

**Department of Health and Human Services  
Centers for Disease Control and Prevention  
Agency for Toxic Substances and Disease Registry**

**ATSDR's Annual Amyotrophic  
Lateral Sclerosis (ALS) Surveillance Meeting**



**June 25-26, 2012  
Summary Report**

This document has not been revised or edited to conform to agency standards. The findings and conclusions in this report are those of the meeting presenters and attendees and do not necessarily represent the views of the Agency for Toxic Substances and Disease Registry.

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## Acronyms

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Acronym	Expansion
AAN	American Association of Neurology
ACA	Affordable Care Act
ACS	American Cancer Society
ALS	Amyotrophic Lateral Sclerosis
ALSRG	Amyotrophic Lateral Sclerosis Research Group
ALSA	Amyotrophic Lateral Sclerosis Association
ALSFRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised
ALSTDI	ALS Therapy Development Institute
APHA	American Public Health Association
APOE	Apolipoprotein E
ApoL1	Apolipoprotein L1
ATSDR	Agency for Toxic Substances and Disease Registry
BMI	Body Mass Index
C9ORF72	Chromosome 9 Open Reading Frame 72
CDC	Centers for Disease Control and Prevention
CD-CV	Common Disease-Common Variant
CD-RV	Common Disease-Rare Variant
CMS	Centers for Medicare and Medicaid Services
COPD	Chronic Obstructive Pulmonary Disease
CPS	Current Population Surveys
CPS-II	Cancer Prevention Study II, ACS
CSF	Cerebrospinal Fluid
CSTE	Council of State and Territorial Epidemiologists
dbGAP	Database of Genotypes and Phenotypes
DoD	Department of Defense
DTHHS	Division of Toxicology and Human Health Sciences, ATSDR
EDTA	Ethylenediaminetetraacetic acid
EMR	Electronic Medical Records
FDA	Food and Drug Administration
FTD	Frontotemporal Dementia
FY	Fiscal Year
GWAS	Genome-Wide Association Studies
HCSC	Health Care Services Coordinators
HDL	High-Density Lipoprotein
HHS	(United States Department of) Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
ICD	International Classification of Diseases
IOM	Institute of Medicine
iPS	Induced Pluripotent Stem
IRB	Institutional Review Board
MDA	Muscular Dystrophy Association
miRNA	Micro Ribonucleic Acid
MND	Motor Neuron Disease
NCBI	National Center for Biotechnology Information (NIH)
NCI	National Cancer Institute

<b>Acronym</b>	<b>Expansion</b>
NCHS	National Center for Health Statistics
NDAR	National Database for Autism Research
NDI	National Death Index
NEALS	Northeast Amyotrophic Lateral Sclerosis Consortium
NHANES	National Health and Nutrition Examination Survey
NIA	National Institute on Aging (NIH)
NIEHS	National Institute of Environmental Health Sciences (NIH)
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
NLMS	National Longitudinal Mortality Study
OMB	Office of Management and Budget
PALS	Persons with Amyotrophic Lateral Sclerosis
PLF	Perilymph Fistula
PMI	Post-Mortem Interval
PON	Paraoxonase Enzymes
PSA	Public Service Announcement
RDC	Research Data Center (CDC)
RNA	Ribonucleic Acid
SNP	Single Nucleotide Polymorphism
SOD1	Superoxide Dismutase 1
SOP	Standard Operating Procedure
SORN	Privacy Act System of Records Notice
SSN	Social Security Numbers
STD	Sexually Transmitted Disease
TBI	Traumatic Brain Injury
TDP-43	Transactivation Response (TAR) DNA binding protein-43
UK	United Kingdom
US	United States
VA	(United States Department of) Veterans Affairs
VAB	(United States Department of) Veterans Affairs Biorepository
VBA	Veterans Benefits Administration
VHA	Veterans Health Administration
WTC	World Trade Center

**Centers for Disease Control and Prevention (CDC)  
Agency for Toxic Substances and Disease Registry (ATSDR)  
ATSDR's ALS Surveillance Meeting**

**Minutes of the Meeting  
June 25-26, 2012**

## **Theme / Purpose**

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**Theme:** Status and Next Steps for the National ALS Registry

**Purpose:** Update stakeholders on the progress of the National ALS Registry and discuss strategies to further enhance the Registry for all stakeholders.

## **Welcome / Introductions**

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**Robert Kingon, MPA, Facilitator**  
**Carter Consulting, Inc.**

Mr. Kingon welcomed everyone, indicating that he would serve as the meeting facilitator. He acknowledged that the annual ALS meeting is always very productive, with many good questions and ideas. After reviewing housekeeping and meeting procedures, he called for introductions. A roster of those in attendance is included at the end of this document.

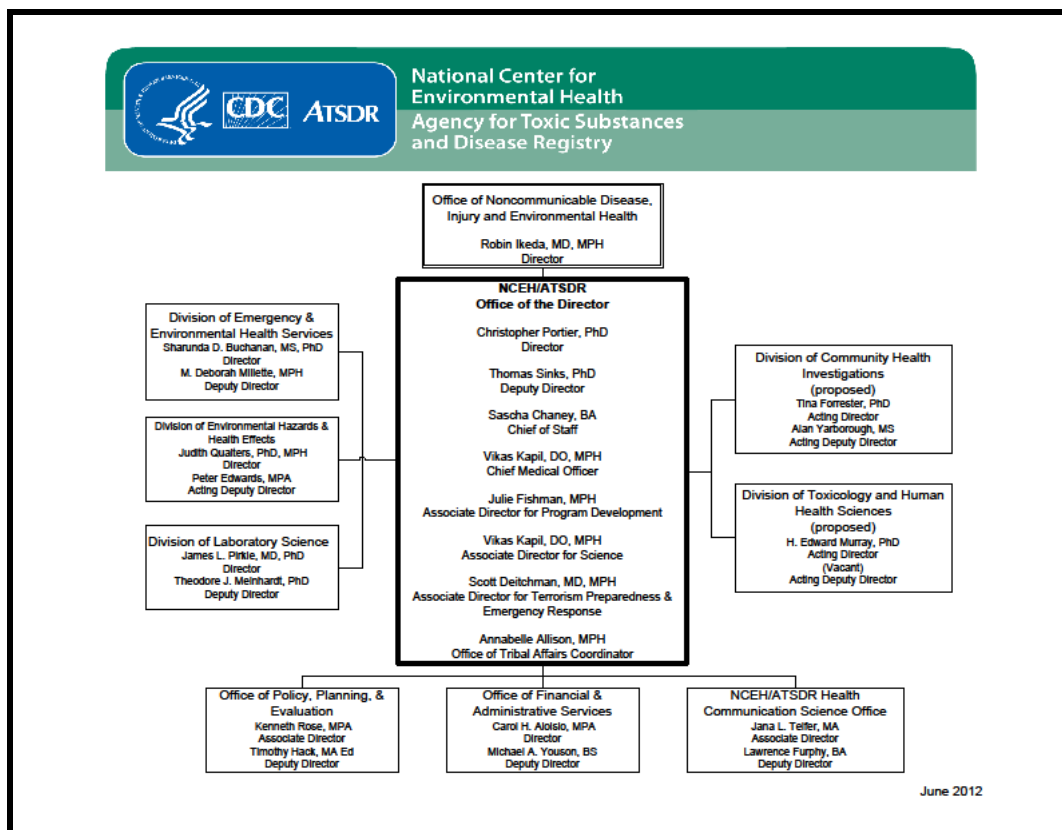
## **Opening Remarks**

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**Christopher J. Portier, PhD**  
**Director, Agency for Toxic Substances and Disease Registry/National Center for Environmental Health**

Dr. Portier welcomed everyone to Atlanta, and thanked them for their attendance and participation. He expressed the ATSDR's gratitude for the time everyone has put into the Registry in order to make it as successful as possible. It is known that ALS is a devastating and fatal disease. It not only affects the people with ALS, but also affects their families, their friends, and everyone around them. No cause for ALS has been readily identified, and everyone holds hope that a cause can be discovered in the near future. The National ALS Registry is a groundbreaking effort to help scientists as they work toward a cure for ALS. Since going live in October 2010, the National ALS Registry has collected demographic and risk factor data on thousands of people with ALS in all 50 states. More people with ALS are signing on every day. The National ALS Registry also has some very exciting new initiatives that ATSDR hoped the participants would enjoy discussing and offering advice on in terms of how to move forward. This included the Bioregistry Feasibility Study, a mechanism that informs Persons with ALS (PALS) about researchers interested in recruiting PALS enrolled in the Registry to participate in their ALS clinical trials and studies; and the State- / Metro-Based Surveillance Activities.

Many people have asked about the reorganization of ATSDR. Since coming to the Centers for Disease Control and Prevention (CDC) two years ago, Dr. Portier indicated that he began studying ATSDR in terms of how it functions, its mission and objectives, and how it could be made more effective. In doing that, he brought in outside consultants who gave him good advice in terms of matching function to organizational structure, to the overall objectives of the agency. As they worked through this, it became clear that ATSDR has one or two very strong functions for which it is responsible, along with the other functions around those. The new organizational structure includes two primary divisions that align with the two main functions for ATSDR. The first main function is to work with communities that have toxic dump sites or other toxic environmental chemicals in the community to evaluate how dangerous those chemicals are and to help such communities work with state and federal partners on clean-up. The first division, Division of Community Health Investigations, was formed around those functions. The other main objective of ATSDR is to build on the science used in those evaluations, build on registries, and conduct epidemiological studies in support of understanding toxic substances and chemicals in communities. The second primary division, the Division of Toxicology and Human Health Sciences, was formed around these science functions. This division includes Environmental Medicine, Environmental Epidemiology, Environmental Toxicology, and Surveillance and Registries. Dr. Portier's hope is that by grouping these together, these sciences will be brought more closely in alignment with each other. The lines between toxicology, epidemiology, and medicine have blurred in the last 15 to 20 years. Molecular epidemiology and molecular science has brought everyone much closer together, so it is not unusual to see toxicologists working with human tissues and epidemiologists working in a clinical setting, and clinicians engaged in epidemiology and laboratory work. By bringing the three major science groups together, Dr. Portier hopes to strengthen their understanding of each other's work as well as the science of the agency. The organizational chart follows:



In closing, Dr. Portier thanked everyone for their participation and indicated that he had to depart shortly for a meeting with his boss.

**Ed Murray, PhD****Acting Director, Division of Toxicology and Human Health Services  
Agency for Toxic Substances and Disease Registry**

Dr. Murray reported that he became the Acting Director for the Division of Toxicology and Human Health Sciences in March 2012. Previously he was the Director of the Division of Toxicology and Environmental Medicine, so he has been involved with the activities of ATSDR for quite some time. Though Dr. Williamson is involved in a detail within CDC, Dr. Murray frequently communicates with him. Dr. Murray emphasized that he has had quite a steep learning curve since taking over this position, and has learned a lot about ALS. Certainly, there is much more to learn about this devastating disease. Although new in the position, he assured everyone that the division and ATSDR are engaged to ensure the success of this registry. However, any endeavor as large as this will depend upon effective collaboration. Collaboration will be necessary with the ALS stakeholders. ATSDR also looks forward to developing new relationships, such as that with the American Academy of Neurology which is helping ATSDR to promote the ALS registry among its constituents, and with the National Institutes of Health (NIH) to conduct epidemiologic and genetic studies to better understand the etiology of this disease. Dr. Murray stressed that as leading experts in ALS, ATSDR welcomed the participants' insight during this meeting in terms of shaping the National ALS Registry. In closing, he wished everyone a successful meeting.

