness that are potentially amenable to treatment interventions.
- Research to evaluate novel therapies based on scientific findings as they emerge. "

5.1.4 ORD Research

Examples of past ORD research in this area are given below.

As part of an ORD-funded Career Development Award, a pilot clinical trial was conducted to determine whether nasal continuous positive airway pressure (CPAP) alleviates the symptoms of veterans with Gulf War illnesses and sleep disordered breathing (SDB). Compared to the nine sham nasal CPAP recipients, the eight participants receiving therapeutic nasal CPAP experienced significant improvements in pain (34%), fatigue (38%), cognitive function (33%), sleep quality (41%), physical health (34%), and mental health (16%) [2].

In a study of potential new treatments for IBS, the expression of glutamine synthetase and its complementary miRNA in blood microvesicles and gut tissues of IBS patients were studied. Data from 19 diarrhea-predominant IBS subjects and 10 controls supported the conclusion that GLUL regulates intestinal membrane permeability and miR-29a regulates both GLUL and intestinal membrane permeability. Targeting this signaling pathway could lead to a new therapeutic approach to the treatment of patients with IBS, especially because small molecules that mimic or inhibit miRNA-based mechanisms are readily available [80].

A randomized controlled multi-site clinical trial was developed through the Cooperative Studies Program to compare the effectiveness of cognitive behavioral therapy (CBT), exercise, and the combination of both for improving physical functioning and reducing the symptoms of Gulf War Veterans Illnesses (GWVI). The results suggested that CBT and/or exercise can provide modest relief for some of the symptoms of chronic multisymptom illnesses such as GWVI [22].

The state of the cardiopulmonary system is important for planning treatments that involve exercise. A study of metabolic responses to maximal exercise in Gulf War Veterans with chronic fatigue syndrome (CFS) was compared with a control group who did not have CFS. Compared with healthy controls, Veterans who report multiple medically unexplained symptoms and meet criteria for CFS do not show a decreased exercise capacity. Thus, it does not appear that the pathology of the GWVs with CFS includes a deficiency with mobilizing the cardiopulmonary system for strenuous physical effort [55].

5.1.5 Research Plans and Funding Mechanisms

VA Researchers will investigate new treatments including, but not limited to:

1) Based on existing evidence, establish a GW Treatment Research Coordinating Center to identify potential pilot study hypotheses. For an explanation of highlighted sections, see page 2.

2) A clear goal to expand the number of treatment trials within the 5-year strategic planning period will be established. A goal of up to 20 treatment or pilot studies in the next five years will greatly increase the chance of obtaining at least one viable and effective treatment for GWI. The goal is dependent on successful identification of potential treatment targets and completion of preclinical development. A more focused and comprehensive commitment to the development of treatment trials for GWI will be made. This will be assisted by the development of an internet-based research portal and by the development of a GW Treatment Research Coordinating Center specifically designed to coordinate several pilot studies per year. A potential location is the Salt Lake City, Utah, VA, which is the site of ongoing activity in the field. Promising pilot studies will then be developed into either larger merit review grants or cooperative studies projects. For an explanation of highlighted sections, see page 2.

3) A more focused effort to identify mechanistic-based treatments for GWVI will be a priority of the VA Gulf War Research Strategic Plan. Examples of studies targeted to reported biomarkers of GWVI will include but not be limited to treatments to regulate neuroendocrine function, coagulation, immune and inflammatory alterations, and neuropsychological and neuroimaging differences reported in ill GW Veterans. Detailed studies of the gastrointestinal microbiome in Gulf War veterans and controls could be performed and may lead to probiotic or antibiotic treatments. Specific therapies from this research could include antioxidants, anticoagulants, immune modulators, IL1 antagonists, and other inflammatory modulators, neuroendocrine modulators, intranasal insulin and other cognitive enhancers.

4) In order to identify at-risk Veterans who could benefit from enhanced preventive medical care including obesity prevention, smoking cessation, and other programs, the VA will implement a mechanism to clearly denote participation in the Gulf War theater in the computerized patient record system. This should assist primary care and specialty providers in their attempts to provide optimal care. For an explanation of highlighted sections, see page 2.

5) More complementary and alternative or integrative medicine therapies could also be implemented and studied for GWV illnesses. Such treatments could include mindfulness based therapies as well as acupuncture, laser acupuncture, Tai-Chi, Qui gong, meditation, nutritional therapies, and probiotics.

6) Cognitive rehabilitation therapy should be studied for the management of cognitive difficulties associated with GWVI.

7) Explicit criteria (case definition) for Gulf War Illness will be adopted and used as uniformly as practical in clinical research on proposed therapies. The NIH PROMIS measures will be advocated for evaluating clinical effectiveness. The PROMIS measures are intended to provide uniform, psychometrically robust measures for use across different interventions and conditions, and as such are ideally suited for the type of symptoms reported by Gulf War Veterans. For an explanation of highlighted sections, see page 2.

VA has an established research infrastructure to support research projects of various sizes and complexity. Current pilot studies will be evaluated for expansion to larger trials. For the Gulf War Research Portfolio, ORD will attempt to:

8) Expand the number of "small projects" in the area of new treatments that could lead to larger studies (Individual Pilot Projects, single-site pilot clinical trials, GW Treatment Research Center).

9) Based on findings, consider replicating promising "small projects" with expanded studies at 2 or three sites (Cooperative Clinical Trial Awards).

10) Also based on findings, transition the most promising treatment studies to a national multi-site (10 or more sites) clinical trial through the Cooperative Studies Program.

The VA funding mechanisms for Symptomatic and Specific Treatments will be initially studied through RFAs and other federal agencies, followed by CSP development of multisite trials. For an explanation of highlighted sections, see page 2.

5.2 DATABASES AND CONTINUED SURVEILLANCE

5.2.1 Goal

To enhance ongoing surveillance efforts of Gulf War and Gulf War Era Veterans, to improve the usefulness of existing databases, and to develop new databases to address specific research questions. Although the 1990-1991 Gulf War was brief, a substantial proportion of Veterans who served in that conflict have reported difficult-to-diagnose health problems since their return from that theater. In addition to considering the chronic undiagnosed symptoms associated with Gulf War service, research studies have provided preliminary indications that a number of diagnosed medical conditions may affect 1991 Gulf War Veterans at excess rates. In the years since the Gulf War, federal committees and scientific advisory panels have regularly identified the importance of coordinating federal data-collection efforts and resources to provide a clearer picture of the health status of 1991 Gulf War Veterans. In particular, these panels have pointed to the importance of monitoring the health of Gulf War Veterans over time to identify the occurrence and prognoses of undiagnosed and diagnosed health conditions affecting this population.

Literature reviews conducted by the Institute of Medicine (IOM), however, continue to indicate there is insufficient information to determine whether or not Gulf War Veterans have been affected by diagnosed medical conditions at excess rates. In addition, studies in recent years have increasingly identified differences in the health and mortality experience of Gulf War personnel who served in different locations and/or had different experiences and exposures during deployment. Findings of this nature highlight the importance of assessing Gulf War data and monitoring health outcomes in identifiable Gulf War Veteran subgroups, including women who served in this deployment. Overall, important questions remain concerning the impact of the 1990-1991 Gulf War on the health and lives of the Veterans who served there.

Currently, multiple large population-based databases, an extensive number of administrative datasets, and a large number of smaller databases provide important information on the health of Gulf War Veterans. However, existing databases are usually stand-alone with limited ability to link to other databases and to other information on Gulf War Veterans. Establishing linkages across databases will facilitate improved understanding of the health status of Gulf War Veterans. This will require breaking down institutional barriers within VA and between VA, the Department of Defense, and academic research centers. Human subject protections will also need to be addressed since informed consent forms signed by Veterans for previous research projects likely did not address the potential to link their data to other data sources. In addition, a data warehouse is needed to serve as a repository for these data as well as an access point for researchers seeking to use data to address research questions on the health of Gulf War Veterans. This warehouse should include the protocols under which the data were collected and information on the structure and content of each database to facilitate usage of these data. For an explanation of highlighted sections, see page 2.

Although some existing databases are longitudinal in nature, most were not conceived to address surveillance of the health of Gulf War Veterans over time. Increased and improved surveillance efforts are essential to understanding the long-term health consequences of having served in the Gulf War.

Two previous studies collected data on treatments used for Gulf War Veterans with multi-symptom illness to determine which of these treatments may be effective. The continuing paucity of effective treatments for Veterans suffering from Gulf War illnesses needs to be addressed. Improved data

linkages and surveillance techniques—coupled with emerging data-discovery methods to identify patterns in unstructured data, such as the electronic medical record—will enhance the ability to identify potentially effective treatments, move them into controlled trials to validate their effectiveness, and institute treatment programs using those treatments found to be effective.

Some population-based research related to Gulf War Veterans has been limited by relatively low participation rates. In addition, studies of Gulf War Veterans who receive VA healthcare services do not take into account the health concerns of Veterans who do not seek VA healthcare services. Other data-collection approaches and database designs—such as disease case registries and a twin registry—may offer advantages over population-based studies in addressing other sections of this strategic plan.

In that regard, twin studies can enable investigators to answer questions about combat-related illnesses and injury, health outcomes, aging and other issues that are not easily answered with other designs. The classical twin method, which capitalizes on the fact that monozygotic (MZ) twins share 100 percent of their genes and dizygotic (DZ) twins share on average 50 percent of their genes, enables investigators to examine the genetic and shared environmental contributions to any characteristic or health condition, such as those related to Gulf War exposure.

Alternatively, the co-twin control design with MZ twins who are discordant for the characteristic of interest is ideal for assessing long-term effects of conditions such as Gulf War Veterans' illnesses that may be linked to environmental exposures. The co-twin control design can be especially powerful if the twin pairs are examined longitudinally to distinguish emerging health conditions related to Gulf War service from general health conditions that arise in a population as it ages.

In addition to the efforts already described, a repository of research results should be developed to keep stakeholders and researchers informed of emerging results. A group also should be formed to regularly review this repository to identify promising directions where additional research should be directed and treatments that indicate potential benefit.

Based on this background and review of previous recommendations and research, the following goals and objectives are put forward and discussed in detail in this section.

- Enhance ongoing surveillance efforts of Gulf War and Gulf War Era Veterans.
- Improve the usefulness of existing databases by linking them and then integrating them into a data warehouse and making them available for use by researchers.
- Develop new databases optimized to address specific research questions.

For an explanation of highlighted sections, see page 2.

These objectives are intended to support the other initiatives in the strategic plan, specifically: assessment of specific treatments; ongoing detection of increased incidence and prevalence of health conditions; and improved case definitions, genetics/genomics, and biomarkers.

5.2.2 IOM Recommendations

In its 2010 report, *Update of Health Effects of Serving in the Gulf War*, the Institute of Medicine (IOM) noted that the path forward for research should include continued health surveillance of Gulf War Veterans over time. The IOM panel recommended longitudinal evaluation of mortality, cancer, psychiatric outcomes and neurologic disorders in deployed and non-deployed Gulf War Era Veterans including, in particular, both amyotrophic lateral sclerosis and multiple sclerosis. Veterans should also be

followed over time to assess rates of diseases of aging, such as cardiovascular and neurodegenerative diseases [41].

5.2.3 RACGWVI Recommendations

In its 2004 report, the RAC concluded "the health of Gulf War Veterans must be carefully monitored to determine if Gulf War service is associated with excess rates of specific diseases, disease-specific deaths or overall mortality." The report provided specific recommendations concerning the use of existing databases and development of population-based research to determine disease rates in Gulf War Veterans overall and in relation to specific deployment exposures. [63, pp 72-76]

The 2004 report also reported that "progress in understanding Gulf War Veterans' illnesses has been hindered by lack of coordination and availability of data resources maintained by the Department of Defense and the Department of Veterans Affairs." To address this problem, the committee recommended that VA and DoD link Gulf War-associated databases, develop a comprehensive library for these data and make federal data resources available to researchers, while adopting appropriate safeguards for their use. [63, pp 84-86]

The RAC added to these recommendations in 2008, calling for epidemiologic research to determine whether Gulf War Veterans, or identifiable subgroups, have excess rates of specific neurological disorders. The report also called for enhanced efforts to determine rates of cancers, respiratory diseases and cause-specific mortality in Gulf War Veterans overall and in Veteran subgroups of interest. [64, pp 313-314]

The RAC later provided specific recommendations aimed at enhancing the capacity of VA Office of Public Health's Longitudinal Survey of Gulf War Era Veterans to provide surveillance of diagnosed and undiagnosed conditions affecting Gulf War Veterans. [65] http://www.va.gov/RAC-GWVI/docs/Committee_Documents/RACSurveyRecs_Final110210.pdf)] For an explanation of highlighted sections, see page 2.

