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Considerations for Designing  
an Epidemiologic Study for  
Multiple Sclerosis and Other  
Neurologic Disorders in Pre  
and Post 9-11 Gulf War  
Veterans

Research Advisory Committee on  
Gulf War Veterans' Illnesses

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# Committee on Designing an Epidemiologic Study for Multiple Sclerosis and Other Neurologic Disorders in Veterans of the Persian Gulf and Post 9/11 Wars

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# Authorizing Legislation and Contract

Public Law 110-389 S.3023 enacted in 2008:

- Directed VA to contract with IOM to conduct an epidemiologic study to determine the incidence, prevalence, and risk of developing multiple sclerosis (MS), and other neurologic diseases as a result of service in the 1990-1991 Gulf War or OEF/OIF/OND.
- The other neurologic diseases the committee was to consider were migraines, Parkinson's disease, brain cancers, and "central nervous system abnormalities that are difficult to precisely diagnose."

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# Authorizing Legislation and Contract

IOM's contract with the VA (signed December, 2014) included:

- “the committee will request data from the VA....The data request will be for existing VA data, rather than for the collection of new data, however, the committee might want the data to be combined in a way that will produce a new data set.”
- a clause regarding the feasibility of conducting the study, specifically: “*Within 60 days of contract end date, provide status report/summary memorandum feasibility of proceeding with study.*”

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# Approach

- Heard from VA representatives and public to:
  - learn about the burden of illness with regard to neurologic outcomes in veterans that have been deployed to the gulf region,
  - gain an understanding of the available data that might be useful, and
  - learn about past and ongoing efforts that have been undertaken in these areas.
- Examined VA utilization reports for MS, migraines, Parkinson's disease, and brain cancer.
- Conducted a literature search to identify published studies on the neurologic diseases of concern in 1990-1991 Gulf War and OEF/OIF/OND veterans.

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# Decision

- Although technically feasible, particularly if data from multiple governmental (e.g., DOD, CMS, CDC) and private sources were available and could be linked to VA data, the committee decided not to go forward with designing an epidemiologic study using only the VA resources available to them.
- If the committee were to use the same datasets and surveys that the VA and other researchers have already used to determine incidence and prevalence of the neurologic conditions of interest, the committee would not advance the knowledge significantly beyond what is currently known.

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# Burden (VA utilization reports)

	<b>Gulf war Deployed (286,995)</b>	<b>Gulf War Nondeployed (269,635)</b>	<b>Unadjusted Odds Ratio (95% Confidence Interval)</b>
Multiple Sclerosis	1,040	1,089	0.90 (0.82-0.98)
Migraines	16,327	14,115	1.09 (1.07-1.12)
Parkinson's Disease	403	487	0.78 (0.68-0.89)
Brain Cancer	342	332	0.97 (0.83-1.13)

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# Burden (VA utilization reports)

	<b>OEF/OIF/OND (1,126,173)</b>
Multiple Sclerosis	1,529
Migraines	58,045
Parkinson's Disease	332
Brain Cancer	458

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# Case Ascertainment

- A diagnosis is entered into medical records using ICD-9-CM codes, but several studies have shown that using a single instance of an ICD-9-CM code in a medical record does not accurately identify the number of true cases.
- Limitations of using ICD-9-CM codes alone to identify cases include coding errors (such as clerical errors, misuse, or omissions), inaccurate diagnoses, and assigning codes prematurely or for uncertain diagnoses.
  - No definitive diagnostic tests for MS and Parkinson's disease exist; instead a diagnosis is made on clinical grounds and ruling out other conditions.
  - The only cases of migraine that would be in the medical record are those cases that are frequent or severe.

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# Case Ascertainment

- Identifying true cases of MS, migraine, Parkinson's disease, and brain cancers with a high degree of precision requires different approaches.
- Methods that accurately identify true cases suitable for estimating prevalence may not be adequate for identifying disease onset required to define incident cases, with the exception of malignant brain cancer.

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# Limitations of Using Existing VA Data

- Constructing a suitable comparison group
- Selection bias from restriction to VA users
- Electronic clinical data
- Survey data

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# Suitable Comparison Group

Several possible comparison groups were discussed by the committee:

- Most deployment information (such as locations, number of deployments, length of deployments) is not available from VA data alone.
- VA has assembled a Gulf War veteran cohort of 621,902 deployed and a random sample of 746,248 era veterans for study that would allow for an adequately powered study to determine whether deployment is associated with increased risk of developing any of the four neurologic conditions of interest.
- Finding a comparison group for OEF/OIF/OND active duty service members is more difficult because as of December 2011, a majority of members in each service branch had deployed at least once to Iraq or Afghanistan.

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# Selection Bias

- Information on veterans who are not using VA services is not captured in the databases, which might lead to missed cases. Only 36% of nondeployed, 46% of deployed Gulf War veterans and 60% of OEF/OIF/OND veterans use VA services.
- Since deployed veterans are more likely to use VA services and be in the system, cases that are missed or not captured by VA might be disproportionately nondeployed veterans, creating a biased comparison.
- Users and nonusers of VA health care might differ in important characteristics that might compromise comparisons between them.

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# Electronic Clinical Data

- Clinical data were not available in electronic health records prior to 1999, which particularly affects health information on 1990-1991 Gulf War veterans.
- Preclinical or prodromal cases are not captured, and time of onset is unknown; that information would be necessary to determine incidence of the diseases of interest.
- Other limitations of administrative data include incomplete records, unrepresentativeness of the target population, and coding errors.

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# Electronic Clinical Data

- Detailed objective measures of possible exposures experienced during deployment, frequency of each exposure, length and route of exposure, are needed to accurately determine whether an aspect of deployment is associated with an increased risk of developing any of the neurologic disorders of interest.
- The only available information on potential exposures is based on self-report measures and surveys that are not included as items in the VA medical records.
- Many potential confounders and effect modifiers are not captured in the medical records or other administrative databases.

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# Limitations of Survey Data

- In general, the limited information collected by the surveys and unconfirmed responses for MS, Parkinson's disease, and brain cancer questions, limit the usefulness of those surveys for use in an epidemiologic study to determine incidence or prevalence of these conditions.
- The sample size of the surveys is too small to provide adequate power to assess the neurologic outcomes of interest with the exception of migraine headaches.

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# The National Health Survey of Gulf War Era Veterans and Their Families

- Response rates ranged from 34% to 70%
- Waves 1 & 2 had no questions related to MS, Parkinson's disease, or brain cancer
- Wave 3 included separate questions on whether a respondent had ever been told by their doctor that they had MS, Parkinson's disease, or brain cancer. If the person answered yes to any of the conditions, the next question asked whether the condition had “been present in the past 4 weeks.”
- All three waves included general questions on headaches, and waves 1 and 3 included specific questions on migraines.
- No questions about head trauma or other injuries.

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# The National Health Survey for a New Generation of US Veterans

- Response rate 34%
- Did not include any questions on Parkinson's disease
- Included separate questions on whether a respondent had ever been told by a doctor that they had MS or any cancer (except skin cancer).
- Asked whether a respondent had ever been told by their doctor that they had migraines, and if yes, to indicate the year they were first diagnosed.
- Included questions on head and traumatic brain injuries.

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# Conclusions

The committee considered each outcome separately, since it judged that appropriate study designs varied according to the outcome under consideration.

After careful consideration, the committee concluded that while technically feasible, it would not proceed with the next steps of designing and implementing a study of the neurologic diseases of concern that is limited to using existing VA data.

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