NEW DRAFT

GULF WAR RESEARCH STRATEGIC PLAN

2012-2016

Highlights indicate material that has been edited or added since the January 23, 2012 version

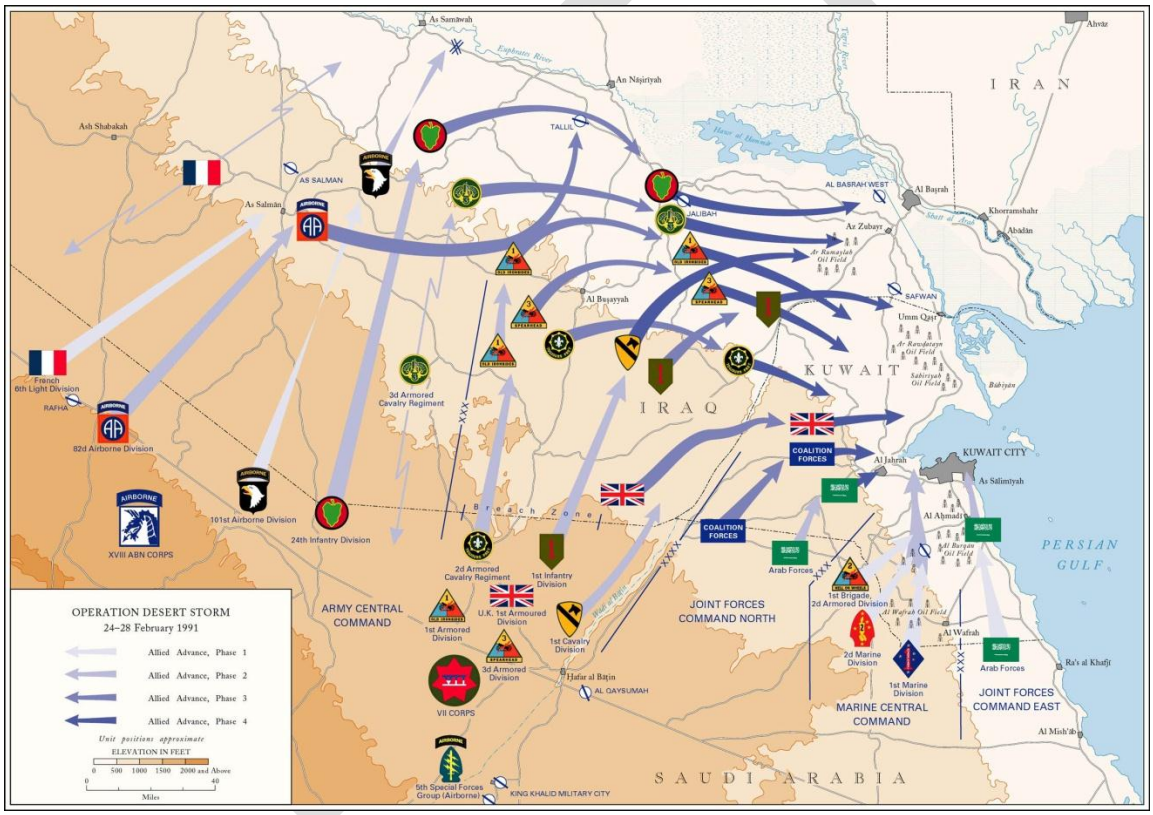

Table of Contents

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 more than 390 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 broadly effective treatments have been identified to date. The VA and CDMRP Gulf War Research programs continue to solicit proposals aimed at identifying new treatments for ill Gulf War Veterans. The health and well-being of Veterans is the main focus of the Gulf War Research Strategic Plan. VA is committed to studying and treating chronic multisymptom illness and any other conditions affecting Gulf War Veterans. No Veteran should feel that his/her particular ailment is less important to VA than any other.

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 [56]. 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 *Gulf War Research Strategic Plan 2012-2016* is VA's response to the IOM report. **Its overall goals are to:**

- **Improve the health and well-being of Gulf War veterans.**

- **Utilize emerging knowledge to prevent similar war-related illnesses in the future.**

As recommended by the IOM, the Plan has two branches that:

- Monitor the health of Gulf War veterans.
- Identify diagnostic biomarkers and treatments for ill Gulf War Veterans.

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 process RFA's frequently and to establish other research projects through executive action give 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 the five-year timetable.

