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

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

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

Secretary McDonald,

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

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

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

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

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

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

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

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

Cautions and Recommendations

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

Cautions:

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

neuroendocrinology, neuroimmunology, and systems biology. The concern surrounding this issue also serves as a reminder that there are very limited treatment options currently available for GWI patients and highlights the need to develop more effective therapeutic and management strategies.

This is an area of great interest to the RAC and one that the Committee will continue to explore and advise on.

Recommendations:

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

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

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

Respectfully,



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on behalf of the Research Advisory Committee on Gulf War Veterans' Illnesses
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