Registration of Individuals with Amyotrophic Lateral Sclerosis (ALS) in the National ALS Registry

Part B

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Principle Investigator:
Oleg Muravov, MD, PhD
Agency for Toxic Substances and Disease Registry
4770 Buford Highway, MS F-57
Atlanta, GA 30341
Phone: 770-488-3817
Fax: 770-488-1537
Email: oim0@cdc.gov

Point of Contact:
Wendy E. Kaye, PhD
Agency for Toxic Substances and Disease Registry
Phone: 770-488-3696
Email: wek1@cdc.gov

B. COLLECTIONS OF INFORMATION EMPLOYING STATISTICAL METHODS

The National ALS Registry coordinator and statistician will conduct periodic statistical analyses on the data in the system. An annual registry report will be generated using SAS (SAS Institute, Cary, NC).The annual report will include information from both individuals who self-register and those from administrative data (Medicare, Medicaid, Veterans Health Administration, and Veterans Benefits Administration). Evaluation of the representativeness of those self-registering will be conducted (see description below). This information will be part of the annual report. It is anticipated that the annual report will include information on:

- Number of people identified with ALS
- Number of individuals who self-identified vs. those obtained from existing data
- Mean age of case
- Sex distribution of the cases
- Racial distribution of the cases
- Geographic distribution of the cases by region
- Distribution of other characteristics such as cigarette use, alcohol use, occupation, service in the military, physical activity, and family history.

The National ALS Registry coordinator may employ the following methodology:

- Data transformation
- Case classification
- Baseline estimation

Registry reports will include data both from those individuals identified using existing datasets and those who self-register. ATSDR evaluated the feasibility of using existing administrative data to identify cases of ALS in four geographically diverse pilot projects including tertiary care facilities for ALS, HMOs, and state based organizations. These four pilot projects matched data from Medicare, Medicaid, the Veterans Health Administration, and Veterans Benefits Administration to data available within the four pilot project sites administrative and clinical databases for a 5-year time period (January 1, 2001 – December 31, 2005). ATSDR provided the pilot projects with individual encounters with an ICD-9 code for any MND (335.2-335.29) for the specific project catchment area. Pilot projects completed a standardized spreadsheet for each individual found in any database indicating in which database(s) a record was located, ICD-9 code recorded for the encounter, as well as the years and types of providers seen. Medical records were abstracted and diagnoses verified. A deidentified dataset was sent to ATSDR for analysis. All individuals who were identified with a possible ALS diagnosis, as indicated by ICD-9 code for any MND, and had their medical record reviewed by a neurologist from the four pilot projects were combined. Approximately 4400 medical records were reviewed. It was possible to develop an algorithm using variables from the administrative data that identified true cases of ALS (verified by a neurologist). The best algorithm had sensitivity of 85% and specificity of 85%. Similar results were found in the individual pilot project analyses.

Basic demographic variables such as age, race, and sex will be available on all individuals regardless of how they were identified. Individuals identified from administrative data will not have all of the OMB approved categories; however the self-reported data will have all OMB categories.

Because we hypothesize that the registry is and will continue to pick up some individuals who are not being picked up in the administrative sources, we will eventually compare ALS cases identified from administrative sources with those ALS cases who self-register. This cannot be done yet because of the lag in data from Medicare and Medicaid. Medicare data for calendar year 2010 and Medicaid data for calendar year 2008 just recently became available and are not yet in-house. Once it is possible, we will try to identify the extent of the potential duplication. We will propose a method for adjusting estimates to account for potential duplication.

1. Respondent Universe and Sampling Methods

This activity is surveillance; respondents are not sampled. Furthermore, no sample selection is involved in this registry. The registry will pull in both individuals with ALS from existing administrative data and will allow cases to self-identify. The primary purpose of the registry is to improve estimates of likely prevalence of ALS and provide basic demographic information including, age, race, sex and geographic area. The tabulation of risk factor information required by Congress is for descriptive purposes only. As the registry matures and more individuals self-register, the information could be used for research (i.e., hypothesis generation). ATSDR allows approved researchers to provide registrants with information about ongoing studies for which they might be eligible. ATSDR plans to compare those individuals who self-register with those identified in the administrative data. ATSDR will then begin to analyze the data provided in the surveys.