The Plan has six major sections:

1.0 Executive Summary

2.0 Introduction and Background

3.0 Evolution of the Gulf War Strategic Plan

4.0 Summary of Gulf War Research Results and Past Federal Research Support

5.0 Gulf War Research Strategic Objectives 2012-2016

6.0 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. Establish a Case Definition of Chronic Multisymptom Illness

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 are most likely to 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, the National Research Advisory Council, 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 [83]. To that end, the PGVCB identified 19 major epidemiological research questions and subsequently added two additional questions in 1996 [84]. 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 390 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[56]. 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."

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 [83, 84]. It is VA's response to the need and opportunity identified by the 2010 IOM report.

In the process of developing the Gulf War Research Strategic Plan, ORD has utilized two federal advisory committees, the Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI) and the National Research Advisory Council (NRAC), as well as ORD's Gulf War Steering Committee (GWSC). An outline of a draft strategic plan was discussed at the GWSC meeting in April, 2011. In June, 2011, a draft prepared by ORD was presented to the RACGWVI by the chairman of the GWSC. Based on the ensuing discussion, the GWSC chairman suggested the formation of ten working groups to recommend modifications and improvements to the draft plan.

The working groups generally consisted of six or more individuals who were either RACGWVI members, NRAC members, GWSC members, VA employees, or scientists/physicians recommended by RACGWVI or VA. More than 45 individuals participated, and nine of the working groups held meetings between September and November, 2011. These groups were responsible for reviewing the sections of the draft strategic plan which dealt with introductory and background material, symptomatic and specific treatments, databases and surveillance, case definitions, genetics and genomics, biomarkers, animal models, coordination among stakeholders, and translation of research into practice.

The recommendations of these groups were submitted for consideration at a GWSC meeting in December, 2011. The GWSC provided guidance to the final working group whose task it was to combine the recommendations of the other nine working groups.

This group held meetings in December, 2011, and January, 2102, in preparation for the upcoming RACGWVI meeting.

In late January, 2012, at a meeting of the RACGWVI, which was also attended by some members of the NRAC and GWSC, the revised draft Gulf War Research Strategic Plan was discussed at length. After the meeting, additional revisions were made based on the recommendations of the RACGWVI and the mission of VA, and the newly revised Gulf War Research Strategic Plan was presented to the entire NRAC at their meeting in late February, 2012. With NRAC recommendations, the draft Gulf War Research Strategic Plan was ready for final review by the RACGWVI and NRAC at their respective meetings in June, 2012.

The *Gulf War Research Strategic Plan 2012-2016* will be reviewed annually by the Gulf War Steering Committee, the National Research Advisory Council, and the Research Advisory Committee on Gulf War Veterans' Illnesses to recommend modifications as needed.

2.3 VA Research and Development Strategic Plan: 2009-2014

The *VA Research and Development Strategic Plan: 2009-2014* is the strategic plan for all research in the VA Office of Research and Development (ORD) [80]. It 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.

The *Gulf War Research Strategic Plan 2012-2016* complements the existing *VA Research and Development Strategic Plan: 2009-2014*. 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.

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?" [83, 84]. 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.
- 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.
- Information on the long-term, cause-specific mortality among Persian Gulf Veterans.

In the revised 1996 Working Plan, 21 epidemiological research questions were formulated [84]. 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* [56]. 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 [48-61].

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 [56].

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* was also comprehensive and provided specific research recommendations [91].

By carefully comparing the RACGWVI and IOM reports, as well as other information [62, 88, 94, 98], 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.

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 [18-25, 75, 76, 85-87].

4.1 Summary of Federal Funding of Gulf War Research 1994-2011

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	$ 10,223,231	$ 0	$ 24,079,983
2011§	$ 5,591,875	$ 34,720	$ 3,145,000	$ 0	$ 8,771,595
Total 1994-2011	$ 125,689,415	$ 39,295,956	$ 254,976,566	$ 14,000,105	$ 433,962,042

* 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 FY2011. DoD estimate does not include CDMRP funds.

The VA estimate for FY2010 includes 40% 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 2012-2016

5.1 Symptomatic and Specific Treatments

5.1.1 Goal

To develop symptomatic and specific treatments for ill Gulf War Veterans. The most urgently needed Gulf War research studies are those that advance identification of effective treatments that can substantially improve veterans' health and quality of life, and this is the focus of the Gulf War research portfolio. To address this important objective, both DoD and VA have funded a growing number of treatment-related studies in recent years. These include clinical studies to evaluate treatments for chronic multisymptom illness in affected veterans, as well as preclinical studies to evaluate treatments to improve neurobiological parameters. 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 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." [53].

