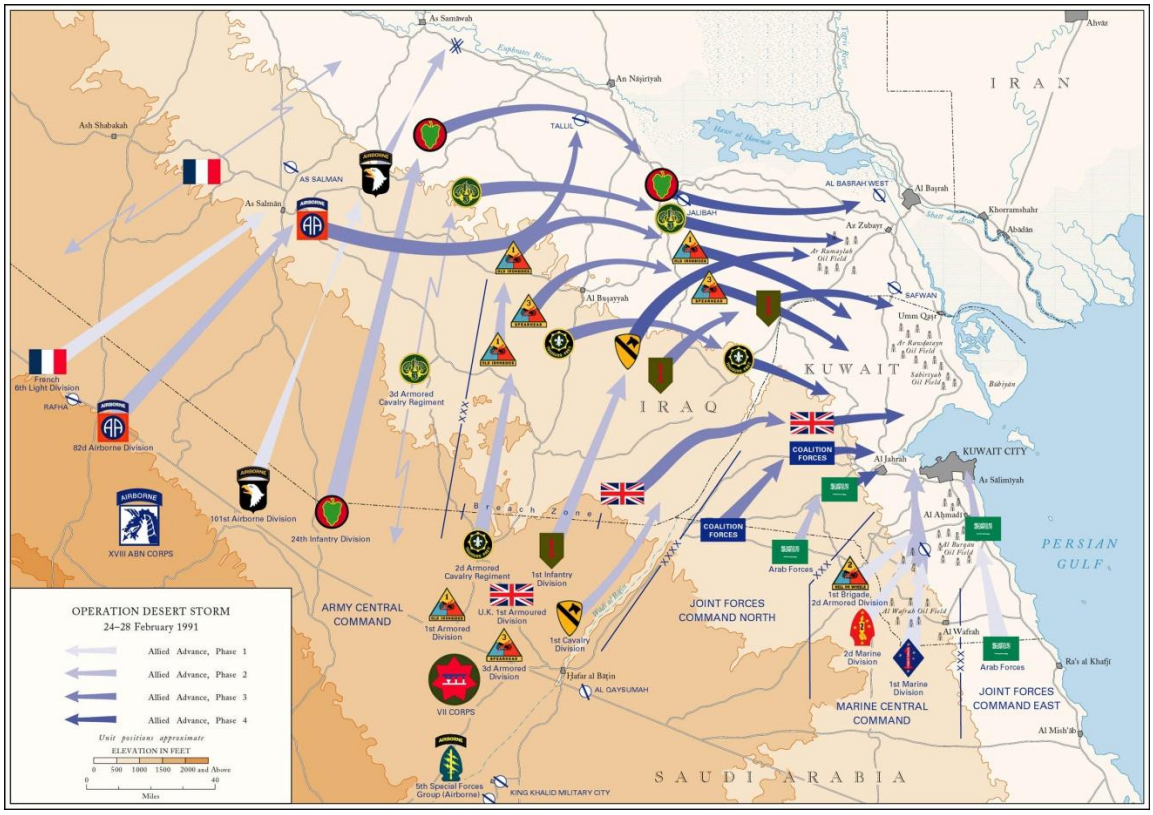
GULF WAR RESEARCH STRATEGIC PLAN

2013-2017

2015 Update



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1.0 EXECUTIVE SUMMARY

After Iraq's occupation of Kuwait in August 1990, the United States deployed military personnel to Southwest Asia in support of Operations Desert Shield and Desert Storm, collectively referred to herein as the Gulf War. At the conclusion of the first year of operations on July 31, 1991, the United States had deployed 696,842 military personnel from all five services and National Guard to the Southwest Asia Theater of Operations (SWATO).

During and after their return from the SWATO, 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.

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 370 research projects related to the consequence of military service in the Gulf War. These studies have yielded substantial insight into the health problems of Gulf War Veterans, including physiological differences between Veterans with multisymptom illness and Veterans of the same era who were not deployed. However, neither diagnostic biomarkers nor broadly effective treatments have been identified to date. The VA and Congressionally Directed Medical Research Programs (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.

In 2010, an Institute of Medicine (IOM) report, *Gulf War and Health, Volume 8*, reviewed the literature and accepted that this multisymptom illness is a diagnostic entity, which it found to be associated with Gulf War service. [1, pp. 204, 256] It further found that the symptoms "cannot be reliably ascribed to any known psychiatric disorder." [1, p. 108] Rather, "it is likely that Gulf War illness results from an interplay of genetic and environmental factors." [1, p. 261]

The IOM report concluded with a call for "a renewed research effort with substantial commitment to well-organized efforts to better identify and treat multisymptom illness in Gulf War veterans [1, p. 261] . . . to alleviate their suffering as rapidly and completely as possible." [1, p. 263]

In the preface to the report, the chairman of the IOM committee emphasized the need "to speed the development of effective treatments, cures, and, it is hoped, preventions."

He stressed that the committee regarded this goal as achievable: "We believe that, through a concerted national effort and rigorous scientific input, answers can likely be found." [1]

The *Gulf War Research Strategic Plan 2013-2017 (2015 update)* is VA's response to the reports of the IOM and the Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI), as well as other information. 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 requests for applications (RFA) frequently and to establish other research projects through executive action give it the flexibility to move at this accelerated pace. The Plan has six major sections:

1.0 Executive Summary

2.0 Introduction and Background

3.0 Evolution of the Gulf War Research Strategic Plan

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

5.0 Gulf War Research Strategic Objectives 2013-2017

6.0 Conclusions

The eight strategic goals that the *Gulf War Research Strategic Plan 2013-2017* 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 2013-2017 (2015 update)* has been formulated to accelerate this progress. The Plan will be reviewed periodically by the National Research Advisory Council (NRAC) and the RACGWVI, and updated as needed.

1.1 Summary of 2015 updates

In all sections where appropriate, old IOM and RACGWVI recommendations were updated and replaced with newer recommendations when available. ORD Gulf War research projects were updated to reflect newly-funded projects. Appendix I was removed.

The most extensive update is to Section 5.3, which now reflects the findings of the new IOM reports regarding research case definitions for Gulf War Illness and treatment for chronic multisymptom illness.

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, collectively referred to herein as the Gulf War. At the conclusion of the first year of operations on July 31, 1991, the United States had deployed 696,842 military personnel from all five services and National Guard to the Southwest Asia Theater of Operations (SWATO).

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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 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. 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. [2] To that end, the PGVCB identified 19 major epidemiological research questions and subsequently added two additional questions in 1996. [3] 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, DoD, and HHS have funded 370 research projects pertaining to the health consequences of military service in the 1990-1991 Gulf War, as reported annually to Congress.