## Overview of the National ALS Registry

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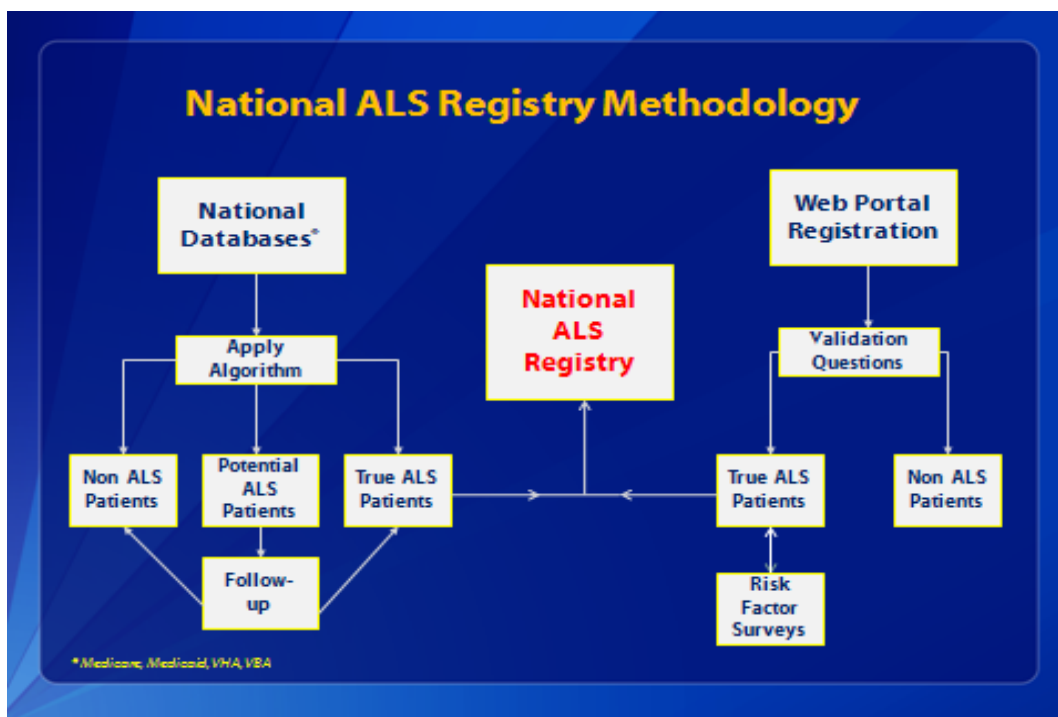
**D. Kevin Horton, DrPH, MSPH****Chief, Environmental Health Surveillance Branch  
Division of Toxicology and Human Health Sciences  
Agency for Toxic Substances and Disease Registry**

Dr. Horton welcomed everyone to Atlanta, and expressed his gratitude to everyone for taking time to attend. As noted, this registry is a critical and vital program to help learn more about ALS. Everyone present was invited because of their particular expertise in treating and working with patients with ALS. As ATSDR has done each year, the agency wanted to solicit feedback in order to make this the best registry possible, and is on a path to making it a world class registry. Recognizing that there were new individuals present, Dr. Horton began with a presentation of some background information.

The ALS Registry Act was enacted as Public Law 110-373 in October 2008. To a large degree, this act was passed because of many of the people in the room to whom a huge debt of gratitude was owed for helping to move this forward. The act directs ATSDR to establish and maintain the National ALS Registry. As specified by the act, which is posted on the ATSDR website, the intent of the National ALS Registry is to describe the incidence and prevalence of ALS, describe the demographics of ALS patients, and examine the risk factors for the disease. While there are incidence and prevalence estimates, they are not population-based national estimates. They are largely based on small-scale studies that are extrapolated out to the United States (US) population. This will be the first true population-based national registry in the country. As such, it is important to hone in on the true incidence and prevalence of the disease;

that is, how common is ALS in the US? It is also important to understand who acquires the disease and how it affects various subpopulations, which is expected to be better understood because this is a population-based registry. One of the most critical components of this registry is to assess the potential risk factors for the disease. Lou Gehrig was diagnosed over 70 years ago. While good progress has been made in learning about the disease, much remains unknown. It is hoped that the Registry will shed light on the disease, help plan future studies, and inform possible treatments. As noted earlier, the Registry was officially launched in October 2010.

With regard to how the Registry functions, a two-pronged approach is utilized to ascertain ALS cases throughout the country. ALS is not a reportable disease in 49 states. Massachusetts has the only state-based registry in the country. That poses a major challenge in terms of capturing and tracking cases of ALS throughout the country. ATSDR has selected two approaches, which it believes are doing a good job of capturing cases. The first approach involves leveraging existing resources in the form of national databases to which ATSDR has access, including the following: Medicare, Medicaid, and a couple of databases from the Veterans Administration (VA). By ATSDR's estimates, these represent approximately 90 million people. ATSDR does not pursue a project without an initial investigation. Pilot testing was conducted before launching the Registry. Through that pilot testing, an algorithm was developed that, when applied to the national databases, allows ATSDR to categorize people in one of three categories: Non-ALS Patients, Potential ALS Patients, and True ALS Patients.



Several critical ingredients go into the algorithm to help identify ALS patients. One critically important ingredient is the International Classification of Diseases (ICD) code for ALS. ICD codes are diagnostic codes used by physicians and healthcare professionals. Unfortunately, miscoding occurs, so ICD codes cannot be relied upon alone. Also important is prescription



drug use. Given that Rilutek® (riluzole) is the only drug currently on the market for ALS that is approved by the Food and Drug Administration (FDA), use of this drug is a sign that someone likely has the disease. Also an important signal is the frequency with which someone visits a neurologist. Once the algorithm is applied to the databases and people are divided into categories, those who are classified as non-ALS patients are not included in the Registry. Those considered to be true patients are entered directly into the National ALS Registry. Potential patients are those for whom there is not enough information to make a determination. These patients are placed in holding while awaiting additional data to determine whether they are or are not cases.

It is known from the pilot testing that not everyone with ALS is going to be identified in these databases. For example, if someone is not a veteran, they will not appear in the VA databases. For those reasons, the decision was made to develop the second approach of online web portal registration. This is largely a safety net to help find the cases that may not be captured through the first approach. To register through the web portal, individuals answer a series of 5 to 6 validation questions. Depending upon the way a person answers, he or she will become part of the Registry or will be classified as not being a case and will not become part of the Registry. The validation questions are the ones the VA used when they were operating their registry during the mid-2000s. Because the VA captured a high percentage of true cases, ATSDR thought it would be beneficial to leverage this resource. They are often asked whether a person will be found through both approaches, and they will be. However, ATSDR has unique identifying information such as Social Security Numbers (SSN) that will allow them to compare patients from the first approach to the second approach to ensure that people are not being counted more than once.

One of the most important things about the web portal is that patients have the opportunity to take brief risk factor surveys, which will help to answer questions about the potential risk factors for ALS. So far, a lot of people have enrolled and have taken the risk factor surveys. While great progress has been made so far, more progress can be made. The risk factor surveys patients can currently complete include: Demographics, military history, life-time occupational history, smoking and drinking history, physical activity, family history of neurodegenerative diseases, and disease progression.

**Current Risk Factor Surveys\***

- ❑ **Demographics**
- ❑ **Military history**
- ❑ **Life-time occupational history**
- ❑ **Smoking and drinking history**
- ❑ **Physical activity**
- ❑ **Family history of neurodegenerative diseases**
- ❑ **Disease progression (ALSFRS\*\*)**

\*Developed and tested by Stanford University's ALS Consortium of Epidemiologic Studies (ACES) program  
\*\* ALS functional rating scale

These topics are mentioned in the literature as having a potential association with ALS. The disease progression module helps to track a person's disease progression over time. Patients are asked to take this survey twice a year, although they are asked to take the other 6 surveys only one time.

ATSDR is very excited about several new registry initiatives, including additional risk factor modules to address feedback about information not currently being requested, a biorepository feasibility study, state- / metro-based surveillance projects, and a clinical research notification system. Dr. Horton emphasized that ATSDR does not want to duplicate efforts. The thought behind the bioregistry is to first evaluate what other biorepositories are doing, consider how ATSDR can work with them, and contemplate how ATSDR can address potential gaps. The state- / metro-based projects are to help the agency determine how effective the Registry is. This effort takes an active case finding approach that will ultimately allow for comparison of state and metro data from participating areas with the data from the National ALS Registry to determine whether cases are being missed. The clinical research notification system is an important component that will allow researchers to link directly with ALS patients to inform them about new clinical trials and other studies for which they may be eligible. This mechanism was launched in May 2012.

A number of new risk factor surveys are under development, including: detailed residential history, residential pesticide exposure, occupations with toxicant exposures, hobbies with toxicant exposures, traumatic brain injury (TBI), electrical injuries, caffeine consumption, reproductive history in females, health care insurance, clinical data, and open-ended questions. These topics are thought to be important by the ALS scientific community, and many have been requested directly by patients. Because these modules must go through Institutional Review Board (IRB) and Office of Management and Budget (OMB) clearance processes, some are not likely to be launched until next year. However, ATSDR hopes to bring some of the new modules to fruition by the end of 2012. ATSDR has worked with various ALS researchers around the country to create the clinical module, some of who were in the room. The intent is to assess how clinical data can be collected on patients. The self-enrollment portion is meant for patients to answer, so the goal is for patients not to have to go to their clinicians for the answers. The agency believes the open-ended question module is very important, given that every ALS patient has a story to tell about his or her disease. This module will include a large text box in which people can describe their disease in terms of what they believe contributes to ALS, and what they think contributed to their own ALS. Perhaps people answering this module will list information that is not captured by the other modules, and perhaps common themes can be observed based on the responses received. Feedback from patients and support groups support this module. While the module will not be easy to analyze because the input will be straight text, ATSDR is willing to address that later in order to acquire honest feedback from patients about what they believe contributes to ALS, and specifically their own ALS.

Regarding the bioregistry component, little is known about the genetics of sporadic ALS. For that reason, ALS has embarked upon a feasibility study that will assess how feasible it will be for the agency to fold a national bioregistry component into the National ALS Registry. This bioregistry would be open to anyone in the US with ALS who is a participant in the National ALS Registry. A feasibility study is currently being conducted to determine what biological specimens could be collected (e.g., blood, tissue, hair, nails) from interested ALS patients who enroll in the Registry, and how frequently specimens should be collected. The protocol is being developed and will soon be submitted to the IRB. Once the protocol is approved by the IRB, it will go on to subsequent pilot testing to ensure that it works the way that is anticipated. One of the most important aspects of the bioregistry is that it would link risk factor surveys from the

National ALS Registry with the specimens collected. In theory, the persons from whom specimens will be collected will have already completed the modules. Many times this information is lacking in biorepositories, so this is expected to be highly useful information for the scientific community at large.

As noted, the purpose of the state- and metro-based surveillance component is to test the completeness of the National ALS Registry. Three state health departments and six metro areas are now taking part in this component. Many of these areas were chosen specifically for their demographics in order to over-represent some subpopulations to ensure that all of the expected information is captured. Data collection from this effort will focus on data from 2009 through 2011. Full datasets are anticipated from the participating states this fall and from the metro areas sometime next year.

In terms of the clinical research notification component, it is known that recruiting for clinical trials and research can be a difficult task. Therefore, ATSDR thought it would be beneficial to open the Registry now to make the data available to researchers to link ALS patients with scientists who are recruiting for clinical trials and studies. This mechanism went live in May 2012, and people are already asking many questions about it. One of the challenges for ATSDR is promoting the research notification component, so the agency is turning to support groups to help promote this component widely to their affiliates so that people know about its availability.