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." [56].

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." [91].
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." [91].

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 [117].

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 [26].

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 [77].

5.1.5 Research Plans and Funding Mechanisms

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. VA Researchers will investigate new treatments including:

- A goal to expand the number of treatment trials within the 5-year strategic planning period will be established in order to increase the chance of obtaining more viable and effective treatments for GWVI. The goal is dependent on successful identification of potential treatment targets and completion of preclinical development. A more focused effort to identify mechanistic-based treatments for GWVI will be a priority. 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.

- Expand the number of “small projects” (pilot trials) in the area of new treatments that could lead to larger studies (individual pilot projects, single-site pilot clinical trials).

- Establish a virtual Gulf War Treatment Research Coordinating Activity to identify potential pilot study hypotheses and track their results as appropriate.

- In order to identify at-risk Veterans who could benefit from enhanced preventive medical care including obesity prevention, smoking cessation, and other programs, ORD will work with the Office of Health Information to develop a mechanism to identify GWVs in the computerized patient record system. This could assist primary care and specialty providers in their attempts to provide optimal care.

- More complementary and alternative or integrative medicine therapies should also be studied for GWVI. Such treatments could include mindfulness based therapies as well as acupuncture, laser acupuncture, Tai-Chi, Qi gong, meditation, nutritional therapies, and probiotics.

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

- Explicit criteria (case definition) for chronic multisymptom illness will be adopted and used as uniformly as practical in clinical research on proposed therapies.

The VA funding mechanisms for Symptomatic and Specific Treatments will initially be through RFAs, then followed by CSP development of multisite trials as warranted by preliminary data and as funding allows.

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. Existing databases should be combined with newly-developed databases as necessary to address specific projects when it is clear that doing so will address a specific problem. 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, it would be useful to have a data warehouse 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 could 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.

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 multisymptom illness to determine which of these treatments may be effective. The continuing paucity of effective treatments for Veterans suffering from chronic multisymptom illness 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 illness 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 chronic multisymptom illness 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 where treatments 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 later in this section:

- Promote ongoing surveillance efforts of Gulf War and Gulf War Era Veterans.
- Work to 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.

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 [56].

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 [90, 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 [90, 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 [91, 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 [92, http://www.va.gov/RAC-GWVI/docs/Committee_Documents/RACSurveyRecs_Final110210.pdf)].

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 [65, 68, 114].
- Multiple large Department of Defense datasets assembled to assess birth-defect rates and pregnancy outcomes in Gulf War Era Veterans [3, 4, 5, 15, 63, 93, 108, 109].
- Multiple large datasets from Department of Defense-sponsored studies of hospitalization rates in Gulf War Veterans [7, 8, 32, 43, 44, 97].
- 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, 2001 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 [78]. 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 Veterans' Illnesses Biorepository (CSP #501B).
- Million Veteran Program (MVP, CSP #G002).
- Gulf War Era Cohort and Biorepository (CSP #585).

5.2.6 Action Plans

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

- Work with OPH to 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.
- Work with VA's National Center for Veterans Analysis and Statistics (NCVAS) to enhance the statistical reporting capabilities in VA's Pre-9/11 Report [78] 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.
- Investigate the possibility of developing 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.
- Investigate the possibility of using the CSP #585 cohort to 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.

Goal 2: Work to improve the usefulness of existing databases by attempting to link them and then integrate them into a data warehouse and make them available for use by researchers.

- Convene a meeting of relevant experts to discuss and recommend possible Gulf War data coordination and linkage efforts at VA.
- Evaluate the issues pertaining to human subjects' protections in order to address the consent and privacy issues impeding the ability to link various data sources.
- Encourage the use of 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.
- Investigate the feasibility of forming a Gulf War Era Veterans' data repository that includes and links federal datasets for this population as necessary and also makes de-identified data available to researchers to address specific questions related to the health of Gulf War Veterans.
- Investigate the feasibility of developing an inventory as part of a data repository that includes protocols for the studies and the structure and content of the databases, including an inventory of data elements in each.
- Promote methods for research data-sharing between VA and DoD in support of the DHWG so that DoD data can be used by VA researchers and vice versa.
- Investigate the feasibility of linking existing earlier databases with MVP and CSP #585 if warranted by specific research projects.
- Work with the OHI to develop a mechanism to identify GWVs in the VA medical record to facilitate identification of potential subjects for research studies and to enable linkage with other databases.
- Encourage VA researchers to provide results in a way that identifies Gulf War Veterans as a group so that meta-analyses and similar comparisons can be conducted and to submit data pertaining to Gulf War Veterans that can be shared appropriately.
- Enhance MVP as a resource for research on Gulf War Veterans to:
    - Co-enroll Gulf War Veterans in MVP and CSP #585.

