SUPPORTING STATEMENT FOR 2900-0649
VA COOPERATIVE STUDIES PROJECT NUMBER 500A, NATIONAL REGISTRY OF VETERANS WITH AMYOTROPHIC LATERAL SCLEROSIS (ALS)
VA FORMS OF THE 10-21047 SERIES

A. JUSTIFICATION

1. Explain the circumstances that make the collection of information necessary. Identify legal or administrative requirements that necessitate the collection of information.

Amyotrophic lateral sclerosis (ALS) is a disease of high priority to the Department of Veterans Affairs (VA) because of ongoing concerns about the health of veterans who served in the Gulf War. Recent evidence indicates that veterans deployed to Southwest Asia experienced a greater risk of ALS than non-deployed veterans, and ongoing efforts are aimed at identifying possible etiologic factors. Additional effort is also needed to systematically identify and track the larger population of veterans with ALS. If the general population incidence rates for ALS hold for veterans (i.e., 1-2 cases per 100,000 persons per year), there may be 250-500 veterans diagnosed with ALS each year, with a prevalence of approximately 1,800. Prior to establishment of this Registry, there was no mechanism in place to ascertain cases of this disease or to follow these individuals over time. This study, VA Cooperative Studies Program (CSP) Study #500A, is developing an ongoing national registry of veterans diagnosed with ALS.

Legal authority for this data collection is found under Title 38, Chapter 5, Section 527 that authorizes the collection of data that will allow measurement and evaluation of the Department of Veterans Affairs Programs, the goal of which is improved health care for veterans.

2. Indicate how, by whom, and for what purposes the information is to be used; indicate actual use the agency has made of the information received from current collection.

The creation of this registry will have significance both for the VA and for the larger U.S. society in understanding the natural history of ALS. First, the registry will provide the VA with crucial epidemiological data on the current population of veterans with ALS, as well as the ongoing identification of new cases. This will help the VA to understand how veterans are affected by ALS and may also assist with early identification of new ALS clusters. Second, this registry will provide an important mechanism for informing veterans with ALS regarding clinical drug trials and other studies that may yield improved outcomes. A National Scientific Review committee will evaluate potential studies and determine when registry participants should be notified (by the VA) about studies for which they may be eligible. Third, creation of this registry will yield an important and rich data source for future studies examining the causes (e.g., genetic and environmental) and course of this disease.

To date, scientists and researchers in the field have accessed data and/or participants from the Registry to conduct additional studies on ALS. These studies have requested the Registry's assistance in identifying and recruiting veterans into ALS-specific studies. These studies have included clinical trials and epidemiological studies aimed at identifying treatments and/or the epidemiology of ALS.

3. Describe whether, and to what extent, the collection of information involves the use of automated, electronic, mechanical, or other technological collection techniques or other forms of information technology, e.g. permitting electronic submission of responses, and the basis for the decision for adopting this means of collection. Also described any consideration of using information technology to reduce burden.

Data collection for the Registry is completed using computer assisted telephone interviewing (CATI). This includes the initial telephone baseline screening (VA Form 10-21047), as well as a biannual telephone assessment (VA Form 10-21047a). Research assistants on the project will conduct these assessments on the telephone and enter data directly into an ACCESS database. The only information collected from participants via paper-and-pencil is the informed consent (VA Form 10-21047b) and medical record release forms (VA Form 10-5345, OMB Approval Number 2900-0260). Although the Institutional Review Board has approved a waiver of documentation of informed consent, participants provide verbal consent over the telephone. We retain a copy of this consent for each patient, signed by the research team member who affirmed that the participant provided verbal consent.

4. Describe efforts to identify duplication. Show specifically why any similar information already available cannot be used or modified for use for the purposes described in Item 2 above.

There are currently no comprehensive data identifying all U.S. veterans with ALS. A careful review of the literature, as well as consultation with experts in ALS research, has also confirmed that this is the first nationwide registry of ALS of any kind in the U.S. It is not possible to identify all veterans with ALS through the use of currently existing databases. Many veterans seek care for ALS outside the VA, so a search of VA health system databases would not identify these individuals. Furthermore, accurate identification of a true ALS case can only be verified by expert neurological review of medical records. Research has shown that there is around a 20% error rate in medical codes used for ALS. Therefore using administrative databases from medical facilities and health care systems would not result in accurate assessment of ALS cases.