### **Discussion Points**

In terms of clinicians and scientists using the clinical research notification resource, Dr. Bruijn inquired as to whether there was currently a mechanism in place to quickly review and determine the legitimacy of requests to share information.

Dr. Horton replied that the web portal is already set up for this component. The application is web-based, and information is required regarding the research objectives, whether IRB approval has been obtained, et cetera. Once ATSDR has a complete package, it will be reviewed. A review panel has been established that is comprised of internal and external members that will be convened as proposals are received. Responses will be made as soon as possible.

Mr. Gibson commended ATSDR on inclusion of the open-ended question. Patients and families have their own stories and would really like a more comprehensive questionnaire. He thought the open-ended question would be highly valuable for acquiring more clues, and allowing patients to feel fulfilled when they participate in this process.

As part of the research notification component, Dr. Boylan inquired as to whether a target turnaround time had been established that the agency will try to achieve as requests are received.

Dr. Horton responded that the target turnaround time is 60 business days. Submitting fully completed packages will help to facilitate this. As soon as an application is received, it will go through an internal screening process and will then be submitted to the panel. He noted that there would be a session during the meeting to further describe this component. The plan is to make the process as user-friendly as possible.

Dr. Kaye emphasized that the main issue is that once an application is approved by the in-house panel, it must be submitted to the CDC IRB for approval in order for communications to

be sent to registry participants. That is out of their control, and can take from one week to three months. They are telling potential applicants that they should allow three months for the application to go through the process.

Dr. Horton added that while it was difficult to give precise timeframes at this point, he thought there would be a better indication once they began receiving proposals. The goal is to turn proposals around as fast as possible, bearing in mind that there are factors beyond their control.

Dr. Traynor thanked ATSDR for their tremendous work in developing a comprehensive registry package that is relevant to patients. There is an increasing recognition of the overlap between ALS and frontotemporal dementias (FTD), and he wondered whether any thought had been given to developing modules to address this.

Dr. Horton responded that ATSDR agrees that this is becoming more recognized, but he did not believe any of the current modules address this. One of the reasons for this type of meeting is to solicit more feedback. Consideration can be given to this. There is also agreement that the national bioregistry will be beneficial to scientists in the US as well as throughout the world. However, this is a process that is going to take time and the government moves at a slower pace. Nevertheless, the goal is to move as quickly as possible to bring all of these components to fruition.

Dr. Gubitx indicated that the National Institute of Neurological Disorders and Stroke (NINDS) at the National Institutes of Health (NIH) recently developed and launched the ALS Common Data Elements, which include some of the information that Dr. Traynor mentioned. Perhaps ATSDR and NIH should compare notes about this. She recognized that it was not simple to incorporate additional questions, but perhaps a comparison could be made of what ATSDR is capturing and what is included in the ALS Common Data Elements, they may find that there are some things that are easy to implement that would not take that much time.

Dr. Horton stressed the importance of leveraging resources.

Dr. Kaye added that the new clinical module asks whether people have had any genetic testing done.

Dr. Traynor inquired as to whether any of the modules ask what the results of any genetic testing were.

Dr. Kaye replied that they do not, and pointed out that this may not be a good idea to do in a federal database.

Dr. Horton asked whether any questions are asked about FTD.

Dr. Kaye responded that they do not, and this may open IRB questions because they are not supposed to be enrolling individuals who are cognitively impaired.

Dr. Gubitx noted that family history could be given by a relative.

## CME Training Module and Tutorial Video

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### Module Update

**Kim Jenkins**  
**Health Education Specialist**  
**Environmental Medicine Branch**  
**Division of Toxicology and Human Health Sciences**  
**Agency for Toxic Substances and Disease Registry**

Ms. Jenkins presented a brief update on the ALS Online Training Module. There are now two modules, the Online Learning Module and the Tutorial for the Registry. The ALS Online Training Module was created for healthcare providers. This module addresses current clinical practice recommendations for diagnosis, treatment, and management of patients with ALS, including communication strategies. This training module is located on ATSDR's website, and is a free course that allows participants to receive free continuing education credit. This is unusual because most continuing education credits incur a fee. The module discusses the importance of the standard diagnostic coding procedures for diagnosis of ALS patients in clinical practice, and information about the new National ALS Registry and the importance of ALS patient self-enrollment in the Registry. Data are received from the Office of Continuing Education regarding how many people are taking the course. The module has been online for about a year and a half, but became active in October 2012. Thus far, 268 continuing education credits have been awarded to the following: 40 physicians (CME), 23 non-physicians (CME), 143 nurses (CNE), 41 other professionals (CEU), and 21 health education specialists (CHES) have been awarded continuing education credit.

The ALS Toolkit has been viewed 31,438 times. Given that the federal government does not allow cookies, it is unknown whether any of these are duplicate views. The top 7 pages viewed include the following: ALS Definition (1126 hits), Communicating with the Patient (1150 hits), Clinical Assessment (832 hits), Welcome Page (683 hits), Treatment and Management (586 hits), ALS Risk Factors (510 hits), and Overview of Module (494 hits). Based on 2011 data, the occupational categories of registrants include the following: Academic / Educational (12), Healthcare (112), Military (2), Non-Profit Organizations (13), Other (18), Other Government Agency (12), Private Industry (2), Public Health Agencies (26), and Unknown (2).

In terms of evaluation of the data, most people strongly agreed (41%) or agreed (54%) that the content and learning materials addressed a need or gap in knowledge; most people strongly agreed (35%) or agreed (63%) that the module is written at an appropriate difficulty level; most people strongly agreed (33%) or agreed (65%) that the length and pace of the module are appropriate (approximately 1 hour); most people strongly agreed (34%) or agreed (61%) that they can apply the knowledge gained from the training; and most people strongly agreed (48%)



or agreed (43%) that the availability of continuing education credits influenced their decision to participate in the training. Many people commented that the module is excellent or good, that they learned a lot, that the training was helpful, that it refreshed their knowledge of clinical assessment, and it was easy to understand and apply, and that this is good work that should be kept up.

### Registry Tutorial Video Update

**Amanda Cadore, MPH**  
**Behavioral Health Scientist**  
**Environmental Medicine Branch**  
**Division of Toxicology and Human Health Sciences**  
**Agency for Toxic Substances and Disease Registry**

Ms. Cadore reported that her group partnered with Dr. Horton's group to create an online tutorial video to help ALS patients learn about the registration process for the National ALS Registry. After playing a sample of the tutorial, Ms. Cadore presented a brief overview. The National ALS Registry was created by ATSDR to gather information needed to understand risk factors that may lead to ALS. DTHHS developed an online tutorial that would assist ALS patients with completing the National ALS Registry registration process. The tutorial video was developed in response to a recommendation made during a previous ALS Surveillance Meeting. Meeting participants suggested that it would be helpful to PALS and personnel at ALS clinics to have an instructional video in addition to the PALS quick start guide to help with the registration process. ATSDR will make the video available for distribution to ALSA clinics and chapters, MDA clinics and offices, and other participating facilities.

A formative evaluation was conducted to ensure the accuracy and effectiveness of the tutorial video. Participants included current ALS patients from the ALS Association Georgia Chapter. These participants reviewed the ALS tutorial video, and were asked to assess the look and the ease of understanding the information, and to evaluate the registration process. They also reviewed the look and feel of the software design. The learning preferences of the participants are audio, video, or a mixture of both. There was also some discussion about the timing and length of the information. Some patients thought the tutorial was too slow because they were very familiar with ALS and the Registry and just wanted to move quickly through, while others needed assistance from family members. In order to address both preferences / needs, a 6-minute video was developed. Participants also provided any additional information they believed would improve the National ALS Registry tutorial process.

In terms of future plans, the Environmental Medicine Branch is also exploring collaborating with the National ALS Registry Team to produce videos focused on how to take registry surveys, how to complete the ALS Research Notification application process, and other registry topics. Other products can be found at the following sites:

ALS module website:

<http://www.atsdr.cdc.gov/emes/ALS/>

Educational resources:

<http://www.atsdr.cdc.gov/emes/index.html>

### **Discussion Points**

Dr. Horton noted that obviously, the target group would be patients. However, it is also critical to reach out to neurologists and other healthcare professionals to make them aware of the Registry. Working with Ms. Jenkins' group is a way to engage doctors, especially non-neurologists who may or may not see patients. There may be opportunities to add new continuing education modules depending upon the overall feedback.

Dr. Brooks observed a major decrease in the utilization of this module from first fiscal year to second. This is an important module for what is known as Disease-Specific Care Certification. He wondered whether ATSDR was partnering with groups like the American Association of Neurology (AAN) and other associations. People who are in clinics could participate in this as a component of their learning, but they may not know about it. He thought ATSDR should increase its marketing efforts, and involve its partners and stakeholders in this regard.

Dr. Horton agreed, indicating that they were fortunate to have someone this year from AAN who would be speaking about how ATSDR and AAN can work together. ATSDR is working with its communications group to disseminate key messages through Twitter and Facebook. He emphasized the importance of collaboration, given that it cannot simply be ATSDR pushing messages out. It must be the collective body of scientists all distributing information about these efforts. ATSDR has been asked by patients and other groups, especially chapters and offices, about the registration process and whether anything could be done to help educate their constituents about the Registry. The tutorial video was just posted to the website a week before this meeting, and it represents another component that ATSDR and its partners and stakeholders can promote together.

Dr. Brooks noted that at the launch of the Registry, there were many "touchy feely white coat type" videos indicating how important this registry is. He wondered whether any instructional /

educational experiences were available for the patient group presentations and / or in-clinic instruction / education. Something is needed that is more “This is my world. Welcome to it” and then something that would go to the depth of this video. Additional videos to go through the questions are imperative.

Dr. Horton replied that there is a resource link on the website that has all of the videos listed. They are all on YouTube as well. What would put this into context might be running the 30-second public service announcement (PSA) that indicates why this is being done. He could envision something like that running in a waiting room to put it into the proper context.

Dr. Kowall inquired as to whether there would be a mechanism to notify registrants when there is a new survey.

Dr. Horton responded that it is a combined approach. On the consent form, registrants have to check whether they wish to be notified about new surveys or studies. If they do, they will receive auto-generated e-mails informing them of new surveys that are available. Work is also being done through ATSDR's communications office, the Amyotrophic Lateral Sclerosis Association (ALSA), and the Muscular Dystrophy Association (MDA) to distribute information through Twitter and Facebook.

Dr. Brooks said it would help him to have a video running in his waiting room. Carolinas Neuromuscular / AKS-MDA Center has been assessing how to use the various materials ATSDR produces to increase the percentage of people involved in the Registry. They have made one presentation in abstract form in that regard. He thought what they were observing among patients was the fatigue effect of the Registry. In many clinic office settings, there are videos about healthcare issues, but they are usually paid for by hospital systems. If ATSDR could get a PSA into that setting, it would be good. He thought another potential advantage would be to make it accessible through an iPad.

Dr. Horton indicated that they also have “Quick Start Guides,” which are one-pagers that can be distributed. Everyone may not be set up for videos, so handouts can be useful. A number of approaches have been used (e.g., handouts, videos, tri-folds, et cetera) to get the message out. Mr. Wildman indicated that ALSA would like to leverage video in order to raise the excitement about the Registry, and get more people enrolled. He noted that he planned to discuss this further during the ALSA presentation.

Mr. Handsfield noted that during this presentation, the consent process was mentioned several times in terms of people having to consent to participate. However, during the first presentation it was reported that people are being brought in to participate from national databases (e.g., Medicare, Medicaid, VA, et cetera). He inquired as to whether a process was in place to acquire consent from them to be part of the Registry.

