

Research Advisory Committee on Gulf War Veterans' Illnesses
Annual Report 2016

1. Origin and Membership

The Research Advisory Committee on Gulf War Veterans' Illnesses was established pursuant to Public Law 105-368. Members are appointed by the Secretary of Veterans Affairs (VA). Committee members who served during 2016 are listed in Appendix A.

2. Committee Activities

The Committee held three scheduled meetings in 2016: April 28th – 29th, in Washington, D.C., August 8th – 9th in San Francisco, CA, and November 7th in Washington, D.C. Additionally, as a follow-up to the April meeting, the Committee held a conference call on June 25th to deliberate and approve a document outlining advice and recommendations to the Secretary of VA. The first meeting of the year was initially planned for January 26th in Washington, D.C.; however, due to complications resulting from a historic blizzard that hit the East Coast, the meeting was postponed. Over the course of its meetings in 2016, the Committee heard from a wide variety of stakeholders, including Veterans, VA research scientists as well as non-VA research scientists, clinicians, medical and science organizations, and policymakers. Diverse perspectives were presented on a range of topics related to Gulf War Veterans' health, which helped inform the direction of the Committee's work in 2016 and will carry through 2017. **In particular, the need to integrate research with clinical care emerged as a priority area and will be a focus of the Committee's work going forward. The recommendations offered by the Committee this year (see Appendix B) provide advice on specific ways VA can make progress on integrating these complementary domains, with key tasks being VA updating its Gulf War Research Strategic Plan and developing a coordinated system of centers (see Appendix C) capable of bolstering research efforts and translating research findings into practice.**

At the April meeting, the Committee welcomed eight new members to its ranks. These members added to the diversity of the Committee by bringing Veteran and civilian viewpoints and expertise in post-deployment health, toxic exposures, epidemiology, cancer research, neurodegenerative diseases, neurological disorders, nursing, and other specialties. To start off the

year, the Committee had an opportunity to engage with Veterans, representatives from the National Academy of Medicine (NAM), and several VA research scientists. In the months preceding this meeting, the NAM (formerly the Institute of Medicine) had released two reports relevant to Gulf War Veterans: “Considerations for Designing an Epidemiologic Study for Multiple Sclerosis and other Neurologic Disorders in Pre and Post 9/11 Gulf War Veterans,” and “Gulf War and Health, Volume 10: Update of Health Effects of Serving in the Gulf War, 2016.” Representatives from each of these NAM committees presented the findings from their respective reports. Following these presentations, during a roundtable discussion the Committee heard directly from Veterans about issues important to them. Several Veteran Service Organizations (VSOs) were represented on the invited panel, including Disabled American Veterans, National Gulf War Resource Center, Veterans of Foreign Wars, and Veterans for Common Sense. There was then a joint discussion between the Committee, VSO representatives, NAM representatives, and VA officials.

On the second day of the meeting, the Committee discussed recent findings and future studies from VA researchers as well as research collaboration with DoD. A representative from the VA Office of General Counsel provided ethics training to the Committee and an update on the VA Office of Research and Development (ORD) Gulf War research portfolio was presented. Throughout both days, there was lively discussion on the research directions VA could take, particularly in the context of the recommendations made in the NAM reports discussed on the first day. The Committee expressed interest to offer advice to the Secretary and VA writ large on how it could chart a fruitful research course as it considered the recent NAM recommendations. However, the Committee decided additional time was needed to formulate a cohesive statement and then reconvene at a later date, but expeditiously, in order to continue discussion on a set of recommendations for the Secretary. Despite an unfinished discussion on what direction VA should take in response to the NAM report, the Committee shared excitement about a number of research opportunities, including the possibility of proactively addressing long-latency health conditions Gulf War Veterans might be at elevated risk for developing. Furthermore, there was recognition that VA has parallel responsibilities to identify therapies that can be deployed in the near-term while also pursuing research that can lead to more targeted and efficacious therapeutic approaches.

In June, the Committee held a call-in meeting open to the public in order to complete discussion on matters that were left unfinished at the April meeting. After discussion and deliberation, the Committee approved a set of recommendations, along with specific advice and cautions that had the full support of the Committee (see Appendix D). The Committee sent this letter to Secretary McDonald soon thereafter. The intent of the document was to help guide the VA toward a sound research course as it considered recommendations from the NAM report, “Gulf War and Health, Volume 10: Update of Health Effects of Serving in the Gulf War, 2016.”