- 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.

- Support projects to 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.
- Promote the development of a separate database focused on the women deployed to the Gulf and their specific health issues.
- Promote the use of existing databases to develop case registries and design case-control studies as appropriate.

5.3 Establish An Evidence-Based Case Definition of Chronic Multisymptom Illness in Gulf War Veterans

5.3.1 Goal

To establish a consensus case definition for chronic multisymptom illness in GWVs, 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 psychological 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. Multiple large population studies [9, 13, 27, 28, 47, 64, 101] have identified similar statistically-defined symptom domains that affect Gulf War veterans at

significantly excess rates relative to veteran comparison groups. The manner in which these symptoms have been assessed, counted, and combined by different research groups in order to define a multisymptom illness complex has been highly variable, however, resulting in substantially different case definitions used by different studies. At least 10 different approaches for characterizing symptomatic illness in Gulf War veterans have been described.[91] Examples include requiring that veterans endorse at least one symptom, [100] or two symptoms out of three types, [28] or five symptoms from a general list,[111] or obtain certain scores on factors defined by principle components analysis of symptoms, [36, 64] or meet chronic fatigue syndrome criteria [115] or have been diagnosed with any of a number of medical and psychiatric conditions.[33] 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. "Chronic multisymptom illness" is used here as an umbrella term, referring to the excess burden of symptoms such as gastrointestinal problems, fatigue, joint and muscle pain, and cognitive problems associated with military service in the 1990-1991 Gulf War.

The lack of a consensus, evidence-based case definition for chronic 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, are too broad, or too narrow, can potentially obscure or misrepresent findings that are important for better understanding chronic multisymptom illness. 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 important that an evidence-based, consensus case definition for use in studies of ill Gulf War Veterans be developed. 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 chronic 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. Once completed, the plan recognizes the need to revisit the consensus case definition over time, as additional data and new insights related to chronic multisymptom illness in GWVs, and illness subgroups, become available.

The case definition process should be completed as efficiently as possible, within a targeted time period, recognizing the 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 chronic multisymptom illness and improving the health and lives of affected Veterans. In the meantime, while a consensus case definition is being developed, researchers should identify and justify the choice of case definition in their studies.

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, [56, 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 [91, 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." [91, 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 chronic multisymptom illness, but did fund a recent study that validated the factor structure for a set of three syndromes previously identified [46]. 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 illness in Gulf War veterans [28, 35-37, 40, 64, 100, 112]. These include a case definition for "Gulf War Unexplained Illness" developed at VA's Portland Environmental Hazards Research Center [100], identification of a unique "Gulf War Syndrome" using factor analysis of symptom data in VA's 1995 national survey of Gulf War era veterans [64], 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 [40].

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

The lack of objective diagnostic markers for chronic 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 by advanced imaging technologies even before symptoms are recognized.

The consensus case definition for chronic multisymptom illness should 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 chronic multisymptom illness and/or illness subgroups.

The plan for establishing a consensus case definition for chronic 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.

- **Expert Consensus Panel.** The case definition effort will convene an expert chronic multisymptom illness Case Definition Consensus Panel to:
  - review existing resources and identify considerations for evaluating chronic multisymptom illness case definitions and
  - establish criteria for a consensus case definition, to be published along with guidelines for its use.

  The panel will include scientists with the expertise required to achieve case definition objectives.

- **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 Chronic 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.

5.3.5.1 "Optimizing" a Case Definition for Chronic Multisymptom Illness in Gulf War Veterans: 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 chronic multisymptom illness cases in GWVs, 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 non-deployed 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 psychological 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

5.3.5.2 Specific Objectives for Establishing a Consensus Case Definition for Chronic Multisymptom Illness in Gulf War Veterans

The action plan for developing and publishing a consensus case definition for chronic multisymptom illness will address the objectives summarized below. The plan recognizes the need for a consensus case definition to be used by all clinical and epidemiologic studies of Gulf War veterans conducted under the strategic plan. Activities will be initiated upon adoption of the strategic plan and implemented with a targeted completion date within two years:

ORD will solicit and fund the development of a consensus case definition.

