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

Part A

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A. Justification

1. Circumstances Making the Collection of Information Necessary

ATDSR is authorized by the Public Health Law No: 110-373, ALS Registry Act (Attachment 1) to (1) develop a system to collect data on amyotrophic lateral sclerosis (ALS) and other motor neuron disorders that can be confused with ALS, misdiagnosed as ALS, or progress to ALS; and (2) establish a national registry for the collection and storage of such data to develop a population-based registry of cases. The objective of this information collection is to develop a population-based surveillance system/registry for ALS. The primary goal of the surveillance system/registry is to obtain more complete information on the likely prevalence of ALS and to better describe the demographic characteristics (age, race, sex, and geographic location) of those with ALS. The secondary goal of the surveillance system/registry is to collect additional information on potential risk factors for ALS including, but not limited to, family history of ALS, smoking history, and military service.

This is a request to continue with revisions for three years, OMB 0923-0041. This data collection activity is a result of several meetings between the stakeholders including scientists, neurologists, advocacy groups, and ethicists and ATSDR. ATSDR developed a proposal to build on work that had already been done and coordinate the extant groups and create a larger database, rather than duplicate effort. The proposal outlined a strategy for identifying people using administrative databases such as Medicare, Medicaid, the Veterans Administration, and health insurance databases, and then to build on that data. ATSDR has funded four pilot projects through contracts to begin evaluating this strategy for ALS. ATSDR worked with outside agencies and organizations such as the Centers for Medicare and Medicaid Services (CMS), the Veterans Health Administration, and the Amyotrophic Lateral Sclerosis Association (ALSA) to obtain information on people with ALS to use as part of the pilot projects. Data indicated that not all persons with ALS will be identified using existing data therefore a self-registration portion is proposed. A bill to amend the Public Health Service Act to provide for the establishment of an Amyotrophic Lateral Sclerosis Registry, S. 1382: ALS Registry Act, was signed into law on October 10, 2008 by President Bush and became Public Law No: 110-373 (Attachment 1). In July 2010, ATSDR received OMB approval to launch the self-registration portion of the National ALS Registry through a web portal, www.cdc.gov/als.

Data Collected in First Three Years

There are limited data on the incidence and prevalence of ALS which is one of the reasons Congress mandated the National ALS Registry. The best estimates come from a paper authored by the NIH[1] that evaluated all papers written on the subject for a 25 year period. Most of the papers meeting the eligibility requirements for inclusion related to ALS came from outside the US and no specific data on the age or racial distribution of the cases are presented. The median annual incidence of ALS was 1.6 per 100,000 (range 0.7 to 2.5) all ages. Prevalence results did not vary widely with a median reported prevalence of 4 per

[1]Hirtz D, Thurman DJ, Gwinn-Hardy K, Mohamed M, Chaudhuri AR, and Zalutsky R (2007). How common are the "common" neurologic disorders? Neurology, 68, 326-337.

100,000 for all ages. There was a weak association with male sex and strong association with older age. The administrative databases used for the Registry were not collected for research, therefore some demographic data, e.g., race, may be less reliable. In addition, coding errors can cause an individual to be omitted. Those who self-register, only provide information on sex, age, and state of residence at registration. All other demographic data, e.g., race and ethnicity are collected in the voluntary surveys.

Given the limited information available and the differences in how the data are collected, it is difficult to make comparisons; however, we feel we can make the following observations. In the first six months that self-registration was available, over 2600 individuals registered. We used the data from the NIH meta-analysis to extrapolate that the self-registration effort is drawing as many as 1/3 of the newly diagnosed cases. However, this extrapolation is not suitable for drawing estimates of expected incidence.

As mentioned above, administrative data are also useful for estimating prevalence (e.g., Veterans Health Administration, Veterans Benefits Administration, Medicare, and Medicaid data). We compared the demographic characteristics of those who- self register with those from these administrative datasets as a way to understand the extent of overlap in these data sources. As not all of these administrative datasets are available for the same years that the registry was in effect (i.e., 2010-2012), we analyzed these data for the 2001-2009 time period. The demographic characteristics of those with ALS in the administrative data sources remained remarkably consistent over this 10 year time period related to the distribution of age (~60%, 60-79 years of age at diagnosis), race (~87% white), and sex (~57% males). Compared with those individuals who self-registered from October 19, 2010 – April 5, 2013 were more likely to be white (94 %), slightly younger (42 %, 60-79 years of age at diagnosis), and no difference related to sex (60% male). This suggests that the self-registration portion of the ALS National Registry may be capturing individuals that would have been missed if only existing databases had been used. The differences in the racial and age distributions could be attributed to access and familiarity with web-based technology and computers.

