Research Advisory Committee on Gulf War Veterans' Illnesses

March 19, 2014 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 March 19, 2014 teleconference meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses.

/signed/
James H. Binns
Chairman
Research Advisory Committee on Gulf War Veterans' Illnesses

Table of Contents

Attendance Record…….……5

Abbreviations…….……6

Meeting Agenda…….7

Welcome, introductory remarks……...……8

Committee Discussion: 2013 Committee Report……8

Public Comment……...……14

Committee Discussion: 2013 Committee Report……..15

Appendix A

Presentation 1 – Committee Discussion: Findings in Brief and Executive Summary……..18

Appendix B

Link to Draft Strategic Plan 2012-2016…….53

Public Comment 1 – International Foundation for Functional Gastrointestinal Disorders……...54

Public Comment 2 – James Bunker……...56

Attendance Record

Members of the Committee
James Binns, Chairman
Roberta White, Scientific Director
James Bunker
Nancy Klimas
Fiona Crawford
James O'Callaghan
Lea Steele
Beatrice Golomb

Committee Staff
Kimberly Sullivan, Associate Scientific Director
Brittany Sutton

Designated Federal Officer
Victor Kalasinsky

VA Office of Research and Development
Robert Jaeger

VA Office of Public Health
Victoria Davey

VA Office of Public and Intergovernmental Affairs
Robert Jesse, Principal Deputy Under Secretary of Health
Jerry Cox, representing Madhulika Agarwal, Deputy Under Secretary for Health Policy and Services

Abbreviations and Acronyms

AChE - Acetylcholinesterase
CFS – Chronic Fatigue Syndrome
GW – Gulf War
GWI – Gulf War Illness
GWVI – Gulf War Veterans Illnesses
IOM – Institute of Medicine
MS – Multiple Sclerosis
RAC – Research Advisory Committee on Gulf War Veterans' Illnesses
VA – Department of Veterans Affairs

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
March 19, 2014

Boston University School of Public Health, 715 Albany Street, Boston, MA 02118

THIS MEETING IS A TELECONFERENCE

Call in Number: 1-800-767-1750, access code 56978

Agenda
Wednesday, March 19, 2014

2:00 – 2:05	**Welcome, introductory remarks**	**Mr. Jim Binns, Chairman** **Res Adv Cmte Gulf War Illnesses**
2:05 – 4:15	**Committee Discussion:** **2013 Committee report**	**Dr. Roberta White, Scientific Director** **Mr. Jim Binns, Chairman** **Dr. Kimberly Sullivan, Assoc. Scientific Dir.** **Res Adv Cmte Gulf War Illnesses**
4:15 – 4:30	**Break**	
4:30 - 5:00	**Public Comment**	
5:00	**Adjourn**	

The March 19th, 2014 meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses (hereinafter referred to as the Committee) was held via teleconference.

Welcome, Introductory Remarks

Mr. James Binns, Committee Chair

Chairman Binns called the meeting to order, and explained that the purpose of the meeting was to review the edited draft of the 2013 Research Advisory Committee (RAC) Report. He then asked Dr. White to begin the report discussion.

Committee Discussion: 2013 Committee Report

Dr. Roberta White, Scientific Director
Mr. James Binns, Committee Chair
Dr. Kimberly Sullivan, Associate Scientific Director

Dr. White welcomed the Committee members and other parties on the call. She stated that the purpose of the meeting was to discuss the executive summary and findings in brief and to review the specific wording of the report. Additionally, the plan was to discuss the recently released Institute of Medicine (IOM) report conclusions regarding devising a more robust case definition of Gulf War illness (GWI). Dr. White reminded the Committee members of the deadline for comments or suggested edits so that the goal of having the report sent to the printing office in time for the April in-person meeting could be possible.

The first paragraph of the executive summary was displayed for the Committee member review and discussion. For the unedited, rough draft of the executive summary and findings in brief sections discussed, please refer to **Appendix A**. Dr. Steele suggested that the Committee acronym be used more consistently throughout the report. She noted that at some points, it was RAC-GWVI (Research Advisory Committee on Gulf War Veterans Illnesses) but in the executive summary it appeared as RAC-GWI (Research Advisory Committee on Gulf War Illness). Chairman Binns stated that it should be RAC-GWVI and Dr. Kalasinsky agreed that this was the correct acronym that should be used in the report.

The first section of the report entitled, 'What is Gulf War illness and how prevalent is it' was shown next. Dr. Robert Jesse, VA Undersecretary of Health, asked whether the acronym GWVI should be used throughout the report and Dr. White stated that the more correct acronym for the illness is GWI. Dr. Golomb then asked whether 'unexplained' should be removed from the section which stated 'unexplained fatigue'. She suggested that the other symptoms should have this word in front of them as well if it was going to be used. The Committee members then agreed to remove 'unexplained' from this section of the report.

Dr. White moved to the next paragraph of the report. She asked a question regarding italicized section titles. There was discussion and general agreement that they should be kept. Chairman Binns stated that styling decisions should be up to the primary author, Dr. White. Mr. Bunker commented on the term '1990-1991 Gulf War'; he did not agree with the labeling of the years. Dr. White stated that the reason the years were labeled was because the research related to veterans whose service that took place during that time period, and as was such, it became necessary to use that terminology. Mr. Bunker also stated that he did not see a place in the report where the Committee recommended that VA do a follow-up study to show any chronic health problems, or treatment studies with Gulf War veterans. Dr. White explained that the report research recommendations section had many pages of specific research recommendations for treatments and follow-up health studies. Chairman Binns noted that this was coming up in the meeting, and would be further discussed at that point.

Dr. White moved to the neurological disorders and cancer research summaries section of the report and asked for comments regarding those sections. Dr. Steele asked about the four identified issues of great concern. She recommended that sleep dysfunction not be as high on the list because she felt that there were other issues of greater concern that should be included instead. Dr. Golomb agreed and commented that she had seen sleep apnea in veterans regardless of the war in her research and clinical practice; she did not think that it was GW specific.

The multisymptom conditions section of the report was reviewed next. Dr. Golomb suggested the word 'similar' be changed to 'overlapping'. Dr. White noted that 'similar' noted real differences between disorders where 'overlapping' did not necessarily, so she preferred to keep the original wording. In the case definition paragraph, the recent IOM case definition report and recommendations were discussed. Chairman Binns thought that the Committee should comment on the IOM's recent recommendations regarding devising a case definition for GWI. The Committee also agreed that the IOM recommendation that the multisymptom illness found in GW veterans should be called Gulf War illness should be noted as well. The Committee members discussed that this GWI case definition development should come from a collaborative effort including different groups of individuals who are educated in GWI research and clinical care. Chairman Binns and Dr. Steele highlighted the inclusion of the three bullet points of developing a case definition from the RAC-GWVI's previous year's recommendations which included performing a literature review, developing an analytic process of data collection, and collecting a consensus of experts in the field to suggest a new case definition of GWI. There was Committee agreement on this suggestion; Dr. White agreed to add the suggested bulleted information to the executive summary and in the review section of the report.

Dr. Golomb commented that an explicit statement should be added regarding the IOM also making a similar recommendation regarding case definitions to highlight that this recommendation was coming from two different scientific committees. There was agreement on

this suggestion. The next section on improving research was discussed next. Dr. Golomb had a wording comment regarding the definition of 'ill health'. Dr. White stated that it was used to include everything that affected GW veterans disproportionately. Dr. Golomb recommended adding 'other forms' ahead of 'ill health', to differentiate from all of the other items aforementioned that would fit into that categorization. Dr. Steele commented using 'reduced functional statuses might be helpful to use. Chairman Binns recommended just removing 'ill health'. Dr. White stated that she would review this section and find suitable wording to express the Committee members' comments.

Mr. Bunker then commented on the child birth defects section and stated that adding a specific recommendation for separating results by gender would be helpful. Committee members noted that generally this is how research has been conducted, and that the greater issue was that these studies were not currently being done at all. Chairman Binns commented that some explicit language included adding gender differences in results might be used when describing these recommendations.