5.2.4 Existing Databases

5.2.4.1 Existing large population-based datasets from federally sponsored research studies of 1991 Gulf War Era Veterans

- Datasets assembled for VA mortality studies of Gulf War Era Veterans (n = ~ 1.5 million Gulf War Era Veterans)
- 1995 National Survey of Gulf War Era Veterans and Their Families (n=30,000 Veterans) (Phases I, II and III) and the 2005 follow-up Longitudinal Health Study of Persian Gulf War Era Veterans and Their Families by the VA Office of Public Health. (Another OPH follow-up study will begin in 2012.)
- Department of Defense study of Navy Seabees (n=12,000)
- Department of Defense-sponsored study of U.K. Gulf War and Bosnia Era Veterans (n=8,000)
- Centers for Disease Control study of Air Force Gulf War Era Veterans (n=4,000)
- CDC and VA study of Iowa Gulf War Era Veterans (n=3,800)
- VA-contracted Military Health Study (n=8,000)
- VA-Portland survey of Gulf War Era Veterans in Pacific Northwest (n= ~1,000)
- VA-Portland Survey of Gulf War Era Veterans in five states (n=1,800)

- Study of Gulf War Veterans returning through Fort Devens, MA (n=3,000)
- VA/CDC datasets on cancers in Gulf War Era Veterans, assembled from multiple large state tumor registries [50, 52, 79]
- Multiple large Department of Defense datasets assembled to assess birth-defect rates and pregnancy outcomes in Gulf War Era Veterans [3, 4, 5, 12, 48, 66, 74, 75]
- Multiple large datasets from Department of Defense-sponsored studies of hospitalization rates in Gulf War Veterans [7, 8, 24, 30, 31, 68]
- Department of Defense's Millennium Cohort Study (original sample > 100,000 Veterans, including at least 9,200 1991 Gulf War Era Veterans)

5.2.4.2 U.S. Federal Gulf War Registries

- VA Gulf War Registry (n=102,000 1991 Gulf War Veterans as of 2007 with ongoing enrollment)
- VA Persian Gulf Spouse and Child Examination Program Registry for spouses and children of Gulf War Veterans (n = ~1,100 in October 2001, discontinued in August 2005)
- Department of Defense Comprehensive Clinical Evaluation Program (CCEP) for 1991 Gulf War Veterans (n = ~32,800, discontinued in 2002)

5.2.4.3 VA Administrative Datasets

- The Corporate Data Warehouse, which contains multiple datasets associated with VHA clinical data (inpatient/outpatient visits, diagnoses, laboratory, pharmacy, mortality files, disability and pension)
- VBA benefits data

5.2.4.4 Gulf War data resources assembled and maintained as a department-wide VA effort

One outcome of the VA Secretary's Gulf War Veterans' Illnesses Task Force was the formation of an inter-disciplinary team of VA employees charged with developing and producing a recurring series of integrated and comprehensive Departmental reports on the Gulf War Era Veteran population. Known as the Gulf War Integrated Project Team, this body generated a two-part reporting structure consisting of a Pre-9/11 Report (August 2, 1990 through September 10, 2001) and a Post-9/11 Report (September 11, 2011 to present). A supporting data system known as the Southwest Asia Veterans System (SWAVETS) will house the data for these statistical reports.

Both the scalable reports and SWAVETS will statistically link selected VA benefits and healthcare data with Department of Defense data. Collectively, the Pre-9/11 Report, the Post-9/11 Report and SWAVETS form a dynamic reporting mechanism for Gulf War Era data.

- **Pre-9/11 Report:** The report provides comprehensive statistics on the use of VA benefits and healthcare services by Gulf War Era Veterans who served at least one day from August 2, 1990 through September 10, 2001 [56]. The generated statistical tables are bucketed into four major profiles: Service member, VA benefits, VA healthcare services, and integrated VA benefits and healthcare services. A portion of these tables address service-connected undiagnosed illnesses (UDX). By breaking out the Pre-9/11 Period into event-based cohorts and sub-cohorts, it is now possible to conduct in-depth analyses of deployed Gulf War military personnel who participated in

events such as Operation Desert Shield and Operation Desert Storm or who may have been in the immediate vicinity of exposure events at Al Jubayl, Saudi Arabia or Khamisiyah, Iraq. VA released the initial Pre-9/11 Report in February 2011.
Post-9/11 Report: Still under development, the initial Post-9/11 Report will provide VA benefit and healthcare service utilization statistics for Gulf War Era Veterans who served at least one day from September 11, 2001 through September 30, 2010. Because the Persian Gulf War wartime period remains open, each successive report will extend the previous report's end date until a date prescribed by Presidential proclamation or law. The Post-9/11 Report expands the scope of the Pre-9/11 Report's benefit portfolio by including utilization information for the following six benefits programs: compensation, education, insurance, loan guaranty, pension, and vocational rehabilitation and employment. VA expects to release the first Post-9/11 Report in spring 2012.

- **SWAVETS:** This population-based data mart contains an individual record for each DoD-identified Pre-9/11 or Post-9/11 Gulf War Era Veteran. Operationally, the SWAVETS data mart serves as a standard analysis and reporting system by integrating key data from both VA and non-VA sources. Such data include DoD demographic information; VA benefits-related information to include service connection status, diagnostic codes and disability evaluations; and VA healthcare-related information to include enrollment, inpatient and outpatient care, ICD-9 codes, and costs. By Spring 2012, SWAVETS will have captured key information on most Gulf War Era Veterans.

5.2.4.5 Other large federal datasets that provide data relevant to the health of Gulf War Veterans

- Department of Defense 1991 Gulf War Troop Location Database: Identifies unit locations during 1991 Gulf War deployment.
- Department of Defense datasets that model unit exposure levels to nerve agents associated with 1991 weapons demolitions at Khamisiyah, Iraq.
- Department of Defense datasets that model unit exposures to contaminants from the 1991 Kuwaiti oil-well fires.

5.2.5 Ongoing VA Funded Projects

Several ongoing projects funded by VA have either been designed specifically to facilitate research on Veterans of the Gulf War or may aid such research.

5.2.5.1 Ongoing OPH Funded Projects

- VA mortality study of neurological outcomes
- VA Follow-up Study of a National Cohort of Gulf War and Gulf Era Veterans
- Research and datasets developed by the War Related Illness and Injury Research Centers (WRIISCs)

5.2.5.2 ORD Funded Projects

These have been referenced earlier in this report:

- Gulf War Postmortem Biorepository (CSP #501B)
- Million Veteran Program (MVP, CSP #G002)
- Gulf War Era Cohort and Biorepository (CSP #585)

5.2.6 Action Plans

Goal 1: Enhance ongoing surveillance efforts of Gulf War and Gulf War Era Veterans.

- Expand the surveillance capacity of the OPH longitudinal survey of 30,000 Gulf War Era Veterans to collect detailed and systematic data on symptoms associated with Gulf War service, on Veteran-reported diagnosed diseases, on medical and self-care treatments used by Veterans with multi-symptom illness, and on VA and non-VA hospitalization and healthcare utilization by this population. For an explanation of highlighted sections, see page 2.
- Enhance the statistical reporting capabilities in VA's Pre-9/11 Report [56] by reporting on the following cohorts: 1) Gulf War Veterans who served in the theater between August 1990 and July 1991;2) Non-theater Gulf War Veteran cohorts that complement existing in-theater cohorts to include those who served between August 1990 and July 1991. For an explanation of highlighted sections, see page 2.
- Develop a "pharmacovigilance"-style surveillance system from the VA electronic medical record to identify emerging trends in incident health conditions that may be specific to Gulf War service. For an explanation of highlighted sections, see page 2.
- Develop a treatment identification surveillance system from the VA electronic medical record to identify treatments given to Gulf War Veterans that may be suitable for further research. For an explanation of highlighted sections, see page 2.

Goal 2: Improve the usefulness of existing databases by linking them and then integrating them into a data warehouse and making them available for use by researchers.

- Convene an expert panel to guide and oversee Gulf War data coordination and linkage efforts at VA. The panel will be supported by a project team specifically tasked with assembling and linking Gulf War data resources across VA, as well as data resources available through other federal agencies. For an explanation of highlighted sections, see page 2.
- Incorporate into the data-linkage effort an evaluation of issues pertaining to human subjects protections and methods required to address those issues. This would include steps to address the consent and privacy issues impeding the ability to link various data sources, to re-contact participants of past studies, and to conduct studies that include Gulf War and Gulf War Era Veterans who do not go to VA for their health care. For an explanation of highlighted sections, see page 2.
- Employ a more flexible consent process, such as currently used in MVP, for future research projects of Gulf War Veterans to facilitate linkage with other data sources.
- Form a Gulf War Era Veterans' data repository that includes and links federal datasets for this population and also makes de-identified data available to researchers to address specific questions related to the health of Gulf War Veterans. (Note that some of the population-based studies used complex sampling schemes that need to be taken into account in data linkages.) For an explanation of highlighted sections, see page 2.
- As part of the data repository, develop an inventory that includes protocols for the studies and the structure and content of the databases, including an inventory of data elements in each.
- Facilitate methods for research data-sharing between VA and DoD so that DoD data can be used by VA researchers and vice versa. Currently, these partnerships are rather difficult to create. For an explanation of highlighted sections, see page 2.
- Link existing earlier databases with MVP and CSP #585.

- Modify the VA medical record to include a field for 1990-1991 Gulf War service to facilitate identification of potential subjects for research studies and to enable linkage with other databases. For an explanation of highlighted sections, see page 2.
- Encourage VA researchers to provide results in a way that identifies Gulf War Veterans as a group so that meta-analyses can be conducted and to submit data pertaining to Gulf War Veterans to the data repository.
- Enhance MVP as a resource for research on Gulf War Veterans to (a) include specific service information to identify Gulf War Veterans and (b) incorporate targeted recruitment of Veterans who were deployed to the Gulf during the conflict.

Note: *Appendix 1 outlines those major activities involved in linking multiple datasets and integrating data into a usable database, based on the experiences of the VA Gulf War Integrated Project Team in developing the Pre-9/11 Report, the Post-9/11 Report and their supporting data system, SWAVETS.*

Goal 3: Develop new databases optimized to address specific research questions.

- Compile retrospective and prospective longitudinal data from medical records of Gulf War Veterans with multi-symptom illness who are treated in the VA system to: (a) provide preliminary information on treatments that appear to be useful for some Veterans or for some symptoms, (b) assess co-morbid conditions and (c) monitor for additional problems that may develop in this cohort.
- Develop a separate database focused on the women deployed to the Gulf and their specific health issues. For an explanation of highlighted sections, see page 2.
- Develop a twin registry of Gulf War Era Veterans. The VA Office of Research and Development has been at the forefront of twin research by developing the World War II (WW II) and Vietnam Era Twin (VET) Registries, which highlight the considerable importance of twin registries to the VA research mission. A registry of Gulf War Veterans who are twins would be an optimal venue to address important clinical, health services and basic science questions regarding the health and well-being of Gulf War Veterans.

  At least two research groups—including William F. Page, PhD, at the National Academy of Sciences and Robert Haley, MD, of the University of Texas Southwestern Medical Center—successfully identified Gulf War Era twins based on an algorithm with the DoD Defense Manpower Data Center (DMDC) database. Both of these efforts were limited by various factors and were discontinued because of changing priorities. However, they can be used as resources to develop a VA-sponsored comprehensive and population-based twin registry that encompasses all Gulf War Era twins from all branches of service on an ongoing basis.

  A Gulf War twin registry, perhaps in the context of a larger effort undertaken by the VA Office of Research and Development to establish a post-Vietnam twin registry, can have transformative impact on our ability to understand the long-term health consequences of having served in the Gulf War.
- Use existing databases to develop case registries and design case-control studies. This may facilitate research on specific medical conditions at increased prevalence in Veterans who served in the Gulf War. For an explanation of highlighted sections, see page 2.

5.3 RESEARCH TO ENABLE DEVELOPMENT OF NEW GULF WAR CASE DEFINITIONS

5.3.1 Goal

To establish a consensus case definition for Gulf War multisymptom illness, and guidelines for its use.

Overview. Since returning from military service in the 1990-1991 Gulf War, studies indicate that at least one in four veterans have suffered from a complex of multiple concurrent symptoms not readily explained by established medical or psychiatric diagnoses. Studies of diverse veteran populations have identified the same general types of symptoms, co-occurring as a "multisymptom illness," that affect deployed Gulf War Veterans at significantly higher rates than veteran comparison groups, and have indicated that few veterans have recovered over time. In the absence of an objective diagnostic test, this multisymptom illness has been defined in research studies on the basis of veterans' symptoms, with different research groups defining the illness in different ways. In the 20 years since the war, however, no single case definition has been generally accepted or widely used. Various terms have been used to refer to this health problem. "Gulf War multisymptom illness" is used here as an umbrella term, referring to the excess burden of chronic, symptomatic illnesses associated with military service in the 1990-1991 Gulf War.