5. If the collection of information impacts small businesses or other small entities, describe any methods used to minimize burden.

Collection of information for this study will not impact small businesses or other small entities.

6. Describe the consequences to Federal program or policy activities if the collection is not conducted or is conducted less frequently as well as any technical or legal obstacles to reducing burden.

This registry is critical because of ongoing concerns about the risk of ALS among veterans. There are two primary parts of participant data collection for the ALS registry. The first part is the initial telephone baseline screening (VA Form 10-21047). This screen is necessary for an initial assessment on whether the veteran may have ALS and whether eligible for the registry. Using a brief survey, individuals who are not eligible on the basis of this screening will not be asked to provide any subsequent data. The second part of data collection involves brief biannual telephone assessments (VA Form 10-21047a), which will be collected at baseline (once a participant has been verified as having ALS by medical record review) and then on a biannual basis. This interview consists primarily of a validated, ALS-specific health status scale (the ALS Functional Rating Scale). Collection of this information is necessary for two reasons. First, it will allow the VA to understand the course of ALS among veterans. Second, it will assist the VA in determining individuals who may be eligible for specific clinical trials on the basis of current health status. Our decision to collect telephone assessment data biannually was on the basis of consultation with experts in ALS research and medical care. Because ALS is a rapidly progressive and fatal neuromuscular disease, substantial changes in patients' health and physical function may occur within a six-month time period.

7. **Explain any special circumstances that would cause an information collection to be conducted more often than quarterly or require respondents to prepare written responses to a collection of information in fewer than 30 days after receipt of it; submit more than an original and two copies of any document; retain records, other than health, medical, government contract, grant-in-aid, or tax records for more than three years; in connection with a statistical survey that is not designed to produce valid and reliable results that can be generalized to the universe of study and require the use of a statistical data classification that has not been reviewed and approved by OMB.**

There are no special circumstances relating to the collection of information for the registry that result in unusual burden, such as requiring information more than quarterly, requiring a response in fewer than 30 days, requiring multiple copies of documents, long-term retention of documents by respondents or the like.

8. a. If applicable, provide a copy and identify the date and page number of publication in the Federal Register of the sponsor's notice, required by 5 CFR 1320.8(d), soliciting comments on the information collection prior to submission to OMB. Summarize public comments received in response to that notice and describe actions taken by the sponsor in responses to these comments. Specifically address comments received on cost and hour burden.

The notice of Proposed Information Collection Activity was published in the Federal Register on August 15, 2006 (Volume 71, Number 157, Pages 46981 through 46982). We received no comments in response to this notice.

b. Describe efforts to consult with persons outside the agency to obtain their views on the availability of data, frequency of collection, clarity of instructions and recordkeeping, disclosure or reporting format, and on the data elements to be recorded, disclosed or reported. Explain any circumstances which preclude consultation every three years with representatives of those from whom information is to be obtained.

Outside consultation is conducted with the public through the 60- and 30-day Federal Register notices. Additionally, the study team includes a group of experts in epidemiology, statistics, databases, and ALS research. In addition, an outside Scientific Review Committee provides consultation. This committee will oversee registry policies and procedures and review proposals for studies that seek to use registry-related data. This committee includes individuals for the VA, the National Institutes of Health, and private institutions and associations. Members of the Committee include the following:

Philip Lavori, PhD
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Ronnie D. Horner, PhD
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Robert Brown, MD, DPhil,
Director, Day Neuromuscular Research Laboratory, Massachusetts General Hospital
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All registry procedures have been examined and approved by the Department of Veterans Affairs Cooperative Study Program. Institutional Review Boards at the Durham VA Medical Center and the University of Kentucky have also approved the protocol and require annual reviews.

9. Explain any decision to provide any payment or gift to respondents, other than remuneration of contractors or grantees.