ATSDR has used a multi-pronged approach for publicizing the existence of the registry. First, ATSDR promoted the information on their ALS website www.cdc.gov/als. Second, ATSDR worked with two advocacy groups, the ALS Association (ALSA) and the Muscular Dystrophy Association (MDA), ALS Division, to promote the registry with their constituents and on their respective websites http://www.alsa.org/research/ and http://mda.org/disease/amyotrophic-lateral-sclerosis. Third, ATSDR has worked with the NCEH-ATSDR Office of Communication to develop a media campaign which has been included in presentations at conferences, advertisements, and social media.

2. Procedures for the Collection of Information

ALS patients will be allowed to voluntarily register for the registry. Case status will be validated using six questions standardized by the Veterans Administration and shown to correctly identify cases 93% of the time (Attachment 4). Once an individual passes validation, he will be permitted to register (Attachment 5). To enable the collection of additional information from registrants who volunteer, a series of short survey modules will be available for completion via a secure web portal (Attachment 6a – previously approved and used surveys Attachment 6b- newly proposed surveys). The previously used surveys were from a survey validated by the ALS

Consortium of Epidemiologic Studies (ACES). The survey has been divided in to short modules because of the physical limitations of the study population. All surveys are designed to be answered only once except for the symptoms survey which can be answered every 6 months. It is anticipated that most participants would complete the symptom survey 3-4 times at most because the average life expectancy of an individual diagnosed with ALS is 2-3 years and the disease is quite debilitating. For the symptoms survey we will use the ALS Functional Rating Scale-Revised (ALSFRS-R), a standard set of questions used by physicians to measure function overtime. Researchers have developed and tested a self-administered version of the ALSFRS-R which showed excellent reliability to change over time. This test is scored in a standard fashion. (Attachment 10) The published version of the self-administered ALSFRS-R was slightly modified to make the question responses more user friendly. Changes to the questions were only grammatical and were reviewed by two ALS researchers to assess impact. It was decided that because the changes were only grammatical no additional cognitive or reliability testing was needed. Below are some examples of changes with the added words bolded.

Original	Change
Need to be fed	**I** need to be fed
Use PEG without assistance or difficulty	**I** use **a** PEG without assistance or difficulty
Not all words are legible	Not all **my** words are legible

The goal of web-based self-administered survey development is to address the most common exposures as specifically as one can with a brief series of questions. The derivation of each new survey module is summarized in Table 1. In keeping with the goal to use data from NHANES or BRFSS surveys as a comparison, ATSDR looked at these two surveys when developing questions for eight of the domains. In most instances neither NHANES nor BRFSS had appropriate questions that could be used except for hormonal and reproductive history (women subjects only). For the trauma history module, we used a survey developed by researchers at Ohio State University (Corrigan and Bogner, J Head Trauma Rehabil 2007;22:318-329) to obtain information on lifetime history of traumatic brain injury. For caffeine history, we adapted a survey from the Fred Hutchinson Cancer Research Center. The remaining modules were adapted from ACES.

We developed two open-ended questions to satisfy a number of requests from patients and patient service organizations (ALSA, MDA and others) to elicit the patient's ideas or thoughts on what may have contributed to the development of ALS. In addition, the ALS Research Group assisted with the development of a module to collect clinical data from participants.

Individuals will be consented prior to registering with the National ALS Registry and completing any survey modules. Participants will not be contacted to take surveys. For all surveys the individual will have to visit the website and log in to his/her personal account. Therefore, if a participant doesn't want to take part any longer, he/she just doesn't log in to the system.