These studies have yielded substantial insight into the health problems of Gulf War Veterans, including physiological differences between Veterans with multisymptom illness and Veterans of the same era who were not deployed. However, neither diagnostic biomarkers nor effective treatments have been identified. Studies by VA and others indicate that as many as 250,000 Gulf War Veterans are affected.
In 2010, an IOM report, *Gulf War and Health, Volume 8*, reviewed this literature and accepted that this multisymptom illness is a diagnostic entity, which it found to be associated with Gulf War service. [1, pp. 204,256] It further found that the symptoms "cannot

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2.2 Development of the Gulf War Research Strategic Plan 2013-2017

The original *Gulf War Research Strategic Plan 2013-2017* was the most recent and substantial revision of the original "Working Plan" put forth in 1995-96. [2] [3] It represented VA's response to the need and opportunity identified by the 2010 IOM report and the 2008 RACGWVI report.

In the process of developing the original Gulf War Research Strategic Plan, VA's office of Research and Development (ORD) utilized two Federal advisory committees, the RACGWVI and the NRAC. ORD's Gulf War Steering Committee (GWSC) was established as a sub-committee specifically to provide guidance and review of the original plan. 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 10 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 9 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 RACGWVI meeting held in January and February 2012.

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. Having successfully completed the intent of its charter, the GWSC was dissolved when the final Gulf War Research Strategic Plan was approved by VA.

In developing this update to the Gulf War Research Strategic Plan, ORD has again relied upon the expertise of our Federal advisory committees. The NRAC and RACGWVI will review this plan periodically to recommend updates as needed.

2.3 VA Research and Development Strategic Plan

The *Gulf War Research Strategic Plan 2013-2017* is informed by and consistent with both the *VA Research and Development Strategic Plan* (new plan currently under development) and the Veterans Health Administration (VHA) *Blueprint for Excellence* (http://www.va.gov/HEALTH/docs/VHA_Blueprint_for_Excellence.pdf).

3.0 EVOLUTION OF THE GULF WAR RESEARCH STRATEGIC PLAN

During deployment to the Gulf, and as Servicemembers began returning from the Gulf, it became apparent that some Servicemembers 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 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 Servicemembers and Veterans. In addition, many Servicemembers 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?" [2] [3] The PGVCB established three primary mission objectives to achieve through interagency coordination:

- Ensure all Veterans receive the complete range of health care 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 1995-96 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. [3] 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

Several IOM reports have been published since the original plan was completed, including:

- *Chronic Multisymptom Illness in Gulf War Veterans: Case Definitions Reexamined.* [4]
- *Gulf War and Health, Volume 9: Long-Term Effects of Blast Exposures.* [5]
- *Gulf War and Health: Treatment for Chronic Multisymptom Illness.* [6]

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. [4] [5] [6] [7] [8] [9] [10] [11] [12] [13] [1] [14] [15] [16] [17] [18] [19]

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. [1] In addition, the RACGWVI has released one report since the publication of the original plan: *Gulf War Illness and the Health of Gulf War Veterans: Research Update and Recommendations, 2009-2013*. [20]

By carefully comparing the RACGWVI and IOM reports, as well as other information, the present *Gulf War Research Strategic Plan 2013-2017 (2015 Update)* identifies the areas of research that appear most likely to succeed in providing new information that will help Gulf War Veterans. [21] [22] [23] [24] [25] [26]

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 joint VA/DoD Deployment Health Working Group (DHWG). [27] [28] [29] [30] [31] [32] [33] [34] [35] [36] [37] [38] [39] [40] [41]

4.1 Summary of Federal Funding of Gulf War Research 1994-2014

Fiscal Year (FY)	VA*	University of Texas Southwestern (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	$ 10,384,231	$ 0	$ 24,240,983
2011	$ 5,537,539	$ 31,472	$ 10,280,922	$ 0	$ 15,849,933
2012	$ 6,723,556	$ 0	$ 11,714,301	$ 0	$ 18,437,857
2013	$ 7,937,878	$ 0	$ 24,540,670	$ 0	$ 32,520,615
§2014	$ 9,737,878	$ 0	$ 2,791,031	$0	$ 12,528,909
Total 1994-2014	$ 150,026,097	$ 39,292,708	$ 301,319,490	$ 14,000,105	$ 504,638,400

* 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 Gulf War research in FY 2014. DoD estimate does not include CDMRP funds.

The VA estimate for FY2010 includes 40 percent of magnetic resonance imaging (MRI) equipment upgrade at San Francisco, California 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 2013-2017

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

5.1.2 IOM Recommendations

The IOM recommended that "future studies funded and conducted by the Department of Veterans Affairs to assess treatments for chronic multisymptom illness should adhere to the methodologic and reporting guidelines for clinical trials, including appropriate elements (problem– patient–population, intervention, comparison, and outcome of interest) to frame the research question, extended follow-up, active comparators (such as standard-of-care therapies), and consistent, standardized, validated instruments for measuring outcomes." [6, p. 191]

Additionally, "the Department of Veterans Affairs should fund and conduct studies of interventions that evidence suggests may hold promise for treatment of chronic multisymptom illness. Specific interventions could include biofeedback, acupuncture, St. John's wort, aerobic exercise, motivational interviewing, and multimodal therapies." [6, p. 191]

5.1.3 RACGWVI Recommendations

"The Committee believes that the first priority of federal Gulf War illness research must be the identification of effective treatments to improve the health of Gulf War veterans and to protect the health of current and future American servicemen and women at risk of similar exposures." [20, p. 77]

The RACGWVI recommended pursuit of treatment approaches based on known mechanistic pathways of Gulf War illness, which could also lead to significant breakthroughs in the treatment of other exposure-related occupational health problems.

Although the perfect animal model of Gulf War illness has not yet been developed, the RACGWVI recommended preclinical animal models be used to develop and test new treatments focused on pathobiological mechanisms of Gulf War illness and the effects of Gulf War theater exposures.

BOX 1:
RACGWVI: Critical Elements of Gulf War Research [20, p. 77]

1. Clear, operationalized case definitions for Gulf War illness and other diagnostic subgroups for whom treatments are designed are essential.

2. Clear, operationalized definitions of the clinical targets for treatment must be included in the research plan.

3. Treatment outcomes must be clearly defined so that it is possible to quantify quantified improvements associated with interventions.

4. Where possible, treatment outcomes should include improvement in measures associated with expressions of underlying pathology (abnormal laboratory and functional assays).