The August meeting, held in San Francisco, began with an update on the ORD Gulf War Research Strategic Plan that runs through 2017. During the discussion that followed, the Committee expressed interest in working with ORD to update the strategic plan for the 2018 – 2022 timeframe. Much of the remaining day was devoted to research presentations showcasing cutting-edge scientific approaches in a range of fields. For example, speakers presented on how blood proteins could serve as indicators and modifiers of brain function and health, the use of next-generation sequencing technologies in pathogen detection, the influence the microbiome can exert in healthy and diseased states, and novel ways video games and other technology can be adapted to confer neurocognitive therapeutic benefits. These thought-provoking presentations and the related discussions helped stimulate new thinking about how researchers might approach investigating and treating health conditions affecting Gulf War Veterans. Notably, the meeting may have helped to seed new partnerships as several VA research scientists in attendance approached the presenters about potential research collaborations. The Committee also received a FACA briefing and an update on changes being made to the VA Chronic Multisymptom Illness Clinical Practice Guideline.

Building off of the research presentations from the first day, the focus shifted on the second day to therapeutic approaches and strategies for integrating research and clinical care. In addition to research talks, an overview presentation of the War Related Illness and Injury Study Center (WRIISC) was provided and led into a roundtable discussion with the three regional WRIISC Directors and the Committee. There was much discussion on how research efforts and clinical efforts might be better coordinated in order to optimize progress and outcomes for both. The Committee identified the need for VA to further integrate research and clinical care in order to improve the health of ill Gulf War Veterans. Two key facets for achieving this will be to establish a robust research strategy and also to develop a coordinated system that synergistically

connects research with clinical care. The Committee committed to exploring these complementary ideas further and to incorporate them in a set of recommendations for the Secretary by the end of 2016.

The final meeting of 2016 was held in Washington, DC on the eve of the presidential election. To start the meeting, the Committee received a briefing on the Secretary's MyVA initiative and engaged with Secretary McDonald about the transformation his administration has been trying to bring about within VA and specific work related to Gulf War Veterans. There was also discussion of priorities identified by the Committee this year and how it can best fulfill its advisory role. Major areas of emphasis during later sessions of this meeting were discussing how VA can best approach its research strategy for health conditions affecting Gulf War Veterans and developing a system of centers that better integrates research and clinical care in a way that meets Veterans' health care needs and advances knowledge of complex chronic conditions. The Committee heard leaders in the research and health care fields present ideas on resources VA can utilize and opportunities it can pursue when developing a research strategy as well as considerations of key factors needed to move VA closer to a learning health system. These presentations led into Committee discussion of its recommendations for 2016, which garnered broad support. The Committee unanimously approved its recommendations and a supporting white paper on a coordinated system of centers. The ideas put forth this year ultimately aim to improve the health of Gulf War Veterans and lay the groundwork for the Committee's work in 2017, which it will develop in collaboration with VA and other key partners.

Representatives from VA, the NAM, DoD, and other federal agencies were invited to attend Committee meetings and participate in discussions with presenting scientists along with Committee members. All meetings were open to the public. Time was reserved at each meeting to allow members of the public to provide comments on the Committee's work and on matters related to Gulf War research.

Committee members have been active participants in all aspects of the Committee's work. The Committee has kept VA leadership and ORD informed of its work on an ongoing basis. This task has been accomplished through attendance and participation of ORD officials at Committee meetings as well as ongoing communications between the Committee Chair, Managing Director, the Secretary's Office, and ORD.

3. Support Activities

Support activities for the Committee transitioned to San Francisco, CA to allow for better coordination with Committee Chair, Dr. Stephen Hauser. The Managing Director for the Committee, Dr. Jon-Eric VanLeeuwen, oversaw relocation of the RAC Office early in 2016. The RAC Office brought on two staff members late in the year to help support the work of the Committee.

In addition to monitoring research pertinent to health conditions and treatments relevant to Gulf War Veterans, preparation of Committee documents, planning and execution of Committee meetings, the staff has primary responsibility for Committee administrative activities and management of the Committee's website.

4. Designated Federal Officer

The Designated Federal Officer for the Committee is Victor Kalasinsky, Ph.D., who also serves as manager for the Gulf War portfolio within the VA Office of Research and Development.

5. Accomplishments

Over the course of 2016, the Committee made great strides in improving the cohesion of its operations and vision. Eight new members successfully transitioned onto the Committee, bringing the total membership to sixteen, and all have become active contributors to the Committee's work. Additionally, the office relocated to San Francisco and staff members were hired to provide adequate support for Committee operations. The Committee met in-person three times, including at least once on each coast, thereby expanding the physical accessibility of the meetings to Veterans. The virtual reach of Committee meetings also increased due to greater use of a web platform for each meeting. The Committee was also active in producing recommendations, transmitting two separate sets to the Secretary. In June, in an effort to be responsive and timely, the Committee held a follow-up call-in meeting on a Saturday in order to approve advice and recommendations intended to assist the Secretary and his administration as they considered recommendations from a recent NAM report that had generated much discussion. A broader set of recommendations was passed by the end of the year that touch on a number of areas but all support the theme of better integration of research with clinical care.