Although there are clearly some differences between those ALS cases identified from the administrative data and those who self-register, this is the largest group of ALS cases on which these data have been collected. These data are a valuable resource for researchers to better describe a large geographically diverse population of ALS cases and develop hypotheses for future research projects.

Revisions Requested

Revisions to the original application are the inclusion of additional risk factor surveys based on the scientific literature and requests from ALS researchers, ALS neurologists, and persons with ALS. This includes 10 additional surveys covering residential history, life-time occupational exposure, home pesticide use, hobbies, hormonal and reproductive history (women only), caffeine use, trauma, health insurance, open-ended supplemental questions, and clinical signs and symptoms. Currently 50 percent of those that register fill out the risk factor surveys; we expect a similar percentage will fill out the new surveys.

The activities described are part of the ongoing effort to maintain the National ALS Registry. As a result, a revision clearance package is being submitted in order to continue data collection following OMB/PRA approval.

PRIVACY IMPACT ASSESSMENT INFORMATION*

Overview of the Data Collection System
The ALS registry allows for web-based collection of data on individuals with ALS. Once an individual is registered he/she can voluntarily participate in on-line surveys of risk-factors for ALS. Data collection is organized in a modular format that is designed to decrease the fatigue burden on participants and can be expanded as additional scientific information becomes available.

Individuals who register will create an account with a password and security questions. Account name and password will be necessary to access the account. Once an account is created or a survey module completed, this information will be removed from the web-based system to a secure server without Internet access.

Items of Information to be Collected
Registry items to be collected include information to make sure that there are no duplicates: Information in Identifiable form (IIF) include: full name, email address, city and state, last 5 digits of the Social Security Number (SSN), month and year of birth. Survey modules to be filled out include information on known or suspected risk factors and disease progression and could include smoking, military service, occupational history, residential history, history of traumatic injury, and symptoms. Personal identifiers will be discussed in further detail, in Section A.10. ATSDR will ensure that several safeguards remain in effect throughout the duration of the registry. These safeguards are also discussed in Section A.10. Screen shots of the web-based instruments can be found in Attachment 4, 5, and 6a of this supporting statement.

Identification of Website and Website Content Directed at Children Under 13 Years of Age
This information collection will involve web-based data collection methods. The registry is directed to persons with ALS who are most likely to be diagnosed between the ages of 55 and 75. Cases are rarely diagnosed below the age of 30 years of age. Others who can register are family members of affected persons or researchers. No content is directed to children under 13 years of age.

2. Purpose and Use of Information Collection

The purpose of this information collection is to gather specific data related to Amyotrophic Lateral Sclerosis (ALS). The objective of this information collection is to develop a population-based surveillance system/registry for ALS. The primary goal of the surveillance system/registry is to obtain more complete information on the likely prevalence of ALS and to better describe the demographic characteristics (age, race, sex, and geographic location) of those with ALS. The secondary goal of the surveillance system/registry is to collect additional information on potential risk factors for ALS including, but not limited to, family

history of ALS, smoking history, and military service. These risk factors were chosen because they are the only known and consistently recognized risk factors for ALS, and we want to obtain baseline assessment of basic risk factors on the registry participants. The method for scoring the ALS Functional Rating is in Attachment 10. It is hoped that additional self-administered risk factor modules will be developed and submitted to OMB for deployment as part of the National ALS Registry. The data collected will be used to describe the characteristics of the ALS Registry participants. Data can also be used to generate hypotheses which could become the subject of research studies.

Privacy Impact Assessment Information*

The information in identifiable form (IIF) will be used for the purpose of recording and clarifying information that has been provided by the registrants and obtained from existing databases and to avoid duplication of reporting of cases. There are no plans to share the IIF with anyone other than ATSDR staff and contractors working on the ALS registry.

Information that might be considered sensitive by a portion of the general public (particularly full name along with self verification of having a diagnosis of ALS) is being collected, so there would be a likely effect on the respondent's privacy if there were a breach of confidentiality. Accordingly, very stringent safeguards have been put in place as described in Section A.10.

3. Use of Improved Information Technology and Burden Reduction

This collection of information will be done using electronic techniques in lieu of paper reporting forms. Screen shots of the validation questions, registration page, and voluntary surveys can be found in Attachments 4, 5, and 6a. Newly proposed surveys are in Attachment 6b. Once registered, cases will have the opportunity to participate in questionnaires that collect information on risk factors. All participation is voluntary. The registration instrument requires collection of only the minimum information necessary for the purposes of the registry system.