The lack of a consensus, evidence-based case definition for Gulf War multisymptom illness has negatively affected the quality of research and impeded progress in addressing this serious health problem. Studies have used diverse approaches for defining symptomatic cases, or have used no case definition at all. Overall, the case definitions put forward have not been systematically assessed to determine if they provide an adequate characterization of the profile of symptoms associated with Gulf War service. Case definitions that miss the mark, or are too broad, or too narrow, can potentially obscure or misrepresent findings that are important for better understandingGWV illnesses. Furthermore, results from different studies cannot be directly compared with one another, and it is not known the extent to which results from individual studies differ as a function of the case definitions used.

It is therefore urgent that VA support rapid development of an evidence-based, consensus case definition for use in studies of Gulf War multisymptom illness going forward. Consistent use of a case definition, which is optimized to identify case subjects that are precisely and rigorously defined, is necessary for advancing better quality and more sharply-focused research. It is essential for successful application of powerful new scientific capabilities such as biomarker identification and genome-wide association studies (GWAS) that could potentially significantly advance understanding of this challenging condition.

This plan outlines a process that can establish a research case definition for Gulf War multisymptom illness. The case definition should be developed by a consensus panel of experts in the field, utilizing analytic results from a comprehensive evaluation of available data resources.

This evidence-based process would prioritize characteristics of specificity, sensitivity, and standardization of symptom assessment in order to identify more homogeneous groups, and subgroups, of symptomatic veterans for research studies. The plan also recommends use of an interim case definition to help to standardize research pending completion of the consensus case definition process outlined here. Once completed, the plan recognizes the need to revisit the consensus case definition over time, as additional data and new insights related to Gulf War multisymptom illness, and illness subgroups, become available.

The case definition process should be completed as efficiently as possible, within a targeted time period, recognizing the urgent need to make available an evidence-based, consensus case definition for other studies conducted as part of the strategic plan. It is hoped that use of a consistent, "optimized" case definition will be instrumental in hastening progress made by the broader research effort focused on deepening understanding of Gulf War multisymptom illness and improving the health and lives of affected veterans.

5.3.2. IOM Recommendations

The Institute of Medicine (IOM) has determined there is sufficient evidence indicating an association between deployment to the 1991 Gulf War and chronic multisymptom illness, [41, p.210] but has not provided recommendations concerning case definitions for this condition.

5.3.3. RACGWVI Recommendations

The Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI) summarized six case definitions that have been developed by different research groups, the differing prevalence estimates associated with various adaptations of those case definitions, and four additional approaches that have been used for characterizing multisymptom illness in Gulf War veterans. [64, pp.25-30] The Committee did not recommend a specific case definition, but its formal recommendations include:

> "Studies of Gulf War veterans should use well-constructed and clearly-described case definitions for Gulf War illness and illness subgroups. Pending more widespread acceptance of an established case definition, preferred case definitions are those that most clearly distinguish the pattern of symptoms in Gulf War veterans from those in nondeployed era veterans, such as the Kansas Gulf War illness case definition." [64, p.315]

5.3.4. VA ORD Previous Research Activities Related to Case Definitions

The Department of Veterans Affairs (VA) Office of Research and Development (ORD) has not previously sponsored research specifically aimed at identifying case definitions for Gulf War multisymptom illness, but did fund a recent study that validated the factor structure for a set of three syndromes previously identified by investigators at the University of Texas Southwestern. [32] Previously, VA's Office of Public Health and Environmental Hazards, as well as the

Department of Defense (DOD), have sponsored projects conducted by VA investigators that have developed different approaches for identifying "cases" of symptomatic illnesses in Gulf War veterans. These include a case definition for "Gulf War Unexplained Illness" developed at VA's Portland Environmental Hazards Research Center [71], identification of a unique "Gulf War Syndrome" using factor analysis of symptom data in VA's 1995 national survey of Gulf War era veterans[49], and a statistically-characterized "high symptom" subgroup identified by investigators at VA's New Jersey Center for Environmental Hazards Research, utilizing symptom data from VA's Gulf War Registry[28].

5.3.5. Plan for Establishing a Consensus Case Definition for Gulf War Multisymptom Illness

The lack of objective diagnostic markers for Gulf War multisymptom illness presents a serious challenge for researchers and clinicians. This challenge is not unique, however. Many familiar medical conditions (e.g. migraines, Alzheimer's disease, fibromyalgia) currently or historically have lacked objective diagnostic tests and so have necessarily been defined on the basis of patients' presenting symptoms. Symptoms for such conditions can also vary to some extent between patient subgroups, necessitating a general, "umbrella" case definition that allows for identification of subgroups of potential importance. Rigorous scientific research can advance progress in addressing conditions initially recognized primarily by their symptoms. We note the significant new insights into Alzheimer's disease and novel therapeutic approaches that have been afforded by identification of the predictive utility of ApoE genotypes, by new insights into the molecular mechanisms of amyloid plaque deposition, and by the capability of identifying amyloid plaques even before symptoms are recognized by advanced imaging technologies.

The consensus case definition for Gulf War multisymptom illness will be developed in close coordination with VA clinical units to provide the most accurate symptom-based criteria possible for characterizing the excess pattern of undiagnosed chronic symptoms associated with military service in the 1991 Gulf War. This characterization should be conducted in close coordination with VA clinical units. It is recognized, however, that no symptom-based case definition is likely to be perfectly accurate or ideal, given the non-specific nature of individual symptoms reported by any population group, including Gulf War era Veterans. Rather, it is important that the consensus case definition be "optimized" to the extent possible using currently available data, according to standards identified by the consensus panel assembled for this purpose. It is also important that the consensus case definition be revisited as appropriate over time, as additional data become available on veterans' symptoms and diagnosed conditions, and as objective biological markers are identified in relation to Gulf War multisymptom illness and/or illness subgroups. For an explanation of highlighted sections, see page 2.

The plan for establishing a consensus case definition for Gulf War multisymptom illness includes two central components, carried out in parallel, to ensure that an evidence-based, consensus case definition is developed in a timely manner.

(1) Expert Consensus Panel. The case definition effort will convene an expert Gulf War multisymptom Illness Case Definition Consensus Panel to: (a) review existing resources and identify considerations for evaluating Gulf War multisymptom illness case definitions and (b) establish criteria for a consensus case definition, to be published along

with guidelines for its use. The panel will include scientists with the expertise (e.g., Gulf War Veterans' illnesses research, classification and evaluation of symptom-based criteria) required to achieve case definition objectives. This will include members recommended by the GWSC and RAC-GWVI, representatives of federal agencies that sponsor research on the health of Gulf War veterans, veterans affected by Gulf War illness, and independent outside experts.

(2) Data Assessment. Development of the case definition will involve a comprehensive analytic effort to evaluate existing case definitions in relation to priorities identified by the expert panel and develop algorithms for revising existing case definitions or establishing new case definition criteria. Analytic results will be provided to the expert panel for their consideration in arriving at a consensus case definition.

The Gulf War Multisymptom Illness Case Definition Consensus Panel should initially review information related to existing case definitions and available data resources, consider additional approaches that might be useful for defining cases, and outline priorities to be weighed in evaluating case definitions. This process will necessarily require consideration of diverse issues, including the pros and cons of emphasizing different characteristics (e.g., specificity, sensitivity, homogeneity, subgroup identification) of the case definition to be established. For example, defining an illness in a highly restrictive way might provide some advantages for specific studies (e.g., biomarker and GWAS studies), but can potentially provide cases that are too narrowly-defined for other research purposes. In contrast, case definitions designed to include a broader range of cases can be overly sensitive, leading to spurious or ambiguous results, e.g., by including veteran "cases" whose chronic symptoms are unrelated to their Gulf War service. The consensus panel will be responsible for weighing different features and approaches to arrive at the "best" case definition possible.

These determinations will be informed by analytic assessments of different case definitions, and specific features of case definitions, using existing population-based datasets, to evaluate strengths and weaknesses in relation to priorities of interest. Case definition algorithms and features can be assessed and compared in Gulf War veterans and nondeployed era veterans to determine, for example, the extent to which they distinguish between the two groups. This might include comparing the impact of different strategies for describing veterans' overall burden of symptoms, for including/excluding specific symptom types, or for assessing the severity level of qualifying symptoms. Criteria that are "optimized" in one population can be further assessed in other datasets to determine the degree to which they effectively characterize the excess symptomatology affecting Gulf War veterans and reliably identify homogeneous groups of cases. Results of these analyses will provide the expert panel with insights that are essential for establishing an evidence-based, consensus case definition.

A. "Optimizing" a Gulf War Multisymptom Illness Case Definition: Priorities to be Considered by the Consensus Panel

Overall, the consensus case definition should provide clear inclusionary and exclusionary criteria, which precisely and consistently characterize Gulf War multisymptom illness cases, and/or homogeneous illness subgroups. Issues to be considered in "optimizing" the consensus case definition include:

- Specificity, i.e., the degree to which the case definition describes a symptom profile specifically associated with military service in the 1991 Gulf War, distinguishing the symptom pattern(s) affecting Gulf War veterans from ambient symptoms reported by nondeployed veteran comparison groups
- Sensitivity, i.e., the degree to which the case definition successfully "captures" the excess symptomatology associated with service in the 1991 Gulf War
- Reliability, i.e., the degree to which veterans' symptoms are ascertained in a consistent, interpretable manner (including symptom occurrence, severity, and duration)
- Portability, i.e., the degree to which the case definition is suitable for use with different study designs and in different research settings (e.g., clinical trials, case-control biomarker studies, population-based surveys)
- Strategy for considering diagnosed medical and psychiatric conditions as exclusionary criteria and/or as comorbid conditions as most appropriate for optimizing specificity and sensitivity for research purposes
- Subgroup identification, i.e., the potential for the case definition to be used in studies that require that subgroups of potential importance are identified or distinguished from one another (e.g., subgroups with prominent symptoms in a given domain, subgroups with/without comorbid conditions, etc.)
- The potential for the case definition, optimized for research purposes, to be used in clinical practice, and any special considerations in that regard
- Other case definition characteristics deemed important by the consensus panel

B. Specific Objectives and Targeted Timeline for Establishing a Consensus Gulf War Multisymptom Illness Case Definition

The action plan for developing and publishing a consensus case definition for Gulf War multisymptom illness will address the objectives summarized below. The plan recognizes the urgent need for a consensus case definition to be used by all clinical and epidemiologic studies of Gulf War veterans conducted under the strategic plan. VA ORD will therefore solicit and fund a comprehensive effort, to be conducted by the most qualified research team, in order to achieve key objectives in a timely manner. Activities will be initiated upon adoption of the strategic plan and implemented expeditiously, with a targeted completion date within two years.

Specific Objectives and Targeted Timeline for Establishing a Consensus Gulf War Multisymptom Illness Case Definition

Targeted Timeline*	Activities/Objectives
No later than 30 days	VA ORD, in consultation with the GWSC and RAC-GWVI, identifies the process by which it will solicit and fund the development of the consensus case definition. Funded activities should include all key elements of the case definition process, including convening the consensus panel and conducting the analytic effort required to establish an evidence-based case definition.
No later than 60 days	Proposals invited from research teams with the expertise necessary for achieving all objectives of the case definition effort.
No later than 120 days	Case definition project site/team selected.
No later than 10 months	Project team obtains datasets that are most informative for providing systematic data on chronic symptoms and diagnosed conditions in population-based samples of Gulf War veterans and nondeployed 1990-1991 era veterans.
	Gulf War Multisymptom Illness Case Definition Consensus Panel convened. Project team provides consensus panel members with comprehensive information on existing case definitions and data resources, and works with them to develop standards and methods to be used in evaluating case definitions and developing analytic approaches useful for revising existing case definitions or developing new case definitions.
No later than 16 months	Initial analytic results provided to consensus panel for review, feedback.
No later than 20 months	Consensus panel completes review of analytic results, develops case definition criteria.
No later than 24 months	Consensus panel completes case definition criteria, submits manuscript for publication.

*Targeted time period following adoption of strategic plan

C. Mechanism for Implementing the Case Definition Objectives

VA will implement the case definition effort using the solicitation and funding mechanisms most capable of supporting: a) expeditious completion of the case definition, b) use of analytic methods that are most scientifically credible for defining cases as objectively as possible, c) project execution by investigators whose research and analytic expertise is most relevant for developing a symptom-based case definition for Gulf War multisymptom illness.

Funding for establishing the consensus case definition will be provided by the VA Office of Research and Development (ORD) through a directed process targeted to achieve the case definition objectives in a timely manner. Eligible investigators may include VA scientists/research teams, investigators from outside VA contracted specifically for this purpose, or collaborative teams that include both VA and non-VA researchers. The project team will be selected based on results of a review process conducted by a panel (to include members recommended by the GWSC and RAC-GWVI) convened specifically for this purpose. The

project team selected will be responsible for addressing all case definition evaluation/ development objectives outlined in the strategic plan within the targeted time period.