There were also comments on the second and third bullets of the section regarding efforts to monitor veterans' health with regard to the VA longitudinal survey and prevalence of multiple sclerosis (MS), Parkinson's disease, and brain cancer rates. Dr. Steele commented on the draft recommendation that the neurological disease surveillance should be done every five years. She thought that would be very useful but it had never been done before. Dr. Golomb thought that this was a good idea as well. There were comments on the use of 'should' versus 'needs' or 'must'. There was agreement among most that 'should' was the word most effectively used. Mr. Bunker wanted to note his dissent with the word usage of 'should', thinking that the language used should be stronger. Dr. Golomb noted that if every recommendation used the word 'must', it would turn the reader off, and make them less likely to listen to the recommendations in the document. Dr. Klimas voiced agreement, stating that using the word 'must' was important and needed to be used carefully.

Assessment in overall disease-specific mortality and assessing rates of medical conditions in children of GW veterans were the fourth and fifth bullets for discussion. There were no comments on these bullets. The sixth bullet was the evaluation of health outcomes in GW veterans and subgroups of potential importance. Dr. Golomb recommended a wording change from evaluation of health outcomes in GW veterans 'and' subgroups of potential importance to evaluation of health outcomes in GW veterans 'in' subgroups of potential importance. This was agreed upon by the Committee.

The next section was on improved methodology in GW research. Dr. Golomb asked for clarification on the third recommendation, which Dr. White provided. Dr. Golomb asked whether the health outcomes term was too generalized, or if specifying to GW veterans would be

necessary. She also asked whether health outcomes should be changed to health conditions. Dr. White said she would take a closer look at this specific wording following the meeting.

Health outcomes and disabilities were included in the next section. Chairman Binns commented that Appendix D was very relevant to him, especially from the perspective of a layman reading the Committee materials. He questioned whether it was important to add a statement that numerous studies have shown that pesticide exposure is associated with similar illnesses in other populations. Dr. O'Callaghan said that he would be hesitant to add this because it may be too broad a generalization. Dr. Golomb and Dr. Sullivan agreed with Chairman Binns. Dr. O'Callaghan thought that it would be too generalizing to say that all pesticide exposures have led to these outcomes. There was Committee agreement on this comment. Dr. White asked whether something this specific would be appropriate for the executive summary; or rather would be more appropriate to add to the content sections. Chairman Binns asked whether there was a scientific and concise way to express this in the executive summary, because it was an important concept. There was agreement with this suggestion. Dr. Golomb agreed with Chairman Binns. Dr. White planned to see if there would be a place for the suggested statement.

Epidemiologic research discussions followed. The first paragraph included organophosphate chemicals. Dr. Steele had a general comment on language usage. She stated that the chemicals were referred to as being in the organophosphate group of chemicals, but much of the literature refers to them as neurotoxicant chemicals or acetylcholinesterase inhibitors (AChE). She suggested making the wording more generic, such as AChE. There was agreement over making this term more generalized. Dr. O'Callaghan agreed, saying that given that very little was known about exactly what exposures to include, the wording should be as inclusive as possible. There was Committee agreement on this point. Dr. Kalasinsky asked that the Committee be more specific regarding the exposures with these occupational groups leading to similar illnesses as GWI. 'Consistent with' did not seem strong enough as wording. Dr. White clarified asking if the wording should state that the size of neurointoxication and some of the other things that are seen in the literature with regard to the associations between GWI and various outcomes are similar to those seen in occupationally exposed groups. Dr. White was going to review this after the meeting to identify the best wording to express this concept.

In the following paragraph, Dr. Golomb commented on the vaccine sentence. She thought that the sentence should read that current results have been conflicting and have shown weak associations because these studies have not adjusted for other exposures. There was some discussion on this; Dr. White explained that the original sentence matched the content in the paper. Dr. Sullivan would provide the citation to Dr. Golomb for further clarification. Mr. Bunker asked a question regarding specificity of research and Dr. White replied that much of the research discussed in the executive summary was high-level concepts and could not get into too much detail. The Committee was in agreement.

The animal studies section of the report was discussed next. Within the recommendations section, Dr. Steele asked a question about the lead-in section to the first point. She asked whether the addition of the word 'immediate' with regard to animal exposure was for a specific reason, as it really has not been used in recent reports. Dr. O'Callaghan suggested that it was used to emphasize the persistent effects of GWI. This was used as an inclusive form, and was intended to be used as such. Dr. O'Callaghan asked whether the fourth recommendation regarding preclinical treatment research using animal models was too diluted. Dr. White asked for him to add detail to this recommendation. Dr. O'Callaghan agreed to send Dr. White further wording for this recommendation. In the paragraph regarding imaging findings, Dr. Sullivan asked whether the spelling of Gulf War theater was correct. It was agreed that this would be checked in prior reports for consistency. In the immune system paragraph, Dr. Golomb had a question regarding the use of the term state-specific. She asked for a rewording, relating to the exercise challenge but not necessarily the state, because some of these effects occur after the challenge conditions. This was agreed upon by the Committee.

Dr. White moved forward to the Committee recommendations regarding pathobiological underpinnings. Dr. Golomb had a comment regarding the first point and asked that the examples be removed because she felt that they may be misleading. Dr. White thought that the examples were important, and that in either direction, the conditions could be misleading. Dr. Golomb thought that it wasn't in either direction. The Committee agreed to remove the sentence. Regarding point seven, Dr. Golomb asked whether it might be premature to have it as a recommendation. This recommendation referred to a need for increased emphasis on the study of alterations in regulatory dynamics, within and across regulatory axes, such as the endocrine, immune, and nervous systems. Dr. White replied that this specific recommendation was discussed and agreed upon at the prior RAC meeting in January. Dr. Klimas agreed to rewrite this recommendation to reflect a more effective wording for the systems biology approach.

In the treatment section of the executive summary, Chairman Binns commented on the introductory paragraphs. He asked whether 'dietary supplements' was specific enough and if individual types should be included. Dr. White stated that this had recently been changed and would be reflected in the next version of the report. Dr. Steele asked whether specific supplements should be included considering some of the studies referenced had not yet been published. Dr. Golomb stated that using a word such as 'promising' may be helpful to use in this section. This was agreed upon by the Committee.

Research recommendations were discussed next. Dr. Golomb commented that this may be a good place to state the distinction between chronic fatigue syndrome (CFS), fibromyalgia, and multiple chemical sensitivity. Dr. Steele agreed. Dr. White thought the Committee needed to be very specific about inclusion criteria for treatment trials or the results would be difficult to

interpret. Dr. White stated that this recommendation was proposed to specifically define the groups that will be studied so that an effective treatment trial would be reflecting effects in participants with GWI and not with CFS or fibromyalgia who may also have GWI. Dr. Steele recommended that in some studies the investigator might choose to consider individuals separately according to criteria rather than a blanket statement. Dr. Sullivan noted that the recommendation was trying to capture the concept that treatment trials should be seeking out individuals that have GWI and those that also meet a set of criteria for other potential illnesses (CFS, fibromyalgia etc.), and not the other way around. It was agreed that the wording would be reconsidered to ensure clarity of the statement. Mr. Bunker asked a question regarding individuals who meet a single criteria for GWI but not the other criteria being excluded from GWI treatment trials. Dr. Steele and Dr. White stated that the individual would probably not get included into a GWI treatment trial if they only present with a single symptom, as generally GWI treatment trial participants present with multiple symptoms. It would be important to be very specific regarding symptoms for a treatment trial because otherwise its effectiveness might be called into question. Dr. Golomb noted the existence of treatment trials regarding veterans that present with single symptoms but not specifically for GWI.

With regard to recommendation number three, Dr. Golomb asked to have the word ‘objectives’ removed. This was agreed upon. Dr. Steele asked a question about recommendation number four calling for objective measures of outcomes. She commented that this sentence should include ‘where possible’. There was Committee agreement on this suggestion. She thought it was important that the studies should not be confined to those where the mechanisms are explicitly known.

Chairman Binns recommended that the last sentence of the second paragraph, regarding Appendix A be used as an internet link reference rather than copying the entire report in the Appendix. Dr. White commented that this reference was already changed to an internet link reference as suggested.