Study participants will not receive monetary or gift incentives.

10. Describe any assurance of confidentiality provided to respondents and the basis for the assurance in statue, regulation, or agency policy.

The Institutional Review Board has approved a waiver of documentation of informed consent for this study. The IRB also approved a telephone script that contains all of the required elements of informed consent and HIPAA authorization. A member of the research team reads this form (VA Form 10-21047b, to the participants and obtains verbal agreement to participate. This verbal script states that all participant information will be kept confidential and will be securely stored. Information on these forms will become part of a system of records that complies with the Privacy Act of 1974. This system is identified as "Veteran, Patient, Employee and Volunteer Research and Development Project Records-VA (34VA11)" as set forth in the 2003 Compilation of Privacy Act Issuances via

online GPO access at http://www.gpoaccess.gov/privacyact/2003.html. If responses reveal information concerning suicidal intent, depression, or other major clinical findings, the participant is informed that his/her primary care physician will be notified immediately.

11. Provide additional justification for any questions of a sensitive nature, such as sexual behavior and attitudes, religious beliefs, and other matters that are commonly considered private; include specific uses to be made of the information, the explanation to be given to persons from whom the information is requested, and any steps to be taken to obtain their consent.

Participants will be asked general questions about their health and functional status, as well as their military history. While individual willingness to answer these questions may vary, questions are not generally regarded as being of a sensitive nature. These questions are necessary for determining eligibility for the registry, as well as monitoring participants' health status over time. Respondents will be informed, both in the consent form and over the phone by the interviewer, that they may refuse to answer any question.

12. Estimate of the hour burden of the collection of information:

a. See details in the chart following this narrative.

This study is beginning its **fourth year**. Information collection activities will include a 30-minute initial telephone baseline screening (VA Form 10-21047). During this same phone call, a verbal consent process will be administered (VA Form 10-21047b). Two 30-minute biannual interviews per year will also be conducted for each participant who is enrolled (VA Form 10-21047a). Based on the present screening rate, it is expected that approximately 450 of these screenings will be conducted during the fourth year. It is also anticipated, based on previous experience with the screener, that only about 53% of those screened will be eligible and consent to participate. These estimates would add a total of 240 new participants. Along with the currently enrolled and active participants (N=900), a total of 1,140 active participants during year 4 are expected. However, based on death rates from the first 3 years of the Registry, about 15% of the sample may die during the year. Therefore, we plan to conduct 2 biannual telephone interviews (VA Form 10-21047a) for each of 969 participants during the fourth year.

During the **fifth year** and **sixth year** of the study, enrollment rates are expected to be similar. Therefore, an additional 450 initial 30-minute telephone screenings (VA Form 10-21047) will be conducted each year. Only about 53% of those screened are expected to be eligible and consent to participate. This estimate will add a total of 240 new participants annually. With an expected annual death rate of 15%, these figures will result in 1,208 participants in the fifth year and 1,078 in the sixth year with whom 2 biannual telephone interviews (VA Form 10-21047a) will be conducted.

		Respondents	Frequency	Responses Annually	Minutes	Divided by 60	Annual Burden Hours
Year 4	10-21047	450	1	450	30	60	225
	10-21047b	240	1	240	20	60	80
	10-21047a	969	2	1,938	30	60	969
Year 5	10-21047	450	1	450	30	60	225
	10-21047b	240	1	240	20	60	80
	10-21047a	1,028	2	2,056	30	60	1,028
Year 3	10-21047	450	1	450	30	60	225
	10-21047b	240	1	240	20	60	80
	10-21047a	1,078	2	2,156	30	60	1,078
TOTAL		5,145		8,220			3,990
div by 3		1,715		2,740			1,330

b. If this request for approval covers more than one form, provide separate hour burden estimates for each form and aggregate the hour burdens in Item 13 of OMB 83-I.

See Subparagraph 12a above.

c. Provide estimates of annual cost to respondents for the hour burdens for collections of information. The cost of contracting out or paying outside parties for information collection activities should not be included here. Instead, this cost should be included in Item 14.

