National Amyotrophic Lateral Sclerosis (ALS) Registry

OMB Control No. 0923-0041 (Expiration Date: 09/30/2016)

Revision

Supporting Statement Part A –

Justification

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Part A. Justification

Goal of the study: As mandated by Congress, the goal is to continue collecting data, with revision, for the National Amyotrophic Lateral Sclerosis (ALS) Registry to better describe the incidence and prevalence of ALS and to identify risk factors for the disease.

Intended use of the resulting data: The National ALS Registry allows estimates of ALS prevalence as well as risk factors. ATSDR endeavors to improve the completeness, representativeness, and accuracy of the Registry data over time.

Methods to be used to collect: self-reporting by persons with ALS (PALS), researchers, and ALS service organizations. The primary revisions proposed include: collection of biospecimens, development of a repository of those specimens, and development of an application process for researchers to obtain access to those specimens.

Subpopulation to be studied: US citizens and legal residents with ALS

How data will be analyzed: descriptive statistics of PALS including number of people identified, number of individuals who self-identified vs. those obtained from existing data, mean age, sex distribution, racial distribution, geographic distribution by region, and distribution of other characteristics such as cigarette use, alcohol use, occupation, service in the military, physical activity, and family history.

A.1. Circumstances Making the Collection of Information Necessary

The Agency for Toxic Substances and Disease Registry (ATSDR) is authorized by the Public Law No. 110-373, the 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 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 Heath 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 (e.g. genetics and environmental and occupational exposures.[2]

In the last three years, the National ALS Registry has had several major accomplishments. In July 2014, the first estimate of ALS prevalence for the entire United States was published in the CDC Morbidity and Mortality Weekly Report (MMWR).[2] The analysis shows that during October 19, 2010–December 31, 2011, a total of 12,187 persons meeting the surveillance case definition of definite ALS were identified by the Registry, for a prevalence of 3.9 cases of ALS per 100,000 persons in the U.S. general population. Incidence cannot be measured because the date of diagnosis was not noted in all patient records.

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 MMWR Surveillance summary includes a list of limitations covering the possible under ascertainment of case, double counting of some cases, and the inability to calculate incidence but that the Registry had published findings for

ALS incidence in smaller defined geographic areas of the United States.[4-9]. More details about the findings and limitations published can be found in Supporting Statement Part B, Section B.1.

Data from and about the National ALS Registry has been presented annually at the American Academy of Neurology meeting, the Northeastern ALS Consortium meeting, and the International Symposium on ALS/motor neuron disease (MND). Persons enrolled in the National ALS Registry can opt to receive emails about research studies for which they may be eligible. As of March 1, 2016, approximately 75,000 emails have been sent for 23 studies over the last three years.

After 5 years of recruitment and self-registration in this system, approximately 1,500 ALS cases enroll each year. The existing Veterans Health Administration, Veterans Benefits Administration, Medicare, and Medicaid data remained remarkably consistent over a 10 year time period, from 2001-2009, related to the distribution of age (~60%, 60-79 years of age at diagnosis), race (~87% white), and sex (~57% males).

In comparison with those cases identified through the national databases, we find that those individuals who self-registered from October 19, 2010 – December 31, 2015 were more likely to be white (95%) and slightly younger (53%, less than 60 years of age at diagnosis). There was no difference in those identified through national databases compared with those who self-registered by sex (~60% male). The difference in the demographics of those who self-register compared with those in the national databases suggests that the self-registration portion of the National ALS Registry is working to identify 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. To date, more than 10,000 PALS have registered and 58% have taken at least one survey. Although this varies by year, in CY2013 1,784 persons with ALS self-registered and approximately 67% took at least one survey.

This is a request to continue the *National Amyotrophic Lateral Sclerosis (ALS) Registry* (OMB Control No. 0923-0041, expiration date 09/30/2016), with revision, for an additional three years. The 60-day Federal Register Notice was published on 04/13/2016 (**Attachment 2**) and is further discussed in Section A.8.

The revisions requested are designed to strengthen the usefulness of the National ALS Registry for researchers. A summary of the requested changes can be found in **Attachment 3**. The revisions include: (1) verification of email address at registration, the ability to add the email address for another person to receive information on behalf of the participant, and zip code (**Attachment 5**), (2) the inclusion of a Global Unique Identifier (GUID) developed by NIH to allow the sharing of de-identified data across studies (**Attachment 5**), (3) the addition of a biorepository component (Section 2A), and (4)

an application for researchers to request epidemiologic data and biological specimens from the National ALS Registry (Section 2A).