Dr. Steele asked about the content regarding the recommendation for genetic susceptibility approaches in treatment and whether there was any substantive information that supported this recommendation. Dr. Golomb thought that biomarker based treatments might be helpful alone without the personalized treatments in this recommendation. It was agreed that the personalized treatments content would be removed from the recommendation. Dr. Klimas recommended keeping the recommendation broad, and using examples following it to be more specific. Dr. Steele preferred a stronger rephrasing for the proof of concept studies recommendations.

Dr. Steele recommended in the bullet regarding the health treatment trials that the word ‘focus’ or ‘central issue’ be included. She also suggested adding studies with new knowledge rather than just current knowledge. Dr. Golomb suggested adding human studies explicitly and then

following it with animal studies so that VA research funding would include both. Dr. Steele recommended a change in heading if these additional recommended changes were to be included, as the current heading would no longer cover the changes. Chairman Binns agreed on this point. Dr. White agreed to consider an additional heading for this section. Dr. Steele asked whether anything regarding specific VA funding should be explicitly included in the report. Chairman Binns asked to delete the last paragraph regarding federal research programs, and move the VA annual reports to Congress section below the three bullets. When done, the new header would not be necessary.

Chairman Binns brought up the question of whether the wording should be changed, because it leads the reader to believe that exposures led to all problems in Gulf War veterans. This was in the second italicized paragraph in the section regarding which exposures and experiences in theater. Unless there was hard evidence, he suggested including a qualifying word, because 'other' can be read as 'all other'. Dr. Steele agreed on this point. The word 'some' or 'a number of' should be included. Additionally, rewording around 'cause' was discussed, because it alone is very strong in science. Chairman Binns recommended the use of 'certain other' to encapsulate necessary wording, which the Committee agreed upon. Dr. Steele added that the word disorders should be removed, and 'certain other adverse health outcomes affecting Gulf War veterans' be used in its place. This was agreed upon, and other places in the report where this wording was used would be changed.

The group had a brief break before the public comment session.

Public Comment

Chairman Binns asked for those who would like to make a comment to identify themselves. Those included: MAJ Denise Nichols and Mr. Ronald Brown.

MAJ Nichols began her public comment by stating that the teleconference was difficult for veterans to follow along who could not see the slides for the discussion. She hoped that some sort of protected webinar might be used in the future so that veterans could follow the meetings easier. MAJ Nichols asked that the Committee include a recommendation for those Gulf War veterans who were ill but were nondeployed. She stated that by definition they are not included in GWI studies, but they should still get the VA health services that they need. She also asked for strong recommendations for follow up studies on affected children. She also mentioned the emergence of dental problems and veterans losing teeth that she would like to see studied further.

Mr. Ronald Brown made the next public comment. He stated that the National Gulf War Resource Center recently asked for an increase in presumptive conditions of brain cancer, lung cancer, and migraines in Gulf War veterans. Congressman Coffman sent a letter to the VA

regarding this. He stated that the science and research supported this request. Chairman Binns noted that the Committee advised only on research, but he thought that many of the members would agree with the actions being proposed on these presumptives. Mr. Brown also asked how more research could be done examining veterans who are alive and suffering from brain cancer. Dr. Sullivan agreed with this point, and added that recommendations like this were included in the report that asked for greater research emphasis on veterans living with these diseases.

The International Foundation for Functional Gastrointestinal Disorders submitted a written statement following the meeting, which can be found in **Appendix B**.

Committee Discussion: 2013 Committee Report

Dr. Roberta White, Scientific Director
Mr. James Binns, Committee Chair
Dr. Kimberly Sullivan, Associate Scientific Director

The findings in brief section of the report was discussed next. Dr. White noted that this was the first look at the findings in brief, which were gleaned from the executive summary. Chairman Binns noted that the term for Gulf War Illness would be changed. In the general conclusions section, Dr. Steele had a comment regarding the reference of the 2010 IOM report as 'the other comprehensive scientific literature review' in that section as well as in other areas of the report. Dr. Steele did not agree that the 2010 IOM report was a comprehensive scientific literature review on Gulf War illness. She stated that the IOM has not provided comprehensive reports; they were charged with examining rates of conditions in Gulf War veterans. The Committee agreed that they would take out the word comprehensive and refer to it as 'a scientific literature review'.

In the section, 'What is Gulf War illness', Dr. Steele asked for a switch in terminology from 'highly' excess rates to 'significantly' or 'markedly' excess rates. The Committee agreed upon the use of 'markedly'. In the prognosis section, Dr. Steele commented that 800,000 troops needed to be changed to 700,000 U.S. troops. In the section about other kinds of health problems, Chairman Binns commented on whether other era veteran groups should be clarified. Dr. White explained that this includes all other veteran groups, including veterans that went to other wars. Dr. Steele also asked that the veterans refer to the first Gulf War as the 1990-1991 Gulf War. Mr. Bunker asked for veterans to be referred to as veterans from other military operations. Dr. Steele commented that they need to be referred to as veterans who were nondeployed. Studies published since 2008 only include those nondeployed era veterans, which is what they will be referred to by the Committee. Chairman Binns commented that there are no other veteran groups of the same era that have been compared to Gulf War veterans since the 2008 report besides the nondeployed veterans, which is why they are the only that should be

mentioned in this section. The Committee agreed on this point. Dr. Steele made the point that it was the same reference regarding ALS in the following sentence, which would be modified.

In the next paragraph, Dr. Steele commented on a wording change, which Dr. White agreed upon.

Mr. Bunker made a comment on the lack of studies on gastrointestinal esophageal reflux disorder (GERD). Dr. Steele commented that it was in fact studied in the VA national survey study. Dr. Steele sent the studies to Mr. Bunker for his reference. There was Committee agreement to take out a sentence that was placed in the executive summary. In the studies of psychiatric and psychological disorders, Dr. Steele commented on a wording change in the first sentence to remove the word 'cause' and replace with 'distinct from', which was agreed upon by the Committee.

In the pathobiology section, the use of the word 'nerves' was questioned by the Committee. The use of this word was meant to clarify the language in layman's terms, but it was noted by Dr. Sullivan that 'nerves' might be misconstrued by some veterans. Dr. Steele recommended the use of 'nervous system' instead, which was agreed upon.

Chairman Binns rephrased a section header to 'Are there available treatments for Gulf War illness?' Dr. Steele asked about studies not yet published and whether there should be explicit language stating that studies are not yet published, but are pending. Chairman Binns pointed out that there was language explicitly stating this in the text. Mr. Bunker mentioned the possibility of adding that the VA does not provide supplemental vitamins to veterans. Dr. Golomb pointed out that they do in fact provide some supplements, but not those that have been found to be useful in Gulf War veterans. Mr. Bunker recommended that the Committee put an explicit recommendation to the VA regarding these supplements. Chairman Binns mentioned that the Committee does not advise the VA formulary, they advise on research on the health of Gulf War veterans. Dr. Klimas suggested using a phrase such as 'as research suggests' to include some sort of treatment suggestion. It was agreed that this would go somewhere other than in the findings in brief. Dr. Steele noted the personalized medicine comment needed to be removed. Dr. White agreed to remove it throughout the report.

Dr. White noted three other topics for consideration. First, instead of making the draft strategic plan an appendix, it would just be referenced as a link in the Appendix A text. A copy of the draft strategic plan can be found in **Appendix B**. The Committee agreed on this point. Dr. White then asked whether Appendix D with the occupational exposure studies should remain. Chairman Binns and Mr. Bunker both voiced agreement with keeping the appendix in the text. The last topic for discussion included Dr. White asking the Committee members to please send any further wording errors in the remainder of the report to her as soon as possible. She asked

whether there were any other issues for discussion before concluding the meeting. Chairman Binns commented on the appendix regarding Committee members' biosketches. He asked if the Committee members could edit their biosketches so that they were no more than ten lines.

Mr. Bunker then asked for a chance to make a comment. He mentioned that the VA longitudinal study that was mentioned in the report was still underway, and he thought it needed to be reworded to show that it was concluded and explicit language that should be added to make sure that it needed to be repeated in a specific number of years. Dr. Steele questioned whether prioritization was needed for the recommendations. It was then decided that there would not be a prioritization of recommendations in the report.