D. Interim Case Definition for Gulf War Multisymptom Illness

It is expected that the process for developing an optimized consensus case definition should require no more than 24 months. In order to standardize research related to Gulf War multisymptom illness in the interim, VA research studies will utilize case criteria specified by the Kansas Gulf War multisymptom illness case definition 72]. If necessary to address research questions for specific studies, additional well-described case criteria may be used in parallel with the Kansas Gulf War multisymptom illness case definition.

As previously indicated, no systematic evaluations have been conducted to determine which of the existing case definitions for Gulf War multisymptom illness most accurately characterizes the excess pattern of symptoms associated with military service in the 1990-1991 Gulf War. Only the Fukuda multisymptom illness case definition [23] and the Kansas GW multisymptom illness case definition have previously been used by multiple research groups. Many researchers believe that the Kansas case definition is best suited because it provides several advantages identified as important for symptom-based criteria. In particular, the Kansas case definition includes features that enhance the homogeneity of veteran cases identified for research studies (e.g., use of systematically-queried symptoms in clearly-defined symptom domains and use of exclusionary criteria for veterans whose symptoms are potentially explained by diagnosed conditions). The Kansas criteria also allow for straightforward subgrouping of cases (based on differences in symptom scores and domains endorsed by veterans) as required for different studies. The Kansas criteria are also preferred because they define a symptomatic illness that appears to be more specific to Gulf War service than the Fukuda criteria. That is, the Kansas case definition defines an illness profile that affects 34% of Gulf War veterans and 8% of nondeployed era veterans, whereas the Fukuda criteria apply to 50% or more of Gulf War veterans and 15-35% of nondeployed era veterans [64].

E. Summary of Goals and Objectives

1. The case definition will be developed by a consensus panel of experts in the field, utilizing analytical results from a comprehensive evaluation of available data resources.

2. This evidence-based process will prioritize characteristics of specificity, sensitivity, and standardization of symptom assessment in order to identify more homogeneous groups, and subgroups, of symptomatic veterans for research studies.

3. The plan also recommends use of an interim case definition to help to standardize research pending completion of the consensus case definition process outlined here. In the interim, VA research studies will utilize case criteria specified by the Kansas Gulf War Illness (GWI) case definition [72].

4. Expert Consensus Panel. The case definition effort will convene an expert Gulf War Illness Case Definition Consensus Panel to: (a) review existing resources and identify considerations for evaluating Gulf War multisymptom illness case definitions and (b) establish criteria for a consensus case definition, to be published along with guidelines for its use.

5. Data Assessment. Development of the case definition will involve a comprehensive analytical effort to evaluate existing case definitions in relation to priorities identified by the expert panel and develop algorithms for revising existing case definitions or establishing new case definition criteria. Analytic results will be provided to the expert panel for their consideration in arriving at a consensus case definition.

6. VA ORD will therefore solicit and fund a comprehensive effort, to be conducted by the most qualified research team, in order to achieve key objectives in a timely manner. Activities will be initiated upon adoption of the strategic plan and implemented expeditiously, with a targeted completion date within two years.

F. Concluding Working Group Comments on the Urgency of Developing a Consensus Case Definition for Gulf War Multisymptom Illness

The case definition working group believes that a consensus case definition for Gulf War multisymptom illness is urgently needed. It is essential for advancing the Gulf War research effort overall and, in particular, to maximize the progress obtained from studies undertaken as part of the present strategic plan. The group wishes to emphasize two points regarding implementation of the plan:

1. The consensus case definition effort should be undertaken in a deliberate, rigorous fashion that is completed as rapidly as possible. The working group estimates that the actual work required for the analytic effort and consensus process can be accomplished in 12 months or less. The tentative timeline provided reflects additional months needed to identify the analytic team and administer the process.

   VA ORD is strongly urged to streamline the administrative process for completing the case definition by utilizing a targeted mechanism for initiating and funding this effort. The usual processes involved in soliciting, reviewing, and funding research proposals will not allow completion of the case definition in the timeframe that will best serve the overall Gulf War research effort.

2. The success of establishing a consensus case definition relies, to a large extent, on the skills and expertise of the case definition expert panel. The working group recognizes that the lack of a consensus case definition, 20 years after the Gulf War, reflects historical complexities and competing views related to Gulf War multisymptom illness. The group urges VA to assemble the consensus panel so as to ensure that: (a) it includes members with the specific skills and scientific expertise required to accomplish the task, and (b) it includes sufficient "independent experts" to avoid impedance of the task by entrenched interests.

5.4 GENETICS/GENOMICS/SYSTEMS BIOLOGY

5.4.1 Goal

Genetic, genomic and systems biology approaches will be applied to advance the understanding of the biological networks involved in Gulf War Illnesses. Molecular sources of inter-individual variation in the response to the environmental toxins which may have caused the diseases will be elucidated. The overarching aim is to define quantitatively genetic and genomic factors which modify the spectrum of symptoms affecting Gulf War Veterans, with a view to enabling predictive personalized therapy for Veterans. This will require comprehensive models describing the biological networks regulating the disease phenotype.

5.4.2 IOM Recommendations

The IOM has noted that "given the high prevalence of persistent symptoms and the steady advances in our understanding of genetics, molecular diagnostics, and imaging, it is now possible to plan and carry out adequately powered studies to identify inherited genetic variants, molecular profiles of gene expression, other epigenetic markers (for example, modifications of DNA structure related to environmental exposures), specific viral exposures, signatures of immune activation, and brain changes identified by sensitive imaging measures that distinguish Gulf War Veterans who have persistent medical symptoms from healthy deployed or non-deployed Veterans." [38]

5.4.3 RACGWVI Recommendations

The RAQCGWVI noted that "a question often asked about Gulf War illness is why some Gulf War military personnel developed chronic symptoms during and after deployment, while others who served alongside them remained well. There is more than one possible reason for this. Genetic and other differences between individuals can dictate different reactions to a given exposure. Additionally, different individuals encountered varying doses and combinations of exposures in theater, over different durations. Identifying specific factors responsible for these differences would provide important insights into the biological nature of Gulf War illness, as well as its causes. It could also help prevent similar problems in future deployments." [64, p 250]

5.4.4 ORD Research

There are no completed studies that explored the association of genetic variants with Gulf War Veterans' illnesses in Veteran cohorts. The Cooperative Studies Program is currently recruiting cohorts that will enable studies into the genetics of Gulf War Veterans' Illnesses. Some examples of past research show the potential of these types of studies in Gulf War Research.

An ORD-funded study entitled "Patterns of Microarray Gene Expression in Gulf War Illness" examined 20,000 genes by microarray immediately before, immediately after and 4 hours following an exercise challenge. Ill Gulf War Veterans demonstrated a dysregulation of immune function cassette genes, as demonstrated by decreased NK cytotoxicity and altered gene expression associated with NK cell

function. Pro-inflammatory cytokines, T-cell ratios, and dysregulated mediators of the stress response (including salivary cortisol) were also altered in ill Gulf War Veterans compared to control subjects [76].

A small mechanistic study used a systems biology approach to assess the immune network response to an exercise challenge in veterans with and without GW multisymptom illness. Statistical analysis of the identified biological networks supported an autoimmune component in GW multisymptom illness etiology [9].

"HIV-1 Genetic Determinants of Drug Resistance Development" was an ORD-funded retrospective cohort study which found that high sensitivity microarray genotyping predicted antiretroviral therapy response better than standard sequencing. This enables VA clinicians to tailor therapy for their patients with the best antiretroviral therapy regimens likely to suppress these resistant variants [51].

ORD researchers conducting genetic research in schizophrenia have found that functional polymorphisms in the core promoter of chromosome 15q14 locus of CHRNA 7 are associated with schizophrenia and with diminished inhibition of P50 auditory evoked responses. This finding is one of few demonstrations of a functional polymorphism in a gene associated with schizophrenia that directly affects a neuronal function. These results support the hypothesis of a familial neurobiological risk factor for the illness, as well as development of a drug to treat the condition [58].

5.4.5 Research Plans and Funding Mechanisms

Genetic, genomic and systems biology approaches can define those genes and networks that govern the clinical responses evoked by xenobiotic compounds such as environmental toxins. Integrating large-scale, high-dimensional molecular and clinical data, as are generated in human genomics studies, holds promise for causally associating such networks with the variable clinical response observed in Gulf War Veterans' Illnesses. While genome sequence is a key driver of variation between individuals, environment sources should also be considered. Age, diet, gender, exposure to xenobiotic compounds, and many other environmental variables have been shown to impact the expression and function of disease genes. These variables are thought to act by regulating the epigenetic status of a cell through modification of chromatin.

Goal One. The VA will enable both established and emerging genetics, genomics and systems approaches by :

(a) recruiting prospectively appropriate cohorts of veterans who volunteer to undergo thorough health assessments and donate biological samples including DNA using the Cooperative Studies Program (CSP) mechanism;

(b) conducting ORD-initiated studies based on the CSP cohorts;

(c) funding investigator initiated studies that access data and biological material collected from the CSP cohorts, or previously recruited cohorts.

Goal Two. Whether studies focus on a small set of genetic variants - for example in biological pathways with relevance in the detoxification of hazardous agents - or genome wide scans for genetic variants to discover those that are associated with the Gulf War Veterans' Illnesses, the overarching principles that will guide genetic, genomic and systems biology research will be the:

(i) design of approaches that enable both discovery and replication;

(ii) in-depth characterization of the clinical phenotype - including longitudinal assessments - to enhance the likelihood of identifying genetic/genomic signals;

(iii) coordination of phenotyping approaches across ill Gulf War Veteran cohorts and research projects to enable comparison of the resulting data and the replication mentioned in (i); this should include external comparison;

(iv) careful selection of control cohorts based on population study principles;

(v) focus on identifying the precise genetic variants that contribute to disease through genetic approaches (e.g, sequencing, quantitative PCR, etc.).

Goal Three. Two cohorts will be developed as the central sources for genomics approaches. The Gulf War Era Cohort and Blood Biorepository (CSP #585) will be primary source for the discovery of candidate genetic variants. The Million Veterans Program (MVP, CSP #G002) is currently not specifically targeting Gulf War Era Veterans for enrollment, but is expected to enroll a number of Gulf War Era Veterans large enough to enable genomic studies on this subgroup. Thus, it is expected that this cohort will have particularly utility for replication studies that follow-up on discoveries made in the Gulf War Era Cohort and Blood Biorepository (CSP #585).

Gulf War Era Cohort and Blood Biorepository (CSP #585).

This large-scale longitudinal study, which is under development, will recruit a cohort of Veterans from the Gulf War era to develop a research database that integrates epidemiological, survey, clinical, and self-reported environmental exposure data. Blood and DNA specimens will be collected to establish the biorepository to enable a deeper level of research. Both users and non-users of VHA Healthcare will be recruited. Participants will also consent to be contacted about enrolling in other research projects.

Challenges and opportunities: This study is currently conducted as a pilot project with the aim to establish standard operating procedures for phenotyping, sample collection and storage (targeted enrollment up to 3000 in the pilot phase). The timeline for transitioning the program into full operation will be accelerated with a goal to complete recruitment at the end of year two of the five year period this strategic plan is covering. This will enable the completion of research studies that are based on this cohort within the governance of this plan. Indeed, it is desired to avail existing data and samples for

research studies already during the recruitment phase. These might for example include smaller targeted genetics studies, which require fewer cases than full human genome scans. These might also include "deep-phenotyping" studies which conduct more comprehensive assessments such as longitudinal electronic medical record analysis [13] , imaging, expression profiling or metabolomics studies; Veterans will be invited to return to the clinical centers for these studies. As these more focused studies will primarily be investigator initiated programs, a web-based system should be installed to inform potential grant applicants of the recruitment status of this cohort in close to real-time and facilitate collaborations. During the recruitment phase a CSP-directed program to obtain genetic/genomic data on cases and controls will be devised, with the intention to collect genome sequence information using next generation sequencing (NGS) technology.

