National Amyotrophic Lateral Sclerosis (ALS) Registry

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Revision

Supporting Statement Part B –

Collections of Information Employing Statistical Methods

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Table of Contents

Part B. Collections of Information Employing Statistical Methods

This data collection does not involve statistical methods; however we have described the respondents. There are no proposed changes to recruitment methods.

B.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. However, there will be some selection for the biorepository component of the Registry due to budget constraints. Individuals asked to participate in the biorepository will be selected from PALS who enroll in the Registry and express and interest in learning more about the biorepository. To better address the congressional mandate to examine genetic and environmental risk factors that may cluster by geographic area, we will select a convenience sample from those who are interested in the biorepository proportional to state population and with at least one person from each state. We will recruit from the harder to fill states, e.g., Wyoming, Rhode Island, first and then distribute the cases throughout the other states. Because recruitment tends to get individuals from the same town to enroll during the same time period, selection in states where we are recruiting multiple participants will be distributed across the states in any given month by stratifying those interested in participating in each state by city and taking a systematic sample from the different geographic areas. Based on our experience with the pilot study, this will give a good distribution of those living in urban and rural areas in addition to good state representation.

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. The following table includes the distribution of selected risk factor data.

Tabulation of Selected Risk Factor Data, October 18, 2010 – December 31, 2013

	No.	%
Smoking Status*		
Current Smoker	305	8.9
Former Smoker	1380	40.4

Nonsmoker	1720	50.4
Ever Smoker	1685	49.4
Smoking Duration		
< 10 years	354	21
10- <25 years	651	38.6
25- <40 years	445	26.4
40+ years	223	13.2
Smoking Intensity		
< 5 pack-years	381	22.6
5 to <15 pack-years	395	23.4
15+ pack-years	895	53.1
Alcohol Consumption Status		
Current Drinker	1443	42.3
Former Drinker	1244	36.4
Nondrinker	703	20.6
Ever Drinker	2687	78.7
Drinking Duration		
< 10 years	361	13.4
10- <25 years	593	22.1
25- <40 years	1084	40.3
40+ years	631	23.5
Drinking Intensity		
Light Drinker	1846	68.7
Moderate Drinker	415	15.4
Heavy Drinker	337	12.5
Military Service History		
Veterans	813	23.5
Nonveterans	2637	76.2
Branch of Military Service		
Army	280	34.6
Navy	181	22.4
Marines	56	6.9
Air Force	155	19.2
Reserves	72	8.9
Coast Guard	17	2.1
More than one branch of military service	48	5.9
Deployment to a War Arena		
Yes	270	33.2

No	542	66.7
Employment Status		
Full-time employed	610	17.4
Part-time employed	168	4.8
Retired	1163	33.1
Disabled	1351	38.5
Full-time student	5	0.1
Homemaker	64	1.8
Unemployed	87	2.5
Other	61	1.7
Job Title Held for the Longest Time (Top 10)		
Teacher, professor or educator	309	8.8
Physician, nurse, dental or health care worker	252	7.2
Secretary, administrative assistant or receptionist	171	4.9
Engineer, architect or draftsperson	158	4.5
Retail salesperson, sales clerk, or sales representative	150	4.3
Manufacturing laborer, production worker, or assembler/fabricator	120	3.4
Accountant, auditor, or bookkeeper	111	3.2
Supervisor or manager of financial or marketing workers	108	3.1
Chief executive or owner	94	2.7
Supervisor or manager of manufacturing or production workers	89	2.5
Industry Worked in for the Longest Time (Top 10)		
Professional, Scientific, and Technical Services	392	11.2
Educational Services	372	10.6
Health Care and Social Assistance	367	10.4
Manufacturing (Metal, Electrical, Transport, Professional)	271	7.7
Other Services (except Public Administration)	222	6.3
Construction	216	6.1
Retail Trade I (Cars, Gas, Furniture, Electronics, Food-Beverage, Clothing)	214	6.1
Finance and Insurance	185	5.3
Manufacturing - (Paper, Printing, Chemicals, Petroleum, Leather, Lumber, Stone)	145	4.1