Additional recommendations from the RACGWVI include:

- Use of Center- and consortium based treatment research efforts to capitalize on multi-disciplinary expertise and multi-pronged approaches to treatment targets and pre-clinical trials.
- Support, through the VA Cooperative Studies Program, for confirmation validation of safety and efficacy from initial Phase I/II trials conducted by the DoD CDMRP.
- Publication of data on effective treatments from VA's 2005 longitudinal survey.
- Reconducting the IOM review of treatments by Gulf War Veterans' medical practitioners ordered by Congress in 2010 (Public Law 111-275, 2010, Section 805)
- Ensure that VA annual reports to Congress on Gulf War illness research funded by VA include only studies and treatment trials in which the health of Gulf War Veterans is the central focus and the study participants are primarily Gulf War Veterans.

5.1.4 ORD Research

A number of treatment projects are currently underway or recently completed. Examples of recent ORD research in this area are provided 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 percent), fatigue (38 percent), cognitive function (33 percent), sleep quality (41 percent), physical health (34 percent), and mental health (16 percent). [42]

In a study of potential new treatments for irritable bowel syndrome (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 glutamate-ammonia ligase (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. [43] A 2015 study in this area found that for patients with IBS with diarrhea, miR-29 targets and reduces expression of proteins that increase intestinal permeability; strategies to block miR-29 might restore intestinal permeability in IBS patients with diarrhea. [44] [45] Trials are underway to test miRNA-based therapies for primary liver cancer and other malignancies (https://www.clinicaltrials.gov/ct2/show/NCT01829971?term=mirna+therapeutics&rank=115).

A randomized controlled multi-site clinical trial was developed through the Cooperative Studies Program (CSP) to compare the effectiveness of cognitive behavioral therapy (CBT), exercise and the combination of both for improving physical functioning and reducing the symptoms of 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. [46]

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 Gulf War Veterans with CFS includes a deficiency with mobilizing the cardiopulmonary system for strenuous physical effort. [47]

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 and approaches for evaluating 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 Gulf War 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 VHA Office of Health Information Governance (10P2C) to develop a mechanism to identify Gulf War Veterans 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.
- Consider replicating small projects when applicable with studies at multiple sites.
- Transition promising treatment studies to a national multi-site clinical trial.

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 1990-1991 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 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, DoD, 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 health 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 health care services do not take into account the health concerns of Veterans who do not seek VA health care 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 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 [1, p. 255]

5.2.3 RACGWVI Recommendations

Ongoing monitoring and surveillance of the Gulf War veteran population is critical as this veteran group ages. Such surveillance should include outcomes such as Gulf War illness; neurological disorders, including Parkinson's disease; autoimmune conditions such as multiple sclerosis; brain, lung and other cancers; cardiovascular disorders and dysfunction; sleep dysfunction; adverse reproductive outcomes and birth defects; general ill health and disability; mortality, and other disorders and outcomes that emerge as important during the surveillance process. The following specific recommendations were made:

1. Ongoing assessment of Gulf War illness and its impact on the health and lives of Gulf War veterans is critical. VA's longitudinal survey currently in process should be extended to add a symptom inventory adequate to define the illness according to existing commonly-used case definitions, as previously recommended by the Committee:

2. Survey data should be used to flag conditions of possible importance and followed up with detailed investigation, including the clinical evaluations that are required to determine specific medical diagnoses affecting Gulf War veterans at excess rates.

3. A study on the prevalence of "multiple sclerosis, Parkinson's disease, and brain cancers, as well as central nervous system abnormalities that are difficult to precisely diagnose" in Gulf War and recent Iraq/Afghanistan war veterans was required by Congress in 2008 (Public Law 110-389, 2008, Section 804) and should be carried out. These assessments should be published at a minimum of five-year intervals.

4. Systematic assessment of overall and disease-specific mortality in all Gulf War veterans and in specific subgroups of interest is essential. The results of these assessments should also be published at five-year intervals.

5. VA's longitudinal survey should be used to assess rates of medical conditions, including neurological and behavioral disorders and birth defects, in children of Gulf War era veterans. Survey data can be used to flag conditions of possible

concern and followed up. It is also important that VA publish results from studies of veterans' children that were conducted over 10 years ago.

6. Evaluation of health outcomes in Gulf War veterans in subgroups of potential importance is critical as some health outcomes are related to specific exposures and experiences in theater. These subgroups can be defined by suspected or documented exposures in theater, geographical locations in the Gulf War theater, or other predictors. [20, pp. 38,81]

5.2.4 ORD Research

A 2013 study examined the research tools of 12 large epidemiologic studies and 2 registries that have focused on 1990-1991 Gulf War Era Veterans to identify gaps and overlaps of efforts to date, and advance the development of future Gulf War Era survey tools. The review found that questions regarding exposures were more similar across studies, while neurocognitive and psychological tools were the most variable. Future surveys need to consider how their design can yield data comparable with previous surveys, and adding specimen and genetic analyses could greatly enhance survey data. [48]

A recent project examined the relative risk estimates for multiple sclerosis (MS) and other demyelinating disease (ODD) based on onset, deployment status, and exposures. Among 696,118 deployed and 1,785,215 nondeployed personnel from the Gulf War era, 1,841 incident cases of definite MS and ODD were identified (387 among deployed, 1454 among nondeployed). Military deployment for 1990-1991 Gulf War Veterans was not found to be a risk factor for developing MS. [49]

5.2.5 Existing Databases

5.2.5.1 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 was completed in 2013 .)
- DoD study of Navy Seabees (n=12,000).
- DoD-sponsored study of U.K. Gulf War and Bosnia Era Veterans (n=8,000).
- Centers for Disease Control (CDC) and Prevention study of Air Force Gulf War Era Veterans (n=4,000).
- CDC and VA study of Iowa Gulf War Era Veterans (n=3,800).
- VA-contracted Military Health Study (n=8,000).
- VA-Portland survey of Gulf War Era Veterans in Pacific Northwest (n= ~1,000).

- VA-Portland Survey of Gulf War Era Veterans in five states (n=1,800).
- Study of Gulf War Veterans returning through Fort Devens, MA (n=3,000).
- VA/CDC datasets on cancers in Gulf War Era Veterans, assembled from multiple large state tumor registries. [50] [51] [52]
- Multiple large DoD datasets assembled to assess birth-defect rates and pregnancy outcomes in Gulf War Era Veterans. [53] [54] [55] [56] [57] [58] [59] [60]
- Multiple large datasets from DoD-sponsored studies of hospitalization rates in Gulf War Veterans. [61] [62] [63] [64] [65] [66]
- DoD's Millennium Cohort Study (original sample > 200,000 Veterans, including at least 35,000 1991 Gulf War Era Veterans and over 9,000 deployed Gulf War Veterans).