A.2. Purpose and Use of the Information Collection

The objective of this information collection request (ICR), *the National Amyotrophic Lateral Sclerosis (ALS) Registry* (OMB Control No. 0923-0041, expiration date 09/30/2016), is to continue a population-based surveillance system/registry for ALS. First approved in 2010 for self-registration, the primary goal of the surveillance system/registry remains to obtain reliable information on the incidence and prevalence of ALS and to better describe the demographic characteristics (age, race, sex, and geographic location) of persons with ALS (PALS). Those interested in participating in the National ALS Registry must answer a series of validation questions (**Attachment 4)** and if determined to be eligible they can register (**Attachment 5**).

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. In 2013, this ICR was approved to collect 10 additional risk factor 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 (**Attachment 6**). The method for scoring the ALS Functional Rating is in **Attachment 6A**. 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.

A biorepository component is being added to increase the value of the National ALS Registry to researchers. As part of registration the participant can request additional information about the biorepository and provide additional contact information (**Attachment 5**). A geographically representative sample will be selected to provide specimens so that genetic and environmental risk factors can be studies. It is important to use the specimens collected for ALS research. The costs to collect, store, and process specimens has to be balanced with the costs on specimen analysis. Therefore, the biorepository cannot collect specimens from all Registry participants that want to participate but is working to collect as many as possible. There are three types of specimen collections, in-home, saliva only, and postmortem. The following table outlines the types of specimens collected in the home and their potential use:

Collection priority	Sample preservative	# tubes	ml / tube	Fractions	Examples of specimen use
Blood					
1	K_2EDTA	1	10	White cells (buffy coat), red cells, plasma	DNA, proteins, red blood cell lipids
2	K_2EDTA	1	6	Whole blood	Lead and other metals
3	Plain, (no anticoagulant	1	10	Serum	Clinical biochemistries, metabolic products, other small molecules
5	PAXgene RNA	2	5	RNA-stabilized whole blood	Intracellular RNA
Urine			9	--	Electrolytes, environmental chemicals, metabolic products
Nail clippings			--	--	Metals
Hair clippings			--	--	Metals
Saliva (Oragene Collection Kit)			2	--	DNA

The brain, spinal cord, cerebral spinal fluid (CSF), muscle, and bone and a small skin samples (to isolate primary fibroblasts will be collected postmortem from up to 40 cases. The procedures and methods used in the pilot study can be found in **Attachment 14**.

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. Information about the sampling scheme can be found in Supporting Statement Part B, B.1. 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 (Section A15) ATSDR will use the information in comparison with the number of PALS self-registering to evaluate how effective the outreach activities are at increasing enrollment in the Registry and completing the survey modules..

A.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 6**. Once registered, cases will have the opportunity to participate in questionnaires on risk factors. The registration instrument requires collection of only the minimum information necessary for the purposes of the registry system.

A.4. Efforts to Identify Duplication and Use of Similar Information

This data collection originated as a result of several ATSDR meetings between the stakeholders including scientists, neurologists, advocacy groups, and ethicists in 2009. In 2010, 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 holds annual meeting with stakeholders to discuss the Registry and get input into future directions.

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.

A.5. Impact on Small Businesses or Other Small Entities

This data collection will not involve small businesses.

A.6. Consequences of Collecting the Information Less Frequently

The average life expectancy for an individual after diagnosis with ALS is 2-3 years. 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 technical or legal obstacles to reducing burden.

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

There are no special circumstances associated with this data collection.

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

A. The 60-day Federal Register Notice was published in the *Federal Register* on 04/13/2016, Vol. 81, No. 71, pp. 21876 (**Attachment 2**). No public comments were received.

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 July 2015 and we are in the process of planning and scheduling the 2016 meeting.

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A.9. Explanation of Any Payment or Gift to Respondents

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

A.10. Protection of the Privacy and Confidentiality of Information Provided by Respondents

This submission has been reviewed by the NCEH/ATSDR PRA Contact 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.* The information in identifiable form (IIF) categories and the system are discussed below.