- 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 will be obtained.
- Methods to evaluate case definitions will be developed.
- Analytic approaches useful for revising existing case definitions or devising new case definitions will be developed.
- Analytic results will be reviewed.
- Case definition criteria will be developed.
- A report will be submitted.

5.3.5.3 Mechanism for Implementing the Case Definition Objectives

The case definition effort will use appropriate solicitation and funding mechanisms most capable of supporting:

- completion of the case definition within the desired two-year timeframe,
- use of analytic methods that are most scientifically credible for defining cases as objectively as possible,
- project execution by investigators whose expertise is most relevant for developing a symptom-based case definition for chronic multisymptom illness in Gulf War Veterans.

5.4 Genetics/Genomics/Systems Biology

5.4.1 Goal

To advance the understanding of the biological networks involved in Gulf War Veterans' Illnesses by applying genetic, genomic, and systems biology approaches. Molecular sources of inter-individual variation in the response to the environmental toxins which may have caused the diseases will be elucidated. Genetic variability has long been suggested as a potential contributing factor in Gulf War illness, and may explain, in part, why some veterans became ill in connection with 1991 Gulf War deployment, while others did not. The overarching aim is to identify genetic and genomic factors which may modify the spectrum of symptoms affecting Gulf War Veterans, with a view that could enable predictive personalized therapy for Veterans. This will require identifying comprehensive models describing the biological networks regulating the disease phenotype. Several studies have provided preliminary evidence that Gulf War illness may be associated with genetic factors [33, 45, 71-73, 79, 106] , including those associated with certain enzymes that act to neutralize adverse effects of neurotoxicant exposures. Questions concerning specific genes that may have played a role in Gulf War illness have focused on genetic variability in enzymes such as paraoxonase (PON1) and butyrylcholinesterase (BChE), which bind and metabolize aceytylcholinesterase (AChE) inhibitors to provide protection from their adverse effects.

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.” [53].

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.” [91, p. 250].

5.4.4 ORD Research

There are no completed studies that explored the association of genetic variants with GWVI in Veteran cohorts. The Cooperative Studies Program is currently recruiting cohorts that will enable studies into the genetics of GWVI. 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 [110].

A small mechanistic study used a systems biology approach to assess the immune network response to an exercise challenge in veterans with and without chronic multisymptom illness. Statistical analysis of the identified biological networks supported an autoimmune component in chronic 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 [67].

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 [81].

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 ill GWVs. 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, among others, may act through epigenetic, mutational, and/or stimulatory means modifying expression in the cell.

Goal 1. The VA will enable both established and emerging genetics, genomics and systems approaches by:

- 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;
- conducting ORD-initiated studies based on the CSP cohorts;
- funding investigator-initiated studies that access data and biological material collected from the CSP cohorts, or previously recruited cohorts.

Goal 2. 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 GWVI, the overarching principles that will guide genetic, genomic and systems biology research will be the:

- design of approaches that enable both discovery and replication;
- in-depth characterization of the clinical phenotype by survey mechanism - including longitudinal assessments - to enhance the likelihood of identifying genetic/genomic signals;
- 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;
- careful selection of control cohorts based on population study principles;
- focus on identifying the genetic variants that contribute to disease through genetic approaches (e.g, sequencing, quantitative PCR, etc.).

Goal 3. Two cohorts will be developed as the central sources for genomics approaches. The Gulf War Era Cohort and Biorepository (CSP #585) will be a primary source for the discovery of candidate genetic variants. The Million Veteran 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 particular utility for replication studies that follow-up on discoveries made in the Gulf War Era Cohort and Biorepository (CSP #585).

- **Gulf War Era Cohort and 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 is targeted 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 [17], 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 exclusively 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:

- Veterans Administration Biorepository (CSP #501) is a cooperative effort to collect high quality biological specimens linked to clinical information from consenting Veterans for use in biomedical research on ill Veterans. Initial efforts have focused on collection of post-mortem 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 Veterans' Illnesses Biorepository (CSP #501B): This pilot project will gather critical information and test the feasibility of developing a collection of high quality post mortem biological specimens 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

To identify biomarkers that may be present in ill Gulf War Veterans. Biomarkers are quantitative biological measures that can facilitate the diagnoses of GWVI and allow monitoring disease progress and a patient's 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.