3. Methods to Maximize Response Rates and Deal with Non-response

There is not a method to deal with non-response to joining the National ALS Registry because it

is unknown who has ALS. We will attempt to maximize the response rate by partnering with ALS advocacy groups and neurologists to publicize the registry.
As such, it is likely that not all persons with ALS will register; it will be difficult to determine the extent of nonresponse bias among those who would not be expected to show up in the administrative data sources. In addition, because we are currently seeing only a 50% response rate for the "risk factor surveys" among those who do register, it is likely that there will be significant nonresponse bias. ATSDR will inform users of this likelihood, and promote the dataset for hypothesis generation rather than hypothesis testing.

Individuals in the National ALS Registry are identified from National databases and self-registration. Those individuals who self-register are more likely to be younger (40-69 years of age) and male than those individuals identified in the National databases. This is likely a result of computer literacy and access. In addition to registering, registrants can provide additional information by taking short surveys. When comparing individuals who took at least one survey with individuals who took no surveys, there is no difference in age or sex between takers and non-takers.

	National Databases 2001-2009			Registration					
				Survey Takers		Survey Non- Takers		Total	
Age	#	%		#	%	#	%	#	%
Under 30	215	0.59		15	0.52	14	0.51	29	0.51
30-39	1126	3.07		82	2.83	71	2.57	153	2.70
40-49	3161	8.63		356	12.29	344	12.45	700	12.37
50-59	5609	15.32		772	26.65	749	27.11	1521	26.87
60-69	10384	28.36		964	33.28	904	32.72	1868	33.00
70-79	11490	31.38		569	19.64	537	19.44	1106	19.54
80 +	4624	12.63		138	4.76	142	5.14	280	4.95
Unknown	10	0.03		1	0.03	2	0.07	3	0.05
Total	36619			2897		2763		5660	
Sex									
Male	20731	56.61		1741	60.10	1679	60.77	3420	60.42
Female	15868	43.33		1156	39.90	1084	39.23	2240	39.58
Unknown	20	0.05							
Total	36619			2897		2763		5660	

Due to the various limitations discussed above, ATSDR will include the following caveat when presenting analytic results:

The data presented (here/today) are a valuable resource to better describe a geographically diverse population of ALS patients and generate hypotheses for future research, however the estimates of incidence and prevalence should not be viewed as complete and the risk factor data are not likely to be representative. Specifically, the rough estimates of incidence and prevalence from the National ALS Registry are based on a combination of administrative data and self-registration, both of which have significant limitations. Coverage uncertainties introduced by the administrative data include coding issues (ICD-9 and ICD-10), benefits eligibility issues (Medicare, Medicaid, Veterans Administration). With respect to the self-registration data, we have not been able to assess the overlap with the administrative data and acknowledge potentially significant response bias (for instance, individuals who self-register are more likely to be younger and more educated). There is not a good basis of comparison for these numbers, as estimates of incidence and prevalence that published in the peer reviewed scientific literature are mostly from, countries other than the United States, however estimates are fairly consistent between countries. We will continue to collect data from both administrative and self-registry sources, with the goal of improving both the completeness and representativeness of the data over time.

4. Tests of Procedures or Methods to be Undertaken

The web site has been tested and continues to be tested to assure its usability. No further procedures or methods are needed at this time.

5. Individuals Consulted on Statistical Aspects and Individuals Collecting and/or Analyzing Data

Individuals consulted on statistical aspects:

Randy Durbin, MSPH, DO
Senior Statistician
McKing Consulting Corporation
2900 Chamblee Tucker Road
Building 10
Atlanta, GA 30341
Phone: 770-220-0608
Email: randydurbin@gmail.com

G. David Willamson, PhD
Agency for Toxic Substances and Disease Registry
4770 Buford Highway, MS F-57
Atlanta, GA 30341
Phone: 770-488-3669
Email: dxw2@cdc.gov

Marchelle Sanchez, MS
Statistician
Agency for Toxic Substances and Disease Registry
4770 Buford Highway, MS F-57
Atlanta, GA 30341
Phone: 770-488-3389
Email: ffw2@cdc.gov

Lorene Nelson, PhD
Associate Profession
Division of Epidemiology
Department of Health Research & Policy
Standford University School of Medicine
Pasteur Drive, Room T233