Million Veteran Program (MVP; CSP #G002)

The VA Office of Research and Development launched the Million Veteran Program (MVP) in early 2011. The MVP is an important partnership between VA and Veterans. The goal of MVP is to better understand how genes affect health and illness in order to improve healthcare for Veterans. MVP will establish one of the largest databases of genetic and health information to be used for future studies that may lead to new ways of preventing and treating illnesses in Veterans and all Americans. The goal of MVP is to partner with Veterans receiving services in the VA Healthcare System who volunteer to share their health information, as well as genetic material. This project is expected to enroll one million users of the VA Healthcare System, with representative sampling from all deployments including the 1990-1991 Gulf War. Veterans who choose to be actively involved in this program will:

- Complete surveys about health and health-related behaviors;
- Provide a blood sample (containing DNA and other substances) that will be stored for future research;
- Complete an optional health assessment;
- Allow secure access to VA and VA-linked medical and health information, including past and future health records; and
- Allow future contact for invitation to participate in additional research studies

Challenges and Opportunities: As the recruitment of this cohort is not targeted towards Gulf War Era Veterans, a mechanism to monitor the sample size of the Gulf War Era Subgroup will be set up. This will allow potential investigators who intend to base their studies on this cohort to assess which projects are feasible and facilitate collaborations. A mechanism will be set up to assess which veterans are enrolled in both cohorts, the MVP (CSP #G002) and the Gulf War Era Cohort and Biorepository (CSP #585)

Other Cohorts:

VA researchers will continue adding data and specimens to develop the research capacity of the ORD biorepository studies. These are available for investigator initiated projects:

- Gulf War Veterans Illnesses Central Nervous System Biorepository (ALS; CSP # 501A) is a cooperative effort to collect high quality biological specimens linked to clinical information from consenting Veterans for use in biomedical research on GWVI. Initial efforts have focused on

collection of central nervous system tissue (brain and spinal cord) from Veterans diagnosed with Amyotrophic Lateral Sclerosis (ALS), which has been reported to occur at higher rates in Gulf War Veterans.

- Gulf War Postmortem Biorepository (CSP #501B): This pilot project is an expansion of an existing project to develop a collection of high quality post mortem biological specimens (not limited to central nervous system) from Gulf War Veterans.

Challenges and Opportunities: There will be a need for a query tool to easily and quickly determine for which cohorts various data elements are available.

5.5 Biomarkers

5.5.1 Goal

Identify biomarkers that may be present in ill Gulf War Veterans. Biomarkers are quantitative biological measures that can facilitate the diagnoses of Gulf War Veterans' Illnesses and allow monitoring its progress and a patients response to treatment. Biomarkers of GWVI may represent molecular or cellular events that can be identified as a link to a specific environmental exposure or to a health outcome. Results from imaging technologies can also be considered surrogate biomarkers when they associate with disease or disease progression.

AS FDA guidelines suggest, biomarker application can be used to predict disease progression or success of therapeutic strategies. Prognostic biomarkers characterize risk for developing a disease or its progression. Predictive biomarkers characterize individual response to particular therapeutic strategies. A pharmacodynamic biomarker displays whether a biological response has occurred in response to a particular therapeutic strategy. While a surrogate endpoint is a biomarker that substitutes for a particular clinical endpoint, this could include neuroimaging as a marker of brain change in conjunction with a particular treatment trial that would display an objective marker of change after treatment.

The path to development of biomarkers has also been summarized by FDA as including biomarker discovery, qualification and then application. The FDA defines these three steps by the following definitions:

A. Biomarker discovery

1. Discovery of a differentiating signature in a measurement as a candidate biomarker

2. In-depth investigations of the mechanisms of action and biological pathways the candidate biomarker reflects. This is the best source of information on the likely relevance, specificity and robustness of the candidate biomarker.

B. Biomarker qualification

1. Development of a robust and practical method for biomarker detection

2. Proof-of-principle in controlled experimental settings

3. Establishing that the biomarker adequately selects and characterizes the presence and / or severity of the outcome of interest in specific patient populations

4. Understanding the candidate biomarkers' clinical performance with regard to the level of sensitivity and specificity achieved under a specific context of use.

5. Identification of clinical factors which might interfere with biomarker interpretation.

C. Biomarker application

1. Use of the biomarker to predict disease progression / success of therapeutic interventions etc. in the context for which it was qualified."

5.5.2 IOM Recommendations

"Many of these symptoms (Gulf War) are difficult to categorize as they have no known cause, no objective findings on clinical examination, no diagnostic biomarkers, no known tissue pathology, and no curative therapy. The inadequate basic understanding of the root cause of these symptoms highlights the limitations of current medical science and clinical practice. The (IOM) committee recognizes that symptoms that cannot be easily quantified are sometimes dismissed—incorrectly—as insignificant, and that they receive inadequate attention—and funding—by the medical and scientific establishment." [64]

The committee recommends rigorous, adequately powered studies to identify biomarkers that distinguish Gulf War veterans who have persistent multisymptom illness (MSI) from healthy deployed or nondeployed veterans. Such biomarkers might include:

- Inherited genetic variants
- Molecular profiles of gene expression
- Other epigenetic markers (e.g., modified DNA structures)
- Specific viral exposures
- Signatures of immune activation
- Brain changes detected through imaging

5.5.3 RACGWVI Recommendations

"Findings from studies of this type can therefore be affected by many of the problems described in relation to Gulf War illness research, that is, potential inaccuracies in identifying "exposed" vs. "unexposed" groups, the lack of useful biomarkers of exposure, and individual variability in specific exposures and vulnerability to those exposures. Given such limitations, it is important that this literature be considered broadly, taking into account patterns of associations across multiple studies and populations. Such studies can potentially provide insights into the pathophysiology of CFS and lay the groundwork for developing biomarkers and treatments." [64, p. 285]

Specific RAC recommendations stated that biomarker research should include:

"Identification of objective measures that distinguish veterans with Gulf War illness from healthy veterans. The Committee places a high priority on identification of biological markers for Gulf War

illness and measurable differences between groups of symptomatic and healthy Gulf War veterans. In light of findings from current and ongoing studies describing associations between Gulf War illness and neurological, immune, endocrine, genetic, and biochemical alterations, the Committee recommends the following research:

- Studies that utilize state-of-the-art neuroimaging technologies to characterize aspects of brain structure and function that may distinguish veterans with Gulf War illness, including illness or exposure subgroups, from healthy Gulf War veterans.
- Comprehensive evaluation of autonomic nervous system function associated with Gulf War illness, as well as illness and exposure subgroups.
- Research that investigates biological and genetic variability potentially linked to differences in vulnerability to Gulf War exposures, including studies that evaluate associations between Gulf War illness and genetic polymorphisms and activity levels of enzymes associated with uptake and metabolism of neurotoxic exposures.
- Studies that evaluate alterations in central proinflammatory and inflammatory processes in Gulf War veterans affected by Gulf War illness.
- Comprehensive evaluation of immune parameters associated with Gulf War illness, including parameters that may differ among illness and/or exposure subgroups.
- Comprehensive evaluation of hypothalamic-pituitary-adrenal axis and other neuroendocrine parameters in association with Gulf War illness, including parameters that may differ among illness and/or exposure subgroups.
- Studies that determine the extent to which other physiological characteristics that distinguish CFS, FM, and MCS patients from healthy controls are also associated with Gulf War illness.
- Studies that utilize new technologies (proteomic, lipidomic, genomic, and metabolomic methods) capable of identifying unique molecular characteristics of Gulf War illness, and of illness and exposure subgroups.

Studies that characterize effects of neurotoxic exposures associated with Gulf War illness. Due to the consistency of findings relating Gulf War illness to neurotoxic exposures during the war, the Committee gives high priority to studies that further characterize specific effects of Gulf War related neurotoxic exposures, and recommends the following research:

- Studies that utilize animal models to characterize persistent molecular, cellular, systemic, and behavioral effects of individual and combined exposure to pyridostigmine bromide, pesticides and insect repellants used in the Gulf War, and low-level sarin.
- Studies that utilize animal models to characterize persistent effects of Gulf War-related exposures, alone and in combination, on central proinflammatory processes and their biological mediators in the central nervous system and target organs." [64]

5.5.4 ORD Research

Some examples of ORD-funded research in this area are given below.

The study "Structural Magnetic Resonance Imaging in Gulf War-Era Veterans" found a significant association between higher levels of estimated sarin/cyclosarin exposure and both reduced white

matter and increased right lateral ventricle and left lateral ventricle volumes. These findings suggested subtle but persistent central nervous system pathology in Gulf War veterans potentially exposed to low levels of sarin/cyclosarin and argue for further investigation of the long-term effects of low-dose sarin/cyclosarin exposures in humans [29].

Tissue factor and Gulf War-associated chronic coagulopathies were studied in a group of 64 Gulf War Veterans and controls. Significant differences between the two groups were observed for three of eight coagulation parameters. The results of this study supported the hypothesis of coagulation system activation in GWI. This is a new potential biomarker for Gulf War Research [6].

The study "Effects of Gulf War Illness on Brain Structure, Function and Metabolism: MRI/MRS at 4 Tesla" examined imaging biomarkers to determine whether US troops who may have been exposed to the organophosphate chemical warfare agents sarin and cyclosarin when a munitions dump at Khamisiyah, Iraq was destroyed after the Gulf War in 1991 have metabolic, structural, or functional changes in the basal ganglia and other regions of the brain, which are not accounted for by confounders such as post traumatic stress disorder (PTSD), depression, and/or alcoholism. The findings suggested that low-level exposure to sarin and cyclosarin can have deleterious effects on brain structure and brain function more than a decade later [11].

In the ORD-funded study "Glucocorticoid Responsivity in Gulf War Veterans" hydrocortisone was administered to GW veterans with (PTSD+, n=12) and without (PTSD-, n=8) chronic PTSD in a randomized, placebo-controlled, double-blind challenge. The PTSD+ group showed greater cortisol and ACTH suppression, reflecting greater peripheral glucocorticoid receptor responsiveness, and did not show an hydrocortisone-induced decrement in delayed recall or retention. Positron-emission tomography demonstrated that while the two groups had comparable relative regional hippocampal [^{18}F]FDG uptake at baseline, only the PTSD- group had an hydrocortisone-associated decrease in hippocampal [^{18}F]FDG uptake. The investigators concluded that the differences in brain metabolic responses between GW veterans with and without PTSD may reflect differences in peripheral and central glucocoid receptor responsiveness [78].

5.5.5 Research Plans

VA Researchers will search for new biomarkers and validate them. Biomarkers of illness, neurotoxicant exposure and risk factors for chronic disease will be specifically targeted. ORD will adopt the FDA strategy of biomarker development by first encouraging investigator-initiated, Program Project and CSP studies of biomarker discovery, then qualification of each identified biomarker and finally applying the biomarkers to assess clinical efficacy of treatment trials in the area of which it was qualified as relevant. Preliminary evidence from multiple studies suggests that GW Veterans' illnesses are associated with significant differences in brain structure and function, autonomic nervous system function, HPA axis measures, immune function, gastrointestinal function and measures indicative of vulnerability to neurotoxicants (i.e. genetic risk factors including PON1 status). Therefore, biomarker development will focus on these areas where initial studies have identified preliminary marker differences in GW veterans with GW chronic multisymptom illness or relevant neurotoxicant exposures. For studies assessing chronic sequelae of GW-relevant neurotoxicant exposures, comparison groups of other occupationally exposed groups will also be compared. Further biomarker qualification in these areas including identifying clinical factors that could cause interference with biomarker interpretation including better defining genetic polymorphisms predicted to have a functional significance and epigenetic modifications of down regulating markers and of risk factors for chronic disease vs. self-limiting symptoms will be

assessed. Finally, identified and qualified biomarkers will be used to predict disease progression / success of therapeutic interventions. Implicit in these studies and strategy will be that specific GWVI case definitions and standard collection of biodata (blood, tissue, imaging) will be implemented whenever possible in order to adequately compare results of biomarker studies and assess biomarker development effectiveness. Also whenever possible, human studies will include blood collection, processing and banking in anticipation of downstream analysis. This could prove instrumental in treatment studies to have pre- and-post-samples to assess for potential surrogate biomarkers.

Initial biomarker development could include but will not be limited to:

- Broad biomarkers of neurologic and/or neurodegenerative effects of GW Veterans illnesses and/or neurotoxicant exposures (examples include):
    - Employing degeneration stains, glial activation stains and/or myelin stains of post-mortem human and animal brain tissue to assess for glial activation (astrogliosis, microglial activation) and/or damaged myelin in GWI or neurotoxicant exposed groups.
    - Cerebrospinal fluid (CSF) analyses of proinflammatory cytokines, genetic polymorphisms and epigenetic markers of or predisposition to GWI.
    - Blood analyses of proteomics, metabolomics and lipidomics as peripheral markers of CNS neuroinflammation.
    - Advanced neuroimaging techniques in-vivo and in post-mortem tissue to identify chronic neuroinflammatory markers or markers of past or current damage to neural cells (neurons, glia).
- Advanced neuroimaging techniques (MRI, PET, DTI, MEG) to further delineate surrogate biomarkers of GWI:
    - These include functional magnetic resonance imaging (fMRI) of resting-state or task activated fMRI to further delineate central nervous system mechanisms of chronic GWI.
    - High resolution structural imaging MRI techniques to enable examination of gray and white matter changes over whole brain simultaneously. This will be done in conjunction with cognitive assessments to compare structural and functional relationships.
    - Diffusion tensor imaging (DTI) or diffusion spectral imaging (DSI) to map and assess the integrity of white matter fiber tracts in the brain and to assess for previously damaged white matter pathways. These analyses will be performed in order to further answer questions regarding structural brain changes and to image past damage to the CNS (including patchy damaged myelin) related to GWI pathology and neurotoxicant exposures.
    - Molecular imaging probes including Positron Emission Tomography (PET) imaging studies using newly devised ligands to identify biomarkers of neuroinflammatory processes associated with glial activation in the central nervous system. These analyses include ligands that target peripheral benzodiazepine receptors (TSPO) on activated microglia or MRI contrast agents including ultra small paramagnetic iron oxide particles (USPIOs) which are taken up by activated macrophages that can cross the blood brain barrier (BBB).