4. Efforts to Identify Duplication and Use of Similar Information

Because ATSDR staff is in communication with The Council of State and Territorial Epidemiologists, advocacy groups, and ALS researchers, it is clear that no nationwide collection exists for this field of study. The literature describes a number of research studies on hospital or physician based cases, but there is no prior history of a national registry. Communications with experts in ALS did not bring to light any similar data collection efforts. No other collective registry exists that tracks ALS nationwide. To date, close to 5,500 persons with ALS have registered and approximately 2,800 (51%) have taken surveys.

5. Impact on Small Businesses or Other Small Entities

No small businesses will be involved in this data collection.

6. Consequences of Collecting the Information Less Frequently

The average life expectancy for an individual after diagnosis with ALS is 2-3 years. Because of this fact it is necessary to allow individuals to register as soon as they are diagnosed. Without prompt registration individuals may become too ill or die before participating.

There are no legal obstacles to reduce the burden.

7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

Special circumstances do exist which require information collection to be conducted in a manner more often than quarterly. Each individual will self-report. Because of the severity of the illness, life expectancy 2-3 years after diagnosis, it is important to allow individuals to register at their convenience.

Other than those mentioned previously, there are no other special circumstances associated with this data collection.

8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

A. A 60-day Federal Register Notice was published in the *Federal Register* on February 12, 2013, vol. 78, No. 29, pp. 9922-9923 (Attachment 2). One non-substantive comment was received and the standard CDC response was sent (Attachment 3).

B. The following individuals were consulted to obtain their views on the availability of data, the clarity of instructions, disclosure, and on the data elements to be recorded and reported. ATSDR holds annual meetings with stakeholders in Atlanta, Georgia. The last annual meeting was held June 2012 and a 2013 meeting will be held on July 30-31 in Atlanta, GA.

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9. Explanation of Any Payment or Gift to Respondents

Participants will not receive any token of appreciation for their participation.

10. Assurance of Confidentiality Provided to Respondents

Registration questions include full name, city and state, email address, month and year of birth and last five digits of the Social security numbers. This information is necessary because case information will be collected from a number of sources and it is imperative that duplicates be identified and consolidated. The primary goal of the registry is to provide accurate estimates of incidence and prevalence which cannot be done without removing duplicate entries. Although information about disease is needed to verify eligibility, the individual responses other than date of diagnosis will not be stored.

PRIVACY IMPACT ASSESSMENT INFORMATION

This submission has been reviewed by the NCEH/ATSDR Privacy and Confidentiality Officer who determined that the Privacy Act does apply. The applicable Systems of Records Notice is 09-19-0001, "Records of Persons Exposed or Potentially Exposed to Hazardous or Toxic Substances."

Data security is of paramount importance and technical, physical, and administrative safeguards are outlined below.

Creating an account
External Users (ALS Patients / External Researchers) must self-register before accessing the ALS Web Portal. Personal information is collected during this registration process and users are allowed to create their own unique username and password. Users are also required to answer security questions which are used as alternative authentication credentials if their password is forgotten. Upon successful registration, users are systematically logged into their accounts. External Users are authenticated against a backend SQL encrypted database.

Internal Users (CDC Employees / System Administrators) are required to be pre-approved by ATSDR management before accessing the ALS Intranet Web Portal. Once a user is approved, ATSDR management sends a request to the System Administrator to create a user account. The request must include the user's CDC User ID, First Name, Last Name, Gender, City, State, Country, and Email in order for the System Administrator to add the user to the ALS System. Users must first log into the CDC network to access the ALS

Intranet Web Portal and are authenticated using Active Directory. No login is required.

The ALS system creates a sequential unique identifier in the database every time a user account is created. This unique identifier identifies each user and is used to link user information inside the system. Another unique identifier (Last 5 digits of SSN) will be used to verify patient data outside of the ALS system.

Login procedures
For authentication purposes, users will be verified using their unique username along with their password. External Users are allowed to self-register online and create their own username. Duplicate checks are implemented during registration to ensure uniqueness of usernames and emails.

Password management
External users are allowed to change or reset their passwords, but are not allowed to retrieve their password. Passwords can be changed via the user's account after the user has been authenticated by providing the old password and can only be changed once every 6 days. If a user forgets his/her password, the password can be reset by providing alternate authentication credentials. These credentials include the user's username, registered email address, and a security question. Passwords are required to be reset every 180 days. Users will be given a 2 week email notice before their password expires. Users will be directed to reset their expired password if they attempt to login after their password has expired.