5.2.5.2 U.S. Federal Gulf War Registries

- VA Gulf War Registry (n=150,000 1991 Gulf War Veterans as of January 2015 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).
- DoD Comprehensive Clinical Evaluation Program (CCEP) for 1991 Gulf War Veterans (n = ~32,800, discontinued in 2002).
- VA/DoD Airborne Hazards Registry (n=32,000 as of February 2015)

5.2.5.3 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.

5.2.5.4 Gulf War data resources assembled and maintained as a Department-wide VA effort

One outcome of the VA Secretary's GWVI 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 Pre-9/11 Report (August 2, 1990 through September 10, 2001).

The report provides comprehensive statistics on the use of VA benefits and health care services by Gulf War Era Veterans who served at least one day from August 2, 1990 through September 10, 2001. [67] The generated statistical tables are divided into four major profiles: Servicemember, VA benefits, VA health care services, and integrated VA benefits and health care 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.

5.2.5.5 Other large Federal datasets that provide data relevant to the health of Gulf War Veterans

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

5.2.6 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.

5.2.6.1 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
    - .Health of Gulf Veterans 20 years after the war
    - Self-reported symptoms of GW and GW-era Veterans reporting chronic multisymptom illness
    - Prevalence of chronic multisymptom illness among GW and GW-era Veterans
    - Clinical and health service utilization characteristics of Veterans who self-report chronic multisymptom illness
    - Correlates of PTSD among 1805 female Veterans of the 1991 Gulf War
    - Life success in GW Veterans
- Research and datasets developed by the War Related Illness and Injury Research Centers (WRIISC).

5.2.6.2 ORD Funded Projects

These have been referenced earlier in this report:

- Gulf War Veterans' Illnesses Biorepository.
- Million Veteran Program (MVP, CSP #G002).
- Gulf War Era Cohort and Biorepository (CSP #585).

5.2.7 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 health care 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 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. [67]

- Investigate the possibility of developing a "pharmacovigilance"-style surveillance system from the VA electronic health 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 health 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 interagency 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 VHA Office of Health Informatics Governance to develop a mechanism to identify Gulf War Veterans in the VA health 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 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.

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

- Support projects to compile retrospective and prospective longitudinal data from health records of Gulf War Veterans with multisymptom 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, to include reproductive health.
- 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 research case definition for chronic multisymptom illness in Gulf War Veterans, and guidelines for its use.

Overview. Since returning from military service in the 1990-1991 Gulf War, studies indicate that at least one in four Veterans have suffered from a complex of multiple concurrent symptoms not readily explained by established medical or psychiatric diagnoses. Studies of diverse Veteran populations have identified the same general types of symptoms, co-occurring as a "multisymptom illness," that affect deployed Gulf War Veterans at significantly higher rates than Veteran comparison groups, and have indicated that few Veterans have recovered over time. In the absence of an objective diagnostic test, this multisymptom illness has been defined in research studies on the basis of Veterans' symptoms, with different research groups defining the illness in different ways. Multiple large population studies have identified similar statistically-defined symptom domains that affect Gulf War Veterans at significantly excess rates relative to Veteran comparison groups. [68] [69] [70] [71] [72] [73] [74] 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. [75] Examples include requiring that Veterans endorse at least one symptom [76] or two symptoms out of three types, [71] or five symptoms from a general list, [77] or obtain certain scores on factors defined by principal components analysis of symptoms, [78] [73] or meet chronic fatigue syndrome criteria [79] or have been diagnosed with any of a number of medical and psychiatric conditions. [80] 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 in Gulf War Veterans" 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.

5.3.2. IOM Recommendations

The National Academy of Sciences, which includes the Institute of Medicine, is chartered by Congress (36 U.S. Code Chapter 1503) to "investigate, examine, experiment, and report upon any subject of science." The aim of the IOM is to help those in government and the private sector make informed health decisions by providing evidence upon which they can rely. Many of the studies that the IOM undertakes begin as specific mandates from Congress; still others are requested by federal agencies and independent organizations.

An IOM study applies the National Academies' rigorous research process, aimed at providing objective and straightforward answers to difficult questions of national importance. IOM consensus studies are conducted by committees carefully composed to ensure the requisite expertise and to avoid conflicts of interest.

The committee's task is developed in collaboration with the study's sponsor; however, once the statement of task and budget are finalized, the committee works independently to come to consensus on the questions raised. In fact, while committees may gather information from many sources in public meetings, they carry out their deliberations in private in order to avoid any external influence.

As a final check for quality and objectivity, all IOM reports undergo an independent external review by a second, independent group of experts whose comments are provided anonymously to the committee members. Relying upon this independent, unbiased view, VA asked the IOM to develop a consensus research case definition for CMI. [4]The IOM convened a committee, carefully composed to ensure the requisite expertise and avoid conflicts of interest, to address the charge as it was provided by VA (see next page).

BOX 2:

Charge to the Committee

Chronic Multisymptom Illness in Gulf War Veterans: Case Definitions Reexamined (2014)

An ad hoc committee will develop a case definition for chronic multisymptom illness (CMI) as it pertains to the 1990–1991 Gulf War Veteran population. The committee will comprehensively review, evaluate, and summarize the available scientific and medical literature regarding symptoms for CMI among the 1991 Gulf War Veterans. The committee will look broadly for relevant information, including, but not limited to:

- Published peer-reviewed literature describing the symptomatology for CMI;
- Published peer-reviewed literature concerning existing case definitions for CMI among the 1990-1991 Gulf War Veteran population;
- Published peer-reviewed literature concerning existing case definitions of CMI among similar populations such as Allied military personnel;
- Published peer-reviewed literature concerning case definitions for other populations with a similar constellation of symptoms;
- Discussions with researchers involved with developing case definitions for CMI in 1990-1991 Gulf War Veterans; and
- Discussions with clinicians who treat Veterans of the 1990-1991 Gulf War.

In addition to reviewing and summarizing the available scientific and medical literature regarding symptoms and case definitions for CMI among Gulf War Veterans, the committee will:

- Establish a consensus case definition along with guidelines for its use.
- Evaluate existing case definitions in relation to priorities identified by the committee and determine whether an existing case definition is adequate, an existing case definition needs to be revised, or a new case definition needs to be established.
- Consider issues such as specificity (the degree to which the definition applies to 1990–1991 Gulf War Veterans), sensitivity (the degree to which the case definition captures the excess symptomatology in 1990–1991 Gulf War Veterans), reliability (the degree to which Veterans' symptoms are determined in a consistent manner), and portability (the degree to which the case definition is suitable for use in different study designs) in evaluating case definitions.
- Consider the potential for the case definition, optimized for research purposes, to be used in clinical practice.
- Consider other case definition characteristics deemed important.
- Evaluate the terminology currently used in referring to CMI in Gulf War Veterans and recommend appropriate usage.