Two significant ways the Committee has offered to assist with realizing this theme are by actively consulting on the development of an updated ORD Gulf War Research Strategic Plan, which will unfold over 2017, and also by proposing VA establish a coordinated system of centers that brings research and clinical care closer together; furthermore, the Committee has outlined key considerations for such a system in a white paper (see Appendix C). The positive developments related to the Committee's operations and vision this year place it in an outstanding position to further build upon its progress in the coming year, guided by the commitment to improve the health of ill Gulf War Veterans.

6. MyVA Alignment:

The activities of the Committee in 2016 aligned with several MyVA goals. The Committee provided advice and made recommendations to the Secretary of Veterans Affairs on proposed research studies, plans, and strategies related to understanding and treating the health consequences of military service in the Southwest Asia theater of operations during the Gulf War. The Committee reviewed recent reports from the National Academy of Medicine (formerly the Institute of Medicine), held roundtable discussions with Veterans, heard updates from VA and DoD personnel, and received briefings about novel medical research that might be applicable to research involving Gulf War Veterans. All of these activities were aimed at improving health care for Veterans and, thus, fed into MyVA goal #1: Improving the Veteran Experience. The Committee also gave considerable thought to a recommendation on VA establishing a coordinated system of centers that would move VA closer to a learning health-research system. This system would lead to better integration of research with clinical care and promote continuous learning, thereby supporting MyVA goal #4: Establishing a culture of continuous improvement. Lastly, the Committee meetings this year spurred collaboration with non-VA scientific investigators and the Committee recommended VA further its efforts to facilitate these valuable partnerships, which closely aligns with MyVA goal #5: Enhancing strategic partnerships.

Submitted:



Committee Chair



Committee DFO

Appendix A
Research Advisory Committee on Gulf War Veterans' Illnesses
2016 Committee Members

Chair

Stephen L. Hauser, M.D., Robert A. Fishman Distinguished Professor and Chair, Department of Neurology, and Director, Weill Institute for Neurosciences, University of California, San Francisco.

Committee Members

Kimberly M. Adams, J.D., Veterans Legal Advocate, Community Legal Aid Veterans Legal Team.

James A. Bunker, Executive Director, National Gulf War Resource Center (NGWRC).

Fiona Crawford, Ph.D., President, Roskamp Institute.

Marylyn R. Harris, R.N., Adjunct Clinical Faculty in Psychiatric Mental Health Nursing at the University of St. Thomas Peavy School of Nursing.

Stephen C. Hunt, M.D., Director and Chief Consultant, Gulf War Veterans' Clinic and Deployment Health Clinic at the VA Puget Sound Health Care System.

Nancy G. Klimas, M.D., Professor and Chair, Department of Clinical Immunology, Director, NSU COM Institute for Neuro-Immune Medicine, Nova Southeastern University.

Katherine A. McGlynn, Ph.D., Senior Investigator, National Cancer Institute.

Jeffrey S. Nast, J.D., Senior Assistant Regional Counsel, Hazardous Waste and Chemical Law, Environmental Protection Agency.

Stephen L. Ondra, Chief Medical Officer and Senior Vice President, Health Care Service Corporation.

Frances E. Perez-Wilhite, North Carolina Military Business Center.

Martin Philbert, Ph.D., Professor and Dean, School of Public Health, University of Michigan.

Scott L. Rauch, M.D., Professor of Psychiatry, Harvard Medical School; Chair of Psychiatry and Mental Health, Partners Healthcare.

Caroline M. Tanner, M.D., Ph.D., Director of the Parkinson's Disease Research, Education, and Clinical Center (PADRECC), San Francisco VA Medical Center.

Mitchell T. Wallin, M.D., Multiple Sclerosis Clinic Director, Washington, DC, VA Medical Center; Associate Director of Clinical Care and Epidemiology, VA MS Center of Excellence in Baltimore.

Scott S. Young, MD, Executive Director and Senior Medical Director, Kaiser Permanente Care Management Institute.

Appendix B

Research Advisory Committee on Gulf War Veterans' Illnesses

2016 Recommendations

The Committee recommends VA:

- **Update the ORD Gulf War Research Strategic Plan for 2018 – 2022.** The strategic plan should continue prioritizing the development of effective therapeutic interventions and management strategies for Gulf War illness (GWI). Unaddressed research directions to consider should include investigation of potential risk factors, biomarkers and treatments for long-latency health conditions (e.g., neurodegenerative diseases and cancers); the use and/or development of technology for understanding and treating health conditions relevant to Gulf War Veterans; studies that disaggregate Veteran sub-groups, such as by sex and ethnicity. The plan should enable tracking of progress toward its goals and take a strategic approach to leveraging VA resources. Additionally, the plan should develop in consultation with the RAC-GWVI and other relevant stakeholders, such as VA's Office of Post-Deployment Health Services.
- **Establish a national hub-and-spoke coordinated system of centers within VHA that integrates research and clinical care in a way that meets Veterans' health care needs and advances knowledge of complex chronic conditions of post-deployment.** The system should have a presence at the national, VISN and local levels but function as an integrated research and care network committed to improving by continuously learning. Success will require effectively using data from disparate sources and forming strategic partnerships so that VA can fully serve Veterans in understanding and caring for post-deployment health conditions, an area where VA is uniquely positioned to lead. Further details for consideration are outlined in an accompanying white paper (Appendix C of the RAC-GWVI 2016 Annual Report) and the Committee intends to work with VA to continue developing these ideas and determine how best to implement solutions that serve our Veterans.
- **Actively seek strategic partnerships by raising awareness of or creating mechanisms for non-VA entities to collaborate with VA investigators in order to enhance research capabilities and incorporate cutting-edge methodologies into Gulf War research.**
- **Form a working group tasked with identifying barriers to recruiting research participants for Gulf War-relevant studies and developing solutions to overcome these challenges.**

- **Develop an approach/guidance to address comparison group (e.g., deployment status) issues and limitations of ICD-9/10 code usage. A major limitation of the ICD-9/10 codes from a research (as well as a clinical) perspective is that GWI does not have a unique code.**

Appendix C

Research Advisory Committee on Gulf War Veterans' Illnesses

White Paper Supporting a Recommendation for Post-Deployment Illness and Injury Centers within the Veterans Health Administration

Introduction

Many Gulf War Veterans suffer from a range of complex chronic conditions, such as Gulf War illness (GWI), chronic pain, neurological conditions and gastrointestinal disorders. These conditions can be debilitating and lifelong. The impact of chronic conditions of post-deployment is also likely to increase given that these conditions afflict Veterans of more recent conflicts as well. Unfortunately, our understanding of these disorders is incomplete and treatment options are lacking. The VA can do more to make progress on these unique military health conditions.

In order to improve the knowledge base and health of Veterans with chronic conditions of post-deployment, it is essential to integrate high-quality research with a strong clinical care system. Research efforts to date have been hampered by studies with small sample sizes, difficulty in recruiting research participants, and siloed data sets, among other issues. Better connecting resources and forming mutually beneficial relationships between researchers, clinicians and patients can help advance the knowledge base on post-deployment health. Information generated in such a coordinated system can and should be used to develop a more evidence-based approach for assessments and treatment. The National Academy of Medicine (formerly the IOM) has championed the idea of a learning health system “[...] in which science, informatics, incentives, and culture are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the delivery process and new knowledge captured as an integral by-product of the delivery experience.”¹ Through deliberate coordination, VA can amplify the capabilities of its integrated research and care network and move closer to a learning health-research system.

The Research Advisory Committee on Gulf War Veterans' Illnesses recommends that VA establish a national hub-and-spoke coordinated system of centers that integrates research and clinical care in a way that meets Veterans' health care needs and advances knowledge of complex chronic conditions of post-deployment. This document outlines core features of such a system and key policy considerations to bring it to fruition. Building the system will require an investment of personnel and data sharing agreements but offers tremendous potential to improve and maintain the health of ill Gulf War Veterans.

¹ Institute of Medicine, The Learning Health System Series (2012): <https://www.nap.edu/catalog/13301/the-learning-health-system-series>

Proposed System Outline

I. Purpose

To develop a coordinated system of centers that uses an integrated and evidence-based approach to support and advance research, education, and clinical care for chronic conditions related to post-deployment.