Transportation and Warehousing I (Air, Rail, Water, Ground, Pipeline)	121	3.4
Years of Employment at Longest Held Occupation		
<= 10 years	514	14.6
10 < time <= 20 years	994	28.3
20 < time <=30 years	1033	29.4
> 30 years	896	25.5

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. The National ALS Registry uses a two-pronged approach to identify prevalent cases of ALS in the United States. The first approach used to identify prevalent cases relies on existing administrative data (from the Centers for Medicare and Medicaid Services, the Veterans Health Administration [VHA], and the Veterans Benefits Administration [VBA]). A pilot tested algorithm is applied to the administrative data that identifies persons with ALS on the basis of encounter codes such as having ALS listed as a code in the visit record or having such a code and having seen a neurologist, a death certificate listing ALS as a cause or contributing cause of death, and prescription for Riluzole.[1] The second approach, which was launched to the public on October 19, 2010, uses a secure web portal (https://www.cdc. gov/als) to identify cases that are not included in the national administrative databases. This approach allows patients to self-identify and enroll in the National ALS Registry if screening criteria are met. An additional advantage of this approach is those who self-enroll in the Registry can take brief surveys that are used to evaluate possible risk factors for ALS.[2] Information is merged into a single record for each person. Merging records for persons identified as having ALS from the administrative databases with those persons who enrolled in the National ALS Registry web portal creates a unique record after data are de-duplicated by using a combination of the last five digits of the person's Social Security number, sex, month and year of birth, and first and last name. This process ensures that persons who are identified in both the administrative databases and the web portal, and those who have records in multiple years, are not counted twice.

In the second report published in the MMWR, August 2016, we report that during 2012 and 2013, the Registry identified 14,713 and 15,908 persons, respectively, who met the surveillance

case definition of ALS. The estimated ALS prevalence rate was 4.7 cases per 100,000 U.S. population for 2012 and 5.0 per 100,000 for 2013. Due to revisions to the algorithm and use of death data from the National Death Index, an updated prevalence estimate has been calculated retrospectively for October 19, 2010–December 31, 2011. This updated estimate showed a prevalence rate of 4.3 per 100,000 population and a total of 13,282 cases. Since the inception of the Registry, the pattern of characteristics (e.g., age, sex, and race/ethnicity) among persons with ALS have remained unchanged. Overall, ALS was more common among whites, males, and persons aged 60–69 years. The age groups with the lowest number of ALS cases were persons aged 18–39 years and those aged ≥80 years. Males had a higher prevalence rate of ALS than females overall and across all data sources. These findings remained consistent during October 2010–December 2013.[3]

Per the terms of clearance, the following limitations were included in the MMWR:

> ‘”The findings in this report are subject to at least four limitations. First, because ALS is not a notifiable disease, ensuring that all newly diagnosed and prevalent ALS cases in the United States are captured in the Registry is challenging and therefore the possibility of under-ascertainment exists. However, the large administrative database methodology that ATSDR is using was vetted through a pilot effort and is expected to identify most of the ALS cases in the United States, given its high sensitivity and specificity.[2] In addition, ATSDR is partnering with national stakeholders to promote the Registry to persons with the disease so they can self-enroll through the Registry’s web portal. Second, although every attempt was made to de-duplicate the files, differences in fields collected by the different sources, misspellings of names, and data entry errors could have prevented records from merging correctly. However, it is unlikely that this occurred in numbers sufficient to affect the overall conclusions. Third, the calculation of ALS incidence with Registry data is not possible at this time because the date of diagnosis is not captured through the large administrative database approach, and cases without a date of diagnosis comprise 68% of cases in the Registry. However, through a separate Registry project, incidence has been calculated and the findings published for ALS incidence in smaller defined geographic areas of the United States.[4-9] Finally, the Registry has been officially active since October 2009 and is still being enhanced. As more persons with ALS enroll and complete surveys, a better understanding of possible risk factors might emerge.”

B.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 voluntary survey modules will be available for completion via a secure web portal (**Attachment 6**). All surveys are designed to be answered only once except for the disease progression survey (**Attachment** 6 – ALSFRS module only) which can be answered three times the first year and twice a year thereafter (rounded up to 3 times per year for burden estimation). It is anticipated that most participants would complete the disease progression 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 disease progression survey we will use the ALS Functional Rating Scale-Revised (ALSFRS-R) (**Attachment 6** – ALSFRS module only), 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 6A**).