The Committee provided three recommendations, see Box 3.

In future Gulf War Requests for Applications, ORD will specify the use of the Centers for Disease Control and Prevention and Kansas case definitions, and will require explicit justification if the proposed research plans to use a different case definition.

Additionally, ORD will attempt to systematically assess existing data to identify additional features of chronic multisymptom illness, as recommended.

BOX 3:
IOM Recommendations: Research Case Definition

Recommendation 1: "The Committee recommends that the Department of Veterans Affairs consider the use of the Centers for Disease Control and Prevention and Kansas definitions because they capture the most commonly reported symptoms."

Recommendation 2: "The committee recommends that the Department of Veterans Affairs, to the extent possible, systematically assess existing data to identify additional features of chronic multisymptom illness, such as onset, duration, severity, frequency of symptoms, and exclusionary criteria to produce a more robust case definition."

Recommendation 3: "The committee recommends that the Department of Veterans Affairs use the term *Gulf War illness* rather than *chronic multisymptom illness*."

Going forward, ORD will use the term "Gulf War Illness presenting as chronic multisymptom illness." As in the past, terminology continues to evolve. There are many other considerations within VA that must be resolved with respect to this terminology.

5.3.3. RACGWVI Recommendations

In the absence of a consensus case definition of Gulf War illness 23 years after the appearance of this condition, it remains difficult to assess and compare research findings in epidemiological, pathobiological or treatment research on the disorder. The Committee recommended the following approaches to the development of such a definition:

1. An evidence-based, expert consensus-driven case definition for Gulf War illness should be developed. This process should include 1) a review of the existing literature relevant to case definitions for Gulf War illness, 2) in-depth statistical and epidemiologic assessment of the strengths and weaknesses of different case definition approaches using datasets that provide representative data on symptoms and medical conditions affecting 1990-1991 Gulf War era veterans and 3) final case definition parameters and guidelines developed by an expert consensus panel that includes scientists experienced in Gulf War illness research and symptom-based case definitions and veterans affected by GWI
2. VA should adopt the name Gulf War illness for the symptomatic condition associated with military service in the 1990-1991 Gulf War. [20, p. 37]

The RACGWVI further recommended that VA work with CDMRP to establish guidelines for improved methodology in Gulf War research that can be included in requests for proposals and subject to research application reviews. Such guidelines should include the following:

1. Systematic methods for assessing symptoms and other health outcomes in Gulf War veterans.
2. Evaluation of health outcomes in Gulf War veteran subgroups of importance—for example, subgroups defined by relevant exposure history or location in theater.
3. Consideration of subpopulations with multiple health outcomes.
4. In evaluating risk factors for Gulf War illness and other health outcomes, use of analytic methods that control as fully as possible for confounding effects of multiple exposures and etiologic factors that may be associated both with the exposures and outcomes of interest. Consideration of the effects of mixed exposures is also key. [20, pp. 39, 80]

5.3.4. VA ORD Previous Research Activities Related to Case Definitions

VA's ORD has not previously sponsored research specifically aimed at identifying case definitions for chronic multisymptom illness in Gulf War Veterans, but did fund a recent study that validated the factor structure for a set of three syndromes previously identified. [81] Previously, VA's Office of Public Health, as well as DoD, have sponsored projects conducted by VA investigators that have developed different approaches for identifying "cases" of symptomatic illness in Gulf War Veterans. [71] [82] [78] [83] [84] [73] [76] [85] These include a case definition for "Gulf War Unexplained Illness" developed at VA's Portland Environmental Hazards Research Center, [76] identification of a unique "Gulf War Syndrome" using factor analysis of symptom data in VA's 1995 national survey of Gulf War era Veterans, [73] 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. [84]

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 illnesses affecting Gulf War Veterans, 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 chronic multisymptom illness in Gulf War Veterans may be associated with genetic factors, including those associated with certain enzymes that act to neutralize adverse effects of neurotoxicant exposures. [86] [87] [88] [89] [90] [91] [92] Questions concerning specific genes that may have played a role in chronic multisymptom illness in Gulf War Veterans 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

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." [1, p. 10]

5.4.3 RACGWVI Recommendations

RACGWVI 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." [75, p. 250]

The RACGWVI notes that "epigenetic and genetic approaches to research on Gulf War illness pathobiology are likely also to be informative." [20, p. 71]

5.4.4 ORD Research

There are no completed studies that explored the association of genetic variants with GWVI in Veteran cohorts, although some involving pain and fatigue are ongoing. CSP 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. [93]

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 in Gulf War Veterans. [94]

ORD researchers are studying a group of dysregulated microRNAs in blood and colon tissue from patients with irritable bowel syndrome. MicroRNAs can modulate certain biological processes, and the goal of the research is to develop preventative or therapeutic approaches to use specific miRNAs to affect genetic and epigenetic control of intestinal pathways in IBS patients. [45]

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 Gulf War Veterans. 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 CSP mechanism;
- conducting ORD-initiated studies based on the CSP cohorts; and
- 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 immediately above; this should include external comparison;
- careful selection of control cohorts based on population study principles; and
- focus on identifying the genetic variants that contribute to disease through genetic approaches (e.g, sequencing, quantitative polymerase chain reaction (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. MVP, CSP #G002 is currently not specifically targeting Gulf War Era Veterans for enrollment, but is expected to enroll a number of Gulf War Era Veterans large enough to enable genomic studies on this subgroup. Thus, it is expected that this cohort will have particularly utility for replication studies that follow-up on discoveries made in the Gulf War Era Cohort and 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 health care 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 3,000 in the pilot phase). The timeline for transitioning the program into full operation is targeted to complete recruitment during the 5 year period this strategic plan is covering. This will enable the conduct 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 health record analysis, imaging, expression profiling, or metabolomics studies; Veterans will be invited to return to the clinical centers for these studies. [95] 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)
VA ORD launched MVP in early 2011. 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 health care 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 VA's health care system who volunteer to share their health information, as well as genetic material. This project is expected to enroll one million users of VA's health care system, with representative sampling from all deployments including the 1990-1991 Gulf War. Veterans who enroll 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;
- 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.

In FY14, 200,000 MVP samples were contracted to be genotyped, and the genotypic data will be made available to approved VA researchers for analysis. A request for applications (RFA) was announced to MVP local site investigators (LSIs) for a beta-test of the data access process and analysis in a secure scientific computing infrastructure. Peer-review and funding will occur in FY15.