Dr. Kaye indicated that ATSDR has a Waiver of Informed Consent and a Waiver of Health Insurance Portability and Accountability Act (HIPAA) Authorization for those data, so they are not consented. They can self-register and consent if they want to provide additional information. De-duplication will be done based on the partial SSN and date of birth.

Regarding the timing of the clinical research notification project, Dr. Bidichandani asked why a CDC IRB review was necessary if there was already an institutional IRB in place.



Dr. Kaye responded that the Registry is covered by the CDC IRB, and any communications to the participants in the Registry are under the purview of the CDC IRB. Therefore, they have to approve it as well. No communications can be sent to the participants without them first being approved by the CDC IRB.

Dr. Horton added that they grappled with this as well, and it is another hurdle. However, they have been told that they have to do this.

Dr. Kaye emphasized that the CDC IRB was not going to be reviewing the protocol for a clinical research notification. They will review the communications. For example, if an investigator would like for ATSDR to send an email and a flyer, those items would be reviewed by the CDC IRB.

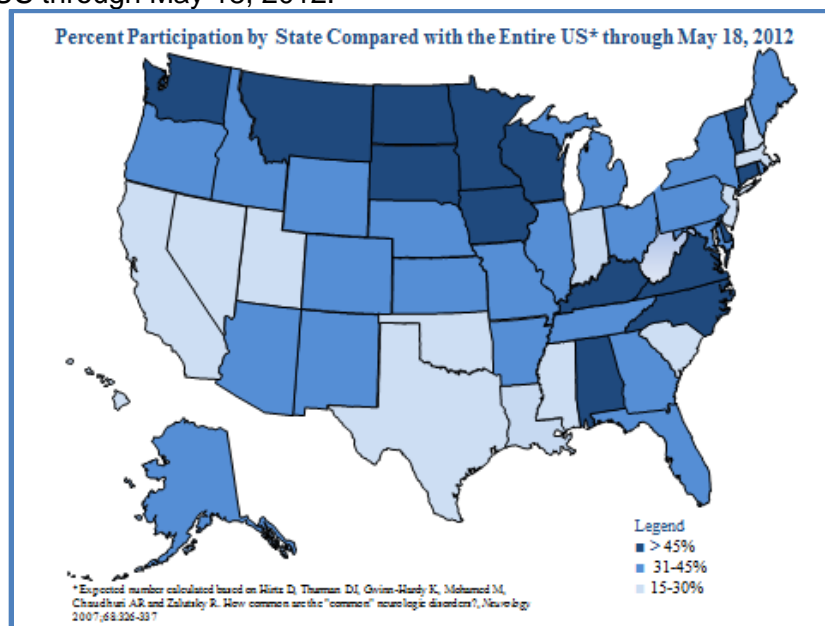
Dr. Sowell added that all the CDC IRB needs to see are the communications materials and documentation that the project is approved by the IRB that has oversight over the project. The CDC IRB will not review anything beyond the communications material and documentation of approval by the IRB of record.

## National Qualitative & Quantitative Data Findings

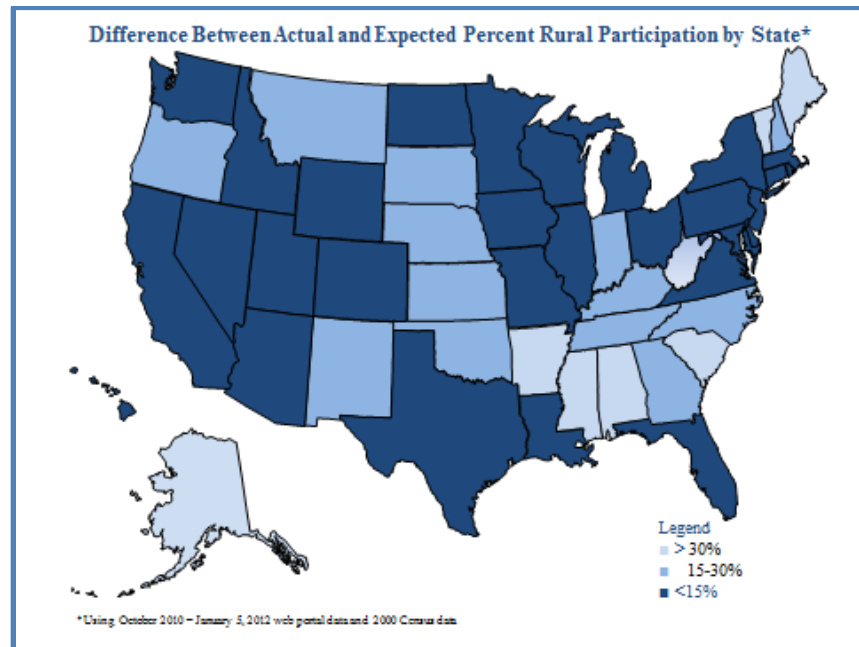
### Qualitative Data

**Wendy E. Kaye, PhD**  
**Senior Epidemiologist**  
**McKIn Consulting Corporation**

Dr. Kaye first presented an update on registration and participation in surveys within the Registry. There are terms of clearance on the OMB approval, which means specific numbers of participants may not be stated at this time. However, approval was received to evaluate participation by state. The following map reflects the percent participation by state compared with the entire US through May 18, 2012:

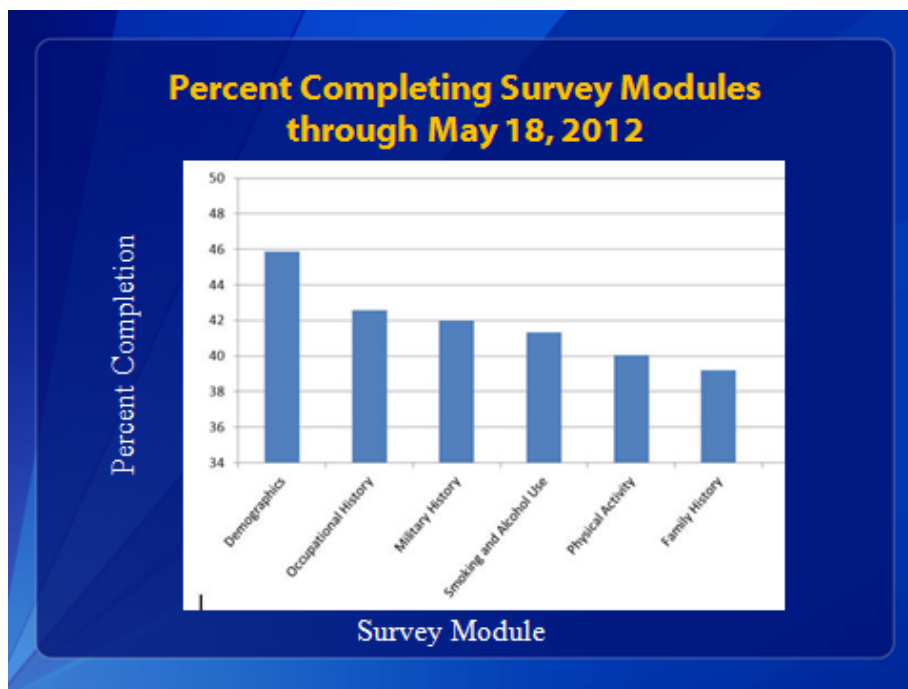


Percentages are lower in the Southwest, South, and on the West Coast. Given the possibility that there may be differences between those in rural and urban areas in terms of participation, assessment was made of participation by state from October 2010 through January 5, 2012. This is very complicated because each city had to be ranked as urban or rural according to the US Census. The results are reflected in the following map:



No overall urban / rural difference was observed. However, there is a major difference in some states such as Mississippi where people in rural areas are registering less than those in urban areas. Using the two maps together, strategies can be developed to disseminate information about the Registry and increase participation.

The following chart presents the percent of participants completing the survey modules.



The highest percentage completed is about 45% for the demographics survey. In general, about a third of the participants actually complete any survey. There seem to be takers and non-takers. There are large groups of people who have taken all of the surveys, and there are others who maybe completed the first or second one and did not complete any more. The physical activity and family history survey modules are the most complicated, which probably also affects the number of participants to some extent. The family history module asks about mother, father, children, and siblings. If someone has a large family, this can result in many questions. The physical activity module involves ranking one's level of physical activity at various ages, which makes it more complicated. The ALS Functional Rating Scale was not included in this information about the percent completing the survey modules, given that people can complete this module every six months so it could not be sorted out by individuals at this point.

In terms of where the Registry data are, ATSDR needs to be able to merge the portal data with the data from the national databases (e.g., Medicare, Medicaid, and VA benefits and health data) on an annual basis. Each of these datasets is on different calendar years, with about an 18-month lag with Medicare data and a somewhat longer lag with Medicaid data, which is causing a problem with the merging of the data. The first complete dataset, which would be for the calendar year 2011, is expected to be completed by Spring 2013. The issue with Medicaid is the fact that it is really run by states rather than the federal government, so the Centers for Medicare and Medicaid Services (CMS) must wait for states to report their data and then merge all of that data. Consideration is being given to using "preliminary" data, and a test will be conducted to determine whether this is possible. That would shorten the timeframe for the availability of the data.

### **Discussion Points**

Mr. Gibson inquired as to whether any thought had been given to mixing up the order of the questions.

Dr. Kaye replied that this cannot be done due to the IRB stipulations, because re-approval would have to be sought continuously. It is not that participants are completing one question in a survey and not finishing the rest. They are just not completing surveys. The surveys do not have names on them—they are numbered. In addition, she thought mixing the questions may also not be a good idea because she would not want someone to complete family history first because it might be discouraging. The demographics module is pretty easy and straightforward. The most important thing is to encourage people to register, participate in the surveys, and complete all of the modules even if they are not relevant. For example, it is important to respond to the military survey even if they were not in the military or to respond to the smoking and alcohol module even if they do neither because “no” responses are significant as well.

Dr. Horton said he thought in general, these response rates are pretty good. It is one thing to enroll, but to go one step further to take the surveys is critical. It was not clear to him whether people do not understand that there are surveys, and that just by enrolling they have done their duty. Or perhaps the agency is not doing a good enough job of letting people know about the surveys. He requested that those present take this message back to their constituents.

Dr. Kaye noted that in the past, once someone registered they automatically went back to their account and had to search for the surveys. Now participants can go directly to the surveys or go to their accounts, which definitely simplifies the process.

Dr. Brooks reported that they have recently heard a lot of complaints about passwords having to be reset, and he wondered how that was impacting survey completion.

Dr. Kaye responded that they now have permission to only change the passwords every 6 months. However, this fact cannot be advertised and they do have to change the passwords every 6 months based on CDC policy. At least they do not have to be changed every 60 days now.

Dr. Horton added that they hear the same complaints and know that this is still a burden. However, this is a CDC issue rather than a National ALS Registry policy. It was a major challenge to get the CDC requirement changed from 60 to 180 days. He has heard anecdotally that people become so frustrated with having to change passwords, they no longer want to participate. This is another major challenge.

Dr. Kaye clarified that this is a Department of Health and Human Services (HHS) policy, not just a CDC policy.

Dr. Brooks found this to be a crucial issue. He wondered whether consideration had been given to the possibility of having a patient advocate to create one of the videos. He thought one of the strongest potential ways to increase patient involvement would be to develop a video of a patient going through the process to help participants relate to this.

Dr. Horton replied that there is a video on the portal currently. Rick Dumas, a patient who normally attends the annual meeting, unfortunately died the week before this annual meeting. He wanted to provide a video because he also thought that if a patient stated why they believe it is important versus a government bureaucrat, it would resonate better with other patients.

