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.

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, 2017

	No.	%
Smoking Status*		
Current Smoker	685	16.2
Former Smoker	3539	31.2
Nonsmoker	4703	52.6
Ever Smoker	4224	47.4
Smoking Duration		
< 10 years	928	22.2
10- <25 years	1552	37.1
25- <40 years	1098	26.3
40+ years	604	14.4
Smoking Intensity		
< 5 pack-years	921	22.1
5 to <15 pack-years	1061	25.4
15+ pack-years	2195	52.5
Alcohol Consumption Status		
Current Drinker	4105	46.1
Former Drinker	3086	34.7
Nondrinker	1710	19.2
Ever Drinker	7191	80.5
Drinking Duration		
< 10 years	2426	35.3
10- <25 years	1624	23.3
25- <40 years	844	12.3
40+ years	2012	29.1
Drinking Intensity		
Light Drinker	5711	82.4
Moderate Drinker	980	14.1
Heavy Drinker	240	3.5
Military Service History		
Veterans	1867	20.6
Nonveterans	7201	79.4
Branch of Military Service		
Army	760	36.9
Navy	451	21.9
Marines	149	7.2

Air Force	410	19.9
Reserves	251	12.2
Coast Guard	39	1.9
More than one branch of military service	-	-
Deployment to a War Arena		
Yes	608	32.7
No	1253	67.3
Employment Status		
Full-time employed	1832	19.7
Part-time employed	450	4.8
Retired	3637	39.1
Disabled	2793	30
Full-time student	7	0.1
Homemaker	586	6.3
Unemployed	1832	19.7
Other	450	4.8
Job Title Held for the Longest Time (Top 10)		
Teacher, professor or educator	755	8.2
Physician, nurse, dental or health care worker	723	7.9
Secretary, administrative assistant or receptionist	467	5.1
Engineer, architect or draftsperson	450	4.9
Retail salesperson, sales clerk, or sales representative	353	3.9
Manufacturing laborer, production worker, or assembler/fabricator	328	3.6
Accountant, auditor, or bookkeeper	305	3.3
Supervisor or manager of financial or marketing workers	253	2.9
Chief executive or owner	252	2.9
Supervisor or manager of manufacturing or production workers	215	2.4
Industry Worked in for the Longest Time (Top 10)		
Professional, Scientific, and Technical Services	1104	12.2
Health Care and Social Assistance	1026	11.7
Educational Services	922	10.5
Manufacturing (Metal, Electrical, Transport, Professional)	677	7.7

Other Services (except Public Administration)	593	6.7
Construction	570	6.5
Retail Trade I (Cars, Gas, Furniture, Electronics, Food-Beverage, Clothing)	512	5.8
Finance and Insurance	482	5.5
Manufacturing - (Paper, Printing, Chemicals, Petroleum, Leather, Lumber, Stone)	378	4.3
Transportation and Warehousing I (Air, Rail, Water, Ground, Pipeline)	303	3.5
Years of Employment at Longest Held Occupation		
<= 10 years	610	26.8
10 < time <= 20 years	522	22.9
20 < time <=30 years	584	25.6
> 30 years	562	24.7

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 April 2022, the sixth annual estimate of ALS prevalence for the entire United States was published in the Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration journal (ALS FTD). The analysis shows that during January 1-December 31, 2017, a total of 17,800 persons meeting the surveillance case definition of definite ALS were identified by the Registry, for a prevalence of 5.5 cases of ALS per 100,000 persons in the U.S. general population. In addition to the Registry's current data sources, the capture-recapture methodology was applied to this report. Capture-recapture is a well-established statistical methodology used to estimate the percentage of missing cases. Using this methodology, 24,821 additional ALS cases (prevalence of 7.7 per 100,000) were identified, leading to a total of 31,843 cases of ALS (prevalence of 9.9 per 100,000) in the United States in 2017. 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 2017.

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

> "The findings in this report are subject to at least three limitations. First, because ALS continues to be a non-notifiable disease, it is challenging to ensure that all newly diagnosed and prevalent ALS cases in the United States are captured in the Registry and, therefore, the possibility of under-ascertainment exists. Even with notifiable conditions such as communicable infections, under-ascertainment exists and, in general, even the best surveillance system will not be able to identify all cases. Second, although every attempt was made to de-duplicate the files using the established algorithm, 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 or in a differential

manner that affected conclusions. Finally, without personally identifiable information including name, date of birth, age, or sex, the Registry is currently unable to match cases from private insurance with national administrative datasets."

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 (Appendix B). Once an individual passes validation, he will be permitted to register (Appendix C). 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 (Appendix E). All surveys are designed to be answered only once except for the disease progression survey (Appendix E2 – 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) (Appendix E2 – 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 (Appendix E2).

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 does not 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 (Appendix M1 and M2). 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 (Appendix S.A-1). 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 (Appendix S.A-2). 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 6A and 6B).

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 three advocacy groups, the ALS Association (ALSA), the Muscular Dystrophy Association (MDA), ALS Division, and the Les Turner ALS Foundation 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 and https://lesturnerals.org/. A monthly summary of outreach activities will be provided by the chapter or districts to the national organizations (Attachment 6A) who will report to ATSDR on a monthly basis (Attachment 6B). 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 CY2017. In addition, CY2017 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 CY2017

	Registry							Portal*			
	Total		Database Only		Portal			Survey Takers		Survey Non-Takers	
Age	#	%	#	%	#	%		#	%	#	%
18-39	517	2.9	254	2.4	14	0.2		262	3.7	385	6.2
40-49	1462	8.2	723	6.7	60	0.8		856	12.1	817	13.1
50-59	3327	18.7	1887	17.6	113	1.6		2029	28.8	1318	21.1
60-69	4792	26.9	3285	30.6	251	3.6		2452	34.7	1498	24
70-79	4168	23.4	3295	30.7	210	3.0		1247	17.7	612	9.8
80 +	1418	8.0	1169	10.9	36	0.5		209	3	137	2.2
Unknown	2116	11.9	122	1.1	6381	90.3		10	-	1473	23.6
Total	17800		10735		7065			7065		6240	
Sex											

Male	11034	62.0	6834	63.7	742	10.5		4191	59.3	3770	60.4
Female	6750	37.9	3901	36.3	486	6.9		2866	40.7	2470	39.6
Unknown	16	0.1			5837	82.6		8	-	0	-
Total	17800		10735		7065			7065		6240	
*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 7.

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

Individuals consulted on statistical aspects:

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