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14. ABSTRACT
Despite considerable research on health issues affecting the nearly 700,000 U.S. veterans of the 1991 Persian Gulf War, fundamental questions and challenges remain. There is still no single, consensus case definition for Gulf War illness (GWI) and little current information related to its characteristics. Nor has there been a comprehensive assessment of rates of more familiar diagnosed medical conditions. Gulf War veterans—many still looking for answers about unexplained health problems—have been anxious to participate in studies, while researchers commonly report enormous difficulty identifying adequate numbers of Gulf War veterans for their projects. This project addresses these challenges with a coordinated research effort. Investigators will use a multifaceted survey research strategy to obtain current information on symptoms and medical conditions from a nationally representative sample of 5,000 1991 Gulf War era veterans. These data will be used to optimize a GWI case definition, based on current symptoms, and to provide insights concerning rates of other medical conditions in Gulf War veterans. Parallel to this effort, the project is inviting a broad national sample of Gulf War era veterans to complete health questionnaires by mail or online, and to participate in the 1991 Veterans Research and Information Network (91VetNet), a national research and information resource for Gulf War era veterans and for investigators. The project was originally designed to be conducted at Baylor University in Waco, but will now be transferred to Baylor College of Medicine in Houston. This represents the final report for study activities completed at Baylor University.

15. SUBJECT TERMS
Gulf War veterans, Gulf War illness, epidemiology, survey research, case definition, research network

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Establishing a 1991 Veterans Research Network

to Improve Characterization of Gulf War Illness

and Provide a National Resource for Veterans and Investigators

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Introduction: Purpose and Scope of Research Effort

Despite considerable research on health issues affecting U.S. veterans of the 1990-1991 Persian Gulf War, fundamental questions remain about the health consequences of military service in that conflict. The signature health problem associated with 1991 Gulf War military service has been Gulf War illness (GWI), the complex of undiagnosed symptoms that have persisted, for many veterans, for 25 years. Studies indicate that at least one in four veterans are affected by this consistent pattern of excess symptoms, variously defined, that is not attributable to established medical or psychiatric diagnoses, and not explained by clinical diagnostic tests.[1-4] This problem has long been the focus of scientific studies, Congressional inquiries, media reports, and scientific review panels.

The need for current population health data to support an evidence-based Gulf War illness case definition. The GWI symptom profile typically includes some combination of cognitive difficulties, widespread pain, and unexplained fatigue—accompanied, in many veterans, by chronic digestive problems, respiratory difficulties, and skin abnormalities. Because there are no objective tests that can be used to diagnose GWI, it is currently identified only on the basis of veterans' symptoms. Twenty-five years after Desert Storm, however, there is still not a consensus, evidence-based case definition for GWI. The 2008 report of the federal Research Advisory Committee on Gulf War Veterans' Illnesses describes eight different approaches used by different investigators to define or characterize GWI.[1] Some case definitions have characterized GWI either very broadly,[5-7] or very narrowly,[8-9] and most were not developed in a systematic, data-driven manner. Despite hundreds of research studies conducted in this population, the lack of a consistent, evidence-based GWI case definition has made study results difficult to interpret and compare and has slowed progress in addressing this problem. Further, there is little available information related to current characteristics of GWI or its impact on the lives of Gulf War veterans.[10]

The need for systematic, population-based data on other medical conditions affecting 1990-1991 Gulf War era veterans. Although GWI has been the most prominent health concern associated with the 1991 Gulf War, it is not the only condition of importance. Twenty-five years after the war, there have been almost no published studies that provide systematic assessments, in nationally representative samples, of rates at which more familiar diagnosed medical conditions affect 1991 Gulf War veterans.[10] Several studies have reported that 1991 Gulf War veterans have an excess rate of amyotrophic lateral sclerosis (ALS),[11-13] compared to nondeployed veterans of the same era, and one study has provided an indication that 1991 Gulf War veterans suffer from an elevated rate of lung cancer.[14] Mortality studies have also reported that the subgroup of Gulf War veterans potentially exposed to nerve agents in connection with the 1991 Khamisiyah demolitions have died from brain cancers at twice the rate of unexposed veterans.[15,16]