Dr. Kalasinsky then asked Chairman Binns whether this meeting officially finalized the report. Chairman Binns confirmed that this was the intention of the meeting. Mr. Bunker mentioned that he emailed statements that he would like to have included in the record, as they were his viewpoints on how the report should have been amended. He submitted an additional document expanding on some of the following points, which can be found in **Appendix B**. He did not think that there were enough sleep apnea follow-up study recommendations, as well as gastrointestinal studies and cancer rate studies. He thought that the Committee needed to be recommending these things more explicitly.

Following Mr. Bunker's comments, Chairman Binns recommended that a blanket statement reinforcing research for treatment studies be considered. The statement could say that VA should consider adopting such treatments where research has shown evidence of treatment efficacy. Dr. White and Dr. Sullivan noted these recommendations were already included in the report, but they would add the word 'quickly' to the recommendation. The Committee agreed that rapid validation of effective treatment studies and rapidly publishing results of these studies was important so that they can be brought to the clinics soon as possible for ill GW veterans.

Chairman Binns thanked the Committee members for their hard work on the report, and concluded the meeting.

Findings in Brief

This report was produced by the federal Research Advisory Committee on Gulf War Illnesses (RACGWI), which was established by Congress under Public Law 105-368. Membership includes veterans of the first Gulf War (1990-91), scientists who have studied illnesses affecting these veterans, clinicians who care for ill Gulf War veterans and a member of the general public. The Committee periodically releases reports that summarize research to date on the health of veterans of the 1990-1991 Gulf War. The most recent report was published in 2008, and the current report updates knowledge from that time by reviewing published scientific papers that appeared after the last report and through December 2013.

The present research review is divided into four sections. The first summarizes the new information available on rates of Gulf War illness and other illnesses and disabilities that affect groups of veterans from the Gulf War (Section 1, Epidemiologic Research). The second reviews the human and animal research that has been carried out to identify the causes of Gulf War illness and other health problems in Gulf War veterans (Section 2: Etiologic Investigations). The third section focuses on studies of the disruptions in normal body functions that underlie the symptoms of Gulf War illness and other health problems (Section 3: Pathobiology of Gulf War illness). And the fourth reviews clinical trials that are underway to treat Gulf War illness (Section 4: Gulf War illness treatment research).

In this section, the findings of the report are described in layman's terms.

General Conclusions

Scientific research published since the preparation of the 2008 Committee report supports and further substantiates the conclusions of the 2008 report that Gulf War illness is a serious physical disease, affecting at least 175,000 veterans of the 1990-1991 Gulf War and caused by exposures to toxic substances. Important progress has been made in improving the understanding of Gulf War illness. Research is beginning to identify probable underlying mechanisms, promising treatments, and biomarkers. However, much work remains to be done.

The other comprehensive scientific literature review of this problem since 2008, the Institute of Medicine 2010 Gulf War and Health report, also called for a renewed federal research effort, and its report concluded that treatments and hopefully preventions can likely be found with the right research.

It is time to applaud and support the scientists working to improve the health of Gulf War veterans and to protect the health of current and future American servicemen and women at risk

of similar exposures. Effective treatments for Gulf War illness could also lead to treatments for other exposure-related occupational health problems.

What is Gulf War illness and how common is it?

Gulf War illness refers to the chronic symptoms that affect veterans of the 1990-1991 Gulf War at highly excess rates compared to other veteran groups and to the US population as a whole. The individual symptoms experienced by ill Gulf War veterans can vary from person to person, but the symptoms reported are similar in the many groups of ill veterans that have been studied since the war. Symptoms typically include some combination of widespread pain, headache, persistent problems with memory and thinking, unexplained fatigue, breathing problems, stomach and intestinal symptoms, and skin abnormalities. This profile of symptoms is not currently explained by other medical diagnoses or by standard laboratory tests.

In the early years after the war, this disorder was commonly called “Gulf War Syndrome” by the media and has since been referred to by a variety of names such as undiagnosed illness, Gulf War illness, chronic multisymptom illness (CMI) and other terms. “Gulf War illness” is the term most commonly used by scientists, clinicians, veterans’ groups, and the Department of Defense

and is used in this report to refer to the group of symptoms associated with military service in the 1990-1991 Gulf War.

Based on its review of the research that has been published since 2008, the Committee concludes that Gulf War illness has been found consistently in all studies of Gulf War veterans and that it is seen in about 25-30% of Gulf War veterans, or about 175,000 to 250,000 of the 800,000 troops deployed to the war in 1990-91. The same conclusion was reached in 2008.

Little new information has become available on whether the health of ill Gulf War veterans has improved over time. The research published in the 2008 RAC report suggests that there is little to no improvement. The effect that aging will have on this vulnerable population remains a matter of concern.

What other kinds of health problems are experienced by Gulf War veterans?

Studies published since 2008 continue to find that veterans from the first Gulf War have poorer general health and greater disability than other veteran groups.

Studies reviewed in this report show that Gulf War veterans have higher rates of ALS than their non-deployed counterparts, that those veterans who were most exposed to the release of nerve gas by the destruction of the Khamisiyah Iraqi arms depot have elevated rates of death due to brain cancer, and that those exposed to oil well fires have higher rates of brain cancer.

Very little other research has yet been conducted to determine rates at which Gulf War veterans have been affected by medical conditions of possible concern, including neurological diseases such as multiple sclerosis or Parkinson's disease, other cancers, sleep disorders and adverse pregnancy outcomes and birth defects.

Persons with disorders like chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivity have similar symptoms to veterans with Gulf War illness, but most Gulf War illness patients cannot be diagnosed with these disorders using standard diagnostic rules. Gulf War illness is a distinct disorder and Gulf War veterans who can be diagnosed with these disorders often differ significantly from non-veteran populations who are diagnosed with them. It may be necessary to consider Gulf War veterans who do and do not meet criteria for these conditions separately in research studies and clinical care.

Studies of psychological and psychiatric disorders in Gulf War veterans since 2008 continue to show that combat and other stressors are associated with post-traumatic stress disorder (PTSD), anxiety, depression and alcohol abuse but that these disorders do not cause Gulf War illness. They are typically reported to occur in less than 10% of Gulf War veterans, far below the rate of these illnesses in veterans of other recent wars and far below the rate of Gulf War illness in Gulf War veterans.

Very little is known about whether service in the Gulf War or having Gulf War illness affects veterans' life expectancy. Much more needs to be learned about this. Despite specific recommendations over many years from both RACGWI and Institute of Medicine panels, research in this area remains seriously inadequate.

Which exposures and experiences in the theater caused ill health and functional disability in Gulf War veterans?

Once it became clear that veterans of the Gulf War had returned home with persistent health problems, the question immediately arose as to the cause or causes of ill health in this veteran group. Although a highly publicized initial argument was that their ill health was due to deployment related stressors and psychological trauma, it ultimately became clear that chemical,

pharmaceutical, and other environmental exposures in theater underlie the development of Gulf War illness. Research in this area has expanded since 2008 and has included research on effects of exposure to specific chemicals and drugs during the war in veterans as well as extensive exploration of the chronic, persistent effects of single and combined exposures to substances and conditions that occurred in theater in animal models.

Taken together, the research reviewed in this Report supports the conclusion in the 2008 RACGWI Report that chemical exposures, not psychological stressors or psychiatric disorders, are the cause of Gulf War illness and other health and functional disorders in Gulf War veterans.

How are basic body functions affected in veterans with Gulf War illness?

A review of the 2008 RAC report and research published since then led the RACGWI to conclude that changes in the brain, nerves, brain hormones, and immune system are associated with Gulf War illness and with other health problems in subgroups of veterans who experienced exposures to specific chemicals and drugs in the Gulf War theater.

What effective treatments are available for patients with Gulf War illness and how should new treatments be developed?

Treatment research has increased significantly since 2008, particularly reflecting the work of the Gulf War Illness Research Program (GWIRP) of the DoD Congressionally Directed Medical Research Program (CDMRP). However, most of these studies are underway, with results pending. Promising approaches that have gone through limited trials to date include Co-enzyme Q10 (a dietary supplement), acupuncture, and use of continuous positive airway pressure (CPAP) during sleep.