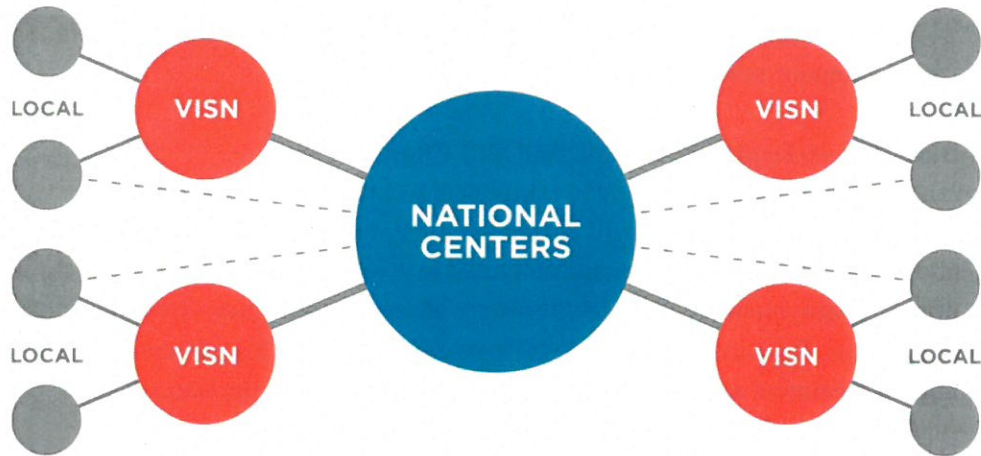
II. Focus Area

The hub-and-spoke system of centers should allow for access to clinicians and researchers specialized in complex, chronic conditions that service members suffer from during post-deployment. For example, associated VHA facilities should have expertise in GWI, other chronic multisymptom illnesses, chronic pain, and chronic disorders resulting from environmental exposures. Complex, chronic conditions that are sufficiently addressed by existing VA clinical centers (e.g., centers for polytrauma or neurology specialty disease centers) do not need to be a focus of this effort. However, there should be an awareness of conditions outside the focus area of the system, including how to manage and refer such conditions (e.g., traumatic brain injury) to other specialized VA clinical centers, so that collaboration can occur when appropriate.

III. Structure and Coordination for Post-Deployment Centers

VA has the resources and expertise to lead in treating chronic conditions related to deployment. However, a structured system is needed to catalyze the development of effective therapies and to provide the best care possible to Veterans regardless of their geographic location. Using a hierarchical hub-and-spoke model will spur research progress, equip clinicians to provide the best available treatments for these complex conditions, and increase Veterans' access to research studies and care. Additionally, this network can use telehealth and e-learning services to expand its reach and create efficiencies in operation. The system should coordinate across three levels:

- **National-level:** These national centers would oversee and coordinate the activities at the regional (i.e., Veteran Integrated Service Network (VISN)) and local supporting levels. The centers should have specialty clinical expertise covering the range of conditions that are the focus of this system, and the VA health care providers should have a defined consultation network for the evaluation and treatment of these unique deployment-related conditions. However, the different centers may have distinct specialties that collectively are able to meet Veterans' health care needs. Through an integrative and evidence-based approach, centers should be at the forefront of research, developing clinical best practices and disseminating education and training pertinent to chronic conditions of post-deployment. The War Related Illness and Injury Study Centers (WRIISC) already engage in many of these activities and could serve as a natural foundation for the center-level presence of this system.



- **VISN-level:** At least one post-deployment clinic within each VISN would provide specialty care within its area, manage referrals to the regional centers, and ensure medical centers in its area maintain a standard level of care. This clinical program should have expertise in GWI, other chronic multisymptom illnesses, chronic pain, and chronic disorders resulting from environmental exposures. Appropriate staffing at this level would be required to enable proper coordination of local sites and communication with the national centers. The post-deployment clinics would also be hubs for relevant research and VA-sponsored registries. There are a small number of post-deployment clinics that could be built upon to achieve a VISN-level presence for this system.
- **Local-level:** Local VA medical centers should offer a standard level of care and also facilitate referrals for research participation and treatment to other parts of the connected system. Having a referral coordinator and team at each VA medical center would be ideal but may not be feasible, particularly in rural areas. Environmental Health Coordinators are already employed in many medical centers and could serve as an initial point of contact and triage patients to these local post-deployment teams. Leveraging telehealth services could expand the team’s coverage and be an efficient way to consult with the VISN Post-Deployment Center and national centers.

ACTIONABLE ITEMS:

- Consider how WRIISCs could be leveraged to provide oversight, education, and support to VISN-level post-deployment clinics and Environmental Health Coordinators.
- Create a VISN-level referral network by creating at least one Post-Deployment Clinic in each VISN without an existing WRIISC.
- Ensure there is an Environmental Health Coordinator or other relevant VA Registry Coordinator at each VA Medical Center site and establish oversight and uniform educational opportunities.

- Develop a cost-analysis estimate for the core elements of this system of centers. This system will require new resource allocation.

IV. Integration of Post-Deployment Research and Clinical Care

The system should function as an integrated research and care network committed to continuously learning. Achieving this will enable the pursuit of targeted research questions and development of more efficacious treatments delivered in a veteran-centric way. That chronic conditions of post-deployment are complex disorders often with unknown etiologies, poses challenges to progress. Research, however, can serve as a key driver for advancing understanding and treatment approaches. Importantly, research—and the knowledge it generates—needs to occur in the scientific, clinical, and patient domains.

Science

Scientific research is a critical component to elucidating underpinnings of disease pathophysiology and potential risk factors. High-quality clinical studies require adequate numbers of patients that are fully representative of the target population. Discoveries can help identify promising treatment directions and serve to provide information valued by clinicians and patients alike. A robust research agenda would benefit from leveraging recent advances in a wide range of investigative approaches, including genomics, proteomics, metabolomics, neuroimaging, and microbiome analyses. Scientific research can also benefit from close linkages with clinical care and patients themselves. Awareness of clinical outcomes can steer research in clinically relevant directions and connections with patients will help facilitate recruitment of research participants and collection of samples for biorepositories.