PRIVACY IMPACT ASSESSMENT INFORMATION

In 2015, the NCEH/ATSDR Information Systems Security Officer (ISSO) has updated his reviewed this system, and a full privacy impact assessment (PIA) has been completed (**Attachment 10**). In addition, ATSDR completes annual Certification & Accreditation for the web portal**.**

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

Overview of the Data Collection System

The ALS registry allows for web-based collection of data on PALS. The registry is directed to all PALS. Most PALS are diagnosed between the ages of 55 and 75 and cases are rarely diagnosed below the age of 30 years of age. Others who can register are family members of affected persons or researchers. Once a PAL is registered he/she can voluntarily participate in on-line surveys of risk-factors for ALS, as described in Section A2. 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.

The primary goal of the registry is to provide accurate estimates of incidence and prevalence which cannot be done without removing duplicate entries. The National ALS 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 last five digits of 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. Name alone is not sufficient to remove duplicates. 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.

Creating an account

Individuals who register will create an account with a password and security questions. Account name and password will be necessary to access the account.

External Users (ALS Patients/External Researchers) must self-register before accessing the ALS Web Portal. IIF is collected during this registration process (full name, email address, city and state, last 5 digits of the Social Security Number [SSN], month and year of birth) 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 Structured Query Language (SQL) encrypted database.

As the number of studies related to ALS increases, it is increasingly important to be able to pool data across studies and biorepositories. The National Institutes of Health (NIH) has led the way in developing the Global Unique Identifier (GUID) https://ncats.nih.gov/grdr/guid which allows the creation of a unique identifier so that data and samples can be shared and linked without sharing IIF. This is especially important when using samples from multiple sources because persons with ALS may be in more than one biorepository. As a revision, during registration we will ask Registry participants if they want to have a GUID added to their records, and if so, they will be asked to provide the information necessary to generate the GUID (**Attachment 5**).

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.

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.

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 cannot 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 cannot be removed and remain in the database permanently. Only the account status can change.

Encryption

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 IIF 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 IIF, a user must be given access to open and close a symmetric key. _

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

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.

ATSDR will merge the self-identified PALS 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. De-identified 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 8A**) 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. De-identified data will be shared and we are working with agency representatives to comply with the Open Data Policy requirements.

Release of data

Researchers may request data from the National ALS Registry and/or samples from the Biorepository. Before release of any data, researchers must attest that they will not attempt to re-identify the data. Data that are only from the administrative datasets will not be released. Data are coded and files do not contain PII. Each data request is reviewed to evaluate the possibility that specific data elements or elements in combination could be potentially identifying and whether or not creating categories for a specific variable, e.g., age, would decrease this potential identifiability. If there is a potential for identification and categorization would eliminate the possibility, we will include the categorical data instead of individual values. If there is a potential for identification and categorization would eliminate the possibility, we will include the categorical data instead of individual values. In other cases, variables may be totally eliminated. One staff member will be responsible for creating the requested data set with the agreed upon variables adjusted as needed. A second staff member, will review the file to reassess the potential for identifiability and make adjustments before any data are sent.

Any of the survey data may be requested matched to the biospecimens. However, any data requests would need to undergo the same non-disclosure review described above. In addition, we will provide a minimal dataset requested by ALS experts that includes the following if available, age at diagnosis, age at symptom onset, age at death, sex, race, state of residence at registration, survival time, immediate relative with ALS (yes/no), immediate relative with

Alzheimer's disease or Parkinson's disease (yes/no), location of symptom onset (e.g., hand, swallowing), and ALS Functional Rating score closest to the specimen collection.

A.11. Institutional Review Board (IRB) and Justification for Sensitive Questions

CDC/ATSDR IRB approval for the ALS Registry protocol was originally obtained on 10/26/09 and the most recent annual continuation was approved on 9/30/15 (**Attachment 9A**). The IRB approved a waiver of documentation of consent for the registration and on-line surveys. The consent form as it appears online is in **Attachment 8A**.

IRB approval of adding a biorepository component was received on 2/12/16 (**Attachment 9B**). Because there will be direct interactions with those who take part in the biorepository and the need to store samples for future study, there are separate consent forms requiring signatures. The biorepository component has four consent forms, in-home collection of biological specimens (**Attachment 8B**), postmortem collection of tissues including brain and spinal cord (**Attachment 8C**), postmortem collection of skin (**Attachment 8D**), and saliva only collection (**Attachment 8E**). Saliva only collections were added to increase the number of PALS who could participate in the biorepository when additional money became available at the end of the fiscal year.

