Research Advisory Committee on Gulf War Veterans' Illnesses

June 23, 2015 Committee Meeting Minutes

Department of Veterans Affairs
Washington, DC

Research Advisory Committee on Gulf War Veterans' Illnesses
Boston University School of Public Health
715 Albany Street, T4W, Boston, MA 02118
Phone: 617-414-1392, Fax: 617-638-4857

I hereby certify the following minutes as being an accurate record of what transpired at the June 23, 2015 meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses.

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

Table of Contents

APPENDICES

Attendance Record

Members of the Committee
Stephen Hauser, Chairman
Roberta White, Scientific Director
James Bunker
Fiona Crawford
Beatrice Golomb
Nancy Klimas
Stephen Ondra
Frances Perez-Wilhite
Scott Young

Committee Staff
Kimberly Sullivan, Associate Scientific Director
Nicole Comfort

Designated Federal Officer
Victor Kalasinsky

Guest Speakers
Dawn Provenzale
James Baraniuk
Stephen Hunt

VA Office of Research and Development
Robert Jaeger
Timothy O'Leary

Acronyms & Abbreviations

ALS – Amyotrophic Lateral Sclerosis
AMPA – α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic
BChE – butyrylcholinesterase
C&P examiner – Compensation and Pension examiner
CBT – cognitive behavioral therapy
CDMRP – Congressionally Directed Medical Research Program
CFS – Chronic fatigue syndrome
CMI – Chronic multisymptom illness
CoQ10 – coenzyme Q10
CPG – clinical practice guideline
CSF – Cerebrospinal fluid
CSP – Cooperative Studies Program
DARPA – Defense Advanced Research Projects Agency
DAV – Disabled American Veterans
DMDC – Defense Manpower Data Center
DNA – deoxyribonucleic acid
DOD – Department of Defense
DU – depleted uranium
EDTA – ethylenediamine tetraacetic acid
EPW – enemy prisoner of war
FY – Fiscal Year
GW – Gulf War
GWECB – Gulf War Era Cohort and Biorepository
GWI – Gulf War Illness
HSR&D – Health Services Research and Development Service
IBS – Irritable Bowel Syndrome
ICD-9 – International Classification of Diseases-9
ICD-10 – International Classification of Diseases-10
IED – improvised explosive device
IOM – Institute of Medicine
IRB – Institutional Review Board
MAVERIC – Massachusetts Veterans Epidemiology Research and Information Center
MBSR – Mindfulness-based stress reduction
MRI – Magnetic Resonance Imaging
MVP – Million Veteran Program
OEF – Operation Enduring Freedom
OIF – Operation Iraqi Freedom
OPH – Office of Public Health
ORD – Office of Research and Development
PACT – Patient Aligned Care Team
PCP – primary care physician
PDICI – Post-Deployment Integrated Care Initiative
PET – Positron Emission Tomography
PEM – Post-Exertional Malaise

PON – paraoxonase
POTS – Postural Orthostatic Tachycardia Syndrome
PTSD – Post-Traumatic Stress Disorder
QUERI – Quality Enhancement Research Initiative
RAC – Research Advisory Committee
RAC-GWVI – Research Advisory Committee on Gulf War Veterans' Illnesses
RCT – randomized control trial
RFA – Request for application
rTMS – Repetitive transcranial magnetic stimulation
SEID – Systemic Exertion Intolerance Disease
SNPS - single nucleotide polymorphisms
US – United States
VA – Veterans' Affairs
VERA – Veterans Equitable Resource Allocation
VFW – Veterans of Foreign Wars
VHA – Veterans' Health Administration
VISN – Veterans Integrated Service Network
VSO – Veterans Service Organizations
WRIISC - War Related Illness & Injury Study Center

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
June 23, 2015

Department of Veteran Affairs, 810 Vermont Avenue, Room 230, Washington, DC
(800-767-1750; access code 56978#)

Agenda
Tuesday, June 23, 2015

8:45 – 9:00	**Informal gathering, coffee**	
9:00 – 9:15	**Welcome, Introductory Remarks**	**Dr. Stephen Hauser, Chairman** **Res Adv Cmte Gulf War Illnesses**
9:15 – 10:00	**CSP 585 Gulf War Era Cohort and Biorepository Update**	**Dr. Dawn Provenzale** **VA Cooperative Studies Program Epidemiology Center - Durham**
10:00 – 10:45	**Georgetown GWI Research Program Update**	**Dr. James Baraniuk** **Georgetown University**
10:45 –11:00	**Break**	
11:00 - 11:45	**Gulf War Deployment Health Clinic**	**Dr. Stephen Hunt** **Puget Sound VA Healthcare System**
11:45 – 12:30	**Development of Specialty VA Clinics**	**Dr. Nancy Klimas** **Res Adv Cmte Gulf War Illnesses**
12:30 - 1:30	**Lunch**	
1:30 – 2:00	**Update of VA ORD Gulf War Research Portfolio**	**Dr. Victor Kalasinsky** **Dr. Robert Jaeger** **VA Office of Research and development**
2:00 - 3:15	**VA GWI Research Program Discussion**	**Dr. Stephen Hauser, Chairman** **Dr. Roberta White, Scientific Director** **Res Adv Cmte Gulf War Illnesses**
3:15 – 3:30	**Break**	
3:30 - 4:30	**Public Comment**	
4:30	**Adjourn**	

Welcome, Introductory Remarks
Dr. Stephen Hauser, Chairman
Res Adv Cmte Gulf War Illnesses

Chairman Stephen Hauser opened the June 2015 Research Advisory Committee (RAC) meeting on Gulf War Veterans' Illnesses (herein referred to as the 'Committee'). Chairman Hauser welcomed those present at the meeting and those listening in on the phone line. Dr. Hauser is a neurologist from the University of California, San Francisco and he said he was delighted to convene the Research Advisory Committee on Gulf War Veterans' Illnesses (RAC-GWVI). Before asking the Committee members to introduce themselves, he framed where the Committee stood and stated what he hoped would be accomplished by the Committee that day.

The Committee last met in April 2015 and focused on selected aspects regarding the science and biology of illnesses linked to toxicant exposures in the Gulf War. He stated that while that meeting kept the Committee up-to-date on biomarkers and animal models and their relevance to Gulf War Illness, today, the goal of the meeting was to focus on clinical research and how basic research was translated to clinical care in the Department of Veterans' Affairs (VA) system.

The Committee members then introduced themselves. Dr. Hauser gave a brief overview of the day's agenda and then introduced the first speaker, Dr. Dawn Provenzale, a professor of medicine at Duke University. She is the director of numerous programs including the Durham VA Epidemiologic Research & Information Center. She leads a large consortium to measure quality of life in veterans and, in particular, lung and colorectal cancer care in VA and non-VA settings.

CSP 585 Gulf War Era Cohort and Biorepository Update
Dr. Dawn Provenzale

Dr. Provenzale greeted the Committee. She appreciated the opportunity to discuss the cohort and biorepository of Gulf War veterans. For the presentation slides of Dr. Provenzale's presentation, please refer to **Appendix A – Presentation 1**. She started off by giving an overview of her presentation as well as acknowledging her study team and organizational partners.

She stated the goal of the Gulf War Era Cohort and Biorepository (GWECB) project (CSP #585), which in summary was to enroll a group of individuals for certain research and to obtain blood specimens from them for a biorepository. The purpose of doing so was to provide valuable tools to examine the prevalence and correlates of medical conditions affecting Gulf War-era veterans, to enhance ongoing research and study chronic diseases that affect veterans with that cohort's demographic profile, and to help target programs to better meet the health care needs of all veterans. She also detailed her two project aims.

She specified the eligibility requirements for participants of this study, which included any member of uniformed services in the 1990-1991 Gulf War Era (deployed and non-deployed; Veterans' Health Administration users and non-Veterans' Health Administration users). She then informed the Committee of where the participants were recruited from. The data collected included a GWECB paper survey, VA and non-VA medical records, and blood specimens. She

provided some specifics regarding the development of the survey and topics covered on the survey as well as details regarding collection of the other data. She next detailed the participation requirements, which included signing and returning all consent forms and providing a blood sample.

She then presented a flow chart depicting an overview of the recruitment process: First, there is an initial sample file received via random sampling from the Defense Manpower Data Center (DMDC) roster. Recruitment packets are mailed to eligible veterans and the study's contracted enrollment coordinating center calls the veteran, confirms eligibility, and obtains a verbal consent. Finally, the blood draw is obtained, and sent to the Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC) in Boston for processing and storage.

Recruitment began on September 2, 2014. There are twenty-two recruitment locations which were selected according to multiple criteria which she briefly outlined. She stated that if a veteran is not close to a recruitment location, there is the option to have a phlebotomist fly to the veteran's location to obtain their blood.

Dr. Provenzale showed her current enrollment data as of June 2015. There were 846 total consented veterans, pending scheduling for the blood collection appointment, and 657 that were fully enrolled and had their blood specimen at MAVERIC. She next provided more information regarding those enrolled including demographics, Veterans' Health Administration (VHA) user status, and deployment status. Approximately 71% were deployed to the Gulf.

Dr. Provenzale wanted to specifically get the opinion of the RAC regarding phone calls, as 5,420 potential participants were released to the call center, and 33% could never be reached by phone. However, they found that those that they did reach by phone and who provided verbal consent to participate in the project tended to follow through with the written consent and actual completion of the blood draw. The overall recruitment rate was 8% with an approximate recruitment cycle length of 206 days.

The next slide provided details for those who chose not to participate in the project. In total, 22% of veterans refused or opted out of the study. Dr. Provenzale then depicted the recruitment challenges on the order of call operations, mail operations, field operations, and overall recruitment and what her team had done to address them. Next, Dr. Provenzale listed their future study directions. She mentioned that at that time, they were in a transition period in the project, as they had reached their target of 10,000 mailings for the first year of the pilot on May 18, 2015 and so were beginning to implement a qualitative research component. She described the ways that her team was conducting this qualitative research in order to understand veterans' perspectives of their project. The remaining future directions all pertained to enhancing their recruitment.

In closing, she provided more information about the Cooperative Studies Program (CSP) 585 project, including websites to visit for more information about the project, the CSP 585 telephone hotline number, as well as the personal contact information for Rick Gray, a CSP 585 Research Assistant. She again emphasized that although they have recruitment locations throughout the

country, veterans do not have to live in one of those cities to participate. They can send a phlebotomist to a veteran outside the recruitment area who wishes to participate.

Lastly, Dr. Provenzale wanted to engage the RAC and obtain the members' advice regarding (1) More effectively engaging Gulf War veterans in this project; (2) Engaging Veterans Service Organizations (VSOs) and which VSOs and other Gulf War Era networks they should connect with; (3) Conferences or events Gulf War veterans might attend; and (4) Implementation of the CSP 585 qualitative activity.

With that, Dr. Provenzale concluded her presentation and opened the floor for discussion. Dr. White was the first to comment, thanking Dr. Provenzale for the presentation. She asked Dr. Provenzale a question about the ultimate total number of participants that she was trying to achieve, given that there was such a low recruitment rate in the first year of the study. Dr. Provenzale responded that for the pilot study, the goal was to mail 10,000 packets and to enroll 3,000 veterans. She then said that ultimately, the goal for the entire cohort was to enroll 30,000 veterans.