The annual cost to the respondents for completing these forms is $19,950 (1,330 annual burden hours X $15 per hour). We do not require any additional recordkeeping.

13. Provide an estimate of the total annual cost burden to respondents or recordkeepers resulting from the collection of information. (Do not include the cost of any hour burden shown in Items 12 and 14).

a. There are no capital, start-up, operation or maintenance costs.

b. Cost estimates are not expected to vary widely. The only cost is that for the time of the respondent. While some respondents will take longer than others, we have chosen an average. The difference in time to complete is due to two factors. First, the length of the screening instrument varies from 3 questions to 23 questions depending upon the veteran's eligibility. Additionally the fragile health status of some of these veterans will determine the length of the assessment.

c. There is no anticipated recordkeeping burden.

14. Provide estimates of annual cost to the Federal Government. Also, provide a description of the method used to estimate cost, which should include quantification of hours, operation expenses (such as equipment, overhead, printing, and support staff), and any other expense that

would not have been incurred without this collection of information. Agencies also may aggregate cost estimates from Items 12, 13, and 14 in a single table.

The annual cost to the Federal Government is estimated at $120,000. The total operational and maintenance costs include salaries for two research assistants who will act as interviewers as well as develop and maintain the CATI screening assessments and databases and prepare reports of the results.

15. Explain the reason for any changes reported in Items 13 or 14 above.

The number of new baseline screenings and biannual interviews differ from prior years. New baseline screenings are fewer, since incident (new) cases are primarily enrolled and prevalent (existing) cases have already been enrolled from when the study began. In addition, the numbers reported here are based on experience from the first three years of this project, rather than the estimated projections before the study began.

16. For collections of information whose results will be published, outline plans for tabulation and publication. Address any complex analytical techniques that will be used. Provide the time schedule for the entire project, including beginning and ending dates of the collection of information, completion of report, publication dates, and other actions.

Since the Registry is not designed to test specific hypotheses, no specific complex statistical analyses are planned. However, we will submit a progress report to the Director of the Department of Veterans Affairs Clinical Science Research & Development Service on an annual basis. This report will contain the following data: Total number of individuals screened, Number screened in previous year, Total number enrolled (verified ALS), Number enrolled in previous year, Number of participants with completed 6-month, 12-month, 18-month (etc.) follow-up interviews, Total number of enrollees who have died (post-enrollment), Number who have died in previous year, Demographic characteristics of enrollees (age, race, gender), Number of enrollees from each military branch/war (self-report), and ALS Functional Rating Scale scores.

17. If seeking approval to omit the expiration date for OMB approval of the information collection, explain the reasons that display would be inappropriate.

VA seeks to minimize the cost to itself for collecting, processing and using the information by not displaying or announcing the expiration date. The survey is conducted by telephone and inclusion of the expiration date would place an unnecessary burden on the respondent because of the need to re-enroll and collect data. Further details are available upon request.

18. Explain each exception to the certification statement identified in Item 19, "Certification for Paperwork Reduction Act Submissions," of OMB 83-I.

There are no exceptions to the certification statement identified in Item 19, "Certification for Paperwork Reduction Act Submissions", of OMB Form 83-1.

B. COLLECTIONS OF INFORMATION EMPLOYING STATISTICAL METHODS

1. Provide a numerical estimate of the potential respondent universe and describe any sampling or other respondent selection method to be used. Data on the number of entities (e.g., households or persons) in the universe and the corresponding sample are to be provided in

tabular format for the universe as a whole and for each strata. Indicate expected response rates. If this has been conducted previously include actual response rates achieved.

The Potential Respondent Universe includes all living veterans with ALS.

Prevalence. The expected annual prevalence of ALS is 5-9 per 100,000 persons. Extrapolating to the population of U.S. veterans (25,349,000 in FY 2001), we expected a prevalence of 1,270-2,280. We have also used VA outpatient data to estimate a more specific prevalence of ALS among veterans. During FY 2001, there were 1,417 veterans with an ICD-9 code of 335.20 (ALS). There are known limitations to using this ICD-9 code to ascertain cases of ALS. Specifically, a false positive rate of 19% has been documented. During previous studies on Gulf War Veterans, approximately 40% of verified cases of ALS were identified via sources other than VA records (i.e., no ALS-related ICD-9 code was found in inpatient or outpatient databases). Using this information, we estimated 1,800 prevalent ALS cases at any time. This estimated prevalence falls approximately in the middle of the expected prevalence (1,270-2,280) in a population the size of all U.S. veterans.

