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14. ABSTRACT Shortly after return from Gulf War (GW) deployment in 1991, some GW veterans began reporting a constellation of health symptoms that did not meet criteria for well-defined medical conditions or syndromes. Symptoms included pain, cognitive deficits, skin rash, gastrointestinal difficulties and sleep problems. The initial attempts at identifying case definition used a one-time cross-sectional health symptom report, which is insufficient for determining a case definition given that symptoms often show remitting and relapsing tendencies. Current estimates suggest that 25 percent of GW veterans (nearly 170,000) have reported persisting multisymptom illness and in order to stimulate more appropriate treatment avenues for ill veterans, it is essential that a refined case definition be found taking change over time into account and examining the impact of symptoms previously reported on current health status. This will be accomplished by employing a longitudinal design with a large longitudinally followed cohort. Current health symptom survey data will therefore be compared with prior survey data. The practical application of this study is to provide a gold standard definition to be used in future treatment trials. The study goals include, devising a new case definition for GW illness, where possible assisting in the management of specific disease states, and collecting outcome data about treatment avenues employed and their efficacy. Year 2 goals have primarily been met including collecting initial data of the first 100 participants.					
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Introduction –

Background and Purpose: Current estimates suggest that 25 percent of Gulf War (GW) veterans (nearly 170,000) have reported some type of persisting multi-symptom illness. Currently used GW Illness (GWI) case definitions have been found to be lacking in sensitivity and specificity with many veterans falling in the false positive and false negative ranges. These GWI definitions, based on cross-sectional studies, allow for reporting of health symptoms only once, and do not consider that symptoms can emerge over time (or remit); thus they likely provide inaccurate representations of veterans' health. Only through the use of longitudinal data, where health symptoms were first measured shortly after deployment and then repeatedly over the following 20 years, would consideration of symptom trajectories and patterns of change over time be possible in order to refine the case definition of GWI. The Ft. Devens, MA cohort was designed as a longitudinal cohort and included nearly 3,000 soldiers. This cohort will be useful in ameliorating the existing problems with case definition. The ultimate goal for this study is to provide a consistent case definition of GWI, which can serve future studies and treatment trials as a valid outcome.

Scope: The true value of a longitudinal prospective design such as the Ft. Devens cohort is that it can capture symptom trajectories that may have been modified by treatment effects. Data mining from the multiple time points during the last 19-years in the Ft. Devens cohort now allows for a more refined case definition of GW illness that can take change over time into account and examine the impact of symptoms previously reported on health, genetic vulnerabilities and treatment outcomes. The practical application of this enhanced case definition of GWI is to provide a gold standard definition for the case ascertainment and evaluation of future treatment trials. Although originally designed as a prospective longitudinal study to compare changes over time, this has not been reported in the Ft. Devens cohort to date. Therefore, the current investigators have a unique opportunity to capitalize on the strengths of this cohort and perform a Time 4 follow up health symptom inquiry to evaluate the utility of prior case criteria and using longitudinal data improve upon case definition classification. The Ft. Devens data, maintained at the Behavioral Science Division for PTSD at the VA Boston Healthcare System, is fully accessible to the current study PI through the password protected shared drive. The existing database will be combined with the current survey findings in order to compare and contrast symptoms in order to determine the new case definition. Reliability of responses will be determined with the use of validity checks as was done with prior datasets.

A question naturally arises how longitudinal characterization could result in a gold-standard case definition for GW illness. This will be accomplished by developing algorithms of risk factors for developing chronic health symptoms that would be encountered by ill GW veterans. The risk factors that would be included in the algorithm equation would include health symptom report, genetic vulnerabilities (PON1 status) and prior treatment effectiveness. This model closely resembles the Framingham Heart Study risk model equations that have used longitudinal health symptom and biomarker patterns to develop risk algorithms for development of chronic disease states including stroke and cardiovascular disease (i.e. heart attacks). This risk algorithm for GW illness could then be translationally employed by VA primary care physicians as well as GW illness researchers.