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).

Gulf War Genome-Wide Association Study within MVP (CSP2006): Based on the 200,000 MVP samples that will be genotyped, a study is currently in the planning phase to assess the number of Veterans with Gulf War Illness within the MVP cohort, and conduct genome-wide association analysis. The study planning includes "deep phenotyping" activities to developing an algorithm to identify and validate GWI cases, using the Center for Disease Control and Prevention and Kansas definitions. The application is expected to be submitted for peer-review in the Spring 2015 review cycle.

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:

- VA 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: This project involves collecting medical records and high quality post-mortem biological specimens from Gulf War Veterans, regardless of their specific health problems.

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 Gulf War Veterans 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 Gulf War Veterans healthy controls. Identified differences relate primarily to brain structure and function, [96] [97] [98] [99] [100] [101] [102] [103] function of the autonomic nervous system, [98] [104] [98] [105] [106] [107] [108] [109] [110] neuroendocrine alterations, [111] [112] [113] immune parameters, [79] [93] [114] [115] and coagulation indicators. [116] [117] 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 Food and Drug Administration (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: [118]

- **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." [1, p. xi] "The committee recommended rigorous, adequately powered

studies to identify biomarkers that distinguish Gulf War veterans who have persistent multisymptom illness 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." [1, p. 10]

5.5.3 RACGWVI Recommendations

Exposure studies in Gulf War veterans to identify the etiologic agents that may have been causative in Gulf War illness remain important because they clarify the physiological basis of the disorder and may help to determine treatment targets for Gulf War illness and other health problems in Gulf War veterans. The RACGWVI recommended that VA research in this area include the following elements:

1. Objective markers of exposure should be utilized whenever possible. These include environmental sampling and modeling of conditions in theater.

2. Identification of biomarkers of exposure and downstream effects of exposures since the war that are present years after the exposure occurred have strong potential for understanding the physiological effects of Gulf War theater exposures and the relationship of these exposures to Gulf War illness. Applicable methods might include genomic, genetic, epigenetic, proteomic, lipidomic and metabolomic assays to explore suspected physiological effects and to identify novel, unsuspected pathways of illness.

3. Research and statistical methods that consider the mixed exposure scenario experienced by Gulf War veterans in theater are essential. These should focus on assessing effects of individual exposures as well as various exposure combinations and mixtures. Mixed exposures include not only mixtures of chemicals but also chemicals combined with heat, dehydration, infection, and other environmental stressors. [20, p. 56]

Research on the pathobiological underpinnings of Gulf War illness and ill health in Gulf War veterans should continue to focus on the central and autonomic nervous systems and on immunological and neuroendocrine outcomes. RACGWVI recommended that:

1. Clear, operationalized case definitions are needed. Findings may differ in differing patient populations, either defined with different Gulf War illness criteria or experiencing different health problems. For example, non-veteran patients with multisymptom illnesses like chronic fatigue syndrome or fibromyalgia may show different patterns of immunological or neurological function than veterans who have Gulf War illness and meet criteria for these disorders.

2. Gulf War theater exposures, age, and other variables likely moderate pathobiological effects and should be carefully addressed in research.

3. Gender should be considered whenever possible in mechanistic and treatment research on Gulf War illness.

4. Since the pathobiological mechanisms underlying Gulf War illness are poorly understood, exploratory probes such as genomics, metabolomics, lipidomics, and proteomics may yield useful information that can lead to more focused research.

5. Epigenetic and genetic approaches to research on Gulf War illness pathobiology are likely also to be informative.

6. In order to effectively pursue "omics" and genetic research, standardized sample collections in research that uses biological specimens can expedite exploratory and hypothesis-driven research. Standard protocols for sample collections should be established and followed.

7. Increased emphasis should be placed on the study of alterations in regulatory dynamics both within and across the principal regulatory axes, including the endocrine, immune and nervous systems. These should include response to standardized challenges at different time scales, i.e., acute response to exercise, circadian rhythm, and monthly cycles as well as long-term illness progression. Analysis should be integrative and deployed across these interacting systems whenever possible using methodologies that formally acknowledge regulatory control.

8. Animal models may be appropriate to investigate mechanistic hypotheses and illness or exposure effects. [20, p. 71]

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. [100]

The study "Effects of Gulf War Illness on Brain Structure, Function and Metabolism: MRI/MRS at 4 Tesla", examined imaging biomarkers to determine whether U.S. 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 Posttraumatic 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. [96]

A further study of apparent structural alterations in the hippocampi of Gulf War Veterans compared the hippocampal subfields of 56 Gulf War Veterans with suspected sarin/cyclosarin exposure to 56 "matched" unexposed Gulf War Veterans utilizing a 4T high-resolution magnetic resonance scanner and found that exposed Veterans had smaller CA2 and CA3/DF subfields. [119]

In the ORD-funded study, "Glucocorticoid Responsivity in Gulf War Veterans", hydrocortisone was administered to Gulf War 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 adrenocorticotropic hormone (ACTH) suppression, reflecting greater peripheral glucocorticoid receptor responsiveness, and did not show a hydrocortisone-induced decrement in delayed recall or retention. Positron-emission tomography demonstrated that while the two groups had comparable relative regional hippocampal [^{18}F] fluorodeoxyglucose (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 Gulf War Veterans with and without PTSD may reflect differences in peripheral and central glucocoid receptor responsiveness. [113]

In a small study of 16 ill and 12 control Gulf War Veterans, researchers determined that ill Veterans with self-reported post-exertional fatigue had objective, autonomic measures that were worse than controls. The cardiovascular function of both groups was observed at several points pre- and post-exertion, with the ill group showing significantly higher baseline heart rate. [120]

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. [116] To further characterize platelet function, researchers studied 43 patients who met the study's inclusion criteria for Gulf War Veterans illness and 21 Veterans who served concurrently but who lacked criteria for the illness. All participants were free of infection and known inflammatory diseases; platelet counts and c-reactive protein were significantly elevated in the Gulf War illness group. This appears to be the consequence of an underlying inflammatory state in chronic multisymptom illness in Gulf War Veterans. [121]

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 Gulf War Veterans.