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

Treatment approaches based on what is known about the underlying physiological changes that occur in veterans with Gulf War illness may be the most effective. Approaches that reflect individual differences in symptoms and effects of exposure to the Gulf War theater should be considered, including personalized medicine. Promising laboratory research is underway to develop cutting-edge treatment approaches by studying the effects of Gulf War exposures in

animals and then targeting treatments for these effects. Effective treatments of Gulf War illness could lead to treatments for other exposure-related occupational health problems. It may be possible to leverage support from other federal health agencies interested in exposure-related diseases and disorders for this effort.

Executive Summary

This report was produced by the federal Research Advisory Committee on Gulf War Illnesses (RACGWI), established by Congress under Public Law 105-368. The Committee periodically releases reports that summarize research to date on the health of veterans of the 1990-1991 Gulf War. The most recent report was published in 2008, and the current report updates knowledge from that time by reviewing published papers that appeared after the last report and through December 2013.

The research review is divided into four sections that summarize the epidemiological issues and research on Gulf War illness, the human and animal research that has addressed causes of the illness and other health problems in Gulf War veterans, studies that focus on the underlying pathobiology of illness manifestations, and the clinical trials that are underway to treat Gulf War illness.

In this Executive Summary, the Committee summarizes its conclusions about the findings from research to date on Gulf War illness and provides recommendations about how to further understand and, most importantly, how to identify and evaluate effective treatments.

The RACGWI members who served on the Committee during the preparation of this report are listed on the second page of this document.

What is Gulf War illness and how prevalent is it?

As described in previous Committee reports, Gulf War illness refers to the complex of chronic symptoms that affects veterans of the 1990-1991 Gulf War at excess rates. Although individual symptoms can vary from person to person, the overall profile of excess symptoms is consistent across populations of Gulf War veterans. Concurrent symptoms typically include some combination of widespread pain, headache, persistent memory problems and other cognitive difficulties, unexplained fatigue, respiratory symptoms, gastrointestinal problems and skin abnormalities. This profile of symptoms is not explained by other medical diagnoses or by standard laboratory tests.

In the early years after the war, this disorder was commonly called “Gulf War Syndrome” by the media and has since been referred to by a variety of names such as undiagnosed illness, Gulf War illness, chronic multisymptom illness (CMI), and various other terms. Gulf War illness, the term most commonly used by scientists, clinicians, veterans’ groups, and the Department of

Defense, is used as an umbrella term throughout this report to refer to the chronic symptomatic illness, variously defined, associated with military service in the 1990-1991 Gulf War.

Based in its review of the data published since 2008, the Committee concludes that all population-based studies conducted since the Gulf War have continued to identify a significant excess rate of chronic symptomatic illness, variously defined, in 1990-1991 Gulf War veterans. The large majority of studies indicate that the prevalence of Gulf War illness is in the range of 25-30% in Gulf War veteran, as reported in 2008.

Little additional information on the *long-term prognosis* of Gulf War illness has become available since 2008. Prior data reported in 2008 suggest that there is little to no improvement in the health of ill Gulf War veterans over time. The effect that aging will have on this vulnerable population remains a matter of concern.

What other kinds of health problems are experienced by Gulf War veterans?

Studies published since 2008 continue to document *poorer general health status and greater disability* among Gulf War veterans. Despite the extensive number of studies conducted with Gulf War veterans in the 23 years since Desert Storm, medical surveillance in this population remains woefully inadequate.

Very little research has yet been conducted to determine rates at which Gulf War veterans have been affected by *medical conditions* of possible concern. As a result, it is not currently known if Gulf War veterans have experienced excess prevalence or incidence rates of most medical conditions. Disorders of concern reviewed in this Report include the following:

1. Neurological disorders. Although neurological conditions are a prominent concern for Gulf War veterans, and research has found an elevated incidence of ALS, rates of multiple sclerosis, Parkinson's disease, and other neurological diseases in Gulf War veterans are currently unknown. Research studies of the prevalence of neurological diseases have not been conducted despite repeated recommendations by this Committee and the Institute of Medicine, and explicit legislation by Congress. The prevalence of these disorders is particularly important because they can be expected to increase as the Gulf War veteran population ages.

2. Cancer. Since 2008, research using state cancer registries has suggested that there may be an increased rate of lung cancer in Gulf War veterans. Brain cancer mortality also appears to be increased in the subgroup of Gulf War veterans with greatest exposure to Khamisyah and oil fire smoke. In general, cancer risk remains unknown and understudied.

3. Sleep dysfunction. A single study published since 2008 has identified sleep abnormalities in a group of Gulf War veterans compared to obesity-matched controls. Sleep disturbance is an extremely common symptom in veterans with Gulf War illness and CPAP treatment has shown some promise in a small treatment trial.

4. Adverse reproductive outcomes and birth defects. No definitive new information is available on birth defects in offspring of Gulf War veterans, and no research has ever been published concerning neurological or other medical conditions affecting veterans' children. It is important that medical and reproductive outcomes be assessed in children of veteran subgroups of interest (e.g. exposure, location, illness subgroups).

Multisymptom conditions, including *chronic fatigue syndrome, fibromyalgia, multiple chemical sensitivity*, share similar symptoms with Gulf War illness but few Gulf War illness patients meet

criteria for them. Gulf War illness is a distinct disorder and Gulf War veterans who meet criteria for these disorders often differ significantly from non-veteran populations who are diagnosed with them. It may be necessary to consider Gulf War veterans who do and do not meet criteria for these disorders separately in research studies, including treatment research

Studies of *psychological and psychiatric morbidity* in Gulf War veterans since 2008 continue to show that combat and other stressors are associated with post-traumatic stress disorder (PTSD), anxiety, depression and alcohol abuse but not with Gulf War illness.

Lack of current information on *overall and disease-specific mortality* among U.S. Gulf War veterans is an important issue. No comprehensive information has been published on the mortality experience of U.S. Gulf War era veterans after the year 2000. The 13 years for which no mortality figures are available represent more than half of the 23 years since Desert Storm. Mortality information from the last decade is particularly crucial for understanding the health consequences of the Gulf War, given the latency periods associated with many chronic diseases of interest. Despite specific recommendations over many years from both the current Committee and Institute of Medicine panels, federal research efforts to monitor the mortality experience of 1990-1991 Gulf War veterans remain seriously inadequate.

How can research on health of Gulf War veterans be improved?

Case definition of Gulf War illness

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

1. An evidence-based, expert consensus-driven case definition for Gulf War illness should be developed, implementing the steps outlined in the draft strategic plan developed by VA staff and outside advisors from this Committee and VA's National Research Advisory Committee (see Appendix A). This effort should involve representatives from VA, a broad spectrum of scientists conducting research in Gulf War veterans, clinicians knowledgeable about the problem, and Gulf War veterans. This effort should be organized through the Gulf War Illness Research Program of the Department of Defense Congressionally Directed Medical Research Program (CDMRP) through its competitive grant proposal process with scientific review.

2. VA should adopt the name Gulf War illness for the symptomatic condition associated with military service in the 1990-1991 Gulf War.

Monitoring the effect of Gulf War service on long-term health

Ongoing monitoring and surveillance of the Gulf War veteran population is critical as this veteran group ages. A plan for such monitoring was included in the plan proposed by a VA Strategic Planning group composed of representatives from RACGWI, VA and DoD (see Appendix A). Such surveillance should include outcomes described in this document, including Gulf War illness, neurological disorders, cancers, sleep dysfunction, adverse reproductive outcomes and birth defects, ill health, mortality and other disorders that emerge as important during the surveillance process. This effort must include the following elements.

1. Ongoing assessment of Gulf War illness and its impact on the health and lives of Gulf War veterans is critical. VA's longitudinal survey currently in process should be extended to add a symptom inventory adequate to define the illness according to existing commonly-used case definitions, as previously recommended by the Committee: "[The current survey instrument] cannot determine the prevalence, progression, or correlates of this illness. . . [I]t is unthinkable that the largest national study of Gulf War veterans

would not provide the data required to evaluate the signature problem of the 1991 Gulf War." (Research Advisory Committee on Gulf War Veterans' Illnesses, 2012).

2. VA's longitudinal survey can be effectively used to assess rates of physician-diagnosed medical conditions in Gulf War and era veterans. Survey data can be used to flag conditions of possible importance and followed up with detailed investigation.