    - Magneto-encephalography studies (MEG) to assess for distinct signature patterns in ill GWVs vs. controls.
- Immune response mediator biomarkers that are associated with chronic inflammation including proinflammatory cytokines, chemokines and other immune functions.
- Hypothalamic-Pituitary-Adrenal axis biomarkers in GWI including cortisol and other measures of neuroendocrine function (including epigenetic studies).
- Blood and CSF studies of proteomics, metabolomics and lipidomic markers in GWI.
- Biomarkers of autonomic system dysfunction in GWI.
- Biomarkers of irritable bowel syndrome (IBS) from altered gastrointestinal flora or microbiome that may relate not only to gastrointestinal symptoms but other symptoms of GWI as well.
- CSP 501B and 585 now pilot studies for brain and tissue biorepository (CSP 501B) and blood biorepository and cohort development (CSP 585) will be developed into full research programs. This extremely valuable CNS tissue and blood bio data will allow for biomarker development studies and analyses as tissue and blood samples will be shared with independent researchers and studies evaluating potential biomarkers of GWI in a more expedient manner. These biorepositories will allow independent researchers with important biomarker hypotheses the ability to analyze tissue and blood samples without the costly and time consuming recruitment of these samples.
- A preclinical Program Project should be implemented to complement the brain and tissue biorepository and blood biorepository and clinical cohort development studies. Core research projects will include an animal tissue biorepository, molecular core, behavioral core and an imaging core.
- In order for the GW biorepositories to provide the most valuable and useful data to GW biomarker researchers, standard procedures for sample collection of blood and tissue samples and standard case definitions for GWVI will be employed. This strategy will allow for reaching the goal of obtaining documented biomarkers of GWI during this 5-year strategic plan period that can be quickly implemented to identify, test and implement effective treatments for GWI.

Promising recent VA pilot studies in biomarkers will be evaluated for expansion to larger studies in the future. VA has the existing research infrastructure to conduct small pilot studies, and move the studies with the most promising results on to larger studies.

The VA funding mechanisms for Biomarkers will be via RFAs, Program Projects and CSP. VA researchers are likely to also leverage funding from other sources.

5.6 Animal Models

5.6.1 Goal

Use animal models to characterize the persistent molecular, cellular and functional effects associated with individual and combined exposures/conditions encountered in the Gulf War. Animal models have advanced science and improved public health. While it may not be possible to develop a "perfect" animal model that reflects all features of Gulf War Illnesses, animal models can readily be used to characterize the wide variety of effects associated with exposures that may underlie the pathogenesis of conditions observed in ill veterans. Animal models have the advantage of providing post-exposure evidence obtained directly from any organ or target tissue. Modeling the persistence of effects due to exposures presumably occurring years earlier in ill veterans can be achieved in a short time frame using rodent (rats/mice) models. Finally, a very wide variety of effect "domains," from molecular to cellular changes, genomic to proteomic, to functional alterations in physiology and behavior, can readily be assessed in experimental animals. The urgent need to identify therapies to treat ill veterans also would also be achieved by screening potential treatments in animal models of GWVI.

5.6.2 IOM Recommendations

The IOM Gulf War Report (vol 8) noted that: "Because the committee was not attempting to link health outcomes to exposures other than deployment to the Persian Gulf theater, for which there is no known animal model, it did not review toxicologic, animal, or experimental studies comprehensively. As noted in the Executive Summary, however; the IOM report called for "a renewed research effort…to better identify and treat multisymptom illness in Gulf War veterans…to alleviate their suffering as rapidly and completely as possible." [41] Studies using animal models constitute components of overall research efforts dedicated to the goal articulated by the IOM.

5.6.3 RACGWVI Recommendations

Most studies that evaluate biological effects of hazardous exposures are done in animals, for ethical reasons. As noted in the RACGWVI 2008 Report, a number of animal studies recently have identified biological effects of Gulf War exposures and combinations of exposures that were previously unknown [1, 70, 73]. Due to the consistency of findings relating Gulf War Veterans illnesses to neurotoxic exposures during the war, the Committee gave high priority to studies that further characterize specific effects of Gulf War-related neurotoxic exposures, and recommended the following research:

• Studies that utilize animal models to characterize persistent molecular, cellular, systemic, and behavioral effects of individual and combined exposure to pyridostigmine bromide, pesticides and insect repellants used in the Gulf War, and low-level sarin.

• Studies that utilize animal models to characterize persistent effects of Gulf War-related exposures, alone and in combination, on proinflammatory processes in the central nervous system and peripheral target organs.

• Studies that identify markers indicative of past exposure to Gulf War-related neurotoxic compounds that can be applied to Gulf War veterans. This includes studies that identify persistent or "downstream" changes in biochemical processes in relation to past neurotoxicant exposure(s), and studies that identify

persistent changes in the central nervous system and in autonomic function associated with exposure to Gulf War-related neurotoxicants.

5.6.4 ORD Research

One example of past research in animal models is given below.

ALS is a disease of concern to Gulf War Veterans. A transgenic mouse model of ALS was used to study the effect of high and moderate levels of exercise on body weight, motor performance, and motor neuron counts in the ventral horn of spinal cords. Moderate exercise delayed the onset of motor deficit by over a week. Motor neuron density in the lumbar cord was significantly higher in the moderate exercise group compared to the sedentary group at 95 days of age. These results show the beneficial effects of moderate exercise on the preservation of motor performance that correlates with higher motor neuron density in the ventral horn of the lumbar spinal cord in mice [10].

5.6.5 Research Plans

The VA funding mechanism for animal models will be RFAs. VA researchers also are likely to leverage other funding mechanisms as well. The Biomedical Laboratory Research and Development Service at ORD solicits proposals that further the goal of improving the health and lives of veterans of the 1990-1991 Gulf War who have a complex of chronic symptoms at an excess rate. Areas of interest include studies in animals (up to and including primates) that can contribute to improved understanding of the pathobiology of GWVI, including research on objective indicators of biological processes or abnormalities in GWVI. The new information on potential origins of GWVI identified in the IOM and RACGWVI reports, combined with the development of novel assessment approaches, provide guidance for topic areas focused on animal models. These could include, but are not limited to, characterization of persistent effects of GW-related exposures, alone and in combination, on:

•sensitive indices of neuropathology used in contemporary neuroscience (degeneration stains, glial activation stains, myelin stains)

•neuroinflammatory processes associated with glial activation in the central nervous system

•autonomic nervous system pathology and function

•systemic immune parameters, with an emphasis on those parameters that sensitize ill veterans to chronic multisymptom illness

•sensitive indicators of altered hypothalamic-pituitary-adrenal axis function

These research studies should be integrated with those from case definition, genomics, and biomarker sections of this document to determine endpoints/markers/systems to be evaluated in animal studies.

Implicit in all of the above topics is the need to rapidly utilize the data obtained to identify, test (in animal models) and implement (in ill veterans) off-the-shelf therapies for GWI.

5.7 IMPROVE COORDINATION AND COMMUNICATION WITH FEDERAL PARTNERS, RESEARCHERS AND THE PRIVATE SECTOR

5.7.1. Introduction

***Institute of Medicine, Report on Gulf War and Health, Vol. 8 (2010): The committee believes that a continued and targeted research program is the most likely path to assist VAs and other health-care providers in diagnosing and treating the health problems of Gulf War Veterans and preventing illness in future Veterans*.[41]**

***Research Advisory Committee on Gulf War Illnesses, Gulf War Illness and the Health of Gulf War Veterans, Scientific Findings and Recommendations (2008): That the Department of Defense and the Department of Veterans Affairs collaborate in establishing a comprehensive federal Gulf War Research plan and a strategy to coordinate and manage federal programs to ensure that priority research objectives are satisfactorily achieved*. [64]**

5.7.2. Inter-Governmental Coordination Efforts

This section describes the VA and DOD agencies that are involved in Gulf War Illness Research.

Within VA, two organizations, the Office of Research and Development (ORD) and the Office of Public Health (OPH), are involved in Gulf War Veterans' Illnesses Research. ORD and OPH internally coordinate and share information on this topic. In early 2011, ORD and OPH initiated formalized quarterly meetings of senior staff and, as appropriate, scientific program managers and VA investigators.

5.7.2.1 Office of Research and Development (ORD)

The Office of Research and Development (ORD) supports the discovery of new knowledge by developing VA researchers and health care leaders and creating innovations that advance health care for our Veterans and the nation. ORD funds research and sets research priorities in four areas: biomedical, clinical, rehabilitation, and health services research.

ORD staff members participate in regularly scheduled meetings of the Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI), the Gulf War Steering Committee (GWSC), and the Gulf War Veterans' Illnesses Task Force.

5.7.2.2 Office of Public Health (OPH)

The work of the Office of Public Health (OPH) includes epidemiological research and large-scale surveillance studies. OPH coordinates and supports Institute of Medicine (IOM) studies that consolidate current knowledge of the Gulf War and other deployment health conditions.

ORD and OPH complement one another in that OPH performs high level surveillance studies (e.g., prevalence, mortality), while ORD performs basic scientific and applied medical research. Results of OPH studies support ORD's research agenda (e.g., increased prevalence of a particular condition in a certain Veteran population could be an indicator that a certain research project may be needed for further study to seek a mechanism and a treatment).

5.7.2.3 Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI)

The Research Advisory Committee on Gulf War Veterans' Illnesses was established by Congress in 1998. It makes recommendations to the Secretary of Veterans Affairs on government research relating to the health consequences of military service in the Southwest Asia theatre of operations during the Gulf War.

5.7.2.4 Gulf War Steering Committee (GWSC)

VA organized a committee of experts from its own internal advisory board and on recommendation from RACGWI to advise on development of this strategic plan in 2010. The group holds conference calls and meets in person on request of VA's Chief Research and Development Officer to advise on scientific and strategic aspects of developing its Gulf War Research portfolio.

5.7.2.5 DOD's Congressionally Directed Medical Research Program (CDMRP)

Outside of VA, ORD coordinates with DOD's Congressionally Directed Medical Research Program (CDMRP), specifically its Gulf War Illness Research Program (GWIRP). In a number of cases, VA investigators have successfully competed for research funding from CDMRP.

CDMRP views Gulf War multisymptom illness as characterized by persistent symptoms such as chronic headache, widespread pain, cognitive difficulties, unexplained fatigue, gastrointestinal problems, respiratory symptoms, and other abnormalities that are not explained by traditional medical or psychiatric diagnoses. CDMRP estimates that this complex set of chronic symptoms may affect as many as 200,000 Veterans of the 1990-1991 Gulf War, of the over 697,000 deployed to that region. The CDMRP GWIRP focuses its funding on projects that relate to GWI.

The vision for the CDMRP GWIRP is to improve the health and lives of ill GW Veterans, and the mission is to fund innovative Gulf War Illnesses research **to identify effective treatments, improve definition and diagnosis, and better understand pathobiology and symptoms**. ORD and the CDMRP (GWIRP) currently maintain several levels of coordination:

1) The VA Gulf War Research Program Manager is invited to present the VA Gulf War research portfolio as part of the GWIRP vision-setting meeting each year. The VA GW research portfolio and upcoming requests for applications (RFAs) are discussed at this time. This allows both agencies to coordinate their research priorities.

2) The VA GW research portfolio and the GWIRP research portfolio are presented and discussed at one or more of the 3 annual meetings of the VA Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI). This allows the RACGWVI to be aware of the activities within each agency's GW research program so that appropriate recommendations may be formulated.

3) Representatives from the GWIRP are invited to present at VA Gulf War Steering Committee (GWSC) meetings so that the committee is aware of the scope and potential overlap between the VA and DOD programs.

5.7.2.6 Deployment Health Working Group (DHWG)

The DHWG is an interagency working group co-chaired by VA (OPH) and DOD that meets monthly (successor to the original Persian Gulf Veterans Coordinating Board). The DHWG reports to VA/DOD joint committees. The DHWG is composed of staff from OPH (environmental health, epidemiology, communications), ORD (including the leads for deployment health research and GW research), and Veterans Benefits Administration (VBA). The working group shares information on deployment health in all areas, environmental exposures, DOD/VA data sharing, surveillance, surveys, research, and other topics as needed. CDMRP and researchers should present programs and findings to the DHWG on a regularly scheduled basis.