Stanford, CA 94305-5405 Email: lnelson@stanford.edu
Phone: 650-723-6854

Person responsible for oversight, data collection, and analysis:

Oleg Muravov, MD, PhD
Principal Investigator
Agency for Toxic Substances and Disease Registry
4770 Buford Highway, MS F-57
Atlanta, GA 30341
Phone: 770-488-3817
Email: oim0@cdc.gov

Wendy E. Kaye, PhD
Point of Contact
Agency for Toxic Substances and Disease Registry
Phone: 770-488-3696
Email: wek1@cdc.gov

Table 1
ALS Registry Module Selection Rationale

Module	Rationale	Source	Time Period	Derived Variables	References
Residence History	include all residences of 6 months or longer (including moves within the same city)	ACES (adapted)*	Lifetime	age of move	1) http://aces.stanford.edu
Lifetime Occupational Exposure	collect broad assessment of pesticides, metals and solvents (required 100 or more days of exposure)	ACES (adapted)*	Lifetime	age first handled age last handled total years handled	1) http://aces.stanford.edu
Home Pesticide Use	include broad classes of pesticides applied in the home and garden and to pets	ACES (adapted)*	Age 10+ years	age first handled age last handled total years handled times/year of use	1) http://aces.stanford.edu

* Note: many questions were adapted to fit a “table format” for data collection, including age first exposed, age last exposed, total duration of exposure, frequency/quantity of exposure

Module	Rationale	Source	Time Period	Derived Variables	References
Hobbies	include common home activities and hobbies with minimum frequency (at least 1 hr/month for one year or more)	ACES (adapted)*	Age 10+ years	age first done age last done total years done hours per month *or* hours/year	1) http://aces.stanford.edu/
Hormonal and Reproductive History (Women only)	collect basic reproductive history	NHANES (unadapted)	Lifetime	age at first menses age at first live birth age at last live birth age at last menses	http://www.cdc.gov/nchs/data/nhanes/ nhanes_09_10/mi_rhq_f.pdf
Caffeine	investigate possible inverse association of caffeine and ALS	Fred Hutchinson Cancer Research Center (adapted)*	Lifetime	age first consumed age last consumed totals years consumed total number drinks	https://www.phenxtoolkit.org/

* Note: many questions were adapted to fit a “table format” for data collection, including age first exposed, age last exposed, total duration of exposure, frequency/quantity of exposure

Module	Rationale	Source	Time Period	Derived Variables	References
Trauma	collect information related to head and neck injuries as a risk factor; some studies suggest electric shock as a risk factor	Ohio State University (unadapted) ACES (adapted)*	Lifetime	age at first injury number of injuries age at first shock number of shocks	1) Corrigan, J.D., Bogner, J.A. J Head Trauma Rehabil, 2007; 22:318-329 2) https://www.phenxtoolkit.org 3) http://aces.stanford.edu
Medical Insurance	collect information on current medical insurance	NHANES (adapted)*	Current		http://www.cdc.gov/nchs/data/nhanes/nhanes_09_10/hiq_f.pdf
Clinical	collect information on signs and symptoms of ALS	ALSRG	Lifetime		

* Note: many questions were adapted to fit a “table format” for data collection, including age first exposed, age last exposed, total duration of exposure, frequency/quantity of exposure

List of Attachments

Attachment 1 Authorizing Legislation: Public Law No: 110-373, amendment to the Public Health Service Act to provide for the establishment of an Amyotrophic Lateral Sclerosis Registry

Attachment 2 60-Day Published Federal Register Notice

Attachment 3 Comments and Response to 60-Day FRN

Attachment 4 Validation Questions

Attachment 5 Screen Shot of the Registration Page

Attachment 6 Text of Voluntary Survey Modules:
6a: Previously approved modules
6b: Proposed modules

Attachment 7 Privacy Statement

Attachment 8 Consent Form

Attachment 9 CDC IRB Approval Letter

Attachment 10 ALS Functional Rating Scale-Revised: ALSFRS: Scoring Sheet

Attachment 11 Privacy Impact Assessment