Clinical Care

The heart of VA’s mission is to care for those that “have borne the battle,” and for their families. Caring for those with chronic conditions of post-deployment comes with significant challenges due to the complexity of the diseases and limited treatment options. Meaningful progress toward identifying biomarkers and efficacious treatments would greatly benefit from a sufficiently large and rigorously constructed cohort of GWI patients, which this system could help establish and maintain. Such a cohort would be a vehicle for more efficient and effective follow-up to promising pilot studies. A closer network of care providers and facilities could lead to better care through improved coordination, giving greater access to specialists and treatment best practices. Research at the clinical level—including clinical trials and implementation research—is also essential to evaluating the effectiveness of treatments and service delivery. Clinical research could be pursued by drawing on established VA research initiatives such as Quality Enhancement Research Initiative (QUERI)² and Point of Care Research (POC-R)³. Findings can feed into training and education for clinicians to ensure treatment plans align with patients’

² <http://www.queri.research.va.gov/>

³ <http://www.research.va.gov/services/csrd/point-of-care.cfm>

values and are delivered in a veteran-centric way, including having sensitivity to the experiences specific to the veteran’s military service.

Patients

More than ever, a patient-centered focus is being recognized as an important part of the clinical and scientific enterprise. From precision medicine to shared decision making, knowledge about the individual—from genetics to environmental exposures—can deepen understanding of specific health conditions and lead to better treatments. Patient engagement is particularly important for chronic conditions of post-deployment where much still remains unknown about the disorders and the current treatment options often amount to managing the conditions. Closer involvement with a network of clinicians and researchers would give patients better access to a range of clinical specialists and the opportunity to participate in studies. Veterans are often willing research participants and, with proper consent and privacy protection, they should be allowed to more easily learn about and volunteer for research studies and clinical trials.

ACTIONABLE ITEMS:

- Explore how QUERI and/or POC-R could be applied to treatment approaches for chronic conditions of post-deployment.
- Reduce barriers for Veterans who are eligible and not eligible for VA health care to volunteer as participants in research studies and to contribute samples to biorepositories.
- Establish a sufficiently large GWI cohort, biobank, and a comprehensive research approach to identify biomarkers and potential therapeutic directions, which remain key unfinished aims of the ORD GW Research Strategic Plan (2013 – 2017).

V. Data Integration

Effectively using data will be critical to the success of the system. This will require data that is accessible, interoperable, and standardized so that it can be analyzed in a meaningful way. VA’s integrated health care system and research divisions provide a wealth of data to draw from, including EHRs, biorepositories, VA registries, and research data. Additionally, incorporating non-VA data sources will also be essential to gaining a more complete picture of a veteran’s health over time. Notable data sources include Department of Defense (DoD) databases, various state and national registries, National Death Index, and even data generated by patients such as through the use of wearable devices. Creating a comprehensive data repository can help spur research forward and improve clinical care, while also creating a more harmonious experience for Veterans. Many databases are already accessible within VA, such as through the Office of Post-Deployment Health Services and the VA Informatics and Computing Infrastructure system, but other databases will require creating new data use agreements.

ACTIONABLE ITEMS:

- Ensure the interoperability of data across VA data sources.

- Ensure the interoperability of data across DoD and VA data sources of interest.
- Identify additional non-VA data sources of interest and develop a plan for making them usable with VA data.
- Enable pooling of data from varied sources and support research, as well as the development of analytical tools, to analyze data sets in aggregate.

VI. Key Partnerships

A core premise of this proposal is a system based on mutually beneficial partnerships between researchers, clinicians, and patients. In order to fully meet the needs of Veterans, though, this VA system will also need to establish partnerships with additional VA stakeholders as well as non-VA stakeholders. These partnerships should enhance VA's research, care, outreach and educational capabilities. Importantly, the focus of this effort—chronic conditions of post-deployment—is one where VA has unrivaled expertise and therefore Veterans would be best served by having this remain a VA-led initiative. Examples of partners VA should collaborate with are noted below.

VA partners

- Office of Research and Development (ORD)
- Specialty Care Services (SCS), including Centers of Excellence and other specialty care centers. Relationships with the Polytrauma and Neurology specialty care programs (MS and Epilepsy Centers of Excellence, and Parkinson's Disease Research, Education and Clinical Centers) should be encouraged.
- Patient Care Services, including Post-Deployment Health Services, Patient Aligned Care Teams (PACTs), and primary care providers
- Million Veteran Program
- Veterans Benefits Administration

External partners

- DoD, including management as well as research branches such as the Congressionally Directed Medical Research Program
- Health and Human Services, including National Institutes of Health, Centers for Disease Control and Prevention, and Centers for Medicare and Medicaid Services
- Universities
- Nonprofit organizations, including Veteran Service Organizations
- Businesses

ACTIONABLE ITEMS:

- Establish MOUs with DoD for data sharing of military demographic, deployment, and medical data.

