National ALS Registry
Proposal to Release State Level Data, Addition of New Data Sources and Request to Modify Self-Administered Survey

Background

Amyotrophic lateral sclerosis (ALS), commonly known as Lou Gehrig's disease, is a progressive and fatal neuromuscular disease. Most persons die within 2–5 years of receiving a diagnosis of ALS [1]. No cure for ALS has been identified, and the lack of proven and effective therapeutic interventions is an ongoing challenge. Treatments currently available, Edaravone and Riluzole, do not cure ALS, but slow disease progression in certain patients [2, 3]. Because ALS, like most noncommunicable diseases, is not a nationally notifiable condition, cases in the United States are identified using a novel, two-pronged approach. The first approach identifies cases from three large national administrative databases (Medicare, Veterans Health Administration, and Veterans Benefits Administration) by using an algorithm with elements such as the ICD code for ALS, frequency of visits to a neurologist, and prescription drug use. The second approach, which was launched to the public on October 19, 2010, uses a secure web portal (www.cdc.gov/als) to identify cases that are not included in the national administrative databases.[4] This approach allows patients to self- identify and enroll in the National ALS Registry if screening criteria are met.

In 2008, the U.S. Congress passed the ALS Registry Act[5]. ATSDR was designated to create and maintain the National ALS Registry (Registry). The main goals of the Registry, as defined by the 2008 ALS Registry Act, are to describe the incidence and prevalence of ALS better, examine risk factors such as environmental and occupational factors, and characterize the demographics of persons living with ALS [5]. The Registry contributes to critical data for further analysis of incidence, prevalence, and causal risk factors.

Since 2010, the Registry has published four national prevalence estimates in CDC's journal of *Morbidity and Mortality Weekly Report* (*MMWR*) [4, 6-8]. The most recent findings from 2015 continue to show ALS has remained more prevalent in whites, males, and persons aged ≥60 years. National mortality surveys of US ALS patients have also found a preponderance of older, white and male cases [9]. ALS disproportionately affects Caucasians more so than any other group. These findings reflect past epidemiological trends for cases identified from 2010 to 2014 and have also been supported by other domestic and international publications.

Currently, the Registry has 18 self-administered patient surveys. These surveys are available for patients to take upon registration and allow researchers to learn more about the risk factors and possible causes of ALS. The surveys are currently taken individually. Preliminary findings from Surveys 1-6 have been published[10].

In 2021-2022, the Registry will publish two prevalence estimates for 2016 and 2017 using the established and validated algorithm as well as an adjusted estimate utilizing capture-recapture.

Capture-recapture will allow an estimate of the number of missing cases of ALS in the U.S. Early *unpublished* findings show the Registry is missing cases predominantly from those who seek care outside of CMS and VA health systems, specifically from private insurance. It is estimated the Registry is missing approximately 44% of cases. ALS, like many other noncommunicable diseases, remains a non-reportable disease at the state level (exception is Massachusetts) and non-notifiable to CDC. The Registry continues to remain the largest source of epidemiological ALS data in the United States.

Justification/Brief Explanation for the Change Request

This is a nonmaterial/non-substantive change request for the National ALS Registry (OMB Control No. 0923-0041 (expiration date: January 31, 2023).

Modification of Self-Administered Survey

Based on feedback from patients, caregivers, researchers as well as the National Center for Health Statistics, Collaborating Center for Questionnaire Design and Evaluation Research (see attachment *NCHS Survey feedback*), we are requesting to modify the surveys to make them more user-friendly and easier to navigate for patients. We feel the enhancements will increase completion rates for all surveys. The evaluation from NCHS is attached and is the basis for these changes.

Therefore, we are requesting to change the current layout of ALS Survey by establishing an Essential Questionnaire and Follow-up Questions in which the questions are categorized into one of the following fields: 1)Registration, 2) Demography, 3) Lifestyle and Factors, 4) Environmental Factors, and 5) ALS-associated and Clinical Factors.

Currently, persons with ALS who register with National ALS Registry are encouraged to take self-directed surveys using an online portal. At the time of survey launch in 2010, the Registry had 7 modules that has since grown to 18 to this date. Table 1 shows the number of completed surveys and the date of survey release from 2010 (Survey 18 was added late 2020). As shown, different modules are designed to capture different attributes of registrants.

Table 1. National ALS Registry: Survey release date and number of completed surveys since 2010

Survey (n=17)	Release Date	No. Completed
Demographics	October, 2010	9910
Occupational history	October, 2010	8994
Military history	October, 2010	8798
Smoking and alcohol history	October, 2010	8639
Physical activity	October, 2010	8288
Family history of neuro. diseases	October, 2010	8067
Disease progression (ALSFRS)	October, 2010	8092
Clinical data (e.g., devices used, body onset)	November, 2013	3533
Open-ended etiological questions	November, 2013	3204

Lifetime residential history	May, 2014	3913
Lifetime occupational history	May, 2014	3891
Residential pesticide use	May, 2014	3641
Hobbies with toxicant exposures	August, 2014	3362
Caffeine consumption	August, 2014	3150
Reproductive history (women)	August, 2014	1702
Health insurance status	December, 2014	2843
Head and neck injuries	December, 2014	2804
Total (as of 7/9/2020)	---	**92,831**

While the Registry strives to obtain responses to all questions, there has been a trend of low participation in the completion of certain survey modules (Table 2).