Dr. Klimas then suggested that Dr. Provenzale get motivated individuals into the study, which would be the self-nominated veterans, and thus the best strategy going forward would be to get people to volunteer. She also suggested that Dr. Provenzale put more publicity on Google or utilize social media, such as a Facebook page or veterans' newsletters. She suggested reaching out to the veteran community for the "super connected" people who would really promote a study and that veterans trust in so that they would enroll. She also suggested changing the way the message was targeted; that a biorepository may sound mundane, so to frame it in a way that made it clear that participation in such a study would be crucial to answering questions about this illness that would address their health needs. To that, Dr. Provenzale asked how she might find those individuals; that is, which groups to engage with and how to best engage them.

Mr. Bunker commented next, noting that this was the 25th anniversary of the start of the Gulf War (GW) Desert Storm and Desert Shield and therefore there were a number of reunions planned happening that year that she should target. He mentioned that the VII Corps would be having a reunion as well as the 1st Infantry Division and other groups. He also said that the War Related Illness & Injury Study Center (WRIISC) in New Jersey has a meeting with VSOs from the Disabled American Veterans (DAV), Veterans of Foreign Wars (VFW), and American Legion once a month and that she could attend that to get the CSP 585 information out to VSOs. He also mentioned that the VA sends a newsletter to GW veterans and that she could discuss with Dr. Kalasinsky how to put this information into the newsletter. Lastly, he mentioned that many records had not been digitized and are often overlooked, so suggested that she look at those records.

Dr. Provenzale asked Mr. Bunker if he could provide a list to Dr. Kalasinsky of those venues to reach out to veterans.

Ms. Perez-Wilhite commented that she is from North Carolina and belonged to the North Carolina Veterans Executive Council, which she said was comprised of major VSO state commanders and had access to roughly 25,000-30,000 veterans. She stated that she'd been

involved with this organization for eight years and that it was relatively effective in dispersing something quickly to veterans throughout the state, so it would be helpful for Dr. Provenzale to come and speak to that group. Ms. Perez-Wilhite stated that next month she would be elected Secretary of the organization, and so welcomed her to come and speak to them. Lastly, she asked whether Dr. Provenzale had processed the data on the female veteran responses. She'd find this analysis interesting to see because she noted that she had met a lot of female veterans that were deployed to the Gulf in August of 1990 who have a lot of gastrointestinal problems.

Dr. Provenzale said that she looked forward to interacting with Ms. Perez-Wilhite to reach out to veterans. She also said that regarding the females, they oversampled in order to obtain 20% females, and that indeed 20% of their sample was comprised of women. She said that in terms of the detailed medical conditions, they were in the process of analyzing the data and would get back to her when they had additional information.

Dr. Hauser had a few questions for Dr. Provenzale regarding the study methods. He clarified that it was one tube of blood being obtained before asking how it was being prepared. Dr. Provenzale answered that it was an ethylenediamine tetraacetic acid (EDTA) tube shipped on a gel pack to MAVERIC where it was then separated into plasma and buffy coat and deoxyribonucleic acid (DNA) was extracted. Dr. Hauser then asked if she was saving the plasma, to which she responded that she was. He then asked her if she had serum. She answered that they did have serum also. However, Dr. Hauser thought that that would require another tube, so she said she would have to double check on whether she had serum or not.

Dr. Hauser then asked whether she was doing an RNA analysis. She mentioned that this was a good point and that others had recommended that she obtain more tubes of blood, including PAXgene tubes for RNA.

The next question Dr. Hauser asked related to the nested cohort that some of the mailings were sent to. He asked whether this was the cohort in which she had an 8% response rate. She said that was correct. He said that this seemed like more of a "convenience cohort" rather than a representative sample and therefore asked if there were ways epidemiologically to convert this to something that resembled a representative cohort. Dr. Provenzale said that her team was certainly thinking about that and that the aim was to get a representative cohort, but their response rates were rather low. She said that as more data was gathered to try to enhance overall recruitment, there would certainly be ways to better understand who the data are coming from and then perhaps they could put targeted recruitment efforts to those that were missing from the sample to enhance the representativeness of the sample.

Dr. Hauser asked whether Dr. Provenzale knew how many (what percent) of the completed samples thus far were from individuals that are symptomatic. She said that those data weren't analyzed.

Dr. Sullivan thanked Dr. Provenzale for her presentation and proceeded to ask a few questions. She said that what she's discovered from her past recruitment studies was that night and weekend calls are most effective because a lot of veterans are still working. She recommended they add weekend calls if they weren't doing them already. She said that another issue was that GW

veterans criticize studies because researchers are collecting a lot of data but then not putting it out or publishing papers, and thus the veterans are unable to see the advances in research resulting from their contribution of specimens. Therefore, Dr. Sullivan recommended that as soon as she could, Dr. Provenzale should start doing the qualitative research component, analyzing any of this data, and sending it to all the veterans that had participated in the study so far. She noted that this would really "sell the study" and help get GW veterans to talk about the study with other veterans and encourage them to participate, because she was sharing the data and getting it out.

Dr. Provenzale thanked Dr. Sullivan for this input and mentioned that they were working with their contract regarding weekend calls and how to best execute them. Dr. Sullivan asked one more question about the sample, which was whether they were still planning to share these samples with other researchers, and if so, when. Dr. Provenzale said that indeed they would be sharing the samples and that the processes were under development at that time yet they were also still in the process of gathering the samples (because they only had 657 at the moment) and the information. Dr. Sullivan encouraged that she begins working on this sooner rather than later because although it's not a very large sample, for some studies it would give a good power analysis. In addition, she mentioned that this was another way to get the data out and to get data published with the samples she already had. Lastly, Dr. Sullivan said that sharing her data with other investigators would expand her outreach as well.

Dr. Hauser thanked Dr. Provenzale for presenting and she thanked him and the guidance of the RAC. She stated that she looked forward to interacting with the Committee in the future.

Georgetown GWI Research Program Update
Dr. James Baraniuk

Dr. Hauser introduced the next speaker, Dr. James Baraniuk. Dr. Baraniuk is an associate professor at Georgetown University in the Department of Medicine. He has trained in internal medicine, allergy, and immunology as well as neuropeptides. Dr. Baraniuk has a longstanding clinical interest in chronic fatigue syndrome and difficult pain syndromes and has used proteomics and analyses of cerebrospinal fluid (CSF) to identify potential biomarkers for these conditions. Dr. Hauser welcomed Dr. Baraniuk and thanked him for coming. For slides of Dr. Baraniuk's presentation, please refer to **Appendix A – Presentation 2.**

Dr. Baraniuk greeted everyone and said that it was an honor to be there. He began by giving an introduction to Gulf War disease. He said that he thought it was interesting that this cohort was exposed and has had the chance of being followed for twenty-five years, making them an excellent longitudinal cohort. He discussed the unique set of exposures that GW veterans were exposed to, going into some detail about specific agents.

He next described the patterns of Gulf War disease. He said that from the patients he'd seen, he concluded that there's a cohort that developed acute symptoms in theatre. However, he stated that the Gulf War Illness (GWI) cohort has not had standard longitudinal neurotoxicological and epidemiological examinations for dysfunctions related to the highest probability exposures.

He was disappointed to see that symptoms had been attributed to MUPS (medically unexplained physical symptoms) or somatoform causes and said that this is still an issue today. He also said that as we learn more about functional somatic syndromes such as chronic fatigue, we'll have a big influence on the 40-60% of patients who chronically go to doctors, accounting for most of doctors' visits and health expenditures.

He discussed the issues preventing the investigation of GWI, which included the fact that medical records were destroyed and that data presented to the IOM does not include sufficiently detailed medical reports.

He then transitioned to talk about cohort effects and noted that under the Fukuda criteria, 15% of those who were never deployed developed GWI symptoms. Then, when Dr. Lea Steele's Kansas criteria came out in 2000, that group was excluded and has hence been totally ignored and lost to follow-up. He was interested in what happened to them as well as other cohorts deployed to the Gulf that he mentioned (which included the 1980's cohort of veterans in the Persian Gulf regions during the Iran-Iraq war, the 1991-2002 Gulf War veterans, as well as Operation Enduring Freedom/Operation Iraqi Freedom veterans). He wondered whether they developed symptoms and said that comparing these groups to the 1990-1991 Gulf War veterans would illustrate how unique the members of this cohort actually are as well as perhaps reveal causes to the symptoms of Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) veterans that are being attributed to post- improvised explosive device (IED) traumatic brain injury, pneumonitis, dyspnea, and burn pits.

He then listed functional symptoms which in the mid-1990's where referred to as psychosomatic in nature. The next slide showed some of the functional biomarkers that correlate with the conditions, disproving the prior belief that "it's all in your head." He said that his aim was to define the objective mechanisms, definitions, and treatments for GWI, chronic multi-symptom illness (CMI), chronic fatigue syndrome (CFS), and fibromyalgia. He then displayed a table depicting the overlap of subjective case designations for fibromyalgia and paused to take a moment to explain the process of central sensitization in a neuron. To summarize, chronic stimulation leads to chronic pain, as glutamate is released in response to the painful stimulus and activates an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor. This is known as hyperalgesia. Additionally, the neuron responding to the painful stimulus becomes hyper-sensitive not only to demyelinated nociceptor neurons, but also to low threshold mechanoreceptors. That is, a light touch will cause pain. This is known as "parallel pain" or allodynia. He went into more detail, describing some of the theories that describe the mechanism of this phenomenon.

He next referred back to the table and discussed CMI (or GWI), outlining the components of that diagnosis. He said that what really made this diagnosis separate from CFS was that this cohort had exposures during the Gulf War in 1990-1991. Essentially, what he was saying was that the symptoms experienced by GW veterans were very similar to the criteria for fibromyalgia and CFS at the time, yet these veterans were being told that their illness was psychosomatic in nature. Yet, as Dr. Baraniuk pointed out, depression is present in 40-60% of all chronic illnesses, so it wouldn't be surprising to have GW veterans with depression also presenting these symptoms. He also noted that symptoms of depression such as fatigue and energy loss, diminished ability to

think or concentrate/indecisiveness, and sleep disturbances overlap with symptoms of fibromyalgia, CFS, and CMI, yet there are other aspects of depression that do not overlap with these conditions and that GW veterans do not present that means they do not merit a diagnosis.

Dr. Baraniuk then asked how we can move forward to objective mechanisms given these shared features. He took a moment to explain the mechanisms of a migraine. He stated that a migraine is the result of a cortical spreading depression, leading to extreme vasoconstriction that spreads outward. This is then followed by vasodilation and the release of many mediators that activate the neurons and nerves in the arachnoid mater and pia mater (meninges, or linings, of the brain). These nerves are extremely branched trigeminal nerves and reach the dura mater and larger vessels, releasing neuropeptides that will dilate those. That dilation then results in a stretch and causes the stretch receptors on the outside of those vessels to feel pain. This message of pain is thought to then move through the trigeminal ganglia into the secondary cervical association area and then through the thalamus to higher regions of the brain, where the pain is experienced as a migraine. He then explained a second theory of the mechanism of a migraine. He provided these two examples because he stated that he thought that this reasonably well-worked out mechanism offers us a model of investigating drugs that may treat GWI.