3. A study on the prevalence of "multiple sclerosis, Parkinson's disease, and brain cancers, as well as central nervous system abnormalities that are difficult to precisely diagnose" in Gulf War and recent Iraq/Afghanistan war veterans was required by Congress in 2008 (Public Law 110-389, 2008, Section 804), and should be carried out. These assessments should be repeated and published at a minimum of 5-year intervals.

4. Systematic assessment of overall and disease-specific mortality in all Gulf War veterans and in specific subgroups of interest is essential. The results of these assessments should also be published at 5-year intervals.

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

era veterans. Survey data can be used to flag condition of possible concern and followed up. It is also important that VA publish results from studies of veterans' children that were conducted over 10 years ago.

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

Improved methodology in Gulf War epidemiologic research

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

1. Systematic methods for assessing symptoms and other health outcomes in Gulf War veterans.

2. Evaluation of health outcomes in Gulf War veteran subgroups of importance—for example, subgroups defined by relevant exposure history or location in theater.

3. Consideration of subpopulations with multiple health outcomes.

4. In evaluating risk factors for Gulf War illness and other health outcomes, use of analytic methods that adequately control for confounding effects of multiple exposures and etiologic factors that may be associated both with the exposures and outcomes of interest. Consideration of the effects of mixed exposures is also key.

Which exposures and experiences in the theater caused ill health and functional disability in Gulf War veterans?

Once it became clear that veterans of the Gulf War had returned home with persistent health problems, the question immediately arose as to the cause or causes of ill health in this veteran group. Although a highly publicized initial argument was that their ill health was due to deployment related stressors and psychological trauma, it ultimately became clear that chemical, pharmaceutical, and other environmental exposures in theater underlie the development of Gulf War illness. Research in this area has expanded since 2008 and has included research on exposure-outcome relationships in veterans as well as extensive exploration of the chronic,

persistent effects of single and combined exposures to substances and conditions that occurred in theater in animal models.

Taken together, the epidemiological and animal studies reviewed in this Report continue to support the conclusion in the 2008 RACGWI Report that chemical exposures, not psychological stressors or psychiatric disorders, are the cause of Gulf War illness and many other health and functional disorders in Gulf War veterans.

Epidemiological research

Overall, studies published since the 2008 report continue show that exposures to chemicals in the organophosphate group are etiologically important in the development of Gulf War illness and in the behavioral and cognitive dysfunction experienced by Gulf War veterans. The evidence is particularly compelling for pesticides and pyridostigmine bromide, and the findings in Gulf War veterans associated with organophosphate exposure are consistent with those seen in other occupational groups. Exposure to the nerve gas agents sarin/cyclosarin (also from the organophosphate group) has been linked in two more studies to changes in structural MRI findings that that are associated with cognitive decrements, further supporting the conclusion from evidence reviewed in the 2008 report that exposure to these agents is etiologically important to the physiological dysfunction that occurs in some subsets of Gulf war veterans.

New evidence has emerged suggesting that oil well fire exposures may be important in the development of Gulf War illness and brain cancer. It is unclear if vaccine exposures may also be contributing to GW veteran health symptoms, because current results have been conflicting and include weak associations. Although exposure to depleted uranium has been demonstrated, with continuing levels in body tissue, its contribution to ill health is unclear: studies on this substance have focused on small groups of individuals.

Most veterans experienced exposures to chemical mixtures in theater and effects of these complex exposures remain unknown. Improved modeling of contributions of individual and mixed exposures would inform the assessment of mixed exposures, as would the development of biomarkers of exposures to specific chemicals in the past.

Exposure studies in Gulf War veterans to identify the etiologic agents that may have been causative in Gulf War illness remain important because they can help to determine treatment targets. The Committee recommends that additional research in this area be carried utilizing objective markers of exposure whenever possible. These include environmental sampling and modeling of conditions in theater. Furthermore, identification of biomarkers of exposure and downstream effects of exposures since the war that are present years after an exposure has

occurred would help enormously in understanding the issues of etiology and possibly physiological effects of Gulf War theater exposures. These methods should include work using genomic, genetic, epigenetic, proteomic, lipidomic, and metabolomic assays for suspected physiological effects and to explore novel, unsuspected pathways of illness. Statistical methods that consider the mixed exposure scenario experienced by Gulf War veterans in theater are essential. These should focus on assessing effects of individual exposures (if possible) as well as various exposure combinations and mixtures. Mixed exposures include not only mixtures of chemicals but also chemicals combined with heat, dehydration, infection, and other environmental stressors.

Animal studies

As noted in the RACGWI 2008 Report, animal studies have identified biological effects of Gulf War exposures and combinations of exposures that were previously unknown. The evidence concerning these effects has burgeoned since 2008, with new animal models of Gulf War illness and exposures in theater. It is axiomatic that animals are not humans and conclusions from animal studies must be used as clues that can be further investigated in appropriate human research. However, the outcomes from animal studies are important because data on exposure-outcome relationships can be collected rapidly and efficiently to provide such clues. Animal models of Gulf War-relevant exposures to individual chemicals, chemical mixtures, and

chemicals plus other stressors have demonstrated alterations in nervous system outcomes (behavior, cognition, neurotransmission, intracellular signaling, molecular and cellular disruptions of axonal transport), liver and cardiovascular function, genomic, proteomic, lipidomic and metabolomic profiles, and mitchondrial changes. These studies have confirmed hypotheses that exposures are important in the development and expression Gulf War illness symptomatology, that health effects due to exposures and exposure mixtures can be delayed and occur after exposure has ended, and that persistent effects can be seen following exposure cessation. Even more importantly, animal models are critical for treatment research. They have identified systemic alterations and physiological changes that can be the target of treatment approaches, and animal models can be used to pre-test promising treatments.

The Committee recommends that research using animal models of Gulf War illness continue to examine the immediate, delayed, and persistent effects of acute exposures to chemicals and chemical mixtures.

1. Future animal model research should focus on studies that characterize persistent effects of Gulf War-related exposures, alone and in combination, on proinflammatory processes in the central nervous system, autonomic nervous system and peripheral target

organs, including those that encompass mitochondrial dysfunction and accumulation of reactive oxygen species.

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

3. Finally, animal research to identify biomarkers indicative of past exposures to Gulf War-related toxic compounds that can be applied to Gulf War veterans is important. This includes studies that identify persistent or “downstream” changes in biochemical processes in relation to past neurotoxicant exposure(s) and that identify persistent changes in the central nervous system and in autonomic function associated with Gulf War-related exposures and conditions. Exploratory biomarker research in animal models that assesses genomic, genetic, epigenetic, proteomic, metabolomics and lipidomic pathways of exposure effect may also be informative.

4. Preclinical treatment research using animal models is also recommended.

What are the physiological mechanisms that underlie Gulf War illness, ill health and functional disability in Gulf War veterans?

In order to understand the health problems seen in the Gulf War veteran population and to generate clues about how to treat their health conditions, is important to learn the underlying pathobiological changes associated with Gulf War illness and with exposures experienced in theater. This Report reviews research on structure and function in the central nervous system (using brain imaging, electroencephalography and cognitive assays) and work that assesses neuroendocrine, autonomic nervous system, and immunological functions.

Overall, the Committee concludes that the evidence to date continues to point to alterations in central and autonomic system, neuroendocrine, and immune system functions in Gulf War illness and in subsets of Gulf War veterans with specific exposures in theater.

Consistent with evidence presented in the 2008 Committee report, new neuroimaging and EEG research has assessed veterans with Gulf War illness and veterans with sarin/cyclosarin exposure. Fourteen of fifteen new studies show *structural and electrical abnormalities in the central nervous system* associated with Gulf War illness and exposure to the nerve gas agents sarin and cyclosarin.

Recent studies on *cognitive function* in Gulf War veterans provide further support for the conclusion of the 2008 report that cognitive dysfunction is a central issue for Gulf War veterans with Gulf War illness and for Gulf War veterans who experienced specific exposures in theater. These findings support the evidence from imaging and EEG probes that nervous system dysfunction is a key element in their ill health.

Studies continue to support the conclusion from the 2008 report that *neuroendocrine function*, as assessed by altered hypothalamic pituitary axis (HPA) functioning in Gulf War veterans, is present and is not consistent with the typical pattern seen in post-traumatic stress disorder.