5.7.2.7 Veterans Service Organizations

ORD and OPH provide briefings to a number of Veterans Service Organizations on at least an annual basis (sometimes more frequently when requested). In addition, VSOs are on the distribution lists for VA press releases and announcements of new publications on Gulf War topics; they receive copies in bulk.

5.7.3 ORD Coordination Efforts Among Researchers

Besides monitoring research that is already funded, ORD also has a responsibility to bring researchers together when appropriate and encourage coordination and collaboration.

5.7.4 Research, Goals and Action Plans

This section outlines the goals for research coordination and communication in this plan, the objectives associated with each goal, and timelines for meeting the objectives. The rationale for these goals and objectives can be linked to the IOM and RACGWI recommendations quoted here.

***Institute of Medicine, Report on Gulf War and Health, Vol. 8 (2010): The committee believes that a continued and targeted research program is the most likely path to assist VAs and other health-care providers in diagnosing and treating the health problems of Gulf War Veterans and preventing illness in future Veterans.*[41]**

Research Advisory Committee on Gulf War Veterans' Illnesses, Gulf War Illness and the Health of Gulf War Veterans, Scientific Findings and Recommendations (2008): That the Department of Defense and the Department of Veterans Affairs collaborate in establishing a comprehensive federal Gulf War Research plan and a strategy to coordinate and manage federal programs to ensure that priority research objectives are satisfactorily achieved. **[64]**

Goals:

1. Scientific coordination of research efforts on Gulf War Veterans' Illnesses using a targeted approach in order to facilitate focused, well-planned research in the areas included in this document (cohorts and survey data; case definitions; genetics/genomics; biomarkers; animal models; treatments; translation) and perhaps others; promote shared use of resources to maximize the efficiency of research efforts and funds; allow thoughtful but flexible and rapid addition of promising new avenues of research that arise in the course of the planned effort; and support on-going discussion of the diagnostic and treatment implications of research findings as they develop.

2. Intra- and inter-agency coordination of funding and scientific initiatives to support a targeted, planned effort that promotes shared utilization of resources for research on Gulf War-related Veterans' Illnesses.

3. Communication of results and hypotheses to the scientific community devoted to the topic of Gulf War Veterans' Illnesses, Veterans, healthcare professionals who treat Veterans, the scientific community at large, and the public.

4. On-going dialogue and communication with Gulf War Veterans and their families regarding the results of the research initiatives and the possible, health, functional and treatment implications of this research

5. Enhance, manage, and coordinate lines of communication among clinicians who treat Gulf War Veterans in VHA, uniformed services (including the Public Health Service) and private sector to provide current research findings, updates to standards of practice, and new modalities of care for ill Gulf War Veterans.

Objectives

Goal 1: Scientific coordination of research efforts on Gulf War Veterans' Illnesses using a targeted approach in order to facilitate focused, well-planned research in the areas included in this document (cohorts and survey data; case definitions; genetics/genomics, biomarkers; animal models; treatments; translation) and perhaps others; promote shared use of resources to maximize the efficiency of research efforts and dollars; allow thoughtful but flexible and rapid addition of promising new avenues of research that arise in the course of the planned effort; and support on-going discussion of the diagnostic and treatment implications of research findings as they develop.

1. Adapt the VA's Gulf War Steering Committee (GWSC) to provide close, regular guidance to the VA Gulf War Research Program. Add members as necessary so that the GWSC includes Gulf War Veterans' Illnesses researchers who have received funding from VA and/or DOD/CDMRP with expertise in each of the identified critical areas (cohorts/surveys; case definitions; genetics/genomics; biomarkers; animal models; treatments; translation, clinical trials). Each member of the GWSC will be responsible for communicating regularly with investigators who are actively involved in research on Gulf War Veterans' Illnesses in the member's specialty. *Ex officio* members of the GWSC should include the ORD Directors of Deployment Research and the Gulf War Research Program, as well as OPH and CDMRP representatives. For an explanation of highlighted sections, see page 2.
2. Virtual meetings of the GWSC will be conducted monthly to discuss research findings in real time, explore possible implications for new initiatives where appropriate, and consider treatment and translational applications of the findings. Each focused area of research will be considered at least every 3 months.
3. Mechanisms will be in place to allow the GWSC to recommend pilot studies or other initiatives that can be funded rapidly with appropriate review in order to pursue new hypotheses and findings that emerge.
4. Mechanisms will be in place to discontinue funding of projects that do not progress appropriately.

Goal 2: Inter-agency coordination of funding and scientific initiatives to support a targeted, planned effort that promotes shared utilization of resources for research on Gulf War-related Veterans' Illnesses.

1. The VA Director of Deployment Research, the Director of the VA Gulf War Veterans Illness Research program and the OHP Chief Consultant for Post-Deployment Health will coordinate research on Gulf War Veterans' Illnesses that is funded and/or conducted by ORD and OPH so that research goals and strategies are efficient and congruent. For an explanation of highlighted sections, see page 2.
2. CDMRP and VA will collaborate on topics for RFAs and research initiatives to be funded through the agencies in support of the scientific goals of the research strategic plan.
3. CDMRP and VA will identify mechanisms to co-fund center and other organized research initiatives on Gulf War Veterans' Illnesses. For an explanation of highlighted sections, see page 2.
4. CDMRP's GWIRP and VA's ORD will communicate regularly with the GWSC through attending the monthly virtual committee meetings or through communication with the GWSC chair.

Goal 3: Scientific communication of results and hypotheses to the scientific community devoted to the topic of Gulf War Veterans' Illnesses, Veterans, health professionals who treat Veterans, the scientific community at large and the public.

1. VA and DoD will improve communication between Gulf War researchers using new online methodologies. For an explanation of highlighted sections, see page 2.
2. VA will convene a meeting of Gulf War Veterans' Illnesses researchers in 2012 to improve sharing of research results. This meeting will be open to healthcare providers, the Veterans and the public. Annual meetings thereafter will be conducted.
3. DHWG will continue to hold monthly meetings to share information between program and research staff of VA and DOD.
4. RACGWI will continue to conduct meetings to review research results and advise VA.
5. VA will continue to communicate with Veterans' groups on Gulf War Veterans' Illnesses research results, treatment options, and policy changes through a variety of mechanisms.
6. VA will communicate with clinical centers such as the Salt Lake City Veterans Healthcare System Clinic in order to gain insights on issues and treatment alternatives that might inform the Gulf War Veterans' Illnesses Research program.

Goal 4: On-going dialogue and communication with Gulf War Veterans and their families regarding the results of the research initiatives and possible health, functional and treatment implications of this research.

1. Develop on-line and face-to-face mechanisms for informing and interacting with Gulf War Veterans and their family members and caregivers on the efforts conducted under the strategic plan. For an explanation of highlighted sections, see page 2.
2. Develop targeted material (e.g., brochures, fact sheets, Q&As) regarding the results of research initiatives for Gulf War Veterans and their families and caregivers.
3. Disseminate material to VHA healthcare facilities for redistribution to Veterans and their family members and caregivers.
4. Distribute information to Veteran Service Organizations and other stakeholders working on behalf of Veterans for redistribution.
5. Make resources available on the ORD website. This material will be linked to OPH's VA Gulf War website and to VA's A to Z website.
6. Establish a mechanism for Gulf War Veterans and their families and caregivers to express areas of interest. For an explanation of highlighted sections, see page 2.

Goal 5: Enhance, manage, and coordinate lines of communication among clinicians who treat Gulf War Veterans in VHA, uniformed services (including the Public Health Service) and the private sector to provide current research findings, updates to standards of practice, and new modalities of care for ill Gulf War Veterans.

1. Enhanced scheduled educational/informational interactive fora with clinicians using multiple modalities of communication media (e.g., webinars, in-person sessions with

internet access, etc) to make sure that the information on research studies and research results are included.
2. Evaluate such to determine the most effective and efficient means of presenting new information and capturing the intended audience.
3. Use several Outlook groups to widely promote forums and webinars.
4. Include the latest clinical and research information on the OPH-maintained VA GWVI website and promote it to clinicians as well as to Veterans.
5. Ensure that the latest research findings are communicated to clinicians through review of shared materials by the GWSC, Director of Gulf War Research program, OPH and RACGWI, and CDMRP.

Timeline for new initiatives:

Goal 1: March 1, 2012: GWSC membership altered as necessary and in place.

June 1, 2012: GWSC begins monthly meetings; mechanisms are in place to support its work.

Fall, 2012: GWSC reports to RACGWI and other advisory groups.

Goal 2: June 1, 2012: VA/DOD coordination and collaboration plans are in place.

Goal 3: Fall 2012: Gulf War Veterans' Illnesses meeting will be held.

Goal 4: May 1, 2012: Develop mechanisms for informing and communicating with Gulf War Veterans and their family members and caregivers on the efforts conducted under the strategic plan.

May 1, 2012: Create one or more resources related to research studies and research findings and establish a mechanism for communicating results through traditional means as well as web, social media, and other emerging technologies.

Goal 5: May 1, 2012: Establish one or more channels of communication and advertise schedule of upcoming educational sessions for clinicians.

5.8 TRANSLATE RESEARCH FINDINGS TO PRACTICE

5.8.1 Goal

Translate research findings into practice as rapidly as possible. Without exception, this is a problem in every field of medical, scientific, and engineering research. It is important to accomplish this translation, so that the benefits of research will be experienced by individuals the research was intended to help.

5.8.2 Research and Activities

VHA's Vision of Excellence includes providing exemplary services that are both patient-centered and evidence-based. For that reason, it is critical that research results that are relevant to Veterans be translated into our clinical treatments and processes of care. It is necessary to identify the barriers to implementing new treatments, whether they are technical or administrative, and to put strategies in place to determine how research can itself accelerate the application of new knowledge in clinical settings.

The translation of research findings can be placed into two categories:

- Type 1 translation, in which basic laboratory findings are turned into treatment concepts that are tested through clinical research studies such as randomized controlled studies. NIH Clinical & Translational Science Awards (CTSA) focus on Type 1 translation.

- Type 2 translation, in which accepted findings from clinical research results are implemented as part of routine clinical care practices. VA's Health Services Research and Development (HSRD) and Quality Enhancement Research Initiative (QUERI) focus on Type 2 translation.

There are also situations in which clinical research findings are equivocal, in which case, a hybrid approach ("pre-implementation") can be used, in which a medical procedure or treatment is provided to patients while additional data are collected in a systematic manner to allow future determinations of comparative effectiveness.

Successful translation requires collaboration between researchers and clinicians to determine the type of research that is appropriate for a given treatment. Clinical findings suggest the types of questions that are most relevant to clinicians and therefore can guide research planning to topics that are more likely to be used in actual practice. In the early phases of implementation, clinicians can also identify what they perceive as barriers to the evidence-based approach suggested by the research findings. Likewise, collaboration might indicate that "de-implementation" be done with a procedure if follow-up research suggests that the procedures/practices are not effective, wasteful of resources, or potentially harmful.

It is not possible to predict in advance whether any specific basic research finding can lead to a treatment concept that stands the test of clinical research. Additionally, initial positive findings in early phase clinical research studies frequently are overturned by subsequent clinical trials. It is important, therefore, to communicate this uncertainty with honesty and sensitivity, and, in particular, researchers interested in translation have a particular obligation to support a trusting patient-clinician exchange. This includes not overplaying preliminary results, however positive they may be initially. Researchers also need to expect the enduring nature of the patient-clinician relationship. A dashed hope based on a flawed research insight could lead to loss of trust in healthcare in general, with potential serious consequences.

VHA has successful models of researcher-clinician collaboration that embrace these principles. For example, Gulf War Veterans are generally pleased with treatment programs at the War Related Illness and Injury Study Centers (WRIISCs) where the physicians use a team approach to treat patients holistically; communication between patients and providers is essential and usually determines whether a patient stays in the VA healthcare system. The WRIISCs, under the direction of OPH, offer a number of special clinical programs for Veterans who have post-deployment health concerns. These programs focus on difficult-to-diagnose or medically unexplained symptoms and military environmental exposure concerns. These Centers are at the forefront of translating research into practice in the VA. The Centers offer a National Referral Program which provides comprehensive multidisciplinary health evaluations The WRIISCs also perform primary clinical research, provide exposure assessment clinics, and tele-health services.

In addition to assuring the implementation of results of clinical studies, WRIISCs have also used the hybrid approach for situations such as Complementary and Alternative Medicine (CAM) treatments, providing a requested treatment while doing the types of assessment needed to establish overall effectiveness. Preliminary results have been positive, but more analyses of CAM programs need to be conducted.