The model that he researched in CFS and GWI studies was exercise-induced exhaustion. He noted that previous studies examining exercise in CFS had participants exercise at a submaximal level on day one, but then on day two they had very poor muscle function and were unable to exercise. It turned out that the amount of oxygen exchanged was a better indicator of that loss of muscle/exercise capacity. Thus, in his studies, they had veterans with GWI and healthy veterans do maximal exercise studies, expecting to see a difference between day one of exercise and day two of exercise, with the control subjects doing well on both days and GWI veterans having a decrease in the amount of oxygen that they could take up. However, this was not what he observed. The subjects did equally well in terms of the cardiopulmonary and musculoskeletal systems. The take-home message from these results was that GWI was different from those groups of CFS who had been tested in that fashion.

After this finding, Dr. Baraniuk switched to submaximal exercise tests. They chose to perform magnetic resonance imaging (MRI) before exercise and after the second exercise. He detailed the multiple modalities of MRI that they performed. One of the things that surprised him was that they were able to find an increase in axial diffusivity in a number of tracts in the brain. They've been trying to figure out why this happens, and he said that the best answer from the literature has attributed it to shrinkage in the diameter of long neurons. They are conducting studies to test this observation's validity as a biomarker.

He then noted that after exercise, one third of his patients developed postural tachycardia (see the pink triangles on page 15 of Appendix A – Presentation 2). This elevated heart rate persisted 24-36 hours after exercise and they've reproduced these findings. What these findings indicate is that in these patients, there is an exercise-induced autonomic dysfunction. This provided his team a model system to look at and now Dr. Baraniuk is investigating ways in which to modulate this autonomic effect. He proceeded to first explain ways in which the brain regulates tachycardia and showed MRI images to illustrate.

He next explained the methods of the cognitive tests used. Participants completed 0-back tasks and 2-back tasks, which he explained are working memory tasks. He then showed the data of what they observed in the cortex of sedentary controls before exercise. There were about four brain regions that were activated in the controls during the 2-back tasks (the more difficult tasks). The next day, there were fewer regions activated, demonstrating that these participants learned.

Those who did not exhibit tachycardia had many more regions in their brain activated one day before exercise. Thus, at baseline they were using many areas as cognitive compensation in order to appear normal. After exercise, they still required those regions (in particular, the caudate nucleus).

In those who did have the postural tachycardia, they did not see any particular brain regions activated. Dr. Baraniuk did note that this was a small sample size which he hoped to expand. However, the findings between the two groups were very different. Continuing on, he mentioned that another way to present this data was to consider which brain regions were functionally connected. He said that there were five regions that were functionally connected such that when one was activated, the other was communicating with it within the network. The DMN stands for the "default mode network," or concentrating on internal thoughts. If one is actively doing a task, the right and left executive areas are activated. He continued to explain which brain regions show activity in response to a certain task, certain thoughts, or certain features of the environment.

Looking at the effective connectivity in these same patients, they found that they did not see much of a change in sedentary controls, as their brains were already efficient. In the group that did not have tachycardia (STOPP group), they had a lot of changes in the areas that were functionally connected. In the group that exhibited postural tachycardia (START group), once again they observed large changes in the brain in response to exercise. He explained the significance of the decrease in activity in specific brain regions of the STOPP and START groups and how it related to their ability to perform the task.

Dr. Baraniuk provided an overview of brain network interactions and how he thought they applied to the nociceptive, hyperalgesia, migraine, attention networks, working memory, exertional exhaustion, fatigue, affect/anxiety and other components of GWI. He showed an example MRI from a study published on depression to illustrate that objective MRI measures lead to study outcomes that can unveil a lot about the disorder and help lead to treatments, similar to the objective outcomes he is hoping for as a result of the MRIs done in GWI studies.

With that, he concluded his presentation and thanked the Committee for their attention.

Dr. Sullivan asked Dr. Baraniuk whether his newly funded Congressionally Directed Medical Research Program (CDMRP) study would be focusing on neuroimaging again. He said that they would be repeating the exact same study as a verification study. He noted that they were at the time in the last stages of Institutional Review Board (IRB) approval and that he had just reworked the budget and that the study should get going after September 2015. Dr. Sullivan confirmed whether he would be comparing axial diffusivity in GW veterans and he said that he indeed was planning to study this. She then asked whether he was also comparing cerebrospinal fluid (CSF) and he responded that he was and that he would be looking for biomarkers in CSF

for GWI. Dr. Sullivan was pleased to hear that his previous study was being validated in a new sample.

Mr. Bunker asked Dr. Baraniuk about a pilot study he had done on Irritable Bowel Syndrome (IBS) treatment. He asked Dr. Baraniuk what kind of a recommendation the Committee could make to the VA in order to fund a verification study or follow-up study on that pilot study to help find a treatment. He noted that IBS is one condition that many GW veterans deal with so a treatment protocol would be very helpful for GW veterans and anyone else suffering from IBS. Dr. Baraniuk responded that he was currently analyzing the data from that study and trying to get a better understanding on what improvements they had an effect on, such as a change in symptom profile, but he was still working with the data. He noted that it would be nice to be able to link the results of that pilot study with a colonoscopy study and also mentioned that some recent microbiome studies would be of value in providing enlightening information. He said that the carnosine at the doses they were able to reach and potentially higher doses could be effective because it would modulate the neurons in the gut. To this, Mr. Bunker asked Dr. Baraniuk if he would like to see the VA do a verification study on that, or whether he would be willing to collaborate with the VA on doing a verification study. Dr. Baraniuk responded that he would be happy to collaborate with VA.

Dr. Baraniuk said that they also have MRI studies from those people but noted that some of these participants did not have any subjective improvements at the endpoints that were looked at, which he proposed was important because he said that most of the things that they used could have been irrelevant as far as improving the long-term pathology in those patients.

Mr. Bunker then said that another major problem within the veterans is migraines. He noted that one of the things that helped him and that Dr. Baraniuk started prescribing to the veterans was topiramate. He mentioned that there was a pilot study with this drug but that it only ran for two weeks, which in his opinion was too short of a period. Thus, he asked whether Dr. Baraniuk had done anything more regarding this and whether he thought there needed to be another study done at a higher dose. Dr. Baraniuk responded that there have been three good studies proposed to the CDMRP but that they weren't funded. When Mr. Bunker asked what Dr. Baraniuk's thoughts were on that, he said that this treatment had a lot of potential. He mentioned that many veterans and CFS patients that came into his clinical research unit met migraine criteria, yet they had just come in from their neurologist and hadn't been diagnosed by their primary care physician (PCP). While in the clinical research unit, they took the opportunity to give them a treatment such as sumatriptan, for example, and their headaches got better to the point where they were practically begging for a prescription. Mr. Bunker lastly noted that the topiramate worked for some migraines but not migraines due to spine injuries. Dr. Baraniuk agreed.

Dr. Hauser asked whether there was anything distinctive about migraine in GW veterans. Dr. Baraniuk remarked that this was an excellent question and said that in women, they thought they would see peri-menstrual aggravation, but they did not. He also mentioned that in the lumbar puncture study, out of 116 people who received a lumbar puncture, 20 of them developed photophobia, phonophobia, and a migraine headache. He said that people with migraines usually aren't supposed to get headaches following a spinal tap, but that this group clearly did and it turned up as a risk factor in a multi-variant analysis.

Dr. Hauser then asked how Dr. Baraniuk selected controls in his MRI study. He said that their controls are sedentary and not exercisers who often have some other health problems, because he said to discriminate a problem between a very healthy group he thought would be trivial and not help them in discriminating the difficult, borderline cases from the actual GWI. To clarify, Dr. Hauser asked that they try to select people with some functional characteristics. He responded that they had chosen individuals with chronic idiopathic fatigue, CFS-like syndrome, and they often had depression profiles.

Dr. Hauser asked whether in persistent orthostatic tachycardia syndrome, the tachycardia was only with orthostasis and thus decreased when people sat. Dr. Baraniuk responded that they have the participants lie down and then stand up, which was very difficult for the patients. This led Dr. Hauser to comment that it seemed a little like Postural Orthostatic Tachycardia Syndrome (POTS) syndrome. Dr. Baraniuk said that in some CFS patients, they were symptomatic before the exercise but that this was mitigated with Gatorade, leading Dr. Baraniuk to think that there was some element of dehydration at play. However, he mentioned that the exercise-induced tachycardia did not respond to the fluids/electrolytes and waned only after 24-36 hours. Dr. Hauser asked if this phenomenon had been described in other populations, but Dr. Baraniuk responded that so far, no, it was just his results. He had seen no reports in a wider population. Lastly, Dr. Hauser asked Dr. Baraniuk for his thoughts of treating this using dopaminergic drugs, but Dr. Baraniuk responded that he wanted to verify these results before moving forward.

Mr. Bunker observed that in this study, they did exercise on a bicycle, but he asked whether the same effect would apply to people doing cognitive exercise. Dr. Baraniuk explained that they used the bicycle because it was a reproducible stimulus, but said that indeed a lot of the patients had mentioned cognitive and emotional induction of their symptoms and he briefly mentioned the "brain fog" common in both CFS and GWI. Mr. Bunker then asked clarifying questions about the proper diagnosis of CFS. He said that he had seen a lot of Compensation and Pension (C&P) examiners deny that a veteran has CFS because the examiner said that the veteran's lymph nodes weren't enflamed or enlarged. Therefore, Mr. Bunker wanted to confirm whether they should be enlarged in CFS or just tender. Dr. Baraniuk responded that the region is not necessarily large in size, but tender because the outside of the lymph node is very densely innervated by nociceptive nerves, so if there were any sort of inflammation there it should be accompanied by pain. Thus he confirmed that patients with CFS do not have large lymph nodes.

Dr. Baraniuk thanked the Committee, who took a short break before reconvening for Dr. Stephen Hunt's presentation.

Gulf War Deployment Health Clinic
Dr. Stephen Hunt

Chairman Hauser introduced the next speaker, Dr. Stephen Hunt, from the Puget Sound VA Healthcare System. Dr. Hunt is a clinical Assistant Professor of Medicine at the University of Washington School of Medicine in the Occupational and Environmental Medicine program, where he is developing strategies for approaching veterans' health care issues from the perspective of military service as an occupation and combat as an environment. He is the national director of the VHA Post-Deployment Integrated Care Initiative, which provides leadership for

the development and support of integrated post-combat care in all VA medical centers nationally. Dr. Hauser was very pleased that Dr. Hunt could join the Committee's meeting and looked forward to his presentation on deployment health clinics. For Dr. Hunt's presentation slides, please refer to **Appendix A – Presentation 3.**

Dr. Hunt thanked Dr. Hauser for the introduction and stated that he too was very pleased to be presenting at the RAC meeting. He particularly wanted to acknowledge the GW veterans present at the meeting, both in relation to their service as well as for their ongoing advocacy after the slow and difficult twenty-five years they've experienced. He said that his presentation would be addressing how patients should be taken care of when there is little understanding of what causes GWI and limited understanding of what treatments are available.