Table 2. Number of completed surveys since 2015 where all modules are actively operational

	Survey completion year[a]								
Module[c]	2015	2016	2017	2018	2019	2020	Row Total	Col %[b]	Row %
Survey 1	1,050	981	698	754	780	599	4,862	-	11.1%
Survey 2	932	871	644	679	686	510	4,322	88.9%	9.9%
Survey 3	914	840	617	662	661	487	4,181	86.0%	9.6%
Survey 4	902	826	603	651	647	470	4,099	84.3%	9.4%
Survey 5	858	783	581	615	607	449	3,893	80.1%	8.9%
Survey 6	824	755	566	597	590	428	3,760	77.3%	8.6%
Survey 9	660	600	454	474	469	328	2,985	61.4%	6.8%
Survey 10	612	576	422	433	446	319	2,808	57.8%	6.4%
Survey 11	606	556	407	427	429	308	2,733	56.2%	6.3%
Survey 13	563	523	394	398	392	291	2,561	52.7%	5.9%
Survey 14	582	510	390	393	384	279	2,538	52.2%	5.8%
Survey 15	590	523	393	401	388	282	2,577	53.0%	5.9%
Survey 17	493	474	356	363	366	349	2,401	49.4%	5.5%
Total	9,586	8,818	6,525	6,847	6,845	5,099	43,720		100.0%
[a]Years when all of survey modules 1-17 are fully available									
[b]Column percentage based on survey 1									
[c]Survey modules 7, 8, 16, and 18 are not shown									

We have a greatest number of completions for Survey 1 which covers the demographic information. Compared to Survey 1, the next module Survey 2 retains about 89% of the respondents' participation. However, this rate of survey completion drops significantly in subsequent modules to 50%, which reduces the number of registrants needed for a more accurate estimation of ALS registrant characteristics. This decrease in participation rate

highlights the need to reexamine the survey organization. Thus, the Registry is proposing to change the existing survey framework by modifying the processes in which the questions are presented to the registrants and assigning the questions to one of the categories mentioned above.

Proposed modifications are summarized as the following:

1. Main modification is the rearrangement of survey questions to yield Essential Questionnaire and Follow-up Questions, for the purpose of grouping existing questions into different survey categories: Registration, Demography, Lifestyle Factors, Environmental Factors, and ALS-associated and Clinical Factors. This modification does not require creating new questions.
    a. The purpose of Essential Questionnaire is to capture broad attributes of ALS registry registrants using a short format of mainly "Yes/No/Don't know" and "Check all that apply" questions that cover all aspect of categories mentioned above in #1.
    b. The purpose of Follow-up Questions is to gain detailed insight based on the initial responses provided in the Essential Questionnaire.
2. Online portal on which the survey is administered will include the survey type header/indicator mentioned above in #1 to provide awareness of different survey categories to the person taking the survey.

The potential benefit to the amendment of survey protocol is threefold. First, the arrangement of questions from 18 modules to the broader categories of Registration, Demography, Lifestyle Factors, Environmental Factors, and ALS-associated and Clinical Factors allows for questions to be siloed based on the characteristic relevance. This change yields better structural organization of existing questions and for the future questions to follow. Second, creating the Essential Questionnaire enables the ascertainment of critical responses during the early stages of registration, rather than relying on the completion of last surveys to capture the critical information (i.e. Survey 17, ALS-associated symptoms first noticed). Third, the modification proposes the Follow-up Questions to accompany the Essential Questionnaire post submission. Follow-up questions will be based on the type of responses given in the Essential Questionnaire, and therefore, questions pertaining only to the individual will appear.

Release of State Level Data and Addition of New Data Sources

Public Seeks more ALS Data

The Registry works closely with patient focused organizations such as the ALS Association, Muscular Dystrophy Association, and the Les Turner ALS Foundation. These groups provide patient services for thousands of ALS patients across the United States. In addition, the Registry

collaborates with neurologists and ALS researchers on joint projects and publications. Every year the Registry's convenes a meeting with these stakeholders to provide updates on its activities.

Since 2010, considerable interest and questions have been directed to the Registry regarding ALS cases in the United States, specifically at the state level. Previously, the Registry launched the State-Metro ALS Surveillance project, which included three states and eight metropolitan areas, to evaluate the completeness of the Registry and better describe demographic characteristics of persons with ALS[11]. The Registry continues to adhere to OMB's terms of clearance language and does not release state level data. Public interest at state level data continues to increase from patients, researchers, clinicians, and partner organizations.