The 2008 RACGWI report discussed a number of scientific publications documenting *autonomic nervous system* dysregulation in Gulf War veterans. Since 2008, the only published study that looked specifically at autonomic function in Gulf War veterans confirmed diminished night time heart rate variability in all three Haley Syndrome Gulf War illness groups.

Six of eight studies conducted on *immune system* alterations in Gulf War veterans since 2008 showed immune dysfunction. Research in this area appears to be narrowing in on changes occurring to the expression of certain cell lines. Additionally, changes occurring during exercise

indicate that immunological manifestations of GWI may be state specific: evidence of underlying immune differences between symptomatic and asymptomatic veterans may only become apparent in specific experimental or clinical settings under "challenge" conditions.

The Committee recommends that research on the pathobiological underpinnings of Gulf War illness and ill health in Gulf War veterans continue to focus on the central and autonomic nervous system, immunological and neuroendocrine outcomes in this population in order to identify targets for treatment interventions and outcomes that should be improved during such treatments.

1. Clear, operationalized case definitions are important for this work. Findings may differ in differing patient populations, either defined with different Gulf War illness criteria or experiencing different health problems. For example, veterans with multisymptom illnesses like Chronic Fatigue Syndrome or Fibromyalgia may show different patterns of immunological or neurological function than veterans without these disorders.

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

3. In some studies that have included female Gulf War veterans, it appears that gender differences may play a role in the pathobiological expression of Gulf War illness and its effects. Gender should be considered whenever possible in mechanistic research on Gulf War illness.

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

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

6. In order to effectively pursue “omics” and genetic correlates of Gulf War illness, standardized sample collections in research that uses biological specimens can expedite exploratory and hypothesis-driven research. Standardized protocols for sample collections should be established and followed.

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

8. Animal models may be appropriate to investigate some mechanistic hypotheses and illness or exposure effects.

What effective treatments are available for patients with Gulf War illness and how should new treatments be developed?

Treatment research has increased significantly since 2008, particularly reflecting the work of the Gulf War Illness Research Program (GWIRP) of the DoD Congressionally Directed Medical Research Program (CDMRP), which is specifically focused on treatments. However, most of these studies are underway, with results pending. Promising approaches that have gone through limited trials to date include dietary supplements, acupuncture and CPAP.

Early results provide encouraging signs that the treatment goals identified in the 2010 Institute of Medicine Report are achievable: "Veterans who continue to suffer from these discouraging symptoms deserve the very best that modern science and medicine can offer . . . to speed the development of effective treatments, cures, and, it is hoped, preventions. The committee suggests a path forward to accomplish these goals and we believe that, through a concerted national effort and rigorous scientific input, answers can likely be found." (Institute of Medicine, 2010, p. x).

It will continue to be important to explore both conventional medical approaches (such as medications or devices) as well as alternative therapies. Treatments based on proposed mechanisms of illness presentation and on specific symptoms are currently under development through two CDMRP-funded collaborative consortia led by Boston and Florida investigators and through other trials by individual investigators. These projects have the potential to identify treatments that address the fundamental physiological conditions underlying the illness, rather than simply the symptoms.

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

This research should include a number of critical elements.

1. Clear, operationalized case definitions for GWI and other diagnostic subgroups for whom treatments are designed are essential. If Gulf War veterans in treatment trials who meet criteria for Gulf War illness also meet criteria for other illnesses such as chronic fatigue syndrome (CFS), fibromyalgia (FM) or multiple chemical sensitivity (MCS), these patients should be considered separately from Gulf War veterans who do not meet criteria for these disorders. This also holds for Gulf War veterans who meet criteria for other disorders and diseases of interest (e.g., neurological conditions such as amyotrophic lateral sclerosis or multiple sclerosis, irritable bowel syndrome, etc.).

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

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

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

Treatment approaches based on known mechanistic pathways of Gulf War illness, biomarker based treatments and therapies based on genetic susceptibility approaches (i.e. personalized medicine) should all be considered. Effective treatments could lead to significant breakthroughs in the treatment of Gulf War illness and other exposure-related occupational health problems. These may require support of intervention development at the proof-of-concept level as well as eventual large-scale clinical trials. It may be possible to leverage support from other federal health agencies interested in exposure-related diseases and disorders for this effort.

Although the perfect animal model of Gulf War illness has not yet been developed, preclinical animal models can and should be used to develop and test new treatments focused on pathobiological mechanisms of Gulf War illness and the effects of Gulf War theater exposures. Highly promising avenues for preclinical animal research are identified in the draft VA research strategic plan (Appendix A of this document).

Center- and consortium based treatment research efforts can capitalize on multi-disciplinary expertise and multi-pronged approaches to treatment targets and pre-clinical trials. The CDMRP treatment consortia are an important step in developing integrated treatments for ill Gulf War veterans as an initial assessment of treatment safety and efficacy in Phase I/II trials. Since CDMRP does not fund larger clinical trials, validation studies through the VA Cooperative Studies Program (CSP) or similar large, multi-site, government sponsored programs are necessary to provide final confirmation validation of initial safety and efficacy from initial Phase I/II trials and pilot studies funded through CDMRP and for initiation of new treatment trials within VA.

Data on effective treatments from VA's 2005 longitudinal survey should be published. Information from veterans with Gulf War illness and their treating physicians on effective treatments should be collected and published. This should include reconducting the IOM review of treatments by treating Gulf War veterans' medical practitioners ordered by Congress in 2010 (Public Law 111-275, 2010, Section 805), which was transformed into a literature review of treatments for mental health problems by a group with no experience in treating Gulf War illness.

VA Annual Reports to Congress on Gulf War illness research funded by VA should include only studies and treatment trials in which the health of Gulf War veterans is the central hypothesis, in which the study participants are primarily Gulf War veterans, and which are consistent with current research knowledge.

Congress should maintain its funding at $20 million annually for five years to support the effective treatment-oriented Gulf War illness research program at the Department of Defense Congressionally Directed Medical Research Programs, for openly-competed, peer-reviewed studies to identify:

1. Effective treatments for Gulf War illness,

2. Objective measures that distinguish ill from healthy veterans, and

3. Underlying biological mechanisms potentially amenable to treatment.

Federal research programs should continue both to solicit proposals from individual investigators and from teams (or organizations) of investigators with all the necessary expertise, working together and focused on a common goal, such as the CDMRP consortia.

Appendix B – Draft Strategic Plan

The Draft Strategic Plan can be found on the RAC website, at the following link:

http://www.va.gov/RAC-GWVI/VA_draft_strategic_plan.pdf

International Foundation for Functional Gastrointestinal Disorders

IFFGD
700 W. Virginia St, #201
Milwaukee, WI 53204

Phone: 414-964-1799
Toll Free: 888-964-2001
Fax: 414-964-7176
Internet: www.iffgd.org

March 24, 2014

Via Email: rwhite@bu.edu

Dr. Roberta White
Scientific Director
Department of Veterans Affairs
Research Advisory Committee on Gulf War Veterans' Illnesses

RE: FR Docket No: 2014-04572

Dear Dr. White:

Thank you for the opportunity to present this written statement regarding the importance of functional gastrointestinal disorders research related to Gulf War Veterans' Illnesses.

On behalf of the International Foundation for Functional Gastrointestinal Disorders (IFFGD), I would like to thank the Committee for its work to understand the health consequences of military service in the Southwest Asia theater of operations during the Gulf War, and to help the veterans with service connected diseases. IFFGD is a 501(c)(3) nonprofit education and research organization. Since 1991 we have been dedicated to improving the understanding of functional gastrointestinal disorders. Our mission is to inform, assist, and support people affected by these painful and debilitating digestive conditions for which too few treatment options exist.

We are grateful to VA for its leadership in recognizing the burden of illness that functional gastrointestinal disorders (FGIDs) have on affected individuals and taking steps to help relieve that burden. Among these steps is the "Presumptive Service Connection" rule issued by VA in 2011 recognizing the positive association between service in Southwest Asia during certain periods and the development of functional GI disorders.