He began his presentation with a personal story about a previous GW veteran patient that he saw in order to illustrate that as we move forward and think of ways in which the research can be shaped to learn more about how to take care of the veterans coming in with their specific symptoms, the patient should always be kept in mind. He remarked that in the 1990's, he noticed right away that the traditional ways of taking care of people clinically weren't going to work for GW veterans. The reason behind this was that veterans who came in to see their PCP received a basic evaluation, but the tests would be negative. Therefore, the clinician would send the patient to mental health. However, once in mental health, they would receive an evaluation and fail to meet any criteria for a diagnosis, so the mental health provider would send them back to their PCP. To address this, Dr. Hunt said that he sought to move away from the paradigm of asking an "either-or" question and instead looked in a more comprehensive way at how to treat GW veterans until more became known about exactly what is going on physiologically and more targeted treatments are developed.

He noted that since then we have learned a lot more about GWI and its causes, that the veterans experienced multiple exposures to various chemicals and that there are many potential physiological consequences. He also noted that as a clinician, one needs to recognize that mental disorders such as depression, Post-Traumatic Stress Disorder (PTSD), and anxiety are physical disorders just as much as they are mental and that they stem from functional changes in the nervous system and physical changes in neuroanatomy. Thus, as a clinician, he realized that veterans needed specific care because he understood that toxic exposures in combination with psychological stressors in the environment lead to worse outcomes than either experienced alone.

He stated that his aspiration for the VA was to be a system that can provide support in an integrated way for people that have all sorts of issues post-deployment. Dr. Hunt then explained their stepped care model for integrated post-combat care that includes tertiary care through the WRIISCs as well as the community, registry clinicians, the C&P examiners, and other services. The clinical care in the VA transformed around this model of integrating physical health, mental health, and social work support. This is known as the Post-Deployment Integrated Care Initiative, 2008 (PDICI).

He noted that focusing on personalized care in GW veterans was crucial because each veteran had their own experiences, exposures, health issues, symptoms, and personal needs. He noted that immediately after a veteran comes back from a deployment is when they should be evaluated

by a team that would examine them in the comprehensive way he discussed.

He mentioned a study in review that he had conducted with Dr. David Kearney on mindfulness. He stated that when they used a mindfulness-based stress reduction (MBSR) approach, they found improvements in cognitive functioning out to six months as well as improvement in pain and fatigue scores and PTSD symptoms.

After discussing his research, he proposed that the Committee focus on point-of-contact care delivery and how it can be improved. He continued by listing the research priorities for enhancing VA point of service for Operation Desert Shield/Desert Storm veterans which included enhancing partnerships, benefits, clinical team education and training, population-based management, medical surveillance, research and development, and outreach.

He then went into more detail discussing each of these points and his ideas on how each could be improved. For example, in regards to clinical team education, he mentioned that he was in the process of putting together a military medicine and deployment health "roadmap" for clinical teams so that all Patient Aligned Care Teams (PACT) would have a "roadmap" resource that tuned them into military culture and history, deployment health, and service-related exposures. This would more systematically educate their teams. He mentioned that they were not challenged by access to good tools and resources with the VA, but that the challenge was ensuring that the dependable system was implemented at every VA center every time with every veteran.

He stated that in the end, research is really about clinical care and clinical care is all about healthy veterans who have the support and resources necessary to live satisfying, productive, and personally meaningful lives. He mentioned that there were some additional slides to his presentation (pages 16 – 19 of Appendix A – Presentation 3) that the Committee could view at their leisure regarding the issue of beliefs; that is, what researchers and clinicians believe to be true about all of this. He stated that these were important to him because it could be a problem if they're working off of guesses or unproven theories and yet there are some things that are known to be certain about the veterans and GWI.

He thanked the Committee for the opportunity to speak, concluded his presentation, and began to receive questions.

Dr. Klimas admired Dr. Hunt's vision of linking every veteran that comes into the VA with the specific care that they need and doing so as quickly as possible after returning from a deployment. However, she noted that the situation is different for GW veterans because they've now been sick for over twenty years. She then said that the biggest complaint she hears when veterans come to her clinic is why it took them over twenty years to realize that there was someone doing work in this field. Thus, in terms of operationalization of this vision, she asked how we could use the VA model to make it into the device that gets a veteran care for this illness. Specifically, she asked how they could connect people to savvy clinicians.

Dr. Hunt said that the "roadmap" is one of those things that would focus on taking military history (learning from what could've been done better with veterans in the past) to better educate clinicians. Their knowledge of military history would lead them to certain presumptions when

they encounter a veteran from a specific branch that served in a specific location or during a specific time. He mentioned that although he liked the WRIISCs, he really liked the idea of a stepped care model, where there are ways to interconnect within the system (via hotlines, for example) that would serve not only new veterans, but also veterans that have any deployment-related health issue going back in time. He then mentioned that by 2008, 84% of VAs had some integrated care platform for returning combat veterans, which was a step in the right direction, although he regretted not having this platform in place sooner (when the GW veterans returned home).

Mr. Bunker noted that there was a program for Desert Storm veterans when they were returning home, but it was stopped because it was said that there was no longer funding for it. He then noted that Dr. Hunt had mentioned the use of the registry exam in his slides and pointed out that one of the biggest problems was that some of the Veterans Integrated Service Networks (VISNs) and hospitals didn't give the registry exam although they were supposed to because it was regulation. Dr. Hunt identified this as a sign that there were VAs that weren't doing things in a systematic way, yet Mr. Bunker said that this was a big problem that needed to be addressed and get fixed.

Dr. Hauser remarked that this issue was one that was also brought up at the April 20-21, 2015 meeting, which led him to ask how far the VA has gone into this integrative model for the 1990-1991 GW veterans that seek that service. Basically, he was wondering how veterans reach Dr. Hunt at the Puget Sound VA. Dr. Hunt responded that at his clinic, they linked their registry exams to their deployment health consultation service. He also mentioned that if a veteran came in through the deployment health clinic, he or she would be connected to a provider. However, he acknowledged that Dr. Hauser's question was not about his particular center, but was in regards to what was happening VA-wide. To this, Dr. Hunt answered that the integrative model was not happening VA-wide, but that was the goal of the "roadmap," to build that sort of awareness into all patient-aligned care teams. He lastly mentioned that they've done a better job with the veterans that served in the 2000s and later than with earlier veterans.

Dr. Hauser then asked whether it would be better to build such a roadmap throughout the VA system with many people, or to have smaller numbers of experts able to see everybody. Dr. Hunt replied that both would be needed; there is a need to have a baseline education of all providers and teams as well as a stepped care model so that there are the WRIISCs or specialty clinics that a person can be referred to when a veteran's needs go beyond a clinician's capacity. He mentioned that there should probably be more of those specialty clinics, which Dr. Klimas would speak about in the next presentation. To that, Mr. Bunker mentioned the "train the trainer" sort of program, which Dr. Klimas would also discuss shortly.

Dr. Ondra directed a question regarding resource utilization and partitioning to Dr. Kalasinsky. Noting that Dr. Hunt's presentation discussed performing health and benefits research in order to improve the delivery of treatment and earned benefits for veterans and improving efficiency in the system, he asked if funding this type of research would take away from the funding for clinical research looking at understanding GWI and developing new treatments. Earlier that morning, he said that he had heard a great deal of frustration from veterans on the health and benefits system efficiency, so although he understood that researching how to improve this

system was very important just like clinical research, he wanted to know how resources would be prioritized for those two areas.

Dr. Kalasinsky replied that the budget for basic care services is separate from the budget of the research office. He then clarified that this Committee's advisory role is on the research side, but as Dr. Hunt pointed out, the research will affect clinical care. While they may have different budgets, he noted that research and clinical care fall under the same part of the VHA so there are people who oversee both sides of those things.

Dr. Sullivan hoped to refocus the Committee on their goal for the day, which was to learn how to best translate the results of research into clinical care. Therefore she questioned how they should translate the research. She iterated the importance of this translation by mentioning that even the best researcher's data would be no use at all if it was not disseminated down to the caregivers. She asked if translation of the research to caregivers was being done in the PACT system. She also asked whether they kept track of the research coming out and if not, how they could accomplish that. Finally, she asked how they could make the clinicians more aware of the research because it was obvious to her that they were not reading all the research that was coming out.

Dr. Hunt responded that there are established channels through patient-care services, but through efforts like the roadmap for deployment health, the goal was to try to educate on a more broad level. He also mentioned that clinical research should be happening for all post-deployment care and not just for specific cohorts like those with heart disease or diabetes. Dr. Ondra commented that the problem of physicians not keeping up with current research was not unique to this cohort, but happens across the VA. He particularly mentioned that adherence to guidelines and an established protocol among oncologists within the VA was very poor. While this did not justify it, it helped to understand the problem. To this, Dr. Sullivan responded that it was different when a GW veteran goes into a VA only to hear from a physician that he or she had never even heard of GWI. That, she said, was a big problem. Dr. Ondra agreed.

Dr. Ondra then asked whether the VA was structured in a way such that more money could be funded to promising studies, while other studies that were not yielding promising results or useful data could be cut funding. He said that this was a much more efficient model for research when it comes to utilizing resources efficiently. He also mentioned that the Defense Advanced Research Projects Agency (DARPA) had a similar model that looked for certain milestones to determine whether the research project would yield the output that was intended and stopping the projects that were missing those milestones which suggested that they would never yield the intended results.

Dr. Sullivan thought that this was a great point and a great mechanism to be able to utilize. She noted that the VA Office of Research and Development (ORD) in fact had that ability and that they've seen merits awarded to an investigator that had a great idea. Mr. Bunker added to that, noting that he knew of a study that received more funding in order for the researcher to examine the cohort of veterans that were closest to Khamisiyah, Iraq (and exposed to sarin).

Ms. Perez-Wilhite thanked Dr. Hunt for his presentation and then asked him a question for

clarification regarding how he assessed and referred veterans that show up to his location. She asked whether he determined his referrals for the patient based off of what he or she would tell him, or based off of which units they were in, or based off of what symptoms they had. Dr. Hunt said that he assessed a patient using what they were telling him and what their symptoms were. Ms. Perez-Wilhite asked only because she said that there had been problems where a veteran may specify which unit they were in only for a doctor to conclude that that unit did not have any exposures or certain exposures, even though units were frequently broken up and sent to different locations.

Dr. Sullivan asked whether Dr. Hunt was doing exposure assessments in his evaluations and if he used them clinically. He said that he was. She suggested that if he was collecting it, that he should consider publishing it because it could be helpful to show that those exposed to a certain toxin exhibit certain chronic symptoms. He said that he would show her some data.

Mr. Bunker noted that Dr. Hunt was involved with Phase III of the GW registry so he asked whether Dr. Hunt or anyone else was interested in looking at those early veterans or bringing them in for a follow-up study. Dr. Hunt responded that he didn't know if anyone was, but he agreed with Mr. Bunker that it'd be very useful to have individual natural histories.

Dr. Hauser asked whether, at Puget Sound, there were clinical practice guidelines (CPGs) that they had for management of specific components of GWI. Dr. Hunt said no, that they use the CPG and guidelines for CMI, IBS, and other similar conditions. Dr. Hauser then asked whether they use that all the time and Dr. Hunt said that yes, they recommend that everyone use the CPGs. Dr. Hauser then asked how the mindfulness studies or cognitive behavioral therapy (CBT) data get incorporated into these guidelines and whether these studies and data were being used for veterans. He said that he asked this because he was again trying to focus on the question of how the research translates to the clinic. Dr. Hunt said that what happens at his clinic is that veterans can now order MBSR and that they have groups for it, so it does get incorporated into clinical care. He then mentioned that a lot of clinics don't even have MBSR, although he did mention that another thing that was happening at the time was transformation of pain care. There was a shift from opioids and medication to a focus on self-care, self-management, complementary innovative techniques (acupuncture), MBSR, and other forms of pain management. He gave this example to illustrate that there are many great tools but that the challenge was putting them together in a systematic way to transform care.