Incidence. The expected incidence of ALS within the general population is 1-2 per 100,000 persons per year. Extrapolating to the population of U.S. veterans, we would expect the annual incidence of ALS to be approximately 450.

Expected Response Rates. Estimated response rates for years four through six are based on response rates from the first three years of the study. During the first three years, 3,311 veterans were screened over the telephone. Of these, 1,913 (58%) screened eligible and 1,759 (53% of total sample) agreed to participate. We anticipate response rates will be similar for succeeding years of the project.

2. Describe the procedures for the collection of information, including:

- **Statistical methodology for stratification and sample selection**
- **Estimation procedure**
- **Degree of accuracy needed**
- **Unusual problems requiring specialized sampling procedures**
- **Any use of less frequent than annual data collection to reduce burden**

All living veterans with ALS will be sought for participation. There are no sampling procedures or stratification. Patients are identified through a variety of commonly used methods in clinical research. The two primary means of identification of participants are: 1.) Use of VA medical databases to identify patients with ALS diagnoses and 2.)A nation-wide solicitation for veterans with ALS, publicized through various ALS and veterans organizations. Once individuals are identified, a thorough review of medical records is conducted to accurately determine whether an individual is eligible for the ALS registry. Baseline and biannual assessments are administered to all individuals who are eligible for the registry. Biannual follow-up was selected because of the rapidly progressive nature of ALS.

3. Describe methods to maximize response rate and to deal with issues of non-response. The accuracy and reliability of information collected must be shown to be adequate for intended uses. For collections based on sampling, a special justification must be provided for any collection that will not yield "reliable" data that can be generalized to the universe studied.

The baseline and biannual assessments are conducted by telephone and are brief. While it is important to periodically assess the health status of registry participants, interviews are purposely kept short to minimize respondent burden and maximize response rates. All interviews are approximately thirty minutes long and are scheduled at the participants' convenience. For follow-up interviews, as many attempts as necessary are made to contact the participant. During the screening questionnaire, contact information for another friend/family member who lives at another residence but who will always know how to reach the participant (i.e., in case of a move) is obtained. By collecting this information, the ability to maintain contact with participants is enhanced. To date, less than 1% of participants have been "lost-to follow-up" (i.e., could not be contacted) or withdrew.

4. Describe any tests of procedures or methods to be undertaken. Testing is encouraged as an effective means of refining collections to minimize burden and improve utility. Tests must be approved if they call for answers to identical questions of 10 or more individuals.

Main components of the telephone interviews are military history questions (established and required by the Department of Veterans Affairs Cooperative Studies Program) and the ALS Functional Rating Scale (ALSFRS). The ALSFRS is a validated scale and is the most frequently used functional rating instrument in studies of ALS patients. Studies have shown the ALSFRS correlates well with objective measures of strength and pulmonary function, has high internal consistency and test-retest reliability, and shows sensitivity to change in health status.

5. Provide the name and telephone number of individuals consulted on statistical aspects of the design and the name of the agency unit, contractor(s), grantee(s), or other person(s) who will actually collect and/or analyze the information for the agency.

Cynthia Coffman, PhD and Jennifer Hoff, MS were consulted on statistical aspects of the registry design. Dr. Coffman and Ms. Hoff are both statisticians with the Biostatistics Unit of the Institute for Clinical and Epidemiologic Research at the Durham VA Medical Center. Both of these individuals are permanent members of the Registry team and will be responsible for any statistical analyses conducted throughout this project. The primary data collection site will be the Durham VA Medical Center. Ms. Barbara Norman will be the primary person responsible for data collection, under the direction of Dr. Eugene Z. Oddone, the principal investigator. All of the above individuals can be reached at the following address:

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