Dr. Brooks stressed that some type of announcement about the anticipated reporting date of the data must be placed on the website so that patients know it is coming. One of the main

responses to their most recent clinic survey of patients was that they did not know where the Registry was headed.

Dr. Horton replied that because there are external factors involved, they are reluctant to make projections about dates that are subject to change. He agreed that people need some type of reasonable estimate, so they have recently started showing the timeline during various presentations throughout the country to let people know what is anticipated. Most of the cases come from Medicare, but preliminary data would be used from Medicaid.

Dr. Kaye clarified that Medicaid data are most often used for those who do not have enough data in one database to help move it them to another category in the algorithm. They are not finding a lot of people in Medicaid who are not also found in Medicare or the VA. Rather they may not have enough information based on the algorithm to be defined as a true case. This is why they believe it will be acceptable from a scientific point of view to use preliminary data for Medicaid and then truncate that down by a significant amount of time.

Dr. Horton added that the VA data are more real-time, so there is not a lag like there is with Medicaid.

Dr. Kaye noted that once they are informed that the 2011 data are actually available, they could probably make a good estimate of how long it will take to receive and analyze the data.

Mr. Wildman asked whether Dr. Kaye was permitted to share the slides about enrollment by state (e.g., the maps that she showed). This would address the issue about data to some extent. Patients wonder where the information is, so anything that could be shared would be beneficial.

Dr. Kaye responded that originally on the website, they envisioned a map that could be "moused" over that would give the number of people registered by state and some basic demographic information, such as 50% of the registrants are men, 30% are White, 20% are African American, et cetera. However, they were told they could not do this. The issue pertains to the denominator. Therefore, she indicated that she would further explore what could be shared. One state has approximately a 90% registration rate based on the expected number of ALS cases in the state. This is believed to be a combination of some states having people who are more receptive, and having ALS centers that are doing a better job of promoting the Registry.

### **Quantitative Data**

**Marchelle Sanchez, MS**  
**Health Scientist**  
**Environmental Health Surveillance Branch, DTHHS**  
**Agency for Toxic Substances and Disease Registry**

Ms. Sanchez began with an explanation of the algorithm that was developed for identifying ALS, Potential, and Non-ALS patients, which are defined as follows:

#### **ALS**

- ☐ ALS ICD-9 in 1 or more years\*\* and death certificate or Rilutek®
- ☐ ALS ICD-9 in 2 or more years and neurologist visit\*\*
- ☐ Age ≤ 65, ALS in Medicare and neurologist visit

- ☐ ALS in one or more years and neurologist visit\*\* with ALS in another source
- ☐ ALS in 3 or more sources
- ☐ ALS in one year and  $\geq 5$  neurologist visits\*\*

#### Potential

- ☐ MND in 1 year and ALS in 1 or more years after MND\*\*
- ☐ ALS in 2 years and no neurologist visit\*\*
- ☐ RX for Rilutek® only

#### Not ALS

- ☐ No ALS visit and no prescription for Rilutek®
- ☐ ALS in 1 year and no neurologist visit\*\*
- ☐ Age < 18 years
- ☐ No ALS in any source
- ☐ Only "Other MND" codes listed
- ☐ Death certificate only

\*\*In the same source

The following table shows the results of the algorithm for 2001 through 2005 Medicare, Medicaid, and Veterans Affairs data where the total number is the number of deduplicated ALS cases:

<b>Results of Algorithm on 2001 – 2005 Medicare, Medicaid and Veterans Affairs Databases</b>							
	Medicare		Medicaid		VA		Total
	N	%	N	%	N	%	N
<b>ALS</b>	<b>15,460</b>	<b>24%</b>	<b>3,456</b>	<b>23%</b>	<b>1,839</b>	<b>16%</b>	<b>16,226</b>
<b>Potential</b>	<b>18,932</b>	<b>29%</b>	<b>3,447</b>	<b>23%</b>	<b>3,023</b>	<b>26%</b>	<b>22,096</b>
<b>Not ALS</b>	<b>31,245</b>	<b>48%</b>	<b>8,050</b>	<b>54%</b>	<b>6,556</b>	<b>57%</b>	<b>44,338</b>
<b>Total</b>	<b>65,637</b>		<b>14,953</b>		<b>11,418</b>		<b>82,660</b>

\*VA includes data from the Veterans Health Administration and Veterans Benefits Administration

Information is being used from the National Death Index (NDI) to identify more people with ALS, especially from the potential group to see if this may change their category. The NDI is a central computerized index of death record information on file in the State Vital Statistics offices and compiled by the National Center for Health Statistics (NCHS). NDI is a resource to aid epidemiologists and other health and medical investigators with their mortality ascertainment activities. NDI death record information begins with 1979 deaths. Death records are added to

the NDI file annually, approximately 12 months after the end of a particular calendar year. The National ALS Registry uses NDI data to determine which registrants have died, date of death, and if the cause of death is listed as a Motor Neuron Disease (MND). NDI data do not have ICD-9 codes, so there is not an ALS-specific code, but it does have ICD-10 code for MND. ATSDR sent records for those determined to be definite or possible ALS per the algorithm to NDI including: Social Security Numbers, Names, Date of Birth, Age at Death (if known), Sex (if known), and Race (if known). NDI returned records with the same information showing the percentage of match and cause / underlying cause of death in ICD-10 codes.

In terms of how the NDI data is being used, one criterion of the algorithm uses death data to identify ALS cases. Date of death for cases of ALS is being used to calculate prevalence. Data are used to remove participants from active accounts in the web portal so that additional communication will not be sent to deceased participants. As a reminder, the first criterion for classification as ALS is "ALS in one or more years (in the same source) and a death certification or Rilutek® prescription." This is the point at which NDI fits into the algorithm. Following the addition of NDI data, a total of 25,453 individuals were categorized as having ALS, as depicted in the following table:

**Cases of ALS Identified from Existing Databases:**  
**National Death Index Data Support the National ALS Registry**

Case Type	2001 – 2005 Total from National Databases*		2001 – 2005 Total Including National Databases and NDI	
	N	%	N	%
<b>ALS</b>	<b>16,226</b>	<b>20%</b>	<b>25,453</b>	<b>31%</b>
<b>Potential</b>	<b>22,096</b>	<b>27%</b>	<b>12,869</b>	<b>16%</b>
<b>Not ALS</b>	<b>44,338</b>	<b>54%</b>	<b>44,338</b>	<b>54%</b>
<b>Total</b>	<b>82,660</b>		<b>82,660</b>	
*Medicare, Medicaid, VHA, VBA				

\*\*9,227 Individuals were categorized as ALS instead of Potential ALS after NDI data were added

Race, sex, and age distribution were determined using national databases only and national databases compared to NDI data. Racial distribution for identified ALS individuals from national databases only was:

- ☐ White 14,106 (87%)
- ☐ Black 1,182 (7%)
- ☐ Other 763 (5%)
- ☐ Unknown 175 (1%).

When compared with NDI data, racial distribution was:

- ☐ White 22,370 (88%)

- ☐ Black 1,638 (6%)
- ☐ Other 1,035 (4%)
- ☐ Unknown 410 (2%).

Sex distribution for identified ALS individuals from national databases only was:

- ☐ Male 8,246 (54%)
- ☐ Female 6,967 (46%)
- ☐ Unknown 13 (0%).

When compared with NDI data, sex distribution was:

- ☐ Male 14,385 (57%)
- ☐ Female 11,031 (43%)
- ☐ Unknown 37 (0%).

Age distribution for identified ALS individuals from national databases only was:

- ☐ 18 – 39 (720, 4%)
- ☐ 40 – 59 (6067, 24%)
- ☐ 60 – 79 (15,126; 59%)
- ☐ ≥ 80 (3343, 13%)
- ☐ Unknown (27, 0%).

When compared with NDI data, age distribution was:

- ☐ 18 – 39 (890, 3%)
- ☐ 40 – 59 (4589, 28%)
- ☐ 60 – 79 (9343, 58%)
- ☐ ≥ 80 (1570, 10%)
- ☐ Unknown (4, 0%).

In conclusion, NDI is a helpful tool in moving potential cases of ALS to the definite category that would not otherwise be found using other algorithm criteria. NDI data are helpful in the administration of the Registry by identifying those who are deceased.

### **Discussion Points**

Dr. Horton noted that there will be more categories for race in the portal.

Dr. Kaye clarified that the death data are not deaths from 2001 through 2005. It is people who were in the Medicare, Medicaid, and VA data during that time frame. NDI data are through 2008, which is why so many more people were captured with the addition of NDI data.

Referring to the definitions for ALS and Not ALS, Dr. Brooks inquired as to whether any sensitivity analyses had been done in any form. The first analysis was by Brody and Hoffman to assess this versus hospital records. The issue is the Not ALS showing up in the death database, which must have come to ATSDR with at least one ALS code.

Dr. Kaye indicated that the Not ALS were not sent to NDI, given that the investigators were 99.99% certain that they do not have ALS. They may have had other codes or other issues that suggested that at some point, someone may have been attempting to rule out ALS. These individuals never had an ICD-9 code specific for ALS.



Ms. Sanchez responded that sensitivity analyses were done for ALS and Unidentified, and sensitivity and specificity were all about 0.85 to 0.87. A sensitivity / specificity analysis has not been done on the NDI data.

Dr. Horton wondered whether a batch of Not ALS should be sent to NDI.

Dr. Kaye indicated that this could be done but had not as of now.

Dr. Horton indicated that a manuscript is currently being written, so the hope is to have these data are published as soon as possible.

## Registry Outreach and Marketing Update

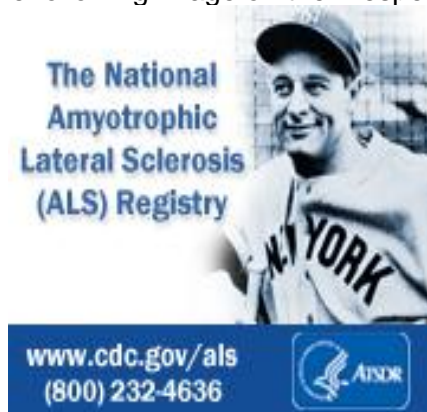
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### Agency for Toxic Substances and Disease Registry

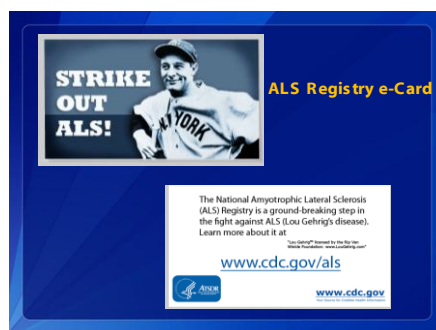
**Jay Dempsey**  
**Health Communication Specialist**  
**Office of Communication**  
**Agency for Toxic Substances and Disease Registry**

Mr. Dempsey reported that the National ALS Registry marketing strategy was to work with partners to generate awareness of the Registry and encourage persons with ALS to self-register; and engage persons and organizations who influence people with ALS in order to reach the largest number of potential registry participants. Audiences include PALS, family members, specialized healthcare providers (e.g., neurologists, physical therapists), ALS researchers who work with patients, and ALS support organizations or entities.