Overall, however, rates of most medical conditions have not been ascertained in 1991 Gulf War veterans. This includes multiple sclerosis, for which a great deal of concern has been raised by Congressional committees, and by veterans' advocates. Data on rates of medical diagnoses in this population are urgently needed, and not only for the insights this information can provide for

veterans and their healthcare providers. In a very practical sense, federal agencies and scientific review panels rely on studies of this type to establish healthcare policies and programs and to determine if veterans should receive disability compensation for diseases that may be related to their military service. Due to the lack of systematic research on diagnosed medical conditions in Gulf War veterans, data are not available to inform veterans, healthcare providers, and policymakers whether U.S. Gulf War veterans are affected by excess rates of most medical conditions of possible concern.

The need for an information resource for 1990-1991 Gulf War veterans and a mechanism to assist investigators in recruiting Gulf War-era veterans for research studies. Scientists conducting research on health issues associated with service in the 1990-1991 Gulf War often face serious challenges in carrying out quality research in an effective and efficient manner. This includes an unfortunate dichotomy with respect to recruitment of 1991 Gulf War era veterans for research studies. On one hand, nearly all investigators report enormous difficulty identifying adequate numbers of symptomatic and healthy Gulf War veterans for studies investigating laboratory markers, treatments, and other clinical parameters. As a result, investigators often have no choice but to enroll nearly all veterans they can identify through any means, yielding less-than-ideal study samples that may not be representative of ill veterans more generally. On the other hand, veterans and researchers commonly indicate that Gulf War veterans *want* to participate in research studies. Unfortunately, though, there is no unified national veterans group or central contact point that can provide 1991 Gulf War era veterans with information related to research or other issues relevant to military service of this period. Veterans of this era, many still seeking answers about unexplained health conditions, are willing and even anxious to participate in research studies, but generally do not know that such studies are being conducted or that they are eligible to participate.

Project Overview. The current project was designed to address these prominent issues with a coordinated effort that utilizes a multipart, national sampling and state-of-the-art survey research strategy. This includes a Computer-Assisted Telephone Interview (CATI) survey of a nationally representative sample of 5,000 1991 Gulf War era veterans, under a contract arrangement with Westat. The CATI survey is designed to provide current data on symptoms and diagnosed medical conditions reported by 3,000 1991 Gulf War veterans, and 2,000 veterans of the same era who did not deploy to the Gulf War theater. In broad consultation with experts in the field, these data will be used to update and optimize a GWI case definition, based on veterans' current health status, and to provide important insights concerning rates of diagnosed medical conditions in Gulf War era veterans.

The project is also obtaining health data from a second, larger sample, referred to as the network sample. This involves contacting 45,000 Gulf War era veterans to invite them to complete health questionnaires by mail or online. These data will be used to further evaluate patterns observed in the CATI sample, including associations between health outcomes and deployment experiences. In addition, veterans in both the CATI and network samples are invited to participate in the 1991 Veterans Research and Information Network (91VetNet). Participating veterans will receive current information on health issues relevant to military service during 1990-1991 and will be notified about studies for which they may be eligible. The network will also serve as a resource

for researchers conducting studies on the health of 1991-era veterans, and can assist them in recruiting veterans who may be interested in participating in their studies.

Overall, the project is designed to provide current, nationally representative data to identify the prevalence and characteristics of GWI, as well as rates of diagnosed diseases reported by 1991-era veterans. These data will be used to inform veterans, providers, and policymakers, and will also be used to optimize an evidence-based case definition of GWI. In addition, the project will provide a current information resource for 1991-era veterans and a recruitment resource for investigators conducting studies in this population. This is expected to have a positive impact on the broader Gulf War research effort, improving studies to advance GWI treatments and diagnostic tests, and provide insights into its pathobiology. This multipart project was originally proposed by investigators at Baylor University in Waco but, as described below, will now be conducted at Baylor College of Medicine in Houston.