For GWVs with chronic multisymptom illness, no laboratory testing methods are available to accurately diagnose individual patients, but studies from different research groups have identified objective biological measures that significantly distinguish groups of ill GWVs healthy controls. Identified differences relate primarily to brain structure and function [11, 12, 31, 38, 42, 69, 70, 103], function of the autonomic nervous system [16, 31, 39, 66, 82, 95, 102, 104], neuroendocrine alterations [29, 30, 113], immune parameters [96, 107, 110, 115], and coagulation indicators [6, 41]. These biological findings are generally considered preliminary, since most have been evaluated in one study, or a limited number of studies, using different measures and methods. Taken together, however, such studies have been useful in providing insights concerning the diverse biological processes that may underlie the causes of chronic multisymptom illness, and point toward areas of research that can potentially lead to useful biomarkers.

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:

- **Biomarker discovery**
    - Discovery of a differentiating signature in a measurement as a candidate biomarker.
    - 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.

- **Biomarker qualification**
    - Development of a robust and practical method for biomarker detection.
    - Proof-of-principle in controlled experimental settings.
    - Establishing that the biomarker adequately selects and characterizes the presence and / or severity of the outcome of interest in specific patient populations.
    - Understanding the candidate biomarkers' clinical performance with regard to the level of sensitivity and specificity achieved under a specific context of use.
    - Identification of clinical factors which might interfere with biomarker interpretation.

- **Biomarker application**
    - 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

There have been several studies demonstrating that chronic multisymptom illness is associated with specific and quantifiable changes detected using blood-based analysis and neuroimaging techniques suggesting that the identification of a reliable set of biomarkers is a realistic goal for chronic multisymptom illness.

According to the IOM, "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." [56]. "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 non-deployed veterans. Such biomarkers might include signatures of immune activation, brain changes detected through imaging, inherited genetic variants, molecular profiles of gene expression, other epigenetic markers (e.g., modified DNA structures), or specific viral exposures."

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." [91, p. 285].

Specific RAC recommendations stated that biomarker research should include:

5.5.3.1 "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." [91]

5.5.3.2 "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." [91].

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 [42].

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 [12].

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 GWveterans with and without PTSD may reflect differences in peripheral and central glucocoid receptor responsiveness [113].

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 chronic multisymptom illness. This is a new potential biomarker for Gulf War research [6].

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. The focus will be to identify biomarkers that are elevated at baseline assessment and will help define disease pathophysiology for ill GWVs. 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. Therefore, biomarker development will focus on these areas where initial studies have identified preliminary marker differences in GW veterans with 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 or success of therapeutic interventions. Implicit in these studies and strategy will be that carefully-defined phenotypes will be used and that specific case definitions and standard collection of biodata (blood, tissue, and 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.

Biomarker qualification studies for areas where initial biomarkers of discovery have shown promise but require further study and validation will include but not be limited to the following (see below). Whenever practical, studies should consider combining qualification of multiple biomarkers in the same study populations (i.e., brain and blood markers of inflammation).

- Advanced neuroimaging techniques (MRI, PET, DTI, MEG) to further delineate surrogate biomarkers of GWVI from promising preliminary studies.

- Immune response mediator biomarkers that are associated with chronic inflammation including proinflammatory cytokines, chemokines and other immune functions.

- Hypothalamic-Pituitary-Adrenal axis biomarkers in ill GWVs including cortisol and other measures of neuroendocrine function (including epigenetic studies).

- Blood coagulation studies of platelet tissue factor and other relevant markers of inflammation

- Broad biomarkers of neurologic and/or neurodegenerative effects in ill GWVs and/or neurotoxicant exposures (degeneration stains, glial activation stains, myelin stains in post-mortem tissue)

- Blood and CSF studies of proteomics, metabolomics and lipidomic markers in ill GWVs.

- Biomarkers of autonomic system dysfunction in ill GWVs.

- Biomarkers of irritable bowel syndrome (IBS) from altered gastrointestinal flora or microbiome that may relate not only to gastrointestinal symptoms but other symptoms of chronic multisymptom illness 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 as appropriate. This extremely valuable CNS tissue and blood biodata will allow for biomarker development and qualification studies as tissue and blood samples will be shared with independent researchers and studies evaluating potential biomarkers in ill GWVs. 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.

- 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.

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 also to leverage funding from other sources.

5.6 Animal Models

5.6.1 Goal

To 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 the illnesses facing GWVs, 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 need to identify therapies to treat ill Veterans could also be addressed by screening potential treatments in animal models, and this emphasis on treatments should guide animal studies as Gulf War research moves forward.