The onset of a functional GI disorder (FGID) can be triggered by severe stress and infections of the digestive system. Deployed military personnel face an elevated chance of experiencing these risk factors and developing a FGID as a result of their service. The relationship between service-related deployment and the onset of a FGID is documented in medical literature, including the 2010 Institute of Medicine (IOM) report entitled, *Gulf War and Health Volume 8: Update of Health Effects of Serving in the Gulf War*.

Functional GI disorders are conditions where normal movement of the intestines, sensitivity of the nerves of the intestines, or the way in which the brain controls some of these functions is impaired. The conditions can affect any area of the digestive tract, from the esophagus to the stomach to the small and large intestines. They are characterized by long-term courses, unpredictable symptom episodes, and disruptive or disabling effects. People who suffer from FGIDs have no structural abnormality, which makes it difficult to identify their condition using routine diagnostic tests such as endoscopies, x-rays, or blood tests.

Functional GI disorders are challenging to patients and physicians. In clinics, patients with FGIDs have normal diagnostic tests. Instead, diagnosis is based on characteristic symptoms that

meet defined criteria. The symptoms are variable, their onset often unpredictable, and their course can vary over time. These variations occur both within an individual, and also from person to person with the same diagnosis. The disorders are influenced by multiple factors, including genetic makeup, environmental influences, and psychological and social factors. The conditions do not fit the traditional linear biomedical model. Consequently, patients often struggle, sometimes for years, to obtain the accurate diagnosis necessary to begin appropriate treatment.

Moreover, adequate treatment for functional GI disorders is lacking. Few effective therapies exist and these do not always work for all persons. Treatment focuses mainly on symptom management over a long term, with varying degrees of effectiveness. All of the above factors contribute to uncertainties that challenge both affected individuals and their physicians.

The functional GI disorders research portfolio at VA has grown in recent years, and is working to advance our understanding of conditions such as irritable bowel syndrome, but more research is needed in this area. Currently, our scientific understanding of FGIDs is limited. As a result, there are no cures and few treatment options. Since these conditions are often chronic and treatment options are limited, they are costly to treat and individuals on disability may have little hope of returning to a productive lifestyle.

Recommendations
IFFGD makes the following suggestions regarding functional gastrointestinal disorders, which we urge you to consider in recommendations you provide to the Secretary of Veterans Affairs regarding proposed research strategies and plans addressing Gulf War Illnesses:

- Streamline logistics set up to harmonize the patient data collected by the Department of Defense (DOD) with data collected by VA.
- Provide investigators with direct access to harmonized patient data and develop questionnaires and other kinds of assessments for tracking FGID patients longitudinally to understand how they are changing, or developing new symptoms or syndromes.
- Educate and increase awareness of these conditions among care providers to facilitate prompt, accurate diagnoses and treatments.
- Educate and increase awareness of these conditions among active duty soldiers and veterans deployed to the Gulf region; work with patient organizations and the National Institutes of Health (NIH) to assist with these efforts.
- Explore opportunities to partner with DOD and NIH to enhance research and improve patient care regarding functional GI disorders.

Thank you for your consideration of our comments.

Sincerely,

Elisabeth Vink

Elisabeth Vink
Program Specialist, IFFGD

James A. Bunker
Executive Director
National Gulf War Resource Center
1725 SW Gage BLVD Topeka, KS 66604

Statement for the record of the March 19 meeting VA Research Advisory Committee on Gulf War. To be a part of the minute of the meeting.

I would like my following commits placed into the minutes of the 19 March meeting Department of Veterans Affairs Research Advisory Committee on Gulf War Veterans' Illnesses (RAC-GW).

1. Whereas this report discusses the research on the pilot study about sleep dysfunction/ sleep apnea (Amin et al., 2011) as a committee, we must make a recommendation that the VA to do a follow on study. The study should look into the side effects of the veterans' medications and SA as a part of the follow on study too. Many of the GW-veterans are on different types of pain pills due to their GWI. The medications given to treat the veterans for CFS and FM type of pain due to the gulf war and the may cause of SA as sleep dysfunction is a part of these illnesses. I believe that this committee needs to be doing recommendation like this in all of the reports.
2. Whereas the VA has never done any studies on GERD or FGID in the desert storm veteran (only a study in OIF) and the symptoms are ranked very high on the surveys. We as a committee must make a recommendation to the VA to undertake a large-scale survey to determine the rate of GERD in the set of veterans from 1 August 1990 to 12 April 1991 and from 13 April 1991 to 30 November 1994. (The end of the cease-fire operation) with a set of non-deployed veterans and a set of GW deployed 1996-1998, and a set of OIF /OEF. The study needs to be using an Endoscopy to check for damage. Barium swallow is not good method to use, as it would miss 2/3 of the veterans with the GERD.
3. The report show cancer of the brain at 2X for veterans in the Nerve gas plum for 2 days or more or close to the oil wells, The report has cancer reports of lung cancer higher in GW-Veterans. We as a committee must

James A. Bunker
Executive Director
National Gulf War Resource Center
1725 SW Gage BLVD Topeka, KS 66604

Statement for the record of the March 19 meeting VA Research Advisory Committee on Gulf War. To be a part of the minute of the meeting.

make a recommendation to the VA for a follow on studies to look at the rates of the cancers and all tumors as well as skin diseases by locations in the gulf, by sex and dates. Of all veterans living and not, The cause of death will under count the number of veterans with cancers. While a veteran can have cancer or other Dx illnesses if his cause of death was something else, like a car wreck the cancer will not be on the death certificate.

4. We talked on the treatment trial of the CPAC but we did not make any recommendation to the VA for a follow on studies. As a committee, we need to have the VA look into this as a form of treatment. Treatment without medication or less of them is what many veterans what. Also for some, just the O2 helps without the CPAC. It might be due to the high rates of sinus problems in the GW veterans. Something we should have the VA look into as the studies do show that Desert Storm Veterans do suffer from a much higher rate of sinus problems than nondeployed.
5. As the report has the research about the rates of multiple sclerosis (MS) in all veterans who served in the Gulf between the years of 1990-2007, Section 804 (Wallin et al., 2012). This study stated that more follow-up work is needed. We need to make sure that is a recommendation that the VA does the follow up study within the next two years. The veterans will need to be reported as per the subgroups of dates and locations of deployments. The locations would be broken down as to the towns in the areas.
6. In this report we talk about research showing significantly higher rates of seizures, nerve pains, and strokes,(Kang et al., 2009) Along with migraines (Rayhan et al., 2013). We need to get the VA do follow-up studies on the headaches and work on better treatments in this area

James A. Bunker
Executive Director
National Gulf War Resource Center
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working with those at Georgetown. Work on better Dx tools for caregivers as some VA caregivers (PA' NP's) do not DX headaches right some of the times. Need to see them in subgroup, we need to get better studies and if more than one type in the groups. Work on more studies of the seizures and treatment. The VA should do follow up studies in the nerve pains. Train caregiver on fine fiber neuropathy Vs dietetic neuropathy or peripheral neuropathy. Studies need to look at some causes too. Migraine can be from most anything, but when a veteran has a neck or head injury, the cause is more likely than not that.

7. Six studies conducted on immune system in Gulf War veterans since 2008 showed immune dysfunction. Research in this area appears to be narrowing in on changes occurring to the expression of certain cell lines. We need to make pointed recommendations for the VA to follow. The VA does need to be doing studies in a larger group.
8. A weak part in many of the research with veterans is not having our full medical history. I had one tell me my nerve problem was from some pills I was on 5 or 6 years after the nerve problem started. We as a committee must make a recommendation to the VA using information in STR and not just VA medical records when studying GWI veterans.
9. Add a subgroup of the southern watch that would have some of the exposures but not all. This group would be able to help control for some of exposure.
10. Baraniuk (2013) found that administering an amino acid supplement containing L-carnosine reduced irritable bowel syndrome (IBS) associated diarrhea (Baraniuk et al., 2013). . We as a committee must make a recommendation to the VA to fund a follow on study with him or do one.

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11. I do not believe we should be using as Appendix A. "Pre-Decisional Draft Strategic Plan for Gulf War Illness Research" it is not a proper thing as per what a Pre-Decisional Draft is. If you have something in one committee that did not go from one Pre-Decisional draft to the next just add it here as your idea.
12.

There are other comments in the draft report I have not made here.