Body –

Progress to date:

- For this 4th complete resurvey of the Ft. Devens cohort, Year 2 has resulted in completion of the design of the online secure web survey. Initial recruitment letters with opt-out postcards were mailed to the Ft. Devens cohort for whom addresses were on file from last contact in 2004.. Individuals for whom opt-out postcards or change of address letters were not received, were sent a letter with a link to the online survey with their unique ID code. Initial feedback from Ft. Devens cohort members who were prior survey respondents encouraged study staff to devise a paper and pencil version of the current survey, which is currently under review by our local IRB? Ft. Devens Cohort contact information collected in 2004 is currently being updated.
- Dr. Kregel obtained access to the prior survey data from the Ft. Devens cohort to compare with the current resurvey study. The database has been updated to include current survey measures.

Study Timeline:

Months 1-6: Finalize Plan for Participant Recruitment

a. Submit human use documents for IRB approvals.

- IRB approval has been obtained from the VA Boston Healthcare System Institutional Review Board, Boston University School of Medicine, and HRPO.

b. Receive health symptom comparison data from Ft. Devens Cohort Studies Time 1, 2, and 3.

- The PI has obtained access to the database stored behind the VA firewall at the VA Boston Healthcare System.

c. Identify current address and contact information for surviving members of the Time I cohort of 2,949 participants.

- Addresses from study participants have been gathered from the last set of Ft. Devens surveys collected in 2004. Study personnel have begun checking contact information.

Months 4-9: Finalize Methods for Web Survey Design

a. Format completed health symptom questionnaires for use with Teleform and website

- Questionnaires have been formatted for web conversion and paper questionnaires were keyed into web format to ensure a consistent and complete dataset for this fourth health symptom survey of the Ft. Devens cohort.
- Paper questionnaires have been reformatted to be consistent with the web survey for participants who prefer to participate through paper surveys.

b. Create website for collection of current health symptom status, health care utilization and treatment usage using web based programming

- The PI and BU Site PI met regularly with the BU data coordinating center staff (DCC) to discuss ways to implement the online survey and programming is completed. Study personnel have also piloted the web survey.

The approved statement of work for year 2 study period is below:

Statement of Work
Redefining Gulf War Inness Using Longitudinal Health Data: The Fort Devens Cohort
Months 9-36
Task 3: Data Collection and Deliverables
3a: send pre-survey letter to original cohort participants with opt-out postcard for those not wishing to participate
3b: Obtain demographic information and information pertaining to current health status and changes in medical or psychiatric diagnoses by use of web-survey and by mail questionnaire for those individuals who do not have access to a computer
3c: Follow-up calls made to individuals who have not responded. Complete health questionnaires on the phone for individuals not otherwise able to participate
3d: Contact a subsample of 200 survey responders to participate in genetic testing
3e: Data cleaning and preliminary analyses will be ongoing as data is collected in order to formulate an advanced algorithm case definition for GW illness.

Months 9-36: Task 3 Data Collection and Deliverables

a. Send pre-survey letter to original cohort participants with an "opt-out" postcard for those not wishing to participate

- Initial recruitment letters were sent to 1600 prior survey participants for whom we had current addresses based on 2004 contact information
- 115 prior survey respondents sent back opt-out postcards
- Updated addresses are being put into the contact database
- The PI is obtaining updated addresses through a secure online database

b. Obtain demographic information and information pertaining to current health status and changes in medical or psychiatric diagnoses by use of web-based survey and by mail questionnaire for those individuals who do not have access to a computer

- 122 completed surveys have been obtained to date.
- Data collection is ongoing.

c. Follow-up calls made to individuals who have not responded. Complete health questionnaires on the phone for individuals not otherwise able to participate

- Based on feedback provided by prior survey respondents and requests for a paper and pencil version, online survey questionnaires were reformatted into paper and pencil questionnaires. These surveys are being reviewed by our local IRB and will be sent to potential participants after all approvals (including HRPO) are obtained.

d. Contact a subsample of 200 survey responders to participate in genetic testing

- Information regarding locality of individuals who have completed the survey is being collected and individuals who live close to the VA Boston Healthcare facility will be contacted in the next month to come in for the blood draw portion of the study.

e. Data cleaning and preliminary analyses will be ongoing as data is collected in order to formulate an advanced algorithm case definition for GW Illness, an assessment of current health care utilization and treatment efficacy

- The Ft. Devens ODS Reunion Survey database has been updated to include data variables from the most recent survey and will be populated as more survey data is obtained. The database remains behind a secure firewall with access to data only by pertinent study personnel.