Body

Task 1. Prepare and Submit Documents to Obtain Regulatory Approvals

This project requires review and approval by the Baylor Institutional Review Board (IRB) and by the USAMRMC's Office of Human Research Protections (HRPO). We also initially understood, based on information provided by DOD officials, that the project would require review and approval by the federal Office of Management and Budget (OMB), under the federal Paperwork Reduction Act (PRA). We were informed that the OMB approval process typically requires a minimum of eight months. We therefore designed the project timeline to allow ten months for obtaining regulatory approvals, as indicated in the Statement of Work.

Our initial strategy was to begin the process and document submissions required for OMB review and approval prior to HRPO and IRB submissions. This was because we understood that OMB approval would be needed to obtain our initial sampling data from the Defense Manpower Data Center (DMDC), and because the OMB approval process typically takes longer than the IRB process. However, in a concurrent study, we were experiencing extended delays and considerable difficulties in connection with the DOD offices responsible for reviewing and forwarding PRA documentation to OMB. Ultimately, after multiple requests and discussions, the DOD Information Management Office determined that study was *not* subject to the federal PRA and that no OMB approvals should be sought. However, since the present study includes a nationwide survey data collection, it was not clear whether it might fall under the PRA. We therefore petitioned DOD's Information Management Office to obtain a firm decision as to whether the project would be subject to OMB review and approval before undertaking the lengthy OMB review process. After multiple submissions and requests over many months, we obtained a ruling in June 2013 from officials at both the DOD Information Management Office and OMB indicating that the project did not fall under the PRA because the data collection had been grant-funded in response to a Baylor proposal, and was neither conducted by nor contracted out by the federal government. The project was therefore not subject to OMB review and approval.

The project encompasses two parallel data collections utilizing a multimodal survey effort that includes the national computer-assisted telephone interview (CATI) survey, as well as mail and online surveys. Data collection for the national CATI survey is to be conducted by our contractor, Westat. We were initially told that Westat would submit the telephone survey to its Institutional Review Board (IRB) for review and approval and therefore prepared human subjects' documentation for the telephone survey, as a separate project submission, to Baylor's IRB for approval. Baylor initial IRB approval for the telephone survey was obtained in September, 2013. After extended discussions and delays related to Westat's IRB process, we determined that Baylor IRB, as the lead institution, would provide all human subjects' oversight for the project. Baylor and Westat therefore worked out an IRB Authorization Agreement (IAA), under which Westat would defer IRB review for the project to the Baylor University IRB.

Because the Baylor IRB would have sole oversight over the project, the Baylor Compliance Office asked that our submissions for all project data collections, including the mail and online surveys, be reviewed in conjunction with the CATI survey. Human subjects' documentation for the remaining portions of the project were submitted to Baylor IRB as an amendment and approved in May, 2014. Human subjects' documentation was initially submitted to the Army Office of Human Research Protections (HRPO) in June, 2014. Full human subjects' approval for the project was provided by HRPO in August, 2014 (HRPO project # A-17630). As of the closing date for project activities at Baylor University, all human subjects approvals continue to be current.

Task 2. Obtain current data on the health status of 5,000 1991 Gulf War era veterans from a national, representative sample using a Computer Assisted Telephone Interview (CATI) Survey

Working with our contractors at Westat, all aspects of survey design and programming for the national CATI survey have been finalized. Although the contract services agreement with Westat was finalized in September, 2014, it was never implemented due to our inability to obtain the required personnel data from DOD's Defense Manpower Data Center (DMDC) for the study, as described below, in order to initiate work on sampling and data collection.