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 Gulf War Veterans with chronic multisymptom illness or relevant neurotoxicant exposures. For studies assessing chronic sequelae of Gulf War-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 (magnetic resonance imaging (MRI), positron emission tomography (PET), diffusion tensor imaging (DTI), and magneto-encephalography (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 Gulf War Veterans 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 Gulf War Veterans 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 Gulf War Veterans.
- Biomarkers of autonomic system dysfunction in ill Gulf War Veterans.
- 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.
- The brain and tissue biorepository and blood biorepository and cohort (CSP #585) supply extremely valuable central nervous system (CNS) tissue and blood biodata will allow for biomarker development and qualification studies. Tissue and blood samples will be shared with independent researchers and studies evaluating potential biomarkers in ill Gulf War Veterans. 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 Gulf War biorepositories to provide the most valuable and useful data to Gulf War 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 Gulf War Veterans, 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.

Animal studies have been used to evaluate the effects of a variety of Gulf War-related exposures and conditions. [75] 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. [122] [123] [124] Further characterization of these effects in animal models may lead to the identification of targets for therapeutic intervention.

5.6.2 IOM Recommendations

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." [1, p. 3] The IOM report called for "a renewed research effort…to better identify and treat multisymptom illness in Gulf War veterans", and studies that couple animal models and biomarkers may be useful in achieving that goal. [1, p. 10]

5.6.3 RACGWVI Recommendations

Studies that utilize animal models (multiple types of species and genetically altered rodents) 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, as well as low-level sarin or sarin surrogate, and environmental stressors such as heat and dehydration, all have been informative to date. Research using animal models in Gulf War illness should continue to examine the immediate, delayed, and persistent effects of acute exposures to chemicals and chemical mixtures. The RACWGVI recommended that future animal model research focus on:

1. Studies that characterize persistent effects of Gulf War-related exposures, alone and in combination, on proinflammatory processes in the central nervous system, autonomic nervous system and peripheral target organs, including those that encompass mitochondrial dysfunction and accumulation of reactive oxygen species.

2. Studies that evaluate systemic immune parameters in animal models, with an emphasis on those parameters that sensitize ill veterans to Gulf War illness, will also be informative.

3. Animal research to identify biomarkers indicative of past exposures to Gulf War-related toxic compounds that can be applied to Gulf War veterans is important. This includes studies that identify persistent or "downstream" changes in biochemical processes in relation to past neurotoxicant exposure(s) and that identify persistent changes in the central nervous system and in autonomic

function associated with Gulf War-related exposures and conditions. Exploratory biomarker research in animal models that assesses genomic, genetic, epigenetic, proteomic, metabolomic and lipidomic pathways of exposure effect may also be informative.

4. Animal models of Gulf War illness are recommended for rapid screening of potential therapies. [20, p. 56]

5.6.4 ORD Research

Examples of past ORD-funded research in animal models are given below.
The prevalence of 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. [125] This same treatment was successfully applied to patients suffering from IBS. [126]

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. [127] These results are encouraging for patients suffering from peripheral neuropathy and other sensory deficits.

Studies of mood and cognitive function following four weeks of exposure to Gulf War illness-related chemicals (including pyridostigmine bromide, permethrin, and DEET) with and without mild stress application have found reduced hippocampal volume and associated deficits in hippocampus-dependent spatial and object memory. Exposure to Gulf War illness-related chemicals and stress causes both hippocampus dependent and hippocampus independent memory impairments, and is also associated with decreased neurogenesis, partial loss of principal neurons, and mild inflammation. These studies suggest that treatment strategies that enhance neurogenesis and suppress inflammation may help alleviate mood and cognitive dysfunction. [128] [129]

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 Gulf War-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

IOM, 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 VA and other health-care providers in diagnosing and treating the health problems of Gulf War veterans and preventing illness in future veterans." [1, p. 10]

RACGWVI, 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." [75, p. 309]

5.7.3. Inter-Governmental Coordination Efforts

This section describes the VA and DoD agencies that are involved in GWVI research.

Within VA, two organizations, ORD and OPH, are involved in GWVI 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. Formalized in 2014 as *OPH/ORD Common Strategies*, this working group focuses on strategically integrating the research

of both offices to produce new findings that will lead to improvements in health and care of Veterans.

5.7.3.1 Office of Research and Development (ORD)

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 RACGWVI.

5.7.3.2 Office of Public Health (OPH)

The work of OPH includes epidemiological research and large-scale surveillance studies. OPH coordinates and supports IOM studies that consolidate current knowledge of the Gulf War and other deployment health conditions. OPH follows IOM recommendations in developing and conducting studies.

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 National Research Advisory Council (NRAC)

NRAC provides advice to the Under Secretary for Health and the Secretary of Veterans Affairs on all research and development sponsored by the VHA, to include ORD's policies and programs.

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

RACGWVI was mandated by Congress in 1998 and held its first meeting in 2002. 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 in 1990 and 1991.

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

Outside of VA, ORD coordinates with DoD's CDMRP, specifically its Gulf War Illness Research Program (GWIRP). In a number of cases, VA investigators have successfully competed for research funding executed and managed by CDMRP.

The CDMRP GWIRP website states that Gulf War Illness (GWI) is 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. It further states that the population of veterans affected by GWI is a subset of the nearly 700,000 who served during the 1990-1991 Gulf War. Studies indicate that

approximately 25% to 30% (or 175,000 to 210,000) of Gulf War veterans continue to experience symptoms associated with their deployment as described above. The CDMRP GWIRP focuses its funding on projects that have the potential to make a significant impact on GWVI.

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." [130] ORD and the CDMRP GWIRP currently maintain several levels of coordination:

- VA Gulf War Research Program Manager is invited to present VA's Gulf War research portfolio as part of the GWIRP vision-setting meeting each year. VA's Gulf War research portfolio and upcoming RFAs are discussed at this time. This allows both agencies to coordinate their research priorities.

- VA Gulf War research portfolio and the GWIRP research portfolio are presented and discussed at annual meetings of the VA RACGWVI. This allows the RACGWVI to be aware of the activities within each agency's Gulf War research program so that appropriate recommendations may be formulated.

- GWIRP contributes funding data and project information to the annual VA GWI Report to Congress

- Electronic coordination through Federal RePORTER, a searchable database of scientific awards from federal agencies.

5.7.3.6 Deployment Health Working Group (DHWG)

DHWG is an interagency working group co-chaired by VA's Office of Public Health and DoD Health Affairs that meets monthly (successor to the original Persian Gulf Veterans Coordinating Board). The DHWG reports to VA/DoD joint Health Executive Council. DHWG is composed of staff from OPH (environmental health, epidemiology, communications), ORD (including the leads for deployment health research and Gulf War research), and 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 VSOs on at least an annual basis (sometimes more frequently when new information or events determine a need). 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 RACGWVI recommendations quoted here.

IOM, 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." [1, p. 10]

RACGWVI, 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." [75, p. 309]

Goals:

Goal 1: To produce focused, well-planned research in epidemiology, case definitions, genetics/genomics, biomarkers, animal models, treatments and translation, and to add promising new avenues of research that arise in the course of the planned effort.