In 2011, the website was updated to be a comprehensive source of information for those seeking ALS information. Specific areas were created on the site for different audiences, and user-friendly tools have been initiated such as the Web Button. The Web Button allows bloggers or websites to place the following image on their respective pages:



Visitors to those sites can click on the button to go directly to the ALS Registry web portal, or call the 800 number provided for more information. The Web Button is being used on a number of websites (e.g., ALSA chapters, NEALS, MDA, PALS websites), and the Podcast is also linked directly from this page. The following E-cards are also available to send:



Over the last year, an analysis has been conducted about how many people have actually been visiting the website. Since the ALS website's inception in November 2010, there have been over 2000 views from the top 5 geographic areas for which the analyses were made (e.g., Washington, Atlanta, New York, Chicago, and Dallas). This informs some general geographic areas that are known to have been reached, and may inform some areas which need more intense focus. The total views of the website since November 2010 have been just over 33,000, so people are actually visiting the site.

During last year's ALS meeting, ATSDR shared information about attempts to leverage social media to share information about the Registry, and these efforts continued during the last year. The audience for those mechanisms has grown considerably. The main Facebook page that shares blanket information from across CDC and ATSDR occasionally features information about the ALS registry and reaches over 208,000 people. Certainly, during appropriate times

## Social Media

- **Facebook**
  - CDC/ ATSDR's Facebook page reaches over 208,000 people
  - Great way to share information and interact with ALS patients and caregivers
  - 127,000 + "impressions" since May 2012 post
  - 200+ visits to ALS Web page
  - Content sharing w. ALSA

The screenshot shows the CDC Facebook page with a post about ALS Awareness Month. The post text reads: "Currently, there is no accurate picture of who has ALS. ATSDR wants to change that. The National ALS Registry gathers information to help scientists learn more about ALS, also known as Amyotrophic Lateral Sclerosis or Lou Gehrig's disease. The more people living with ALS participate in this registry, the more accurate registry information will be." It includes a link to "www.cdc.gov/als" and a "Like" button. Below the post, several user comments are visible, such as "Laurie Ann Walling You have that right! So do I, want to change that!" and "Sherry Anderson ICHORD'S NEW VIDEO FROM ALS".

ATSDR will share information about ALS, such as ALS Awareness Month in May. The post in May 2012 had over 120,000 impressions. That may not mean that anyone actually clicked on the information featured on the Facebook page, but people saw it in the news feed that is a part of Facebook. A spike in web traffic is observed when a product is featured on the social media

channels. For example, the May 2012 post generated just over 200 visits to the ALS webpage. There have also been content sharing initiatives with ALSA. One of the takeaways from last year's meeting was a request for a dedicated space in social media for the ALS Registry. There are a number of factors that prevent this, but there is dedicated space on CDC, ALSA, and MDA channels. It makes a lot of sense to share content with each other when possible. Dr. Portier has a Twitter page that he uses on a daily basis. The follower count on his profile is just over 3200. He shared at least one message per week during ALS Awareness Month. A sporadic roll out of messages via Dr. Portier's page since February 2012 has generated 187 visits to the ALS web page and 85 retweets. The page that features general information from CDC and ATSDR on Twitter reaches over 94,000 people. There is also an ALS Registry Flickr album, which has been viewed just over 2600 times.

There is a survey on the ALS webpage. What has been learned from that is that PALS are hearing about the Registry in a variety of ways, including ALSA / MDA / Support Group (50.5%), Doctor / Physician (16.5%), Internet Search (10.3%), Other (9.3%), Family Members / Friends (4.6%), News / Media (3.6%), Twitter / Facebook (2.1%), and the ATSDR website (3.1%). It is key that over 50% of PALS are hearing about the Registry through support groups, and this will inform some of the work that will be done with ALSA and MDA. Mr. Dempsey also shared information about registry product distribution for requests that are received on a regular basis, which is shown in the following table:

<b>Registry Product Distribution</b>				
<b>Product Type</b>	<b>ALSA</b>	<b>MDA</b>	<b>Clinics, Centers, Physicians, General Public</b>	<b>Total</b>
<b>Patient Guides</b>	<b>5735</b>	<b>596</b>	<b>7861</b>	<b>14192</b>
<b>Provider Guides</b>	<b>491</b>	<b>334</b>	<b>925</b>	<b>1750</b>
<b>Fact Sheets</b>	<b>900</b>	<b>855</b>	<b>2566</b>	<b>4321</b>
<b>Quick Start Guides</b>	<b>830</b>	<b>446</b>	<b>2436</b>	<b>3712</b>
<b>Continuing Ed. Guides</b>	<b>100</b>	<b>156</b>	<b>510</b>	<b>766</b>
<b>Doctor Office Posters</b>	<b>37</b>	<b>141</b>	<b>477</b>	<b>655</b>
<b>Total</b>	<b>8,093</b>	<b>2,528</b>	<b>14,775</b>	<b>25,396</b>

As of May 2, 2012

In terms of proposed future plans, based on information from the survey, some targeted promotional work is planned in select publications relevant to persons with ALS, their families and caregivers, and ALS professionals. ATSDR also hopes to implement a broadened outreach campaign using national media outlets (e.g., USA Today, the Today Show, 60 Minutes). It would be impactful to get a good piece on a national news show, and the agency is working with outside partners on this strategy. Broadened outreach is also planned via social media (e.g., Facebook, Twitter, radio advertisements, PSAs, YouTube style videos, chat rooms, and online

communities). Mr. Dempsey emphasized that social media is not the “be all, end all” concept on marketing, but it is known that people are discussing ALS in the social media space, so these opportunities will be leveraged whenever possible. There was discussion earlier in the morning about utilizing videos, which works very well in the social media space. Research shows that if there is a video featured on a social media page or a web page, there tends to be an exponential increase in use of that page. Targeted outreach to military publications, professional webinars targeting clinicians, and tutorial videos for the National ALS Registry (e.g., completing surveys, using clinical notification mechanism) are also planned.

### **Discussion Points**

Dr. Horton emphasized that again, this points to the collaborative effort. ATSDR is at the bottom of the list in terms of how PALS hear about the Registry, which is reasonable. The most “bang for the buck” comes from ALSA, MDA, and physicians who work with patients on a daily basis unlike ATSDR. This speaks volumes about why these relationships are critical, and he expressed ATSDR’s gratitude for what its collaborators are doing to help promote the Registry.

Mr. Gibson noted that during the last ALS meeting, just “Support Group” was shown rather than ALSA / MDA / Support Groups. It was indicated during that meeting that most of the “Other” category was comprised of ALSA / MDA. He wondered whether that was still the case and if there was any way to update the numbers.

Dr. Horton responded that the last time he checked, the “Other” category did include comments about support chapters. Therefore, the 50.5% should be higher. This can be refined to make it more accurate, but this is a good snapshot that shows how people are finding out about the Registry. Regardless of whether it is 50% or 60%, ALSA, MDA, and other support groups are leading the charge. Regarding product distribution, there is a mechanism on the website where people can go to request information. Products are shipped free of charge via FedEx. ALSA and MDA are sending out a lot of products. Clinics and offices are requesting increasingly more information. As much as anyone can let their affiliates know that they can request these products at any time, ATSDR is happy to send it out.

Mr. Wiebe indicated that they refer physicians to the CDC website, so he was curious about whether there is an identifier when people request information through that site.

Dr. Horton replied that there is a field that asks for the requester’s affiliation. This is an internal tracking mechanism for ATSDR. There have been many inquiries and requests for these materials, and ATSDR will continue to ship them out as needed. As far as using the national media (e.g., USA Today, 60 minutes, et cetera), the impression that he gets from these groups is that they want to see data before they will dedicate a full piece to a topic. This is understandable, but the agency is in a holding pattern on this until the data can be presented. It is not that they have not been trying. There is an Office of Communication within ATSDR and CDC, and they routinely pitch ideas to various syndicated groups.

## **Amyotrophic Lateral Sclerosis Association**

**Steve Gibson**

**Vice President, Government Relations and Public Assistance**

**Amyotrophic Lateral Sclerosis Association**

Mr. Gibson reported that ALSA is very excited to be partners with ATSDR. The National ALS Registry has a very special place in all of the people at the ALSA's hearts. For the most part, ALSA's audience is similar to ATSDR's and includes the following:

### **Outreach & Awareness**

- **Raise Awareness of the ALS Registry**
  - Patients & Families
  - Caregivers
  - Veterans and other Organizations
  - Public
  - Press
  - Targeted States
- **Assist with Enrollment**
- **Most Importantly...**
  - Accomplish goals of the Registry: advance research to find the cause, treatment and cure



3

Though veterans comprise such a small percentage of people who have ALS, ALSA has found that veterans' organizations are a great outlet to the public in general because not many people remember Lou Gehrig anymore. This is especially true on Capitol Hill where the average age of the staffers is in the 20s. ALSA has made great strides on Capitol Hill on getting them to support ALSA's efforts, even when they had no constituents in the area. The focus on veterans' organizations continues to be a good asset for them. In addition to assisting ATSDR with awareness, ALSA plans to assist with enrollment in terms of disseminating materials and information about the research project to get people enrolled.

In terms of ALSA's project, an ALS Registry Chapter Toolkit has been developed. All chapters will receive this toolkit, and ALSA has done this for a number of initiatives in terms of having everything turnkey in one place. It may not be newly created. It is a gathering of information in one place. Many executives and clinicians are very busy, so having information in one place is very important. Last year, over 40 million people visited Minor League Baseball games. That number continues to grow, and ALSA is one of the official charities of Minor League Baseball. It is amazing because it is a launch pad for Major League Baseball, because Minor League Baseball organizations use their winter meetings that they hold for all of the trades for Major League Baseball. This offers a major awareness opportunity. There are also a new website and outreach tools, which continue to be a challenge for people.

In order to select tools, ALSA engaged in an ALS Registry Listening Tour during the Fall / Winter 2011 to figure out what is important to chapters. This included an hour-long call with all chapters, for which there was 100% participation. Participants included executive directors and clinicians, who were asked a series of questions about what tools they use from ATSDR in order to capture a lot of information. It was found that there are a lot of great "Best Practices,"

### Listening Tour Feedback

- Best Practices:
  - Information, Handouts
    - Center/Clinic
    - Support Groups
    - Homevisits
    - Events
  - Newsletters/Website/Email
  - Social Media
  - Enrollment Assistance



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including handouts, information from visits, homecare managers, newsletters, social media, and so forth that are available to share. Most importantly, many challenges were identified. The single greatest challenge is access to technology. That is more than just access to the internet. Mr. Gibson listed the following challenges:

- Computer access
  - ☐ No wireless/internet access
  - ☐ No computer at clinic, support group etc.
  - ☐ Progression of the disease
  - ☐ No email
  - ☐ Fear of technology
- Supporting Materials
  - ☐ Lack of Time and Resources
  - ☐ Lack of Information/Not Familiar with Registry

**Patrick Wildman**  
**Director, Public Policy**  
**Amyotrophic Lateral Sclerosis Association**

Mr. Wildman emphasized that the ALS Registry Listening Tour guided ALSA on what to do in terms of giving its chapters the tools to help share best practices and overcome some of the

challenges identified. There are three sections in the toolkit (e.g., Overview, Promoting the Registry, and Enrollment). The toolkit will be distributed to chapters in notebook form, and will be a “one-stop-shop” for chapters to get the word out about the Registry. The Overview includes background and history to educate chapters about the Registry, a flow chart to give an overview of the Registry, and a summary of the existing and planned modules. The Promoting the Registry section includes a check list of activities for chapters, information about best practices in the field, print and electronic newsletter articles that chapters can send out, a list of handouts and information about how to acquire them, about a year’s worth of social media (e.g., Facebook posts and Tweets) that chapters can send out, web tools, talking points, and Minor League Baseball. There seems to be a lull and people are not energized. With this toolkit, ALSA hopes to keep the energy flowing throughout the year. The Enrollment section includes a check list, best practices information, Quick Start Guide, FAQs, information about how to create an Email account, and help and resources. This is a living document, so responses to additional questions will be added.