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Animal studies have been used to evaluate the effects of a variety of GW-related exposures and conditions [91]. Recent animal-based studies of exposures implicated in chronic multisymptom illness reveal the involvement of subtle cell-signaling processes that may underlie persistent symptoms exhibited by ill veterans [1, 99, 105]. Further characterization of these effects in animal models may lead to the identification of targets for therapeutic intervention.

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." [56] The IOM report called for "a renewed research effort…to better identify and treat multisymptom illness in Gulf War veterans" [56], and studies that couple animal models and biomarkers may be useful in achieving that goal.

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 Report [91], a number of animal studies recently have identified biological effects of Gulf War exposures and combinations of exposures that were previously unknown [1, 99, 105]. Due to the consistency of findings relating chronic multisymptom illness 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

Examples of past ORD-funded research in animal models are given below.

The prevalence of irritable bowel syndrome (IBS) in Gulf War Veterans is so high that the condition is presumptively connected to service during the 1990-1991 Gulf War. In order to study IBS, VA researchers have developed a rat model of chronic visceral and somatic hypersensitivity in the colon. It was found that the application of intracolonic lidocaine reversed the effects of hypersensitivity in the rats [116]. This same treatment was successfully applied to patients suffering from IBS [89].

In another project, the femoral nerve in the mouse was used to study motor neuron regeneration for treating peripheral nerve injuries. By using surgical procedures on the

muscle and removing Schwann cells from the nerve, it was possible to influence the tendency of the neurons to project into the quadriceps muscle or the skin [74]. These results are encouraging for patients suffering from peripheral neuropathy and other sensory deficits.

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 (BLRD) 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 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 chronic multisymptom illness 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.
- 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 utilize the data obtained to identify, test (in animal models) and implement (in ill veterans) off-the-shelf therapies for GWVI.

5.7 Improve Coordination and Communication with Stakeholders

5.7.1. Goal

To improve coordination and communication among Federal partners, researchers, and the private sector.

5.7.2. 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 [56].

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 [91].

5.7.3. 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.

5.7.3.1 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.

5.7.3.2 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 funds VA investigators to perform 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).

5.7.3.3 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 theater of operations during the Gulf War.

5.7.3.4 Gulf War Steering Committee (GWSC)

VA organized a committee of experts from its own internal advisory board and on recommendation from RACGWI to facilitate the development of this strategic plan in 2011. 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.

5.7.3.5 DoD's Congressionally Directed Medical Research Programs (CDMRP)

Outside of VA, ORD coordinates with DoD's Congressionally Directed Medical Research Programs (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 veterans who have Gulf War Illness," and the mission is to "fund innovative Gulf War Illness research to identify effective treatments, improve definition and diagnosis, and better understand pathobiology and symptoms." [14] ORD and the CDMRP (GWIRP) currently maintain several levels of coordination:

- 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.
- The VA GW research portfolio and the GWIRP research portfolio are presented and discussed at one or more of the three 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.
- 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.

5.7.3.6 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.

5.7.3.7 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.

5.7.4 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.

5.7.5 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 in the Introduction (Section 5.7.2).

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; allow 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.

- Involvement of the ORD's Gulf War Steering Committee (GWSC) in providing regular advice for the VA Gulf War Research Program. Members will be added as appropriate.
- To supplement face-to-face meetings, virtual meetings of the GWSC should be conducted as needed to discuss research findings and provide advice regarding possible new initiatives, treatments, and translational applications.

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

- ORD and OPH will coordinate research on Gulf War Veterans' Illnesses that is funded and/or conducted by VA so that research goals and strategies are efficient and congruent.
- Representatives from CDMRP and VA will meet regularly to discuss topics for RFAs and research initiatives to be funded through the agencies in support of the scientific goals of the research strategic plan.
- Representatives from CDMRP's GWIRP will be invited regularly to the GWSC meetings to discuss DoD's research program.

Goal 3: 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.

- ORD will work to improve communication among Gulf War researchers using new online methodologies.
- VA will convene a meeting of Gulf War researchers in 2012 to improve sharing of research results. Regular meetings thereafter will be conducted, consistent with VA travel policies.
- VA will continue to participate in monthly meetings of the DHWG to share information about research programs with DoD.
- RACGWI will continue to conduct meetings to review research results and advise VA.
- ORD will continue to communicate with Veterans' groups on research results, treatment options, and policy changes through a variety of mechanisms.

- ORD will communicate with clinical centers in order to gain insights on issues and treatment alternatives that might influence the Gulf War 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.