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

Goal 3: To communicate hypotheses and results to the scientific community devoted to the topic of GWVI, Veterans, health professionals who treat Veterans, the scientific community at large, and the public.

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

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

Objectives:

Goal 1:

1. Coordinate the scientific research efforts on GWVI using a targeted approach in order to facilitate focused, well-planned research from cohorts and survey data, and on case definitions; genetics/genomics, biomarkers; animal models; treatments; translation.
2. Add new avenues of research that arise in the course of the planned effort.
3. Support on-going discussion of the diagnostic and treatment implications of research findings as they develop.

Goal 2:

1. ORD and OPH will coordinate research on GWVI that is funded and/or conducted by VA so that research goals and strategies are efficient and congruent.
2. 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. Transparency and avoiding duplication are also key issues to address.
3. CDMRP and VA will coordinate activities, where possible, to maximize combined program impact.

Goal 3:

1. ORD and OPH will continue to convene meetings of Gulf War researchers to improve sharing of research results and ideas.
2. VA will continue to participate in monthly meetings of the DHWG to share information about research programs with DoD.
3. RACGWI will continue to conduct meetings to review research results and advise VA.
4. ORD and OPH will continue to communicate with Veterans' groups on research results, treatment options, and policy changes through a variety of mechanisms.
5. ORD and OPH will communicate with clinicians in order to gain insights on issues and treatment alternatives that might influence the Gulf War research program.

Goal 4:

1. ORD and OPH will continue to develop methods of communicating with Gulf War Veterans and their family members and solicit their input regarding areas of interest. We will develop online mechanisms of presenting the Gulf War research portfolio.
2. ORD and OPH will develop targeted material (e.g., brochures, fact sheets, Q&As) regarding the results of research initiatives for Gulf War Veterans and their families and caregivers.
3. ORD and OPH will disseminate material to VHA health care facilities for redistribution to Veterans and their family members and caregivers.
4. ORD and OPH will communicate research findings and distribute information to VSOs and other stakeholders working on behalf of Veterans for redistribution.
5. ORD and OPH will make resources available on their Web sites and link to other VA sites such VA's A to Z Web site.

Goal 5:

1. OPH and ORD will determine the most effective and efficient means of presenting new information and capturing the intended audiences.
2. ORD and OPH will incorporate research results into educational/informational interactive forum with clinicians (Webinars, in-person sessions with internet access, etc.).
3. Construct several Outlook groups to widely promote forums and Webinars.
4. Provide the latest clinical and research information for inclusion on Web sites.
5. 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 Blueprint of Excellence states that VHS will provide 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 respect the enduring nature of the patient-clinician relationship. A dashed hope based on a flawed research insight could lead to loss of trust in health care 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 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 health care system. 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. WRIISCs also perform primary clinical research, provide exposure assessment clinics, and telehealth services.

In addition to assuring the implementation of results of clinical studies, WRIISCs have also used the hybrid approach for situations such as integrative medicine (formerly 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 integrative medicine programs need to be conducted.

WRIISCs are also an educational resource for combat Veterans, their family members and loved ones, and Veteran health care 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 health care providers across the VA.

VA is also committed to clinician education and training. OPH has developed accessible, flexible and user-friendly training regarding health aspects of the Gulf War including GWVI 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. More collaborative work on clinician education and training is planned between OPH and ORD.

OPH programs, including its Environmental Health Program 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 Operation Enduring Freedom/Operation Iraqi Freedom 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 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 health care 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 integrative 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.

5.8.4 Health Services Research and Development

Beginning in spring 2014, VA Health Services Research and Development (HSR&D) has issued solicitations for proposals regarding research on the care of Gulf War Veterans. The primary purposes of this initiative are to facilitate innovative research that improves, identifies, and encourages implementation of policies, procedures, and practices that benefit the overall well-being and level of care for Gulf War Veterans.

Specifically, the solicitations sought proposals that aim to:

- Advance our knowledge of the health care provided to Gulf War Veterans and its impact on long-term health outcomes;
- Understand the Gulf War Veteran's experience of care in VA and outside VA and identify ways to improve that experience;
- Identify promising models for improving care of Gulf War Veterans and ways to expand the use of those models; and
- Use knowledge of the care of Gulf War Veterans to improve the care of all Veterans with deployment related health problems.

6.0 CONCLUSIONS

The first "Working Plan" for Research on Persian Gulf War Veterans' Illnesses was published in 1995-1996. [2] [3] 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 percent of Gulf War Veterans suffer from multisymptom illness compared to 10 percent of Veterans who did not deploy; [84] [57] imaging studies that have shown alterations in brain structure in Gulf War Veterans exposed to sarin/cyclosarin; [97] [100] and a pilot study demonstrating the efficacy of CPAP to partially relieve some symptoms of multisymptom illness. [42]

The leadership of VA's ORD 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 2013-2017 (2015 update)* 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 2013-2017 (2015 update)* will be reviewed periodically by NRAC and RACGWVI, and updated as needed.

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APPENDIX II. 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)
FM	Fibromyalgia
fMRI	functional Magnetic Resonance Imaging
GLUL	Glutamate-Ammonia Ligase
GWAS	Genome-Wide Association Studies
GWIRP	Gulf War Illness Research Program
GWRSP	Gulf War Research Strategic Plan
GWSC	Gulf War Steering Committee
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
MCS	Multiple Chemical Sensitivity
MEG	Magneto-Encephalography
MMUS	Multiple Medically Unexplained Symptoms
MOU	Memorandum of Understanding
MRI	Magnetic Resonance Imaging

MVP	Million Veteran Program
MZ	Monozygotic
NCVAS	National Center for Veterans Analysis and Statistics
NGS	Next Generation Sequencing
NIH	National Institutes of Health
OPH	Office of Public Health
ORD	Office of Research and Development
PCR	Polymerase Chain Reaction
PCS	Patient Care Services
PET	Positron Emission Tomography
PGIRCC	Persian Gulf Interagency Research Coordinating Council
PGVCB	Persian Gulf Veterans Coordinating Board
PHS	Public Health Service
PON1	Paraoxonase/arylesterase 1
PTSD	Posttraumatic Stress Disorder
QUERI	Quality Enhancement Research Initiative
RACGWVI	Research Advisory Committee on Gulf War Veterans' Illnesses
RFA	Request For Application
RRD	Rehabilitation Research and Development
RWG	Research Working Group
SDB	Sleep Disordered Breathing
SWATO	Southwest Asia Theater of Operations
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