User names are unique and can not be changed. Users must contact the System Administrator by phone or email to retrieve their username. The System Administrator is required to ask verification questions before releasing any information to the user; which can include the user's First and Last Name, Month & Year of Birth, City, State, and two security questions.

The status of an account will change to inactive if the user has not logged into his/her account in 6 or more months. Users will be given a 2 week email notice before their account is inactivated. Users will be required to contact the System Administrator by phone to re-activate their account. The System Administrator will be required to verify the user by asking verification questions which include the user's First and Last Name, Date of Birth: Month & Year (ALS Patients only), Address: City, Province/State, Country, and 2 security questions.

No personal information or credentials can be sent to a user's email, only notices or confirmations.

User accounts can not be removed and remain in the database permanently. Only the account status can change.

Encryption
Information in Identifiable Form (IIF) fields will be masked on the Graphical User Interface because of the sensitivity of the data. For example, month and year of birth will be masked.

All Personally Identifying Information (PII) data which includes the last 5 digits of the SSN

will be encrypted using AES_256 (Advance Encryption Standard 256 bit) encryption, the strongest encryption standard supported by SQL Server 2008.

To encrypt/decrypt data in database columns designed to hold PII data, a user must be given access to open and close a symmetric key. _

Minimize collection of identifiable information
The information required for registration has been limited to only that needed to make sure that an individual truly has ALS and is not already part of the registry. Address information has been limited to city and state, and email address; birth information has been limited to month and year of birth, and only the last five digits of the SSN will be collected.

Physical Controls
Production and test servers are stored in a server room secured by the CDC. Access tools are in place to secure entry into CDC buildings (Guards, ID Badges, Key Card, Cipher Locks, and Closed Circuit TV).

Data management
On a quarterly basis, data will be downloaded from the web-based portal and provided to ATSDR. ATSDR will merge the self-identified individuals into the registry after first checking for duplicates. The registry will be maintained on a secure server or stand-alone hard-drive. Access to the data will be limited to approved study personnel. Deidentified data sets will be used for data analysis. There will be an opportunity for respondent consent. A screen providing Privacy Act information will appear prior to the registration screen on the website (Attachment 7). A copy of the consent document is included (Attachment 8) outlining the intended uses of the information collection and that there are no plans for identifiable data sharing other than with ATSDR staff and contractors working on the ALS registry. The CDC IRB has granted a waiver of consent for possible participants to complete the validation questions because these questions just determine eligibility and the data are not stored unless the person is eligible for the registry. Consent will be sought prior to registering or completing any surveys.

IRB Approval

CDC/ATSDR IRB approval for the ALS registry protocol was originally obtained on 10/26/09 and a continuation was approved on 10/10/12. Documentation is included (Attachment 9).

11. Justification for Sensitive Questions

Registration questions that might be considered sensitive by a portion of the general population include full name, month and year of birth, last five digits of the Social Security Numbers, and self verification of diagnosis of ALS. This information is necessary because case information will be collected from a number of sources and it is imperative that duplicates be identified and consolidated.

The National Registry is a combination of individuals identified through existing datasets

and self-registration. The administrative data sets, Medicare, Medicaid, Veterans Health Administration, and Veterans Benefits Administration use SSN as a unique identifier. It will be necessary to use the SSN to make sure that there are no duplicates in the ALS registry. This is true for eliminating duplicates between the VA data and the Medicare data, for example, and adding the individuals self-identified via the web portal.

Prior to initiating the registry we analyzed approximately 362,000 unique patient records, ATSDR found that using the last four digits of the SSN and last name returned many duplicate matches. Month and year of birth cannot be used for verification because most of the patients fall within a narrow age range and Medicare data are known to contain many inaccuracies in these fields. An additional analysis of the data showed that using the First Initial, Full Last Name and last 5 digits of the SSN returned no duplicate matches for the available file.

ATSDR has received approval from the IT security and OMB for last five digits of the SSN. In addition, ATSDR has completed and maintains full Certification &Accreditation (C & A) for the web portal. (Attachment 11)

The primary goal of the registry is to provide accurate estimates of incidence and prevalence which cannot be done without removing duplicate entries. Name alone is not sufficient to remove duplicates. Epidemiologic characteristics such as sex and geographic location are routinely collected because of their significance in describing effected populations and evaluating resource allocation.