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,[1] and self-verification of diagnosis of ALS. Epidemiologic characteristics such as sex and geographic location are routinely collected because of their significance in describing effected populations and evaluating resource allocation.

One variable necessary to calculate the Global Unique Identifier (GUID) is sex at birth. This might be considered sensitive by those who have had a sex change. This information is not permanently stored. This information is only kept long enough to generate the GUID and validate the number and then it is wiped from the system. Those who do not want to provide that information can decide not to participate in the GUID process.

[1] 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.

A.12. Estimates of Annualized Burden Hours and Costs

A. Burden hours are included in Table 1, and represents an increase in total time burden from 1,375 as approved in 2013 to the currently requested 1,883 hours, a net increase of 508 hours. The description of how the increase in burden is distributed is below.

Based on past Registry experience, it is assumed that approximately 90 percent of persons to be screened (n=1,670) will yield 1,500 individuals successfully registered each year. The initial screening questions which determine eligibility are expected to take 2 minutes and registration to take 10 minutes, an increase of 3 minutes over the previously approved 7 minutes due to the inclusion of the GUID (**Attachment 5**). Registered individuals will have the opportunity to complete short surveys related to risk factors for ALS and demographic characteristics. [2] 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. For purposes of estimation, we are rounding up to 3 times annually.[3] 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. Based on our experience with the pilot study, those who participate in the in-home portion of the biorepository will spend approximately 30 minutes having specimens collected and answering a few questions needed to process the specimens (**Attachments 12A**) and those who provide saliva specimens will spend approximately 10 minutes each, and in all, 222 additional burden hours are requested for 325 PALS' participation in the in home portion of the biorepository and 350 PALS' participation in providing saliva. The annual burden of the Registry is expected to increase 341 hours for PALS compared to 2013 estimates.

[2] In the 2013 ICR, the 16 different five-minute surveys were described as one form requiring different 16 annual responses. To be more accurate, we have revised them as one group of 16 voluntary survey modules requiring a total of 80 minutes to complete. In its entirety, this group of survey modules will require one annual response. The requested time burden remains 1,000 hours annually.

[3] In the 2013 ICR, the estimated number of responses for the "twice yearly surveys" was approved as 2.3 times per year per respondent; although, described as three times the first year and twice a year thereafter. In keeping with the requirement to express the burden table in whole numbers, we have revised the number of "disease progression surveys" by rounding up to 3 times per year. This resulted in an increase of requested time burden from 144 hours approved in 2013 to 188 hours in the current ICR.

Researchers will be able to request epidemiological data collected by the National ALS Registry as well as the specimens collected by the biorepository. In order to assure the appropriate use of data and specimens, researchers much complete an application form and provide documentation of IRB approval and institutional support. Completion of the National ALS Registry Research Application Form (**Attachment 11A**) and record gathering should take approximately 30 minutes. Those who receive data and/or specimens much provide an update on a yearly basis along with documentation of continued IRB approval. Completion of the Annual Update Form (**Attachment 11B**) and record gathering should take approximately 15 minutes. In all, we are requesting an additional 24 burden hours for researchers.

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. They provide ATSDR with information on their outreach efforts in support of the Registry on a monthly basis (**Attachment 13A and 13B**). In all, we are requesting an additional 143 burden hours for service organizations.

Table 1: ESTIMATE OF ANNUALIZED BURDEN HOURS

Type of Respondents	Form Name	No. of Respondents	No. of Responses per Respondent	Average Burden per Response (in hours)	Total Burden (in hours)
Person with ALS	ALS Case Validation Questions	1,670	1	2/60	56
	ALS Case Registration Form	1,500	1	10/60	250
	Voluntary Survey Modules	750	1	80/60	1,000
	Disease Progression Survey*	750	3	5/60	188
	ALS Biorepository Specimen Processing Form	325	1	30/60	163

	and In-Home Collection				
	ALS Biorepository Saliva Collection	350	1	10/60	59
Researchers	ALS Registry Research Application Form	36	1	30/60	18
	Annual Update	24	1	15/60	6
ALS Service Organization	Chapter/District Outreach Reporting Form	135	12	5/60	135
	National Office Outreach Reporting Form	2	12	20/60	8
Total					1,883

* The disease progression survey is taken initially 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. For purposes of burden estimation, the number of annual responses has been rounded up to 3 times (**Attachment 6** ALSFRS Module only).