The attendance at Minor League Baseball is about the same as at Major League Baseball. That is primarily because there are 30 Major League Baseball teams and there are 160 Minor League Baseball teams throughout the country. With 41 million people in the audience, and that is just attendance alone, it does not include broadcasts, this offers a tremendous opportunity to get the word out about the National ALS Registry. Initially, ALSA created simple advertisements for programs that teams could place in their programs in order to leverage the connection between ALS and military service. ALSA has found that with their interactions on Capitol Hill and generally, once the military service connection and ALS are mentioned, people’s interest is peaked.

During the Baseball Winter Meetings, a lot of interest was generated among a number of teams. ALSA created a focus group of teams throughout the country who are interested in helping spread the word about the Registry. From that focus group, a campaign was created called “Tribute to Our Military Heroes,” which leverages the connection between ALS and military services and includes a number of turnkey elements. This is a very flexible program that is designed for teams and ALSA chapters to work together to create a program that works best for them to raise awareness about the Registry. Part of this entailed the creation of a website that includes a variety of information, such as information about events, links to the ATSDR portal and the Ecards mentioned earlier and video links to PSAs that are designed to be played



## Minor League Baseball



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during games on the video board as well as during broadcasts. During games, teams and chapters can have a booth to distribute registry literature and information, hold on-field ceremonies, and give out flyers and stress balls. Turnkey information is provided to teams to help them implement these programs that include: instructions, press releases, flyers, order forms, newsletters, sample talking points to use in the booth during a game, social media information, fact sheets, registry information, and chapter contact information. Turnkey information is also provided to chapters that includes instructions, press releases, newsletters, and social media information.

ALSA is creating a new section in its website devoted to the Registry. The goals of this section are to make it easier for PALS, families, and chapters to find information; make the section appealing to different audiences (e.g., PALS – Peer to Peer, Caregivers and Families, Veterans); and make the section more interactive, including videos and photos. Mr. Wildman shared some screenshots of the draft pages. The concept is that people with ALS are heroes,





because enrolling in the Registry can advance the understanding of the cause and ultimately the cure and a means of prevention. The child in the red cape was used because consultants have indicated that a child will get more interest, and Mr. Wildman invited feedback about the page from the participants as well. There are pages to appeal to caregivers, veterans, and people with ALS. Throughout the site, there are links to fact sheets, brochures, videos, enrollment instructions, et cetera. A section of the site will be dedicated to videos, which can be accessed from a variety of places other than the ALSA website, such as through YouTube. A map of the country will be included so that people can mouse over states to see videos from people who post their own videos about why they enrolled in the Registry and why it is important to them. Peer-to-peer communication is much different than communications from ATSDR and ALSA. Mr. Wildman shared a video of PALS promoting the Registry. Pending IRB approval, ALSA plans to break that video up, with a lot of additional footage as well in order to be able to use it in social media venues. The video is completely unscripted. It is people with ALS sharing their own feelings and views about the Registry. People can also upload their own videos.

ALSA is promoting the Registry in the field through the provision of tablets through chapters that can be taken to home visits, support groups, and clinics to introduce people to the Registry, show them what it is and how to enroll and answer their questions. Because there are people without access, it is important to ensure that technology is provided for them to assist in enrollment. Given that some areas do not have internet access, a mobile device is provided to the chapters along with the tablets so that they can get online regardless of the availability of wireless technology. Because not everyone knows how to use tablets, guides are also provided. The tablets are preloaded with the Registry as a bookmark, and it comes up as the homepage.

### **Discussion Points**

Dr. Horton noted that since all of this is targeted primarily toward patients, it will have to go through IRB approval. All of the toolkit information has been submitted to internal ATSDR clearance, and it will soon be sent to IRB. The hope is that within the next month, this process will clear the information as well. While there is a series of checks and balances, ATSDR believes this will be a very valuable way to promote the Registry, and ALSA has done some really exciting things.

Dr. Brooks applauded the efforts being made for this initiative. Given the deployment of iPads and other tablets to patients from a variety of sources, he suggested that video be included that shows patients using a tablet. He thought he heard that there would be a "State of the Registry" paper published before the actual release of data, so he stressed the important for this to be an open access paper so that people do not have to go through a library to access it. He also wondered why an outside organization for a national, publically supported, opt-in registry needed to go through CDC's IRB.

Dr. Kaye replied that it is because ALSA has a contract with ATSDR; therefore, they are serving as ATSDR's agent.

Mr. Wildman indicated that ALSA enrolled a number of people during the advocacy conference in May, and they got some great photos of people using the tablets at that time as well.

Dr. Horton added that this was the first registry to his knowledge that was using technology like this to take a registry to the people. It will be interesting to assess whether there have been spikes in enrollment since going wide with these tablets. Using technology where possible and reaching those in rural areas who do not have access puts them well on the way to increasing

enrollment. With the limited dollars available for this program, ATSDR is trying to get the most “bang for the buck,” and a lot of full page ads have been placed in various patient magazines through MDA and ALSA. He wondered from a clinician’s standpoint whether it would make economic sense to place ads in clinical journals. He has heard pros and cons about this mechanism.

Dr. Sorenson responded that for the most part, all of his journal reading is done electronically online now and he could not remember the last time he had opened a journal. The way he accesses the journals electronically, they do not have ads on line. However, there are ads directly on the neurology website. If that is an option, it would be better than placing them in journals.

Dr. Traynor added that a hard copy of *Neurology Today*, published by the American Academy of Neurologists, is disseminated to all neurologists.

### **Muscular Dystrophy Association**

**Sanjay Bidichandani, MD**  
**Vice President—Research**  
**Muscular Dystrophy Association**

Dr. Bidichandani emphasized that the MDA is extremely supportive of the ALS Registry, though they have a slightly differently relationship with ATSDR than ALSA in that the MDA does not have a contract. MDA does this because they believe it is worth doing. He explained that the national MDA office is located in Tucson, Arizona and that there are 200 offices throughout the country that have health care service coordinators and other MDA staff. The national office’s primary role is to support MDAs 200 neuromuscular disease clinics, 42 of which are ALS centers. There is also the ALS Clinical Research Network, which is comprised of 5 centers that are funded to conduct clinical studies and trials as part of the MDA network. Currently, \$25 million dollars are allocated to 71 research grants specifically for ALS. MDA has a partnership with ALSTDI as part of Augie’s Quest through which over \$30 million has been raised over the past few years. The \$25 million is broken down primarily into basic research grants of \$15.7 million (N=43). The figure of \$25 million is important because at any one time, MDA has approximately 300 active grants that total approximately \$100 million. That is a fourth of MDA’s research budget. MDA cares for people with 45 different conditions. Also funded from that \$25 million are 4 translational research grants totaling \$4.7 million (mostly Augie’s Quest: \$3.2 million), 5 clinical research network grants totaling \$1 million, 12 training grants totaling \$2.2 million, and 7 miscellaneous grants totaling \$1.4 million.

In addition to the clinics and research, MDA also provides advocacy, medical equipment, support groups, and educational seminars. These allow MDA to touch individuals with ALS and get the message across about the ALS Registry. MDA also administers influenza vaccines, and multiple publications are sent out through the MDA website either in hard copy or electronically. An annual conference is convened, which alternates between a clinical focus and science focus every other year. The clinical conference was a great site to get the message across because clinical directors and various clinic team members attend that meeting. ATSDR featured ALS Registry exhibits. There is a significant amount of discussion about ALS during these conferences, and everyone is welcomed to attend. The next science conference will be convened in March 2013. In addition to the national conferences, MDA has begun a symposium series dedicated to a specific topic for small groups of individuals. Recently, a

symposium was convened on ALS, and there will be at least one symposium focused on ALS each year.

ATSDR has been placing full-page ads in MDA's *QUEST Magazine* (circulation 130,000) and *MDA / ALS News Magazine* (circulation 22,500). Many individuals do not have access to computers and / or the internet, so these are hard copy magazines that are disseminated. These magazines are going to be fused into one. MDA also creates a number of online communications, including advocacy and research newsletters. The CDC ALS button has been placed on the MDA website and Facebook page, MDA has been tweeting, and MDA and ATSDR have been re-tweeting each other's tweets.

National ALS Registry information dissemination efforts to members of the MDA PALS / CALS community include the following:

- ☐ MDA publications
- ☐ MDA website button / links
- ☐ Exhibit space at MDA sponsored meetings (including national conferences)
- ☐ Information at seminars, support groups, and local events
- ☐ New person registration packets and MDA clinics
- ☐ Information from MDA HCSCs & MDA Clinic Teams

National ALS Registry information dissemination efforts to MDA staff members nationwide include the following:

- ☐ Staff trainings
- ☐ Monthly DDHCS calls and ATSDR update distribution
- ☐ Supply field office distribution from the national office and online replenishment for seminars, support groups, and local events
- ☐ New person registration packets and MDA clinics
- ☐ Inclusion of updates and reminders in MDA's internal staff publications and intranet site

National ALS Registry information dissemination efforts to MDA-supported researchers include the following:

- ☐ Research update / eBlast
- ☐ Advocacy Alerts
- ☐ Exhibit space at MDA sponsored meetings (including national conferences)

National ALS Registry information dissemination efforts to MDA-supported clinicians include the following:

- ☐ Materials distributed from MDA field offices to MDA clinics
- ☐ Presence of MDA HCSC at MDA clinics
- ☐ Research update / eBlasts
- ☐ Advocacy Alerts
- ☐ Exhibit space at MDA sponsored meetings (including national conferences)

National ALS Registry information dissemination efforts to MDA community supporters (e.g., volunteers, donors, sponsors, congressional champions, et cetera) include the following:

- ☐ Advocacy alerts (The MDA Voice, Take 5, et cetera)
- ☐ MDA publications
- ☐ ALS Registry materials & displays at MDA events, seminars, clinics, symposia, support groups, et cetera

## **Discussion Points**

Mr. Wiebe indicated that once a month, ATSDR shares with MDA and ALSA the listing of states that are lagging behind and the states that have had no new registrants in the last two months. MDA shares that with its staff across the country who then can engage in more targeted outreach to those areas in order to help improve registration.

Dr. Horton said he had noticed an uptake in the number of MDA tweets and Facebook posts in the last couple of weeks, which ATSDR really appreciates. He expressed his hope that ATSDR could be placed on a regular rotation.

Mr. Wiebe replied that MDA has been active with social media, but is becoming more active. He said that he would follow-up about a regular rotation.

Dr. Bidichandani added that MDA is actually putting up two Tweets per day currently.

Dr. Horton indicated that when ATSDR attended clinical meeting in March, some clinical staff approached them who knew very little about the Registry and some who said they knew nothing about it. He wondered how this could be changed, and whether MDA's outreach was impacting this. It seemed like all of the clinical directors attending the meeting knew about the Registry, but it was not clear to him whether that was filtering down to their staffs such that those who are actually seeing / treating patients know about the Registry so that they can inform them about it.

Mr. Wiebe responded that historically, MDA has always reached out to its clinical directors as a primary point of contact. Over the last several months to a year, they have realized that information may not be trickling through quite as well as it could be. Thus, they are trying to do more to reach the entire clinic teams.

Dr. Horton emphasized that ATSDR would provide as many materials as possible to ensure that the effort to increase awareness continued.

Dr. Brooks noted that the MDA has a unique group of Health Care Services Coordinators (HCSC) in each district. Carolinas Medical Center has worked closely with their HCSCs to discuss registry issues for the ALS component, and is also involved in synergy in other neuromuscular disease registries as well. One issue Carolinas Medical Center has identified that there are competing registries. Some patients may be entered into a local registry and may not think about the National ALS Registry. In addition, there may not be local enthusiasm about the CDC registry when they are trying to get their own registries in place. He thought there needed to be education from ALSA and MDA regarding how important this is at the HCSC and ground levels.