Dr. Hunt commended the Committee for the work they've always done and said that as a nation we will never let up after a war is over. He wanted to continue pushing for post-deployment care, building on what has been learned from past successes as well as things that did not go as well.

Dr. Ondra had one more comment before leaving for the afternoon, since he would not be present for the Committee discussion. He said that while it was important to go back and look at things and continue the basic physiology research, there should also be an emphasis on a look for new tools. He said that he'd really like to see future research at the VA in GWI use the tool of genetics to better understand why some people suffer from this illness and others don't when they had similar exposures. He wanted to use genetics as a different tool to unlock new paths of research and different treatment, rather than continue to focus on what has been focused on for

the past twenty-four years. In summary, thinking about resource utilization, he said he'd like to see more resources utilizing these new tools, to see if the door to new lines of research could be opened in addition to what was already being done, but again he stated that allocating these resources will be an important question for discussion.

Mr. Bunker asked Dr. Hunt if he thought it'd be advantageous for the VA to open up another WRIISC in the Midwest, such as in Minneapolis or Kansas City, because WRIISCs are crowded and also, veterans there had a hard time getting to some of the WRIISCs due to their location on the east and west coast. Dr. Hunt said that they need the tertiary stepped care model so that any center could provide more than what they had been able to provide locally.

The Committee thanked Dr. Hunt for his presentation.

Development of Specialty VA Clinics
Dr. Nancy Klimas

Dr. Nancy Klimas, a member of the Research Advisory Committee, spoke next about the development of specialty VA clinics for GWI. Please refer to **Appendix A – Presentation 4** for Dr. Klimas' presentation slides.

She stated that the goal of her talk was to orient the Committee about what was available at that time in terms of health care systems within the VA in order to inform their discussion about the translation of research into clinical care. She began with an overview of what she'd speak about in her presentation followed by some background. Dr. Klimas developed a specialty clinic at the Miami VA Medical Center because she was interested in GWI, was doing research in this area, and wanted to help her patients who were frustrated that they had nowhere to go for research studies. The clinic was a success for the patients, who felt like they were being thoroughly evaluated and really listened to. She said that when tele-health was launched by the VA, other VAs across the country began calling her for telephone consultations (although this led to some issues because clinicians are not paid if they consult patients from other VISNs).

She then discussed what resources the VA offered already, including the WRIISCs. She also noted the disadvantages of the WRIISCs, which includes that they are small and have many patients, forcing doctors to choose which patients they think would benefit most by doing a virtual consultation before an on-site consultation. She then explained this process of accepting a patient in more detail and noted that it was about a nine month period from when a patient is referred to a WRIISC to when they are accepted into a WRIISC.
She then discussed some of the funded research studies that are conducted at WRIISCs. She noted that the WRIISCs work collaboratively in their research studies and that they are performing excellent research. However, again she noted that the problem is that there are 250,000 GW veterans that need care and only three WRIISCs.

She then discussed the clinical and research training that goes on at the WRIISCs. She mentioned that all three WRIISCs offered fellowships which could be in different areas such as neurology or neuropsychiatry. They also provide experiences for their local residents and medical students to care for veterans.

Dr. Klimas next discussed registry exams, which are a requirement for every VA. She commented that the registry exam was not just for GWI, but also for other toxic exposures such as depleted uranium (DU) and burn pit exposures. She said that in her opinion, the registry exams were the best way to get a patient visiting the VA into care. However, she also said that the person conducting the registry exam usually delivers it but then does not provide the patient with any further resources.

She moved on to talk about the role of the Environmental Health Coordinator. She informed the Committee that every VA was supposed to have someone with this title, but that who had the title (whether it was a patient advocate or a social worker, for example) depended on who the VA assigned. She continued to identify the existing resources that the Committee could draw from to improve and make more comprehensive and cohesive. Dr. Klimas then mentioned patient advocates, which are heavily utilized by Gulf War patients. The patient advocate directs patients to certain doctors to meet their needs and they do so with personal knowledge of the doctors and the different facilities. She said that patient advocates are a great resource and she was glad to see that every VA had one.

She next noted that the Patient Aligned Care Team (PACT) was the mechanism in place at the time for trying to integrate care. The PACT was a team she said that was composed of a PCP, nurse, nurse practitioner, clerk, and other supporting staff. She explained how the PACT system worked for a veteran and what the PACT's role was. She stated that PACTs could work for GWI if the PACT was knowledgeable about GWI, noting that the challenge would be providing the training. She said that the PACT was designed for complex care delivery, so focusing on PACTs could be an option the Committee considers in order to provide better care for GW veterans. She noted that PACTs also still allowed for integrating complementary tools within the VA such as yoga and acupuncture.

Dr. Klimas said that when they do see a patient in a primary care setting, they have a host of referrals available to them, which she listed. She then provided some background as to how the "train the trainer" program was first started back in the 1980's in an HIV clinic. She said that they took experts from across the country to create a curriculum and then asked for three people from every VA to attend a training: a social worker, a physician, and a nurse. These people were then responsible for going back to their VA and not only providing great health care, but training every single person in their VA about the illness. She said that the program was very successful.

After this, Dr. Klimas began to outline the options for addressing better care in GWI. She stated that specialty clinics, like the one created for HIV, were one option. She then went into more specifics on this. She recommended not having a specialty clinic just for GWI, but forming an environmental medicine clinic, for all of those who experienced toxic exposures such as Vietnam veterans. She said that her Chief of Staff had asked her to create an environmental medicine division of the Department of Medicine, where they aim to create a properly staffed and trained environmental medicine program including a full-time clinician, nurse practitioner, and the appropriate support staff. She also noted that she was partnered with Nova Southeastern University (her research institute) and would create a similar environmental medicine division with the appropriate staff there as well. She commented on the importance of research and said

that her vision for both the VA and the university would be that every patient also served as a research subject, signing the consents necessary to obtain a natural history and follow the patient over the course of their care.

She continued, saying that the time had come for an environmental medicine program. She recommended that there should be at least one in every VISN, so that the clinicians can get paid but also to address regional educational needs and train the next generation of caregivers on environmental medicine.

The next option that she discussed was to train expert clinicians via a "train the trainer" model. She suggested that this be done with or without an environmental medicine clinic. She said that it was not very costly, but that they would need to work with the clinical side to develop the curriculum and funds necessary to implement this program. She recommended that this be done at every VA hospital, whether through a Health Services Research and Development Service (HSR&D) mechanism or through some other mechanism.

She concluded by asking, "If not now, then when?" She suggested putting together an ad-hoc committee and working with VA leadership to quickly get a program in place. Lastly, Dr. Klimas encouraged everyone to go on the webpage through the link she provided in her presentation to review the IOM report regarding the new criteria and clinical case definition for CFS.

Dr. White began the discussion. She mentioned that she had called for an environmental clinic in 1993 and that there had been one in Boston that she ran then. She recommended considering an environmental occupational medicine clinic that would address occupational insults that go beyond just toxicants. Dr. Klimas responded that there were different certification programs (two certification programs), although these were not true fellowships. Her goal was to create a true fellowship (and quickly). Dr. White said that the VA had always needed this as well as the veterans themselves so she thanked Dr. Klimas for restating the importance of that need. Dr. Klimas said that they just had to find a mechanism to operationalize the program, which she wanted to accomplish at the meeting.

Dr. Hauser then asked if the clinician in the clinic model, whether it is WRIISC, the PACT, or an environmental and occupational medicine clinic, would be the PCP for the patient in all aspects, including those unrelated to environmental health and exposures. Dr. Klimas confirmed that indeed the clinician in the specialized clinic would be the patient's PCP. She suggested taking the PACT model and forming an environmental occupational team in the PACT model. She thought that the PACT model would be a great way to operationalize this program because it was already in place at the VA and they were comprised of specialized teams that were also primary care deliverers. She suggested that to implement the program, there be a PACT in every hospital which would be accomplished using the "train the trainer" model. Those brought in for the training would become the members of the PACT at that hospital. In her opinion, this was the fastest way to operationalize the program. She stated that the WRIISCs would still be there for a second opinion, or even better would be to have an expert environmental medicine team in every VISN, which would allow for regional expertise and accessible, knowledgeable care for those without easy access to the WRIISC locations.

Dr. Sullivan thanked Dr. Klimas for her presentation and for her important recommendations. She agreed that it was important to act right away to ensure that environmental medicine be included in the care being done at the VA.

Dr. Hauser announced that the Committee would take time to go over their preliminary recommendations before breaking for lunch. Dr. Hauser asked Dr. Ondra to give his recommendations so that they could be considered in the Committee discussion, since Dr. Ondra would not be present that afternoon. Dr. Ondra's recommendation was to place an emphasis on studies that take advantage of genetics, which he thought that would open new doors to the research pathways they had been focusing on for a long time. He was very optimistic about the opportunity and promise of genetics because of the way that it personalizes medicine and care, making better use of the finite resources in health care.

The Committee took a lunch break before reconvening for the afternoon.

Update of VA ORD Gulf War Research Portfolio
Dr. Victor Kalasinsky

Dr. Hauser announced that Dr. Victor Kalasinsky would be updating the Committee on the current VA Office of Research and Development (ORD) Gulf War Research Portfolio. For Dr. Kalasinsky's presentation slides, please refer to **Appendix A – Presentation 5.** Refer to **Appendix A – Document 1** for the updated VA ORD funding portfolio.

Dr. Kalasinsky began by stating the mission and vision of the VA ORD. He gave some background on the VA Intramural Research Program and then showed a diagram that depicted the different branches of the office. He outlined the process that the office goes through when receiving and evaluating study proposals. He mentioned the six Requests for Applications (RFAs) that VA investigators could apply for in the Gulf War research program from three different service programs: Biomedical Laboratory Research and Development, Clinical Science Research and Development, and Health Services Research and Development. The Committee reviewed those RFAs (BX-15-011, BX-15-012, CX-15-011, CX-15-012, CX-15-013, and HX-15-017). He mentioned that for the fall, the service programs would be re-written and combined in a way that made it easier for the VA ORD to process them. However he noted that the same subject material would be covered and they'd keep the same number of RFA's essentially, so all of the topics aforementioned would still be in the portfolio of requests.

Dr. Sullivan asked whether the pilot grant RFAs included treatment pilot funding. Dr. Kalasinsky responded that it did not and that all clinical trials were in the CX-15-013 regardless of the size of the trial. He clarified further by stating that if a researcher proposed a small trial, it would go under the CX-15-013 and would be evaluated on whether a small trial would be useful or not, depending on the particular study.

He acknowledged the advisory committees that the VA ORD had and then gave the links for the VA ORD GW Research Strategic Plan. He listed the eight focus areas of the strategic plan. Dr. Kalasinsky then overviewed the VA ORD GW research funding from 2006-2015. He noted that the funding for Fiscal Year 2015 (FY2015) was an increase than in previous years and he hoped

to increase the budget for FY2016 as well.