Months 30-36 Dissemination of data

- These items will be begun towards the end of year 2 into year 3

a. Present preliminary results at local and national conferences

b. Draft manuscripts pertaining to health symptom patterns, current diagnoses, health care utilization and newly devised case definition of GW illness

Key Research Accomplishments:

- Potential study participants have been identified from the Ft Devens cohort, those previously surveyed upon arriving home from deployment to the Gulf War and at subsequent time points thereafter. Opt-out post cards were received from less than 10% of the total group who received the initial mailings suggesting continued interest from the Ft. Devens cohort in participating in this continued longitudinal health survey study of GW veterans.
- Paper and pencil questionnaires that have been used for prior Ft. Devens survey studies were adapted for computerized use with special care taken to ensure ease of self-administration. However, with feedback from the prior survey respondents, comparable paper surveys have also been designed for those who wish to participate through paper and pencil versions of the survey.
- Random numbers were generated so that each potential survey participant will have a de-identified code number when completing the survey.
- Longitudinal health symptom data has been collected from prior survey time points and entered into a database that will allow for combination with subsequently collected data from the current survey time point (Time 4).

Reportable Outcomes:

A poster was presented at the International Neuropsychological Society meeting in February, 2013 on the qualitative findings in neuropsychological tests in a cohort of Gulf deployed pesticide applicators from prior CDMRP grant funding. Manuscript is in preparation.

Grant funding recently obtained:

Title: GW110054 - "Intranasal Insulin: A Novel Treatment for Gulf War Multisymptom Illness" (PI: Gollier, Co-PIs Kregel; Sullivan)

Supporting agency: Department of Defense (W81XWH-12-1-0585)

Specific aims: (1) To assess the efficacy of two different doses (10 IU BID and 20 IU BID) of daily intranasal insulin for eight weeks on memory and attention functioning in GW veterans with CMI. (2) To assess the efficacy of two different doses of intranasal insulin on overall physical health and mood in GW veterans with CMI. (3) To characterize the effect of different doses of intranasal insulin on other symptoms that are characteristic of or associated with CMI (e.g., fatigue, pain, sleep quality, subjective cognitive function). (4) To assess the safety of two different doses of self-administered intranasal insulin in GW veterans with CMI.

Title: Identification of Plasma Biomarkers of Gulf War Illness Using "omic" Technology" (PI:Crawford; Co-I Kregel)

Supporting Agency: CSR&D (CX000469-01A1)

Specific aims: The aim of this project is to develop a plasma biomarker panel by using targeted "omic" investigations and screening an additional GW Veteran population to qualify the

biomarker findings from the discovery phase by determining the reproducibility of the diagnostic specificity and sensitivity of the candidate biomarkers under investigation. This novel and innovative proposal addresses many of the outstanding needs pertaining to issues related to GWI, a) diagnostic biomarkers, b) differences in biological responses due to genetic heterogeneity, c) personalized medicine. Biomarkers may also be identified which can be used as surrogates for evaluation of therapeutic efficacy.

There is no scientific or budgetary overlap.

Title: Brain Immune Interactions as the Basis of Gulf War Illness: Gulf War Illness Consortium (GWIC) (PI: Sullivan)

Supporting agency: Department of Defense (CDMRP/GWIRP GW120037)

Specific aims: The GWI consortium aims to identify validated biomarkers of GWI in both preclinical and clinical models using longitudinally studied cohorts of GW veterans to devise a neuroinflammatory profile risk of GWI.

Conclusions to date :

1. Gulf War veterans who have been followed longitudinally for health survey studies in the past continue to be interested in participating in current health survey studies. A small percentage of potential participants opted-out of participation for this time 4 study of the Ft. Devens cohort from the initial recruitment mailings. It is possible to adapt paper and pencil questionnaires for use in internet survey format that is acceptable to most GW veterans. However, some GW veterans still strongly prefer a pencil and paper format. To ensure the highest rates of study participation for large surveys of GW veterans, offering multiple modalities for participation is recommended.