Although we have had multiple discussions with DMDC on this matter, we have yet to submit a formal data request to obtain information on 1990-1991 Gulf War era veterans for use in developing the national samples to be contacted for the project. This is due to a major setback encountered in two previous and separate studies that also required us to obtain data from DMDC, including names and contact information for Gulf War era veterans in our target samples. These delays involved new requirements raised by the DMDC Privacy Office in the Spring of 2014. In contrast to prior experience and DOD assurances involving DMDC data acquisition for use in federally-funded research studies, DMDC Privacy Office officials informed Baylor that DMDC data could only be approved for release to a federal entity and that the receiving IT system must be certified according to federal (e.g. FISMA, DIACAP) guidelines, or a corporate equivalent. After learning of these new requirements, we investigated multiple possible avenues for addressing them. Again, these requirements had not been in place when we initially developed the project, nor after the project was funded by CDMRP. Possible solutions have included working with identified DOD collaborators and with partnering institutions or corporate entities to download and manage the DMDC data on a certified IT system. We are grateful for the input and extended efforts of our CDMRP Program Officer who worked with us to identify solutions. This included a potential partnership with the Army Analytics Group to facilitate access to the DMDC data needed for this project. However we learned in Spring 2015 that the Army Analytics Group was unable to work out a solution with DMDC and so could not assist us in accessing these data. We continue to work to develop a solution that will allow us to obtain the DMDC data for the project, utilizing suitable IT security provisions that support our use of these data in compliance with the new DMDC IT security requirements.

Study and instrument design for the CATI, mail, and online surveys have been finalized and we have long been ready to proceed with the CATI national survey. However, no activities have been undertaken to initiate sampling and data collection, pending suitable arrangements that allow us access to DMDC data that provide the location and contact information for 1991 Gulf War era veterans required to establish our national sample.

The delays caused by our inability to obtain DMDC data have caused considerable uncertainty regarding the timeline for the project. The study was initially designed to allow our survey contractor, Westat, to receive the DMDC data since Westat routinely works with DMDC data utilizing its secure DIACAP-certified data enclave. Even were that deemed acceptable to DMDC, however, it was also essential that we address DOD IT security requirements at our institution. This is needed to allow Westat to turn over DMDC data to Baylor for developing the samples to be contacted for the mail and online surveys, and for data management and analyses.

Because of the serious concerns raised by these and related challenges, the Principal Investigator worked to identify a new institutional affiliation that would provide a FISMA-certified IT system, supporting the level of data security needed for housing DMDC data for this and other CDMRP-funded projects.

Note that no subject recruitment or data collection activities have been initiated and no research results are yet available.

Task 3. Obtain health data from a broad sample of at least 10,000 Gulf War era veterans via mail and web-based surveys and establish the 91 Veterans Research and Information Network (91VetNet)

In anticipation of receiving sampling information from DMDC, we previously finalized key aspects of study and instrument design for the mail and online surveys, to be conducted in-house at Baylor (that is, not through our contractor). This included work on practical aspects of implementation of the mail and online surveys, focusing on IT and execution details associated with launching the web survey and printing/mailing/scanning the mail survey.

However, no subject recruitment or data collection activities have been initiated and no research results are yet available.

Tasks 4 – 5. Data Assembled and Analyzed; Preparation of Publications, Information Update, and Final Report

No activities completed or underway at this time. No data have been collected or analyzed, and no research results are yet available.

Project Timeline and New Location

As previously described, extended delays resulting from DOD's initial misdirection concerning OMB approvals, our inability to obtain DMDC data, and additional institutional delays caused considerable concern regarding the timeline required for completing the project. We therefore requested a 12 month extension without funds (EWOF) for the project on August 17, 2015. However, it also became clear that it was unlikely that the project could be completed in an acceptable timeframe under current circumstances. Therefore, in December 2015, the PI accepted a new faculty position at Baylor College of Medicine (BCM), where additional research resources will be available at BCM and the Texas Medical Center in Houston. Baylor University has agreed to return remaining grant funds for this project to DOD, so they can be made available to BCM to complete the project there. Specifically, we expect that the enhanced capabilities at BCM for FISMA-compliant IT management will allow us to work more effectively with our contractors at Westat and complete the project in a more reasonable timeframe.

Key Research Accomplishments

Only regulatory submissions and work on finalizing study design and instruments have been accomplished to date. Data collection has not yet been initiated.

Reportable Outcomes

There are no manuscripts or other reportable outcomes at this time.

Conclusion

No research results are yet available; no conclusions can be drawn at this time.

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