He said that the VA ORD received seventeen grant applications in the Spring 2015 cycle and that they were reviewing them that month and would be finished with the reviews in June. He provided a listing of the clinical trials that were currently funded and noted that a new trial called 'A Randomized Control Trial [RCT] of Duloxetine and Pregabalin for the treatment of GWI in Veterans' would start on July 1, 2015.

Dr. Kalasinsky then listed the ongoing studies investigating biomarkers/mechanisms and took particular note of the National Health Survey of Persian Gulf War Veterans and their Families. He explained that while that project was an old one, it had been mentioned by the RAC that some of the data had not been published. The VA ORD checked back into that and found that the principal investigators on that project had moved or left the VA and had gone in different directions. Once they were found, the VA ORD discovered that there wasn't enough information on the family members to put together a publication. Thus, the VA ORD decided to look back at the CSP study data, which resides at a CSP site, and re-analyze it for publication.

Dr. Klimas asked whether there was a biorepository in that study, but Dr. Kalasinsky wasn't sure. He said that he would look into that as well. Dr. Sullivan wanted to confirm that this was not new data, but old data that had been collected and he confirmed that indeed it was old data that would be re-analyzed. Dr. Klimas suggested that when the VA ORD looked at the biorepository, they should reexamine the consents as well and see if they'd be allowed to do genomics or whether they would need to re-consent to do so. He said he would look into that.

Dr. Sullivan asked if this was the data that had been lost. Dr. Kalasinsky responded no, that this was completely different data. Dr. Crawford asked about the specifics of the 'Multimodal Biological Assessment of Gulf War Illness' study and Dr. Kalasinsky replied that there were a number of studies utilizing Positron Emission Tomography (PET) scans, MRI, and various other methods to study biomarkers. Dr. Crawford asked if the principal investigator of that study was collecting blood. She commented that it'd be interesting if they put blood data together with the neuroimaging data. He said that he didn't think they were, but that he'd have to check.

He then listed five GW research projects that were selected for funding that would be doing genomics. He then noted the GW research biorepositories and the two ongoing IOM studies that he had mentioned at the April 2015 meeting.

He concluded his presentation and opened the floor for questions.

Dr. Sullivan had a question regarding the CSP 585. She said that she was aware that this study received pilot funding and would eventually receive larger funding. Having said this, she asked whether the ~$2 million awarded for funding was for the pilot study or the larger study. Dr. Kalasinsky responded that it was allocated for the pilot phase. Dr. Sullivan then asked what the funding would be for the larger study and if that had not been determined, when it would be decided. He said that the CSP 585 study was just collecting the specimens and data for the pilot, so it would not be until the pilot was finished and the project evaluated that they would decide.

Dr. Klimas asked how tightly the Million Veteran Program (MVP) was linked with the CSP 585. He said they weren't exactly the same, although he noted some overlaps, including that Dr. Provenzale used the MVP baseline survey as the starting point and then added specific GW questions for the CSP 585 survey. He also noted the differences, such as that the CSP 585 study included veterans that use VA healthcare and those who don't, whereas the MVP was users of VA healthcare only. Dr. Klimas addressed that the CSP 585 study only had an 8% rate of completed study participants but she recalled that the MVP had 10,000 GW veterans collected. She identified that a solution to this problem of recruitment for the CSP 585 would be to survey all of the identified MVP participants with the CSP 585 survey too. However, Dr. Klimas noted that the MVP survey does not make clear who has GWI and who does not.

Dr. Crawford then asked Dr. Kalasinsky what the mechanism would be for identifying or nominating and inviting or accepting new Committee members to replace the longstanding RAC members that would be replaced in the next few months. He said that the VA would put a notice in the federal register and solicit nominations. She asked who would review the applications and nominations and he replied that a number of people at VA would. Dr. Klimas asked whether there would still be a Scientific Director position on the Committee and Dr. Sullivan commented that that was something that, in the past, would be up to the Chairman to negotiate. Dr. Crawford said that the composition and forward operations of the Committee were relevant to the Committee and she believed they should be discussed in a public forum, whether in the next session that day or in another session. Mr. Bunker disagreed.

Mr. Bunker asked Dr. Kalasinsky if he knew whatever happened with his recommendation to Secretary McDonald that a coenzyme Q10 (CoQ10) follow-up study be done. Dr. Kalasinsky said that they were looking into the possibility of doing a CoQ10 study.

Dr. Hauser asked Dr. Kalasinsky how the three large VA initiatives connected with the DOD efforts, especially the DOD 80 million sample serum repository which could be useful for a number of biomarkers including genetic studies. Dr. Hauser then asked whether there had been applications to go after that huge stored DOD database. Dr. Kalasinsky explained that there was no formal connection between the VA repositories and the DOD repositories, but noted that some of the researchers that work for the VA get funded by the DOD, so he would look more into those questions as they moved forward. Dr. Hauser proposed that getting access to the Armed Forces Health Surveillance Center repository and aligning a current study with that repository might be a faster way to achieve the numbers needed for genomics studies. Dr. Kalasinsky said that he would certainly broach this subject with the DOD.

Dr. Klimas voiced that an issue researchers had was getting access to veterans with GWI. She had a hard time understanding who was allowed access to which registry and the process for a researcher to gain access to the registry. She commented that this was a barrier for new investigators trying to get into the field so resolving it would be helpful. She even suggested that something the RAC could propose would be for the VA to develop a mechanism for access to VA and DOD resources and clarify who would have access to what. She also suggested that the VA update their website to show those who want to become new investigators all of the resources that are available including access to subjects and the biorepositories.

Dr. Kalasinsky said that they could edit the website and that this did not require a formal recommendation from the Committee. With respect to accessing the registry, he said he'd heard the same thing from other investigators, which is that some had ready access to registry files and others had none, so they were working with the Office of Public Health (OPH) to resolve that. He mentioned that each of the repositories would have their own guidelines for requesting materials.

Mr. Bunker asked the scientists what the advantage was in having access to the registry files. Dr. Klimas explained that for principal investigators, the registry provided access to people for recruitment for participation in research studies.

The Committee thanked Dr. Kalasinsky for his presentation.

VA GWI Research Program Discussion
Dr. Stephen Hauser, Chairman
Dr. Roberta White, Scientific Director
Res Adv Cmte Gulf War Illnesses

Dr. Hauser began the Committee discussion by stating that the Committee would discuss the recommendations that they had recently suggested. He made a comment regarding the strategic plan, saying that while it was very inclusive, the Committee had an opportunity to improve its operational specifics. Dr. Hauser suggested focusing on the specific things that could be done that are actionable that could potentially have impact by either pushing an area of inquiry forward, or putting it to rest. He iterated that the more specific the Committee was in its recommendations, the better chance they had of communicating forcefully to result in impacts. To see the document that guided the Committee discussion, please refer to **Appendix B – Document 1.**

The Committee reviewed Appendix B – Document 1, the most recent and pressing recommendations, as well as a document which compiled all of the previous recommendations made by the Committee in the past. Dr. Sullivan noted that in the previous recommendations document, the Committee could see which recommendations had been made repeatedly and had either not been addressed at all or had not been fully addressed, and thus the Committee could certainly choose to recommend the same thing again if they felt that it was still important.

The Committee recommendations in Appendix B – Document 1 were categorized into three groups: (1) Integrating research outcomes into clinical care and making the two services more collaborative and interactive; (2) Improving study methods for gene-exposure outcomes, case definitions, exposure group surveillance, and categorization of groups by dates of service; and (3) Develop larger treatment trials from prior promising pilot treatment studies.

The Committee began discussing the first category: integrating research outcomes into clinical care and making the two services more collaborative and interactive. Dr. Klimas noted that this was not so easy to operationalize. She said that this was wonderful conceptually, but in hospitals required a director to oversee the Veterans Equitable Resource Allocation (VERA) dollars coming in for research as an opportunity to integrate the clinical and research sides. She also explained that the VA has an indirect rate and that the director has a lot of authority over how the

funding is spent, whether that was on research services or clinical operations. She asked for Dr. White's opinion on this.

Dr. White initially discussed her experiences, commenting on how her VA environmental clinic was tied inexplicably to her research. She said that she thought her VA supported her patients also being her research subjects because of the fact that they had the funds to allow her to have clinical space in her center and also because she could see patients while also conducting research. She also mentioned that some of the work she did was through cooperative study mechanisms. The idea she suggested was that a good way to utilize a number of VA mechanisms would be to have a system in place at environmental clinics where some research as well as clinical care was done as well as cooperative studies, and thus patients across all clinics could be identified as having a certain exposure or certain features of GWI that made them candidates for a certain intervention.

To summarize, she stated that it would be best if people engaged in the research as well as ran the clinics, as opposed to facilitating the transfer of information and data from researchers to clinicians. In her opinion, having clinicians engaged in the topic would improve clinical care and seeing patients in person would also motivate the clinician to seek the answers in research and give them ideas to pursue certain research avenues, based off the symptoms they see in their patients.

Dr. Klimas agreed and noted the VA's unique position to accomplish this because they have access to physician scientists. She stated that this is the vision that the Committee ought to strive for and that they could recommend such a system on a timescale that would affect the patients they are trying to care for.

Dr. Hauser noted two other points he and Dr. White had previously discussed. The first was to have "immediately deployable SWAT teams" to confirm exciting observations that remain unconfirmed. The second was that implementing the type of clinic discussed would satisfy the VA's wish that more veterans utilize the VA system. It would also increase the number of individuals who are satisfied with their care and want to participate in organized research.

Mr. Bunker questioned how they could improve communication among VA doctors across the country so that VA doctors could realize certain observations were more common in GW veterans than they may have anticipated. Dr. Hauser stated it could be done through the type of network that Dr. White proposed.

Dr. Klimas stated some suggestions to improve clinical care. One was that the Chief of Staff of hospitals should partner with researchers to "train the trainer." Another suggestion was to have a "superteam" in every VISN to be the go-to team working between WRIISCs and individual hospitals, which she thought could possibly be done by an HSR&D application, but she wasn't completely sure. Dr. Sullivan suggested working with the VA Quality Enhancement Research Initiative (QUERI) program to figure out how to make this work. Mr. Bunker noted that the compensation and pension (C&P) examiners would need to be involved too.

Dr. Young commented that he really liked this proposal idea and that he had expertise in

operating between divisions of research and the front-end clinicians. He said that an important area was to bring in front-end clinicians (whether they are hospital-based, ambulatory specialists, etc...). He discussed that he has found that the timeline and standards for actionable data are very different between researchers and clinicians. For a researcher, the timelines are long and standards for data are fairly high, compared to clinicians' short timelines because they need to take care of people as soon as possible. As a clinician, he said he would accept data with not as high a P value because he would look at the data continuously and his interpretations and conclusions would likewise evolve continuously. Thus, while both views are important and have strengths, he recognized that researchers and clinicians have different opinions on what is actionable or not actionable and have differing views on integrity and timelines.

Dr. Hauser added that the goal of these centers would be initially to improve care and satisfaction of care and therefore proposed perhaps that's the way the success should be judged at the first step: by the amount that the centers improve the quality of life of the veteran. Dr. Hauser then asked Dr. Klimas and Dr. White whether this should be launched in a pilot way at a few sites to see how it works, or be launched in a bigger way immediately. He also asked what the appropriate timeline for implementation would be.