- Identify additional academic, non-profit, community, and business partners of interest and develop a plan for formalizing a relationship.

Appendix D

Research Advisory Committee on Gulf War Veterans' Illnesses

Letter to Secretary McDonald (June 2016)

University of California

San Francisco



Department of Neurology

School of Medicine

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June 28, 2016

To: Hon. Robert A. McDonald
Secretary of Veterans Affairs

From: Stephen Hauser, M.D.
Chair, Research Advisory Committee on Gulf War Veterans' Illnesses

Subject: RAC Advice Related to NAM's *Gulf War and Health, Volume 10*
Recommendations

Secretary McDonald,

Earlier this year the National Academy of Medicine (formerly the Institute of Medicine) released a report entitled, "Gulf War and Health, Volume 10: Update of Health Effects of Serving in the Gulf War, 2016," which happens to be the last volume for this series. The reports in this series have served as valuable resources that summarize the published scientific and medical literature at a given time. In addition to organizing a wide breadth of knowledge and making recommendations, the reports also stimulate discussions on important issues among a variety of stakeholders. We commend VA for holding listening sessions following the release of this report in order to better understand the perspective of veterans, and we encourage VA to continue consulting widely on these complex issues.

We hope that the advice, cautions, and recommendations we offer in this letter prove informative to you and your administration as you consider the recommendations from the National Academy of Medicine (NAM). We offer these comments with the intent to help VA plot a course aimed at improving the health of ill Gulf War Veterans.

An overarching theme of the NAM Volume 10 report is an emphasis on pursuing treatments and management strategies that address the varied health conditions of Gulf War veterans. The Research Advisory Committee on Gulf War Veterans' Illnesses (RAC) fully supports such a direction. The NAM also recommends research into Gulf War veteran sub-groups, long latency health issues, and

identifies the need to draw on new technologies and to form partnerships, with which the RAC also concurs.

Although there are several NAM recommendations the RAC agrees with, which we outline below, there are other areas where the RAC takes a different perspective from the NAM. In these instances we offer an alternative approach for the VA to pursue. Additionally, there are limitations and perception issues that we note related to broader Gulf War research areas that will be important for VA to consider in its research agenda going forward.

Advice and Recommendations related to Gulf War and Health, Volume 10.

The National Academy of Medicine was tasked with reviewing, evaluating, and summarizing the available scientific and medical literature regarding health effects in Gulf War veterans, and with providing recommendations for future research on Gulf War veterans' health. Among the recommendations from the Gulf War and Health, Volume 10 report, there are many that the RAC supports. These include:

- VA and DoD partnering to incorporate, “emerging diagnostic technologies and personalized approaches to medical care into sufficiently powered future research to inform studies of Gulf War illness and related health conditions.”
- Pursuing follow-up, “assessments of Gulf War veterans for neurodegenerative diseases that have long latencies and are associated with aging.”
- Conducting, “further assessments of cancer incidence, prevalence, and mortality.”
- Investigating, “Sex-specific and race/ethnicity-specific health conditions... in future studies of Gulf War veterans,” along with a reanalysis of existing data when feasible.
- Placing “top priority on the identification and development of effective therapeutic interventions and management strategies for Gulf War illness. The Department of Veterans Affairs should support research to determine how such treatments can be widely disseminated and implemented in all health care settings.”

Cautions and Recommendations

The RAC has concerns with certain aspects of the Gulf War and Health, Volume 10 report. Some concerns pertain to issues peripheral to the report while others relate to directions that could result were the NAM recommendations adopted in full. In the sections below, we highlight issues VA should consider when developing its plan for moving forward, and in some instances we recommend VA pursue an alternate path.

Cautions:

- **Validity of comparison groups** – from discussions on the Volume 10 report’s findings a broader issue concerning comparison groups has come to light. Specifically, the validity of comparison groups based on deployment status or health conditions identified by ICD-9 codes have been called into question. There is reason to believe that “non-deployed” veterans may have deployed to later conflicts. Secondly, ICD-9/10 codes may not be reliably reported. Moreover, there are fundamental limitations in the ICD system with regard to characterizing GWI. For example, GWI has no ICD code and even its name—GWI or multisystem illness—has varied in the literature. Furthermore, some codes are limited and lack continuity from one version to the next (e.g., CFS has a code in ICD-9 but not ICD-10). These issues go beyond the NAM’s Volume 10 report and impact the Gulf War research field more broadly, and possibly other VHA research. Reliance on these designations should be further explored; in particular, findings resulting from these designations may need to more clearly delineate the comparison groups. The RAC can work with VA on this issue and offer further advice.
- **Timeliness of published data** – the task charged to the NAM Volume 10 committee was to review, evaluate and summarize the available published literature related to 1990 – 1991 Gulf War veterans. Although this approach is very useful and can offer key insights, it has the notable limitation that published literature does not fully reflect the current state of a field. New findings are continuously emerging and these require periodic reassessment of underlying concepts of causality and pathophysiology. As we noted in our 2015 recommendations, potentially important preliminary data need to be followed-up expeditiously. Investigators should also strive to publish their results in a timely manner.
- **Brain-body interconnectedness for GWI** – there is concern that the NAM’s first recommendation may be interpreted in a way that leads to re-focusing Gulf War illness (GWI) research and treatment towards a primarily mental health approach. It should be noted that the NAM Volume 10 committee concurred with previous NAM committees in its statement that, “Gulf War illness is not a psychosomatic illness” (pg. x) and furthermore, “that Gulf War illness is not a mental health condition.” (pg. 82). Recognizing that many veterans have been suffering for over twenty years without much relief, VA has the parallel responsibilities to identify treatments that care providers can deploy today and also to pursue research aimed at developing more targeted and effective therapeutic approaches. While pre-clinical research should include studies that recognize and investigate the complex relationship between the brain and body, research questions should not focus exclusively on this interplay. Furthermore, exploration of the brain-body connectedness should focus on biological determinants and span a range of disciplines, including

neuroendocrinology, neuroimmunology, and systems biology. The concern surrounding this issue also serves as a reminder that there are very limited treatment options currently available for GWI patients and highlights the need to develop more effective therapeutic and management strategies. **This is an area of great interest to the RAC and one that the Committee will continue to explore and advise on.**

Recommendations:

- **The RAC appreciates the NAM report's acknowledgement of Gulf War illness as the signature health concern of 1990 – 1991 Gulf War veterans, and recommends VA do the same.**
- **The RAC recommends VA continue investing in preclinical Gulf War research, including exposure and animal studies when appropriate, that aligns to the larger goal of developing effective therapeutic interventions and management strategies.** The NAM identified key challenges investigators should consider when developing their studies and concluded that animal studies have not been successful at suggesting pathogenic mechanisms leading to GWI, and that development of an animal model of GWI may not be possible. The RAC disagrees with these conclusions. While we would agree there is no comprehensive pre-clinical model of GWI, animal models of Gulf War exposures *have* been developed and *have* identified mechanisms through which such exposures might contribute to GWI. With the right study designs, the RAC believes animal research can serve as an important tool for exploring reverse and forward translation opportunities. Furthermore, there may be new ways to approach exposure studies and animal models to better incorporate cutting-edge research methods, which could yield novel insights and, it is hoped, accelerate progress toward effective therapies. For example, systems and computational biology provide exciting new directions for bringing together pre-clinical and human data. Application of approaches such as these to the problem of Gulf War health outcomes research could significantly advance our understanding of how complex systems can be perturbed. The RAC will continue to explore and advise on this issue.
- **The RAC recommends VA continue to conduct well-designed population-based epidemiological studies with appropriate validation regarding disease-specific prevalence, morbidity and mortality in Gulf War veterans.** There should be a focus on cancer and neurological disease based on positive results from prior NAM reviews and studies in Gulf War era veterans. Additionally, the RAC takes the perspective that epidemiological studies exploring circulatory, hematologic, respiratory, musculoskeletal, structural gastrointestinal, genitourinary, reproductive, endocrine and metabolic, chronic skin and mental health conditions could still yield new insights if designed in a methodologically rigorous way. This latter point is in partial contrast to the NAM's fifth recommendation. Such analysis should include exposures, when data can be determined with

reasonable validity, in relation to geographical deployment. The RAC does agree with the NAM that ensuring timely and effective treatments should be a priority.

- **The RAC recommends VA regularly consult with its funded investigators and others in the field in order to understand the current state of the research.** As previously noted, published results may not fully reflect the most up-to-date understanding in a given area. As VA considers the recommendations offered by this Committee and the NAM, it should also seek the input of researchers and medical practitioners when deciding on the most promising directions for research and care.
- **The RAC recommends VA continue to seek expert external independent input, such as from the NAM, to review, evaluate and summarize scientific literature on health issues relevant to Gulf War veterans. Importantly, committee membership should be balanced among relevant disciplines and include some members with Gulf War illness expertise.**

Respectfully,

A handwritten signature in blue ink, appearing to read "Stephen L. Hauser".

Stephen L. Hauser, M.D.
on behalf of the Research Advisory Committee on Gulf War Veterans' Illnesses
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