Limitations of Data

Since ALS is a non-notifiable disease to CDC/ATSDR, the Registry will inherently miss cases. The Registry is acutely aware of the limitations of capturing all ALS cases in the U.S, specifically those who seek care from private insurance and minorities. In order to improve the representativeness of the Registry, especially for the self-registered online portal, the Registry has undertaken a targeted approach to recruit more minority patients. These efforts include:

- Working with partner organizations such as the ALS Association, Muscular Dystrophy Association, and the Les Turner ALS Foundation to inform and educate patients and caregivers about the Registry. This will include targeting states with higher minority populations such as California, Texas, New York, and Florida.
- Utilizing digital platforms such as Facebook, Twitter, and Google Ads as well as a patient-oriented newsletter (released quarterly) to communicate Registry's activities and events.
- Presenting at regional and national patient symposiums where Registry staff give platform talks and answer questions from patients and caregivers.

Note, COVID-19 has impacted these activities in 2020, but the Registry continues to implement strategies to improve minority representation.

Proposed State Level Data Release

The National ALS Registry proposes the following release of state level data for OMB's review and consideration:

- Registry will publish these data (incidence, prevalence, and mortality) in a peer-reviewed journal prior to making data available to the public. Data, specifically to ALS cases, will be listed in either a tabular format (e.g., table) and/or a gradient map of the United States. The gradient map will show the number of cases via a population legend. Attached is a table showing the number of state prevalent cases from 2012-2016, please note data from 2016 are unpublished.
- Cases counts will only be released for states with more than 16 ALS cases and is consistent with practices by the United States Cancer Statistics[12]. This is based on where cases or deaths are small and tend to have poor reliability[13]. In addition, the Registry will

add the following limitation/disclaimer: The National ALS Registry identifies the majority of ALS cases; however, patients who seek care outside Medicare and/or the Veterans Administration are known to be underrepresented. Data from this state are not available.

- Rates per each state will not be calculated and only national prevalence rates will be shown.
- State data will be released for each calendar year beginning with 2017. The state will be represented in a table format alphabetically.
- Case counts will be reported only at the state level and not at the county or city level.
- Develop an online public platform where de-identified ALS cases (incidence, prevalence, and mortality) can be viewed by individual states and regions adhering to all the limitations and disclaimers.
- The Registry is also analyzing national incidence data. Once completed, these findings will be published in a peer-reviewed journal. The Registry requests the same proposed release of data for incidence as prevalence.

In order to be transparent about missing data, the Registry will state clearly on all publications and any online public platform the following:

- The Registry does not represent all ALS cases in the United States. The cases from those who seek care outside the administrative systems (e.g., CMS, VA) as well as minority patients are missing.

Inclusion of ALS Cases from New Data Sources

Since inception, the Registry's main sources of data have been CMS, VA, and the online self-registration portal. These three sources have been critical to estimate the national epidemiological trends. However, as evident from yet to be published capture-recapture findings, the Registry is estimated to be missing 44% of cases. In order to improve case-ascertainment and completeness, the Registry seeks approval to add cases from other sources listed below. These sources will include personal identifiable information (PII) such as full name, date of birth, social security number (when available), state of residence, and gender. This information will be needed in order properly match existing cases in the Registry and add new ones that are not present to the numerator. The Registry will adhere to all strict requirements for data privacy and security. The inclusion of new cases will only be added prospectively, that is, for years 2017 and beyond and prior estimates will not be changed. By seeking and adding cases from new data sources, this will also address criticism from the public that the National ALS Registry data are incomplete.

Sources of ALS cases:
- State ALS registries such as the Massachusetts ALS Registry
- Non-profit ALS organizations such as ALS Association, Muscular Dystrophy Association, Les Turner ALS Foundation, Answer ALS
- National ALS multidisciplinary clinics affiliated with academic research institutions and/or hospital systems

- Health insurance companies and neurologists

Conclusions

The establishment of the National ALS Registry fills an important scientific gap by providing estimates of epidemiological trends of this disease and facilitates further study of risk factors and etiology. Furthermore, the enhancements to the Registry also increase its potential for ALS research and detection of more cases. As more persons with ALS enroll and complete surveys, a better understanding of possible risk factors might emerge. The National ALS Registry thanks OMB for reviewing this proposal and stands ready to answer any further questions.

SUPPLEMENTAL DOCUMENTS

A.   ALS Registry Protocol V23e_clean
B.   ALS Registry Protocol V23e_track changes
C.   APPENDIX E – Survey_mh_v3_Clean_updated
D.   APPENDIX E – Survey_mh_v3_trackchanges_updated
E.   NCHS survey feedback_2020
F.   Essential Questionnaire – Clinical Factors
G.   Essential Questionnaire – Demography
H.   Essential Questionnaire – Environmental Factors
I.   Essential Questionnaire – Lifestyle Factors

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