Dr. Klimas said she thought the Committee needed to be ambitious because if more time was spent modelling a system, it would be years until something was actually implemented. She looked to Dr. Kalasinsky for input regarding the timeline and also to inquire whether they'd be overstepping the boundary of the Committee by creating a task force.

Dr. Klimas remarked that she didn't think that establishment of a high-level occupational medicine clinic with such a "train the trainer" type of program, which creates a trained cadre of people at each site, was unreasonable to ask for. She had spoken with Dr. Hunt earlier and he said that he achieved it in his program by training people more local and then getting those people to train others at the regional sites. However, Dr. Klimas thought it'd be faster if there was actually a task force that created recommendations to the Secretary, who implemented the recommendations and identified individuals in specific hospitals to then go and receive training at a regional resource.

Dr. Klimas then noted that the actual training is more important than the implementation. She said that someone would need to put the training together in a way that it became a comprehensive, in-depth way to assess and care for the patients which evolved with new research findings.

The environmental clinics she suggested be established should be a national mandate to the VISN to establish. The goal would be staged levels of care (national, regional, VISN, WRIISC) which she thought would be possible without a huge investment. Dr. Hunt commented on this, saying that the more that what the Committee proposes fits in with what's already established at the VA and complements it, the more the Committee will succeed.

Mr. Bunker noted that it would not be difficult to convey to Congress the importance of these centers and the need for funding because of the various exposures that not only GW veterans experienced, but many other veterans as well from serving in different theatres. He mentioned a

few different exposures (such as burn pits and Agent Orange) and said that the Committee would urge that this is of high importance.

Dr. Sullivan seconded that, mentioning that VA hospitals were created to service veterans because they have specific needs that weren't being met at regular hospitals, such as PTSD and mental health, blast-related injuries, and also environmental exposures. She also said, however, that environmental exposure health care issues weren't currently being addressed fully by the VA. She also noted that PTSD has a national center, and suggested that perhaps there should be a national center for Environmental Health within the VA that would give it the status, recognition, and importance that it deserves.

Dr. Hauser said that the mandate issue should be thought through in order to ensure that the people running the centers are people that care about GWI, veterans, and environmental exposures.

Ms. Perez-Wilhite had a question for the Committee. She asked whether in the past, task forces had resulted from Committee recommendations and if so, whether they were successful. Dr. Sullivan responded, saying that a research strategic plan came out which was a combination of many research advisory groups contributing. She also mentioned a recommendation to have a separate group that dealt with clinical issues, but said that it disbanded quickly, only lasting about a year. Those were the two she could think of at that moment and noted that they certainly didn't meet the expectations of what the Committee was recommending.

The challenge, Dr. Hauser noted, would be to write this in a short yet effective and passionate way. The goal would be to finalize this before the September meeting, so that then if necessary the Committee could decide which elements would be retained or not. After contributing and revising, the Committee members could see if it had gotten to the point where it could be voted on at the September meeting.

It was concluded that the next three points on the document (under the first Committee recommendation category) for the Committee to review would be natural extensions if the first point was implemented. Thus, the first point (just discussed) would be the most impactful item and thus the Committee decided to try to make actionable.

Mr. Bunker commented on the point "in addition to self-reported outcomes, researchers should obtain up-to-date results of veteran's physical evaluations from clinic visits." He asked whether it would help a researcher to get a veteran's military records, because it would help give details regarding their place of deployment and also what may have happened to them while deployed. He said that this would perhaps require a consent form to get access to the veteran's C file, but he thought that if it was possible it'd probably be helpful. Dr. Hauser said that the IOM had also recommended this, as well as the President's advisory committee on what to do in future conflicts. Dr. White said that a long time ago, they had suggested there be a medical record that followed the veterans from the time they enlisted through the end of their deployment.

Mr. Bunker said that an obstacle was getting the different branches of the military to have the same type of medical record. He also said that for a VA researcher to have access to the C file, a

veteran should just be able to provide consent which would give a researcher access to the military files. Dr. Hauser asked whether a veteran can currently get his or her DOD medical records from their clinician. Mr. Bunker said that the DOD medical file becomes part of the VA file. Thus, to allow a VA researcher to get access, presumably the only obstacle should be obtaining consent from the veteran to gain access to those files. Dr. Sullivan mentioned that to give researchers access to DOD records may have been a recommendation made already and included in the strategic plan. Dr. Kalasinsky said that he believed the Committee had not yet recommended that for the strategic plan.

Dr. Young said he was a proponent of self-reported outcomes as a research method. He asked whether the VA had the capability of doing certain levels of data analysis: the ability to do natural language processing and machine learning or machine auditing of the metadata, because he said that sometimes the VA provides rich data, but not in the terminology that those in health care are used to seeing. Dr. Kalasinsky said that there are some research avenues that allowed natural language processing once the researcher had access to the medical records, but he wasn't sure if that was true for the clinics. He asked for Dr. Klimas' input on this. She responded that no, clinicians do not have natural language processing and can't search records by phrase. Dr. Young thought that such an analysis would be a very rich analysis and that the understanding would be more comprehensive than what's obtained from clinical trials alone. He was a big proponent for this analysis but understood that it requires certain capabilities.

Dr. Klimas thought that this was a great idea. She mentioned how there was no IC-9 or IC-10 code for GWI so the clinician had to find these "words" in the medical record to try to decipher who had GWI or who was diagnosed with something else but similar like chronic fatigue syndrome. She urged for having some form of consistency to easily identify which veterans have GWI (as opposed to finding GWI patients by finding GW-era people with comorbid conditions, which is difficult). She thought that using natural language strategies would be much more helpful to find those who might be ill. Dr. Sullivan noted that there was a group at the Bronx VA who had success using these methods as well.

Dr. Young mentioned that they had information scientists who were doing research, going into patient discussion forums and finding the words that patients were using to describe certain medical terms (like "depression" for example), and then correlating that back to clinical terms. He said that the words people were using to describe their symptoms never would've shown up in a search. He also thought that this was providing really rich data which allowed clinicians to better understand their patients' ailments; yet again he acknowledged that this required people with specific expertise outside of the medical research field.

The Committee moved on to discuss the second recommendation category: Improving study methods for gene-exposure outcomes, case definitions, exposure group surveillance, and categorization of groups by dates of service.

There was some discussion regarding the need for improved case definitions, which has been an ongoing process. Dr. Kalasinsky noted that the IOM was no longer working on it, but he had heard that other groups were continuing to refine definitions, so there was still work going on. Dr. Sullivan said that this was recommended in the strategic plan and that while some groups

were doing studies, there was nothing being done on a larger scale. Dr. Hauser asked Dr. Sullivan to confirm whether indeed a research group was being formed to advise on this issue. Dr. O'Leary responded that there wasn't, but said they had been thinking about the issue and there was some work going on sponsored by DOD which he explained. Dr. White commented that this approach would be a data-driven way of looking at what is seen in the study relative to the two different criteria for GWI and chronic multi-symptom illness. She asked whether this would be done with an eye toward developing a model GWI definition that could then be validated, which would be different than what had been done in the past. Dr. O'Leary said that it wasn't. One thing that he wanted to know was what sort of criteria would be used in validating a case definition. He noted that what constitutes validation is very interesting and what one typically sees is clinical evolution that varies. One question he said the Committee and the VA should focus on was whether they wanted a typical research case definition (highly specific, not necessarily sensitive) or something that maximizes the amount of people who can receive clinical care. To this, he added, what is the gold standard for a clinical case definition? In summary, he said that's what the Committee could really advise on: what would constitute the ideal case definition.

Dr. Golomb agreed that the clinical case definition should be distinct from the research case definition, particularly because having GWI doesn't preclude the occurrence of other conditions that may want to be precluded from the research setting. This was a problem that needed attention as GW veterans continue to age and so have more of the conditions that are exclusionary criteria.

Dr. Klimas asked for confirmation that there was a newly funded study that was going to tackle this. She was asking whether the Committee would recommend that the VA put together a case definition working group or workshop, or rather wait for the study to do its job. Dr. O'Leary said that following the advice of the Committee, they did this study because the original recommendation made by the Committee put in the strategic plan was that it should be data-driven. He thought that the challenge was the lack of strongly unified approaches to data evaluation. He mentioned that the last meeting had shown a correlation between genetics and GWI and so perhaps genetics could be included in the case definition. Dr. Golomb said that she didn't think these types of genetics would factor into the case definition because the genetics really affected the outcomes given the magnitude of the dose. However, she did state that other aspects of genetics may prove to play a role.

Dr. O'Leary looked for guidance on the approach because he was not convinced that the problem would be solved by simply forming another committee without a unified base of data and clear set of decision criteria on what would constitute great criteria for a clear case definition. The Committee determined that the question of case definitions was important to continue to consider but maybe not to focus on at that time, but soon, because there were great studies going on which would soon provide answers so that the Committee could better answer the case definition question.

The Committee moved on to the next point in the category regarding improving study methods. Mr. Bunker commented that this recommendation was one he had been making for a long time. Dr. Sullivan introduced the problem, which was that the way veterans are categorized as

deployed and non-deployed, particularly in the OPH studies, acknowledges that the Gulf War ended on February 28th or March 1, 1991. However, several of the biggest exposures (including the Khamisiyah detonations) happened from that point forward, so veterans that came in after the date March 1, 1991 are considered non-deployed in the studies. Dr. Sullivan had assumed these people were not considered in studies at all, but it turned out that they are in the non-deployed (comparison) groups in some of the studies. This is a big problem for exposure studies, as it altered the case and control groups in important ways. There are 70,000 people that are in this grouping.

The next recommendation which followed after this was regarding the Khamisiyah group: the GW veterans with the closest proximity to the Khamisiyah detonations (and thus at the highest risk of sarin exposure) should be followed as a surveillance group, due to this group being at the highest risk of brain cancer and perhaps other disorders. Dr. Sullivan explained that this group included the most exposed individuals because these people were already highlighted as a high risk group. Dr. Sullivan suggested that a study be done in this group of people specifically, which is about 15,000 people. Dr. Hauser asked whether these 15,000 people were easily identifiable, and Mr. Bunker confirmed that they would be easily identifiable because the DOD knows who was in that area. In addition, each person within the units has a unique unit identifying code by military company. Also, the DOD had already identified who this group was when they performed their plume models. Dr. Sullivan noted that including these veterans as an exposure group would also solve the earlier point about groupings after March 1, 1991. Dr. Sullivan emphasized that it was extremely important that the OPH fixes these case and control groupings. Dr. O'Leary said that he would talk to people in OPH about it. Mr. Bunker also noted that there were people in the non-deployed group who were later deployed to OIF and that those people were then exposed to mustard gas during their deployment. He suggested that anyone who'd ever been deployed to a desert environment should be pulled out and that these people shouldn't be compared as controls to the exposed GW veterans because they may have had exposures also.