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.

In addition to fulfilling the two-part Congressional mandate, the Registry is designed to be a tool for ALS researchers. Now that the Registry has matured, ATSDR will make data and specimens available to approved researchers. A respondent type was added to allow researchers to access data and specimens collected by the Registry (**Attachment 11A and 11B**). For those who agree to participate in the in-home portion of the biorepository, we will schedule an appointment for a trained phlebotomist to come to their homes at a convenient time to collect the specimens (**Attachment 12A**). Because we have to get specimens to the lab the next day, appointments are only scheduled Monday through Thursday at a time that would allow the phlebotomist to deliver the specimens to a FedEx facility for next day shipping. For those who agree to provide a saliva specimen, we will mail them a self-collection kit with instructions for the collection and pre-paid postage to return the kit to the laboratory (**Attachment 12B**). In

addition, ATSDR is also collaborating with ALS service organizations to conduct outreach activities through their local chapters and districts as well as on a national level. ATSDR will collect summary information on their outreach efforts in support of the Registry (**Attachment 13A and 13B**).

B.3. Methods to Maximize Response Rates and Deal with No Response

There is not a method to deal with non-response to joining the National ALS Registry because it is unknown who has ALS. 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. A monthly summary of outreach activities will be provided by the chapter or districts to the national organizations (**Attachment 13A**) who will report to ATSDR on a monthly basis (**Attachment 13B**). 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.

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 58% response rate for the "risk factor surveys" among those who do register, it is likely that there will be nonresponse bias. ATSDR will inform users of this likelihood, and promote the dataset for hypothesis generation rather than hypothesis testing.

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 self-registration portion of the Registry is, and will continue to identify some individuals who are not identified in the administrative sources, we will compare ALS cases identified from administrative sources with those ALS cases who self-register. All Medicare, VHA, and VBA data are only available through CY2013. Registries need time to mature, therefore we have chosen to present this comparison for CY2013. In addition, CY2013

is the most recent year that includes all data sources because of the lag in availability of data from CMS.

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 female 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 little difference in age and no difference in sex between takers and non-takers.

Comparison of Registry Data by Source and Survey Status for CY2013

	Registry							Portal*			
	Total		Database Only		Portal			Survey Takers		Survey Non-Takers	
Age	#	%	#	%	#	%		#	%	#	%
18-39	567	3.6	234	2.3	333	5.7		178	5.7	155	5.7
40-49	1667	10.5	771	7.7	896	15.3		473	15.1	422	15.5
50-59	3502	22.0	1806	18.0	1696	28.9		963	30.7	732	26.9
60-69	4908	30.9	3090	30.8	1818	31.0		971	31.0	846	31.1
70-79	3695	23.2	2832	28.2	863	14.7		448	14.3	413	15.2
80 +	1513	9.5	1315	13.1	198	3.4		82	2.6	116	4.3
Unknown	56	0.4			56	1.0		18	0.6	38	1.4
Total	15908		10048		5860			3133		2722	
Sex											
Male	9941	62.5	6417	63.9	3524	60.1		1882	60.1	1639	60.2
Female	5947	37.4	3611	35.9	2336	39.9		1251	39.9	1083	39.8
Unknown	20	0.1	20	0.2							
Total	15908		10048		5860			3133		2722	

*Unknown survey status for 5 participants because of missing or invalid SSN.

The demographics of those in the biorepository pilot project were similar to those who were in the self-registration component of the Registry. Because the Biorepository participants are only taken from the self-registration component of the Registry, the differences in the demographics

between those who self-registered and those identified from the Registry (administrative data plus self-registration data) also apply to those in the Biorepository. We will make sure to provide this information to researchers who request samples and will include this as a limitation in any publication initiated by ATSDR. In addition, ATSDR is working to increase minority participation in the self-registration portion of the Registry and the Biorepository.

B.4. Test 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 for the Registry. The procedures and methods were tested as part of the pilot study. Details about the pilot study can be found in **Attachment 14**.

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

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List of Attachments