B. Burden costs are included in Table 2. The ALS patients will be members of the general public and the researchers are expected to be neurologists. The hourly wage rate of $22.71 for ALS patients and ALS service organization staff and $93.74 for researchers is based on the US Department of Labor, Bureau of Labor Statistics May 2014 National Occupational Employment and Wage http://www.bls.gov/oes/current/oes_nat.htm#29-0000.

Table 2: ESTIMATE OF ANNUALIZED BURDEN COSTS

Type of Respondents	Total Burden Hours	Hourly Wage Rate	Total Burden Costs ($)
Persons with ALS	1716	$22.71	$38,970.36
Researchers	24	$93.74	$ 2,249.76
ALS Service Organization	143	$22.71	$3,247.53
Total	1,883		$44,467.65

A.13. Estimates of Other Total Annual Cost Burden to Respondents and 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.

A.14. Annualized Cost to the Federal Government

Data analysis by ATSDR may result in action taken by the ATSDR 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 $10,922,466 as itemized below.

Annual ATSDR personnel costs $979,822.

Additional expenses will be incurred by ATSDR in order to operate a successful surveillance program/registry.

- In addition contract staff will contribute to this program: a Senior Scientist (30%), a Program Analyst (100%), Epidemiologist (25%), and Statistician (100%) for a total of $600,000.
- 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 ($651,000).
- ALS service organizations conducting outreach spend approximately 10% of their time meeting reporting requirements ($80,000).
- A contractor will be in charge of the biorepository operations including but not limited to specimen collection, analysis, storage, and distribution of samples $1,310,000. Lesser expenses may include computer resources, telephone calls, and recruitment materials (approximately $20,000).

The estimated annual cost to the government is $3,640,822.

A.15. Explanation for Program Changes or Adjustments

Change in respondent burden is based on program change (**Attachment 3**). These include the minor revisions to registration, indicating interest in the biorepository and providing the requested contact information, and agreeing to add GUIDs to their record and the required data to do so which increased registration time from 7 to 10 minutes. The GUID increases the value of the data by allowing it to be combined with data from other studies without compromising privacy.

The 2013 application included 16 1-time surveys at 5 minutes each and in this application the surveys are represented as a total if the individual took all 16 surveys, i.e. 80 minutes, which is a better representation if a registrant chooses to do all of the surveys. The requested burden hours remains the same at 1,000 hours. In addition, the original application had the disease progression survey (**Attachment 6** ALSFRS Module only) at 2.3 times per year because it can be taken 3 times in the first year and 2 times per year thereafter, however this has been rounded to 3 times per year in this application, resulting in a net increase in requested hours in 2016 of 44 hours due to rounding.

The original application has been revised to include a biorepository component to the National ALS Registry. There is a need for additional specimens from ALS patients to further ALS research. Although there are some other sources for specimens, they are limited by being from specific clinical practices or geographic areas. The National ALS Registry presents a unique opportunity to obtain specimens from a geographically representative group of ALS patients. In addition, these specimens can be coupled with extensive epidemiological data. The time to complete the specimen collection and answer a few questions necessary to analyze the specimens (**Attachment 12A**) has been added. We have also added the time to collect saliva from a second group of PALS (**Attachment 12B**).

A respondent type was added to allow researchers to access data and specimens collected by the Registry (**Attachment 11A and 11B**). The activities described and the revision requested are part of the ongoing effort to maintain the National ALS Registry. A second respondent type was added to collect information from ALS service organizations regarding outreach activities (**Attachment 13A and 13B**). This information will assist ATSDR in evaluating the effectiveness of the outreach activities.

A.16. Plans for Tabulation and Publication and Project Time Schedule

The National ALS Registry 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 has been conducted. 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 (e.g. create age categories)
- Case classification

Registry reports will include data both from those individuals identified using existing datasets and those who self-register.

CDC will aggregate the data provided by the registrants on a yearly basis and will publish updated prevalence estimates of ALS in an MMWR Surveillance Summary. In addition, survey data will be analyzed to generate hypotheses for future studies.

Table 3: TIMELINE

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 .

A.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.

A.18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.

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List of Attachments