The third point under Committee recommendation category #2 was Dr. Hauser's recommendation, which stemmed from Dr. Lea Steele's presentation in April 2015. This was after she reported that specific genetic variants are associated with symptom reports. Dr. Hauser's recommendation was to perform an independent confirmation study of reported association of rare butyrylcholinesterase (BChE) variants associated with GWI in deployed veterans, stratified based on their self-reported exposure histories. He also wanted to assess the feasibility of sequencing the entire gene (both exons and introns) and extend this to other candidate genes (such as PON1, PON2, and PON3) and to Amyotrophic Lateral Sclerosis (ALS), where rare paraoxonase (PON) variants are also associated with disease. Finally, he suggested that other repositories be used for this (including MVP or coupled with the DOD serum repository).

Dr. White thought that this was a wonderful recommendation. However she thought that the piece regarding sequencing the entire gene and extending to other candidate genes should include the phrase "and exposures." She said the genetics work should be on gene-environment interactions. Dr. Hauser agreed that that would stratify GWI based on exposures. She asked Dr. O'Leary whether they were doing that. He responded that he hadn't verified for all three PON genes but he verified that most of the reported BChE variants were covered in the exome chip

that they were currently using. If they verified a linkage there, in the PON genes, then going back and doing the targeted sequencing would make sense. In summary, he would hold the targeted sequencing until they had more information on that. He mentioned that this was intended as a gene-environment study, but they had to observe that the power for detection of a GWI-environment relationship is modest at best. He said it takes immense sample sizes to do a good gene-environment study, so the failure to observe something would not mean there was not proof for it, but rather it'd more likely mean that they were simply short in power. He did also mention that by sequencing the entire gene there would be a significant number of errors. Their studies were working on this though. They would soon have all the genomics on these patients, but not everything else required for a good gene-environment study.

Dr. Sullivan asked Dr. O'Leary whether they had environmental exposures for the MVP participants yet. He responded that they had access to various environmental exposure data on these people. She mentioned that if he had access to the information, it would be critical to include the gene-exposure aspect. To that he commented that he had faced similar obstacles as the other researchers in getting certain pieces of information and that there were certain limitations. The Committee determined that even though OPH was conducting this study, the VA should continue to support other work in candidate gene/single nucleotide polymorphisms (SNPs)/sequencing analysis studies for GWI before hearing the results of the OPH study. This remains an important area for additional study, so the Committee did not want to limit anyone while waiting for the results of this one study.

The Committee next moved onto Dr. Golomb's recommendation, the final point in the second Committee recommendation category. Her recommendation was that the notion that "all health problems of GW veterans" need to be considered under GW research funding be revisited. This is because other conditions that affect GW veterans have other pockets of funding available whereas GWI doesn't. For many of the other conditions like PTSD, she mentioned, GW veterans actually normally have lower prevalence of these illnesses than veterans that were deployed to other settings. She commented that diverting the resources to conditions other than those that are specific to GW veterans does a great disservice to the special allocation of funds for GWI and GW veterans. Dr. Klimas commented that she agreed that their pool of resources had become diluted considerably. She gave a specific example where Gulf War money was taken and given to another pet project.

Dr. Klimas did mention however, that comorbid conditions really do matter and that they don't really have a handle on comorbidity as much as they'd like to have in this illness. Dr. Golomb said she didn't have a problem with studying comorbidity as it affects GWI, but that taking the GWI funds to study anxiety or PTSD wasn't right. Dr. O'Leary commented that it comes to a single appropriation and that they had not been able to give research a score that merits funding as much as they'd like. Therefore, the OPH didn't see a particular reason to want to return that money to the treasury when it expired, so they do repurpose the money. He also said that they do not have a cap on GWI-related funding, making this an artificial issue from his perspective. He stated that if it came to the point where there was a lot of meritorious research, he would gladly fund it all, but he said that at that time that wasn't a real issue. They were not denying funding to anybody that did well in front of a scientific evaluation committee. Dr. Golomb then asked whether the scientific evaluation committee was appropriately experienced in GWI research. Dr.

O'Leary commented that the members of the review committee were public information and that anyone is welcome to comment.

The Committee ended discussion in order to provide sufficient time for public comment.

Public Comment

Major Denise Nichols spoke for public comment to mention things that she thought could be included as recommendations by the Committee in September. She recommended that the Committee video record the meeting as a live webinar or tape it so that veterans or researchers at other universities can watch and get involved. She also recommended that the RAC print the slide presentations or make them available to the public prior to the meeting to help veterans with neurocognitive disabilities better follow the presentations. In addition, she asked that veterans who travel to the RAC meetings or research centers for a study are compensated and/or provided a place to stay. She said that at the September meeting, she wanted to hear an official policy recommendation from the Committee on including funding for travel expenses for veterans. She petitioned for better standard protocol testing for GW veterans that come into the VA. She said that the environmental center idea was great and that should be moved into medical university training programs too, but again reiterated that a GW veteran who comes into a VA presenting symptoms should be given standard protocol testing or some form of a comprehensive clinical evaluation. She also asked that veterans that have seizures not be excluded from studies. She also wanted the data from the pre-9/11 group and asked the Committee to make a policy recommendation to investigate the diagnoses, deaths, or causes of death of pre-9/11 veterans (by age group if possible). She suggested promoting research projects or studies recruiting via posters or cards hung centrally inside every VA hospital. Also, she said that a task force for veterans at each state level could help with publicity for research and bringing up issues with the VA in each state. Finally, she noted that it was critical that the new Committee members joining the RAC soon are knowledgeable, experienced, and have a good research track record specifically relevant to GWI.

Michael Jarrett spoke for public comment. He's a GW veteran and has worked with Ron Brown and helps to educate his fellow veterans. He said that he passes information along to GW veterans about the RAC and therefore supported what Denise had said, saying that many veterans would like to participate in research but can't afford to travel to the centers such as in New Jersey or Boston, and so would like the Committee to consider compensation for veterans when funding a study. He next read a statement submitted to Secretary McDonald by Ronald Brown, President of the National Gulf War Resource Center, which can be found in **Appendix C – Document 1.** To summarize his statement, Ronald Brown petitioned to make leukemia and aplastic anemia presumptive service-connected conditions, due to their benzene exposure from petroleum projects, particularly the oil well fires during Operation Desert Storm. He commented on how Roberta Wedge of the IOM had already shown (at the April 2015 meeting) a correlation between leukemia and aplastic anemia and benzene exposure. He listed other benzene exposures including wearing uniforms covered in oil, eating food contaminated by oil and soot, and other exposures. This written statement was submitted for the record.

Paul Johnston spoke next for public comment. He is from the 144th supply company from

Hammington, NJ. He stated that 90% of his unit hadn't heard of the WRIISCs. In fact, he had only heard of it since he was present at the last meeting. He lauded the Committee for their recommendations made; he would love to see what was discussed at today's meeting implemented. He too suggested getting the meeting videotaped so he could give it to his doctors and men in his unit to watch at their leisure. He also said that this would enable those in his unit to see for themselves and get their questions answered instead of having to rely on his own poor memory. He even suggested uploading the meeting to Youtube as a simple and quick way to disseminate the messages from the meeting. He said that for his unit to see progress being done on their behalf would be a great boost for their morale.

Ronald Brown spoke next for public comment. He apologized for not being able to make the meeting. He wanted everyone to know that data from the National Gulf War Resource Center on brain cancer should be available within the next two weeks.

Kirt Love spoke next for public comment. He is a disabled combat veteran and veteran's advocate. He summarized his written statement which he submitted to the Committee. His written statement can be found in **Appendix C – Document 2.**

Marsha Young spoke next for public comment. She thanked the RAC for taking the time to listen to the veterans. She presented herself as a Desert Storm veteran. She was very happy to hear the discussions about translating research topics into clinical practice. She said that there had been many studies done by RAC, DOD, and others demonstrating diagnosable conditions directly related to exposures during Desert Shield and Desert Storm. She said that it was time to put together protocol testing for presenting and non-presenting Desert Storm veterans. April 21, Desert Storm veterans met with Dr. Clancy (the VA Undersecretary of Health) at the VA headquarters and had a round table discussion to offer suggestions. Her suggestion to her was to develop protocol testing and patient-centered care. Another suggestion presented by David LaShell and Valerie Mullikan was to create an environmental toxic exposure center of excellence or clinics, and so was pleased with Dr. Klimas' presentation. She thought that the WRIISCs were self-limiting and appeared to be benefiting scientists more than the veterans. She felt like they were restrictive; she hadn't been able to get in for eight months, due to her being told that she was unsafe to travel due to having seizures (yet she did not have seizures before she deployed to Desert Storm). After stating that she attended a "train the trainer" program, she said that accountability is a core value that needed to be implemented across the VA. She asked that they look at other maladies besides chronic fatigue syndrome and fibromyalgia, such as seizure disorders and headaches, which are shared among many veterans yet receive little attention. She asked that the Committee bring to the attention of Secretary McDonald the lack of information flow up and down within the organization as well as place mechanisms of accountability on all levels of the hierarchy. Lastly, was asked whether there was any news to report on research from their allies, which Secretary McDonald had suggested they engage in at the September meeting. She thanked the Committee for their time.

Edward Bryan spoke next for public comment. He is a disabled GW veteran. He noted that there has not been any treatment for GWI or chronic multi-symptom illness and stated how badly the veterans needed help and treatment. He said that the Committee needed to push for hearings and round table discussions for treatment to be fully funded. He said that it seems as though no VA

hospital knows about GWI and asserted that the doctors need to know about the research. He urged that the Committee needed to work together with the VA to get answers and he suggested that Secretary McDonald get a round table discussion together immediately. He said that he would submit his comments to the RAC.

Venus Hammock spoke next for public comment. She is a disabled GW veteran of the US Army. She stated that she has been disabled due to exposures in Saudi Arabia and Iraq. She had been advocating for many years the study of environmental exposures as an occupational health risk. She also said that she wanted the meeting video recorded and for the slides and presentations to be accessible to the public. She thanked the Committee for their efforts and said that, as soon as the website allowed, she would submit a formal statement.

Greg Wappel spoke next for public comment. He is a Desert Storm US Marine Corps veteran. He provided his personal account, stating that throughout the 1990's he was told that there was nothing wrong with him, until later in about 2012 it was finally recognized that he had a condition. He asked the Committee to think about their environmental outreach so that they may educate individuals, because he said that he could not find anyone in the Richmond area very familiar with it and his physician was not familiar with the WRIISC processes. He stated that the Committee should think about how to best provide the correct information to veterans' organizations, as there is an information overload online. Lastly, he mentioned to Dr. Golomb that he had sent her an email and asked if she would be on the lookout for that. He thanked the Committee for their time.

Shawn Scott of the US Army spoke last in the public comments. He presented himself as a military policeman who handled a lot of enemy prisoners of war (EPWs). His squad had been in a close area during the Khamisiyah detonation. His orders were then destroyed, so the DOD had no proof that he was anywhere. He personally filed an MBC1 report with his lieutenant, which had also disappeared. He also stated that the meeting should be broadcast as a WebEx seminar. He submitted a statement to the RAC to be included in the record. His statement can be found in **Appendix C – Document 3.** He thanked the Committee for their time.

Major Nichols stated that public comments could be sent to rac@bu.edu. Chairman Hauser thanked everyone who attended the meeting and listened in on the phone line and the Committee wished the veterans safe travels home. The Committee decided that the last two recommendation points would be discussed at the next meeting in order to have ample discussion time. Dr. Hauser stated that the Research Advisory Committee would meet again on Tuesday, September 29, 2015, and with that, the meeting was adjourned.