12. Estimates of Annualized Burden Hours and Costs

A. Burden hours are included in Table 1. During the next three years approximately 1500 individuals are expected to participate. The initial screening questions which determine eligibility are expected to take 2 minutes and registration to take 7 minutes. Registered individuals will have the opportunity to complete short surveys related to risk factors for ALS and demographic characteristics. There are 16 such surveys which take approximately 5 minutes each to complete and are completed only once. There is one survey related to progression of disease that can be completed three times the first year and twice a year thereafter which also takes approximately 5 minutes. Because some people's disease progresses more rapidly, clinicians recommended adding the survey at 3 months to make sure everyone had the opportunity to take the survey a second time. In years 2 and 3, the survey would be taken at the yearly anniversary and at 6 months. If an individual was eligible, registered in the National ALS Registry, and completed all the surveys, the total burden would be 99 minutes. If an individual decides to take surveys, these can be done at any time and do not need to be done in one session. Surveys can be saved for completion and submission at any time.

Table 1: ESTIMATE OF ANNUALIZED BURDEN HOURS

Type of	Form Name	No. of	No. of	Average	Total Burden

Respondent		Respondents	Responses per Respondent	Burden per Response (in hours)	(in hours)
Person with ALS	Validation questions (Screener) for suspected ALS cases	1670	1	2/60	56
	Registration Form of ALS cases	1500	1	7/60	175
	Cases of ALS completing 1-time surveys	750	16	5/60	1000
	Cases of ALS completing twice yearly surveys*	750	2.3	5/60	144
				Total	13 75

* The disease progression survey is taken initial and then 2 additional times the first year (0, 3, 6 months). Because some people's disease progresses more rapidly, clinicians recommended adding the survey at 3 months to make sure everyone had the opportunity to take the survey a second time. In years 2 and 3, the survey would be taken at the yearly anniversary and at 6 months.

B. Burden costs are included in Table 2. The ALS cases will be members of the general public. The hourly wage rate of $21.74 is based on the US Department of Labor, Bureau of Labor Statistics 2011 National Occupational Employment and Wage http://www.bls.gov/oes/current/oes_nat.htm#00-0000.

Table 2: ESTIMATE OF ANNUALIZED BURDEN COSTS

Type of Respondents	**Total Burden Hours**	**Hourly Wage Rate**	**Total Burden Costs ($)**
Persons with ALS	1375	$21.74	$29,893

13. Estimates of Other Total Annual Cost Burden to Respondents or Record Keepers

There are no capital or maintenance costs incurred by respondents because the information will be entered via the Internet from any location. There are no costs or burden to respondents for recordkeeping.

14. Annualized Cost to the Government

Data analysis by ATSDR may result in action taken by the Division of Toxicology and Human Health Studies in response to the required CDC mandate in maintaining preventive health activities and surveillance systems. The action taken will vary, depending on the analysis.

The total cost to the federal government for the collection of this information for the three year ongoing project is $3,300,000 as itemized below.

Annual ATSDR personnel costs $420,000

Additional expenses will be incurred by ATSDR in order to operate a successful surveillance program/registry. Four staff will contribute to this program: a Senior Scientist (25% contribution=$75,000), and a program analyst (100% contribution = $100,000) A contractor will be used to maintain the web portal for case registration and participation in surveys in addition to providing public user support 40 hours per week ($500,000). Lesser expenses may include computer resources, telephone calls, and recruitment materials (approximately $5,000).

The estimated annual cost to the government is $1,100,000.

15. Explanation for Program Changes or Adjustments

Change in respondent burden is based on program change. The original application has been revised to include 10 additional risk factor surveys based on the scientific literature. The topics covered by the 10 additional surveys include residential history, life-time occupational exposure, home pesticide use, hobbies, hormonal and reproductive history (women only), caffeine use, trauma, health insurance, open-ended supplemental questions, and clinical signs and symptoms. The activities described are part of the ongoing effort to maintain the National ALS Registry. .

16. Plans for Tabulation and Publication and Project Time Schedule

Statistical Analysis Plan:

CDC will only provide the “self-registration” data combined with data from administrative sources, to create a single prevalence estimate. CDC will aggregate the data provided by the registrants with that available from administrative sources on a yearly basis. The data will not be broken out by geographic area until an appropriate approach for non-response bias has been developed and approved in the form of a nonsubstantive change.

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.

A. 16-1

Activity	**Time Schedule**
Surveillance Activity	Ongoing data collection
Summary Reports	Every year after OMB approval
Yearly Evaluation	Each year after OMB approval

We also plan to publish selected summary reports on CDC's public website www.cdc.gov/als .

17. Reason(s) Display of OMB Expiration Date is Inappropriate

Exemption from displaying the expiration date for the OMB approval of forms is not being requested.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.