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

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A. Justification

1. Circumstances Making the Collection of Information Necessary

Progressive muscular wasting disease was first described in 1850 by Aran, and in 1860 by Duchenne. In 1869, the French neurologist Jean-Martin Charcot described a unique condition characterized by deterioration of both lower and upper motor neurons, and this condition was termed amyotrophic lateral sclerosis (ALS).[1] The Greek term amyotrophic translates to 'no nourishment to the muscle' which leads to muscular wasting; the term lateral refers to an area in the spinal cord where motor neuron pathways are located; and the term sclerosis describes the scarring or hardening in the spinal cord that results when these motor neurons deteriorate.[2] Many people know ALS as Lou Gehrig's disease, named after the famous baseball player who, in 1939, retired because of his illness.

In addition to ALS, several other less common conditions are classified under the general term of motor neuron disease (MND). ALS accounts for 85 percent or more of all motor neuron cases, and most individuals who are initially diagnosed with these other conditions will ultimately progress to include both upper and lower motor neurons and thus will be diagnosed as having ALS.[4,5]

Other neuromuscular disorders can mimic ALS. Differential diagnosis of ALS requires a neurological exam as well as neurophysiological tests and other tests to rule out non-motor neuron diseases and the other motor neuron diseases with restricted presentations.[6] False-negative rates can be high in the early stages of the disease.[6] In a review of 33 patients with a definitive diagnosis of ALS, fourteen were misdiagnosed upon initial presentation of symptoms.[7] False-positive misdiagnoses are less common but have been shown to occur in 7 to 8 percent of cases.[8,9] The diagnosis of ALS will become more uniform worldwide as the World Federation of Neurology El Escorial criteria and its subsequent revision are utilized.[10-12] Only the most recent[13] of the studies evaluated in this review relied upon these criteria for case definition. Thus, there is likely some degree of disease misclassification and inconsistency in case identification between studies.

Amyotrophic lateral sclerosis (ALS) is a complex neurodegenerative disease of unknown etiology, but it is believed to be the result of a combination of genetic and environmental factors. The search for environmental risk factors associated with ALS has yielded intriguing but, at times, conflicting results. Epidemiologic studies provide supporting evidence for some of these agents as potential risk factors for ALS, but additional studies that address issues of exposure assessment, sample size, and latency are warranted.

The ATSDR Registry Program is based on the premise that diseases cannot be diagnosed, prevented or controlled until existing knowledge is expanded and new ideas developed and implemented. In accordance with this principle ATSDR is requesting approved clearance for data collection for the Registration of Individuals with Amyotrophic Lateral Sclerosis (ALS) in the National ALS Registry. Data collection is authorized by Public Health Law No: 110-373, ALS Registry Act (Attachment 1).

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 to start from scratch. The proposal outlined a strategy for identifying people using administrative databases such as Medicare, Medicaid, the VA, and health insurance databases, and then to build on that data. ATSDR has funded pilot projects 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. All pilot projects worked with abstracting existing data and did not involve any interviews. Preliminary 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. The activities described are part of the effort to create the National ALS Registry. As a result, a clearance package is being submitted in order to allow data collection immediately 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 can be expanded as additional scientific information becomes available as well as to decrease the fatigue burden on participants.

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. It is ready for online use as soon as OMB/PRA approval is obtained.

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, 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 instrument can be found in Attachment 5 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 reliable information on the incidence and 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.

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. 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.

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 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 May 28, 2009, vol. 74, No.101, pp. 25552-25553 (Attachment 2). We received comments from two advocacy groups, the ALS Association (ALSA) and the Muscular Dystrophy Association (MDA) (Attachments 3a and 3c). The responses can be found in Attachments 3b and 3d. In general, the comments were supportive of a National ALS Registry and a self-registration option. Both groups offered to assist ATSDR with publicizing the Registry which will be important to maximize participation. No comments were made regarding costs or burden.

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. A meeting was held in Atlanta, Georgia, June 24-25, 2009.

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9. Explanation of Any Payment or Gift to Respondents

Participants will not receive any cash payment or gift for participating.

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 data 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 required to login into their account using their username and password. 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 60 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.

Usernames are unique and can not be changed. Users must contact the System Administrator by phone 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 & day of birth, City, State, Country, 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 2005.

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.

On a quarterly basis, ATSDR will provide back to the web-based portal a dataset which is deidentified, including only state, age, race, and sex. This dataset will be used to populate the surveillance/registry map available on the website.

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.

CDC/ATSDR IRB approval for the ALS registry protocol was obtained on 10/26/09. Documentation is included (Attachment 9).
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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 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. Approximately 6,000 individuals are expected to participate. The initial screening questions to determine eligibility are expect to take 2 minutes and creating an account 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 6 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 twice a year which also takes approximately 5 minutes. If an individual was eligible, registered in the National ALS Registry, and completed all the surveys, the total burden would be 49 minutes.