The WRIISCs are also an educational resource for combat Veterans, their family members and loved ones, and Veteran healthcare providers. Their educational programs provide information on topics ranging from environmental exposures and deployment health conditions, to self management techniques for chronic health concerns.

Once a promising technology or treatment has been selected to go forward, it continues to be subject to an adoption process that varies widely. One method is to set up specialty centers, where a particular treatment or treatment program is available. Another method is by developing educational programs for both Veterans and healthcare providers in the VA.

VA is also committed to Clinician Education and Training. VA is developing accessible, flexible and user-friendly training regarding health aspects of the Gulf War including Gulf

War Veterans' Illnesses to educate primary care physicians, compensation and pension examiners, environmental health clinicians, mental health professionals and social workers about the health effects, including gender specific health effects of service in the 1990–1991 Gulf War.

OPH programs, the Environmental Agents Service, and WRIISCs are coordinating with Patient Care Services, the Office of Academic Affairs, Veterans Integrated Service Networks, and VA Medical Centers to improve training on the unique exposure concerns of 1990–1991 Gulf War Veterans as well as returning OEF/OIF Veterans, and provide educational and clinical tools for evaluation of exposure risk and the health outcomes relevant to these risks.

5.8.3 Research and Action Plans - Funding Mechanisms

When Gulf War research results show a successful treatment, each successful treatment will be translated into clinical practice.

Moving treatments that have been shown to be successful in the research laboratory to clinical practice require different combinations of the following:

- Establish an evidence base through large well-designed research studies that can be published in leading journals.
- The VA Quality Enhancement Research Initiative (QUERI) is aimed at improving the quality of healthcare for Veterans. QUERI contributes to this effort by implementing research findings and innovations into routine clinical practice. As treatments and technologies emerge from research and are ready to be translated, appropriate knowledge from QUERI will be used to facilitate the transfer.
- Continuing education of VA healthcare providers is important because of the constant advances that are being made in research and the need to incorporate recent advances.
- ORD will coordinate with the War Related Illness and Injury Centers and disseminate research findings to these three centers.
- ORD will encourage Gulf War Researchers to apply for the Career Development Awards available through VA to build research capacity.

Research and clinical studies that involve Type 1 and Type 2 translation need to be encouraged and supported. Hybrid implementation and the principles of "pre-implementation" and "de-implementation" are important components of translating research into practice.

There needs to be close collaboration between clinicians and researchers in designing research projects irrespective of whether Type1 or Type 2 translation is anticipated.

Many different kinds of research that can produce new treatments need to be supported. These include research programs involving biomarkers, genetics and genomics, pharmacogenomics, proteomics, lipidomics, and other basic medical research topics.

Use of complementary and alternative medicine (CAM) will continue to grow. Where high quality evidence exists, research results from non-Veteran studies should be evaluated for potential implementation in VHA.

Pilot research projects evaluating possible new treatments should be encouraged. It is likely that ORD support of these studies would be a reasonable pathway for translating research into practice.

The outcomes of any new treatment procedures need to be subjected to rigorous statistical evaluation. Tracking patient outcomes would be essential to evaluating the utility of such projects. This might include reviewing records, tracking patient satisfaction, determining cost effectiveness, monitoring follow-up visits, and tracking medication usage and other indicators of wellness.

The VA funding mechanisms for translation of research results into practice will be initial studies through RFAs and CDMRP, followed by CSP development of multisite efficacy trials. WRIISC and QUERI mechanisms will be ultimately used for implementation studies. For an explanation of highlighted sections, see page 2.

6.0 CONCLUSIONS

The first "Working Plan" for Research on Persian Gulf War Veterans' Illnesses was published in 1995-96. Progress in medical and scientific research since this first Gulf War "Working Plan" was put forward include mapping the human genome, advances in medical imaging, and advances in medical informatics and electronic health information, to name but three technologies that were not available in 1995-96.

Examples of advances made by VA researchers have included: a survey of 30,000 Gulf War and Gulf War era veterans showing that 35% of Gulf War veterans suffer from multisymptom illness compared to 10% of veterans who did not deploy; imaging studies that have shown alterations in brain structure in Gulf War Veterans exposed to sarin/cyclosarin; and a pilot study demonstrating the efficacy of Continuous Positive Airway Pressure (CPAP) to partially relieve some symptoms of multisymptom Illness.

The leadership of VA Office of Research and Development, in preparing this Strategic Plan for Gulf War Research, has recognized that these and other substantial advances have been made. Collectively, they suggest new and innovative approaches to future Gulf War research.

The overall goal of the *Gulf War Research Strategic Plan 2012-2016* is to improve the health and well-being of Gulf War Veterans and to utilize emerging knowledge to prevent similar war-related illnesses in the future.

Progress has been made in Gulf War Research, yet much work remains to be done to fully achieve effective treatment and prevention of multisymptom illness and similar conditions . This Plan has been formulated to accelerate this progress and to identify diagnostic biomarkers and effective treatments within the timeframe of the Plan. The *Gulf War Research Strategic Plan 2012-2016* will be reviewed annually by the Gulf War Steering Committee and the Research Advisory Committee on Gulf War Veterans Illnesses, and updated as needed.

Appendix I. Major Activities Involved in Linking Multiple Datasets into a Usable Interactive Database

Based on the experience gained by developing the Pre-9/11 Report, the Post-9/11 Report and their supporting data system, SWAVETS, members of the VA Gulf War Integrated Project Team offer the following high-level overview of the major activities involved in linking multiple datasets and integrating data into a usable database. Not all of the activities listed below will be required for all linkage projects. Similarly, some linkage projects may require additional tasks not documented here. In considering the outlined activities, several points deserve emphasis:

- While much of the work in any data linkage project will focus on determining how data may be matched across multiple datasets, such projects must also incorporate all applicable requirements relative to information protection and information security.
- Successful linkage projects require up-front consideration of both information technology-related and administrative parameters.
- Efficient linkage projects typically require that multiple activities be conducted in parallel.

Information Protection

1. Develop a comprehension of Federal and organizational (agency-specific) requirements that results in the implementation of measures that meet or exceed privacy, information security and protection of human subject requirements.
2. Ensure compliance with all aspects of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), if applicable.
3. Verify compliance with Confidential Information Protection and Statistical Efficiency Act (CIPSEA) requirements, if applicable.

Information Security

1. Verify that an applicable Authorization to Operate (ATO) is in place for the information system(s) to be used in the data linkage project.
2. Ensure compliance with the certification and accreditation (C&A) requirements.
3. Check to make sure that the linkage project team has completed all agency-required training pertaining to information security and healthcare data utilization.
4. Ensure that project team members have undergone appropriate background checks, if applicable.
5. Double-check that all appropriate contracting requirements have been met, if applicable.
6. Ensure that inter-agency relationships are formalized through current memorandums of understanding (MOUs).
7. Ensure that protocols for data sharing and data transfer are current and in place through appropriate data agreements.
8. Work with the Information Security Officers to ensure that appropriate clearances have been obtained for data access and data sharing.

Information Technology

1. Define the operating environment for the data linkage project, including identification of both the development and the production servers and the platform (e.g., SQL, Oracle, etc.) that will be used.
2. Determine how the users will access or interface with the linked datasets (e.g., dashboards).
3. Verify that server capacities are adequate to support the linkage project.
4. Develop disaster recovery procedures in the event of a catastrophic event.

Administration

1. Establish the scope and objectives for the effort.
2. Identify the data to be used in the data linkage project.
3. Determine authoritative sources for all data to be used in the linkage project.
4. Develop standardized definitions for the study cohort and for all characteristics (variables) of interest for the study population.
5. Develop business rules and associated data requirements for selecting and retrieving data from the defined authoritative data sources.
6. Identify the data integrator for the linkage project. (Note that the data integrator may be an individual, a group of individuals, an organization or an agency.)
7. Develop a data dictionary, a user's manual and other documentation for the linkage project.
8. Determine requirements and procedures for user acceptance testing and user training.

Data Selection

1. Identify the datasets to be integrated.
2. For each data table, identify the variables of interest and develop a structure for that data table.
3. Create a master person-table (one record per individual; no duplicates). This master table defines the study cohort and serves as the centerpiece of the database.
4. Perform data checks to identify and remove duplicates, invalid records, etc., from the master person-table.

Data Linkage

1. Develop a structure for the linked datasets. Again, note that the master person-table serves as the center of this structure, and that supporting information is connected to this master person-table through selected characteristics. (See next bullet.)
2. Select appropriate identifier(s) to link the master person-table to other data tables. The selected identifier (e.g., social security number, scrambled social security number, etc.) or set of identifiers should be chosen in a way that results in the greatest number of accurate, usable records.
3. Define the desired sets of linked data tables that will be needed to support the project.
4. Develop multidimensional models, using the available data, to create data "cubes," in accordance with the project objectives.
5. Note that different identifiers may be used to support different linkages.
6. Note also that datasets are matched on a linking variable or set of variables. Data linkage does not involve appending datasets except, on occasion, during updates (see below).

Data Validation

1. Develop appropriate procedures for verifying and validating linked data.
2. Perform validation checks throughout the entire course of the linkage project.

Data Reporting and Analysis

1. Define the specific reports and analyses required to support the linkage project objectives.
2. Determine the format for the required reports and analyses.
3. Determine how the reports and analyses will be transmitted and shared with the project team.
4. Implement the reporting and analysis in accordance with the defined requirements.
5. If the linkage project includes an exploratory analysis component, determine who will conduct the analyses, how the data will be transferred to the analyst, and the platform on which the exploratory analyses will be conducted.

Training

1. Determine whether end users will require training to fully understand and utilize the linked data.
2. Determine how the training should be delivered.
3. Implement the training program in accordance with the defined requirements.

Updates and Maintenance

1. Determine how frequently the data will be updated.
2. Determine the mechanism for updating the linked datasets.
3. Determine whether the updated information will be delivered as a "write-over" of the original dataset(s), or whether new data will be appended to the existing data files.
4. Implement the updates in accordance with the defined requirements and schedule.

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APPENDIX III. – List of Abbreviations

ACTH	Adrenocorticotropic Hormone
ALS	Amyotrophic Lateral Sclerosis
BBB	Blood-Brain Barrier
BLRD	Biological Laboratory Research and Development
CAM	Complementary and Alternative Medicine
CBT	Cognitive Behavioral Therapy
CCEP	Comprehensive Clinical Evaluation Program
CDMRP	Congressionally Directed Medical Research Programs
CFS	Chronic Fatigue Syndrome
CNS	Central Nervous System
CPAP	Continuous Positive Airway Pressure
CSP	Cooperative Studies Program
CSRD	Clinical Sciences Research and Development
CTSA	Clinical and Translational Science Awards
DHWG	Deployment Health Working Group
DoD	Department of Defense
DSI	Diffusion Spectral Imaging
DTI	Diffusion Tensor Imaging
FDG	Fluorodeoxyglucose (F-18)
fMRI	functional Magnetic Resonance Imaging
GLUL	Glutamate-Ammonia Ligase
GW	Gulf War
GWAS	Genome-Wide Association Studies
GWIRP	Gulf War Illness Research Program
GWRSP	Gulf War Research Strategic Plan
GWSC	Gulf War Steering Committee
GWV	Gulf War Veteran
GWVI	Gulf War Veterans' Illnesses
GWVITF	Gulf War Veterans Illnesses Task Force
HHS	Department of Health and Human Services
HSRD	Health Services Research and Development
IBS	Irritable Bowel Syndrome
IOM	Institute of Medicine
KTO	Kuwait Theater of Operations
MEG	Magneto-Encephalography
MMUS	Multiple Medically Unexplained Symptoms
MRI	Magnetic Resonance Imaging
MSI	Multisymptom Illness
MVP	Million Veteran Program
NGS	Next Generation Sequencing
NIH	National Institutes of Health
OPH	Office of Public Health
ORD	Office of Research and Development

PCR	Polymerase Chain Reaction
PCS	Patient Care Services
PET	Positron Emission Tomography
PGIRCC	Persian Gulf Interagency Research Coordinating Council
PGVCB	Persian Gulf Veterans Coordinating Board
PHS	Public Health Service
PON1	Paraoxonase/arylesterase 1
PTSD	Post-Traumatic Stress Disorder
QUERI	Quality Enhancement Research Initiative
RACGWVI	Research Advisory Committee on Gulf War Veterans' Illnesses
RFA	Request For Application
RRD	Rehabilitative Research and Development
SDB	Sleep Disordered Breathing
SWAVETS	Southwest Asia Veterans System
TSPO	Translocator Protein
UDX	Undiagnosed
USPIO	Ultra-Small Paramagnetic Iron Oxide
VA	Department of Veterans Affairs
VBA	Veterans Benefits Administration
VHA	Veterans Health Administration
VISN	Veterans Integrated Service Network
VSO	Veterans Service Organization
WRIISC	War Related Illness and Injury Study Center