- Work with OPH to 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.
- Work with OPH to disseminate material to VHA healthcare facilities for redistribution to Veterans and their family members and caregivers.
- Work with OPH to distribute information to Veteran Service Organizations and other stakeholders working on behalf of Veterans for redistribution.
- Make resources available on the ORD website and link the website to other VA sites such as OPH's VA Gulf War website and to VA's A to Z website.

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.

- Provide information on research studies to OPH so that they may incorporate research results into their educational/informational interactive forum with clinicians (webinars, in-person sessions with internet access, etc).
- Work with OPH to determine the most effective and efficient means of presenting new information and capturing the intended audience.
- Construct several Outlook groups to widely promote forums and webinars.
- Provide the latest clinical and research information to OPH for inclusion on their website.
- Ensure that the latest research findings are communicated to clinicians through meetings, seminars, webinars, and other means.

5.8 Translate Research Findings To Practice

5.8.1 Goal

To 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 OPH 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.
- Use the VA Quality Enhancement Research Initiative (QUERI) program to facilitate the translation of appropriate treatments and technologies from research to clinical practice. 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.
- 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.
- Coordination by ORD with the War Related Illness and Injury Centers to disseminate research findings to these three centers.
- Encourage Gulf War Researchers to apply for the Career Development Awards available through VA to build research capacity.

- Encourage and support research and clinical studies that involve Type 1 and Type 2 translation. Hybrid implementation and the principles of "pre-implementation" and "de-implementation" are important components of translating research into practice.
- Encourage close collaboration between clinicians and researchers in designing research projects irrespective of whether Type1 or Type 2 translation is anticipated.
- Support research in many different areas that can produce new treatments. These include research programs involving biomarkers, genetics and genomics, pharmacogenomics, proteomics, lipidomics, and other basic medical research topics as outlined in earlier sections of this document.
- Evaluate complementary and alternative medicine (CAM) research results from non-Veteran studies for potential implementation in VHA in instances where high quality evidence exists.
- Encourage pilot research projects evaluating possible new treatments. It is likely that ORD support of these studies would be a reasonable pathway for translating research into practice.
- Require that the outcomes of any new treatment procedures are 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, followed by CSP development of multisite efficacy trials. WRIISC and QUERI mechanisms will be ultimately used for implementation studies.

6.0 CONCLUSIONS

The first "Working Plan" for Research on Persian Gulf War Veterans' Illnesses was published in 1995-1996 [83, 84]. 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 [40, 63]; imaging studies that have shown alterations in brain structure in Gulf War Veterans exposed to sarin/cyclosarin [12, 42]; and a pilot study demonstrating the efficacy of Continuous Positive Airway Pressure (CPAP) to partially relieve some symptoms of multisymptom Illness [2].

The leadership of VA Office of Research and Development and others who prepared this Strategic Plan for Gulf War Research, have 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, the National Research Advisory Council, 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
ATO	Authorization to Operate
BBB	Blood-Brain Barrier
BLRD	Biological Laboratory Research and Development
C&A	Certification and Accreditation
CAM	Complementary and Alternative Medicine
CBT	Cognitive Behavioral Therapy
CCEP	Comprehensive Clinical Evaluation Program
CDMRP	Congressionally Directed Medical Research Programs
CFS	Chronic Fatigue Syndrome
CIPSEA	Confidential Information Protection and Statistical Efficiency Act
CNS	Central Nervous System
CPAP	Continuous Positive Airway Pressure
CSF	Cerebrospinal Fluid
CSP	Cooperative Studies Program
CSRD	Clinical Sciences Research and Development
CTSA	Clinical and Translational Science Awards
DHWG	Deployment Health Working Group
DMDC	Defense Manpower Data Center
DoD	Department of Defense
DSI	Diffusion Spectral Imaging
DTI	Diffusion Tensor Imaging
DZ	Dizygotic
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
HIPAA	Health Insurance Portability and Accountability Act
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

MOU	Memorandum of Understanding
MRI	Magnetic Resonance Imaging
MSI	Multisymptom Illness
MVP	Million Veteran Program
MZ	Monozygotic
NCVAS	National Center for Veterans Analysis and Statistics
NGS	Next Generation Sequencing
NIH	National Institutes of Health
OHI	Office of Health Information
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
RWG	Research Working Group
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
VERA	Veterans Equitable Resource Allocation
VHA	Veterans Health Administration
VISN	Veterans Integrated Service Network
VSO	Veterans Service Organization
WRIISC	War Related Illness and Injury Study Center