Table 1: ESTIMATE OF ANNUALIZED BURDEN HOURS

Data Collection Instruments	No. of Respondents	No. of Responses per Respondent	Average Burden per Response (in hours)	Total Burden (in hours)
Validation questions (Screener) for suspected ALS cases	6,000	1	2/60	200

Registration Form of ALS cases	4,667	1	7/60	544
Cases of ALS completing 1-time surveys	2,334	6	5/60	1167
Cases of ALS completing twice yearly surveys	2,334	2	5/60	389
Total				2300

B. Burden costs are included in Table 2. The ALS cases will be members of the general public. The hourly wage rate of $17.42 is based on the US Department of Labor, Bureau of Labor Statistics 2007 annual average hourly earning of private sector employees (http://www.bls.gov/ro3/fax_9250.htm).

Table 2: ESTIMATE OF ANNUALIZED BURDEN COSTS

Type of Respondents	**Total Burden Hours**	**Hourly Wage Rate**	**Total Burden Costs ($)**
ALS Cases	2300	$17.42	$40,066

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.

14. Annualized Cost to the Government

Data analysis by ATSDR may result in action taken by the Division of 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 $2,400,000 as itemized below.

Annual ATSDR personnel costs $220,000

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=$40,000), and a program analyst (25% contribution = $35,000) 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 training materials (approximately $5,000).

The estimated annual cost to the government is $800,000.

15. Explanation for Program Changes or Adjustments

This is a new surveillance data collection.

16. Plans for Tabulation and Publication and Project Time Schedule

Statistical Analysis Plan:

CDC will aggregate the data provided by the registrants on a yearly basis.

A. 16-1

Activity	**Time Schedule**
Activation	1 - 2 months after OMB approval
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 website during the second year of this project.

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 certification for Paperwork Reduction Act Submissions.

B. COLLECTIONS OF INFORMATION EMPLOYING STATISTICAL METHODS

The ALS Registry coordinator and statistician will conduct periodic statistical analyses on the data in the system. Statistical analyses will be done using SAS (SAS Institute, Cary, NC) annual statistics will include:

- Number of people identified with ALS
- Mean age of case
- Sex distribution of the cases
- Racial distribution of the cases
- Geographic distribution of the cases
- Other descriptive statistics

The ALS registry coordinator may employ the following methodology:

- Data transformation
- Case classification
- Baseline estimation

1. Respondent Universe and Sampling Methods

This activity is not research; respondents are neither recruited nor sampled. Furthermore, no sample selection is involved in this registry. The registry will identify individuals from existing data and will allow cases to self-identify.

2. Procedures for the Collection of Information

ALS patients will be allowed to voluntarily register for the registry. Case status will be validated using six questions standardized by the Veterans Administration and shown to correctly identify cases 93% of the time (Attachment 4). Once an individual passes validation, he will be permitted to register. To enable the collection of additional information from registrants who volunteer, a series of short survey modules will be available for completion via a secure web portal (Attachment 6). We are using a survey validated by the ALS Consortium of Epidemiologic Studies (ACES). The survey has been divided in to short modules because of the physical limitations of the study population. All surveys are designed to be answered only once except for the symptoms survey which can be answered every 6 months. The ALS Functional Rating Scale-Revised (ALSFRS-R) is a standard set of questions used by physicians to measure functioning overtime. Researches have developed and tested a self-administered version of the ALSFRS-R which showed excellent reliability to change over time. The published version of the self-administered ALSFRS-R was slightly modified to make the question responses more user friendly. Individuals will be consented prior to registering with the National ALS Registry and completing any survey modules.

3. Methods to Maximize Response Rates and Deal with Non-response

There is not a method to deal with non-response because it is unknown who has ALS. We will attempt to maximize the response rate by partnering with ALS advocacy groups and neurologists to publicize the registry.

4. Tests of Procedures or Methods to be Undertaken

The web site has been tested and will continue to be tested until deployment. No further procedures or methods are needed at this time.

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

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List of Attachments

Attachment 1 Authorizing Legislation: Public Law No: 110-373, amendment to the Public Health Service Act to provide for the establishment of an Amyotrophic Lateral Sclerosis Registry

Attachment 2 Federal Register Notice

Attachment 3 Comments and Response to 60-Day FRN
3a ALSA Comments to 60-Day FRN
3b Response to ALSA Comments
3c MDA Comments to 60-Day FRN
3d Response MDA Comments

Attachment 4 Validation Questions

Attachment 5 Screen Shot of the Registration Page

Attachment 6 Text of Voluntary Survey Modules

Attachment 7 Privacy Statement

Attachment 8 Consent Form

Attachment 9 IRB Approval