Mr. Gibson said that they discovered on their Listening Tour that there is confusion about the registries. Some people think that registering with a chapter is registering with the National ALS Registry. In the checklist for chapters is to really emphasize that there are various registries, as well as the importance of completing the surveys. Just because someone is in the Medicare, Medicaid, and VA does not mean they are achieving the full goal of what the National ALS Registry is designed to do—the risk factor surveys.

Dr. Horton noted that ATSDR has a feedback mechanism and receives a lot of feedback. One person has posed this question a number of times, "On the day of diagnosis or maybe a week or two afterward, why don't neurologists take the time to educate people about the Registry?"

His response to this person has been that this is largely dependent upon how important the practitioner thinks this is. While ATSDR cannot make physicians tell their patients about the Registry, it is a very good point that at or near the time of diagnosis may be a critical window of opportunity to let the newly diagnosed patient know about the Registry.

Mr. Handsfield said that when he introduced himself, he did not indicate that his family is impacted with ALS. His wife was diagnosed last January. Even though clearly something was going on with his wife for a couple of years, receiving that diagnosis was pretty overwhelming. The amount of information they were given was rather overwhelming as well. They are still in the grief process 6 months later, and his wife is just now starting to ask how to get involved in clinical trials. She has not registered yet, although she probably will at some time. Because patients are already overwhelmed just by the diagnosis, maybe the plan should be to introduce the Registry 6 months post-diagnosis, perhaps during the third multi-disciplinary clinic visit.

Dr. Horton agreed that they want to be sensitive and not overly aggressive. He just wondered whether there is a magic timeframe if a physician wants to do this. He thought what Mr. Handsfield suggested sounded reasonable. It is a balancing act, and everyone probably approaches it differently.

Dr. Brooks thought information overload and timing issues were important points, but ATSDR needs to realize that part of the participation by the patients comes from information of importance that the agency is releasing to them. There must be a continual relationship between what goes into the Registry and what comes out of it that may impact on the potential causes of ALS.

## State- / Metro-Based ALS Surveillance

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**Laurie Wagner, MPH**  
**Research Associate**  
**McKing Consulting Corporation**

Ms. Wagner explained that the purpose of the state and metropolitan-area surveillance project is to:

- ☐ Use data to evaluate the completeness of ATSDR's National ALS Registry
- ☐ Obtain reliable and timely information on the incidence and prevalence of ALS and better describe the demographic characteristics (e.g., age, race, sex, and geographic location).

The states that are participating include Florida, New Jersey, and Texas. The metro areas include Atlanta, Chicago, Detroit, Philadelphia, Los Angeles, and San Francisco. In order for

## Participating Sites

Current Participating Sites



states to participate, they were required to have at least a population of 4 million and states were specifically selected to over-represent some minority populations (e.g., Hispanic, African American) compared to the US population. Metropolitan areas were required to have at least 1.5 million, and were also selected to over-represent some minority populations (e.g., (African-American, Asian-American). In terms of the state and metro project site areas combined, the African American population is over-represented in comparison with the US, Asian-Americans

## Combined State- and Metropolitan-Area Demographics

Race	US Total Population		All Project Sites	
Total:	%	308,745,538	%	80,749,953
White alone	72.4	223,531,770	64.9	52,412,676
Black or African American alone	12.6	38,901,938	15.5	12,520,709
American Indian and Alaska Native alone	0.9	2,778,710	0.5	429,833
Asian alone	4.8	14,819,786	6.6	5,359,045
Native Hawaiian and Other Pacific Islander alone	0.2	617,491	0.1	105,133
Some other race alone	6.2	19,142,223	9.3	7,478,336
Two or more races	2.9	8,953,621	2.5	2,055,221
Hispanic or Latino	16.3	50,325,523	28.7	23,201,691

are higher than the US population, and the Hispanic or Latino ethnicities are higher than the US population as well.

IRB has been a challenge overall; however, Dr. Kaye is highly specialized in dealing with IRB issues, so there have not been many problems. It is just very time-consuming. The state and metropolitan area-based surveillance was determined to be research at CDC / ATSDR because it will contribute to generalizable knowledge about the National ALS Registry. Approval was received from the CDC / ATSDR IRB in June 2010. Individual state and metropolitan areas consulted local IRBs to determine if the activity is considered human subjects research and obtain IRB approval. New Jersey, Florida, and California determined that the project is not considered human subjects research. Texas received IRB approval from the Department of State Health Services. Philadelphia received IRB approval from the Pennsylvania Department of Health. Atlanta, Chicago, and Detroit relied on CDC's IRB determination. In addition to the local, state, and federal IRBs, some of the institutions decided to go through their own IRBs, so some of the universities and hospitals had additional IRBs.

To prepare a comprehensive, up-to-date list of practicing neurologists to contact, data were obtained from the American Medical Association, which was supplemented by internet searches. ALS specialists were identified and sub-specialties that are unlikely to see ALS patients (e.g., pediatric neurologist) were removed from the list. This resulted in the final list that was used for mailing and contacting physicians. Project materials were then mailed to each provider in the study areas, and follow-up calls were placed to each physician to confirm whether these providers see ALS patients. For states, 2069 physicians were contacted. Of those, one-third diagnose and / or treat ALS patients (N=704), 1346 were determined not to treat or diagnose ALS patients, and the status was never determined for 19 of the Texas neurologists. The answers to a few questions are still pending at this time for some of the practices. For the metropolitan areas, Atlanta and Detroit have been collecting data for about 6 months. Philadelphia has been collecting data along with New Jersey because of the overlap of the practices. Chicago, Los Angeles, and San Francisco have been collecting data for about a month. The total number of physicians that need to be contacted in the metropolitan areas is 2200. Of those, 229 physicians have been identified to diagnose or treat ALS patients. About 1000 do not diagnose and / or treat patients, and contact is pending for over half of the physicians. Because Los Angeles and Chicago have such large numbers, they have not contacted all of their physicians, so they are still in the unknown stage.

Case ascertainment was conducted by collecting case reports from participating neurologists for all ALS patients diagnosed or treated from January 1, 2009 to December 31, 2011. The case report form includes 15 brief questions that are completed by physicians and submitted to the surveillance project. These forms include identification, demographic, and diagnosis information. After completion by the physicians, they were submitted to each site. Through May 31, 2012, for the states there have been 4380 ALS cases reported. These reports came

## Results: Cases\* Reported State-Based ALS Surveillance through May 31, 2012

	Florida	New Jersey	Texas	Total
Cases Reported	1825	909	1646	4380
Practices Reporting	90	54	96	240
The overall expected number of cases, based on 2010 US Census is 4219				
*Includes duplicate reports				

from 240 practices. This does include duplicates, and additional cases may have been received since that timeframe. Overall, 4319 cases are anticipated for these areas combined. Through May 31, 2012, the metropolitan areas have collected 380 ALS case reports from 15 practices.

Their overall expected number of cases is 2165. Chicago and Los Angeles have not received any reports yet, and San Francisco has received only 4. While Atlanta has not received the anticipated number of reports yet, Ms. Wagner has contacted every office.

For quality assurance, cases were selected for verification. Case verification documents the signs and symptoms of a patient with ALS, and EMG reports were collected if available. This information was then sent to the consulting neurologist, who determined whether cases were truly ALS cases. Through May 31, 2012, a total of 447 case verifications were completed. Of those 447, only 10 were deemed not to be ALS. Most of the cases that were submitted were truly ALS cases. For quality assurance to assess the completeness of reporting, the states have been asked to use existing data such as death certificates and hospital billing data to identify possible cases that have not been reported. The total number of cases identified through death certificates and not through case reports is 1544. The total number of cases identified through hospital discharge data is 1331, with only Florida and New Jersey reporting to date. New Jersey found 38 duplicates between death and hospital discharge data. This information has not yet been received for Texas and Florida, although there is some overlap between the two.

Throughout this project, some unique challenges have been encountered. Texas is comprised of a vast geographic area with rural populations that have medically underserved populations. New Jersey is in close proximity to large referral centers that are outside the state in Philadelphia and New York City. Therefore, much of the case ascertainment has been conducted in Philadelphia and New York City. Florida and San Francisco have large transient populations, and it is difficult to track their medical services. For Philadelphia and Detroit, there



are a number of homeless patients who seek care, and it is difficult to determine if they reside within the project areas. For the metropolitan areas, patients have to reside within certain zip codes, so it is very important for the metropolitan areas that a place of residence be determined. Atlanta, Chicago, and Los Angeles are sprawling metropolitan areas with numerous and dispersed medical centers.

Data analysis plans are for ATSDR to assess the completeness of the National ALS Registry. McKing Consulting Corporation will describe the methods that are used and will conduct analyses for combined state data and metro data. States and metropolitan projects will calculate area-specific incidence and prevalence rates. The states' data should be complete by summer of 2012, and the metro data should be available by summer of 2013.

### **Discussion Points**

Dr. Bradley noted that comparing the maps Dr. Kaye showed earlier in the morning and these data, it was obvious that because the data collection and analyses are not complete, no conclusions could be drawn at this point.

Ms. Wagner responded that the data are still being submitted, and while Texas still does not have the hospital discharge data and cannot follow-up on it, at least the number that may be missing can be filled in.

Dr. Horton inquired as to whether any feedback had been received about the rationale for why some facilities are not reporting.

Ms. Wagner indicated that she has called and followed up with several offices in Atlanta, including visiting them in person. They have good intentions, but they may not have the time, staff, or coverage. Even if she goes in person, sometimes they cannot identify the cases for her.

Dr. Kaye added that some practices are trying to transfer to electronic medical records (EMRs) under the Affordable Care Act (ACA), and they cannot use their systems yet so they cannot find people. As Ms. Wagner mentioned, others have good intentions but cannot find the time to do it. Others have said they do not want to participate if they are not required by law to do this and there is no penalty for not doing so.

Dr. Horton asked whether these are all larger practices or if there are some "mom and pop shops," and if so, what their responses have been.

Dr. Kaye responded that there are practices with just one or two cases. About half of the cases are from "mom and pop" sources. That could be from groups that are much smaller than a referral center that have from 1 to 20 cases.

Dr. Knorr mentioned that in Massachusetts, a lot more reports are from private neurologists than anticipated. They thought most of the cases would be reported from the large centers. He requested clarity regarding how duplicate reports are being identified.

Ms. Wagner replied that initially the states collect the data. When they go to another facility, they are supposed to check for the names, but they still get entered because the data that comes to her still has duplicates. While they are not supposed to take duplicates from the same

facility, it is okay if someone has been to 5 places. They have the identifiers (e.g., names, Social Security Numbers, date of birth, et cetera).

Dr. Knorr asked whether Philadelphia and New York City had any difficulties with the IRB process.

Dr. Kaye replied that they all received IRB approval eventually, although some took longer than others. A lot of the facilities in New Jersey did not require approval within their own facilities because the public health department deemed it to be public health surveillance rather than research, therefore making it reportable under state law. Some universities are relying on the CDC IRB, some went through their own IRB process, and some were told by their IRB's they were not engaged in research and did not need IRB approval.

Dr. Knorr noted that because Massachusetts has ALS as a reportable disease, it makes a major difference. They updated their regulations, so no physicians declined to supply information. They may not have all liked it, but no one refused. Their participation is about 85%, and they believe they know why some are not submitting cases. For example, some are not submitting cases because they do not have any, some have retired, and some have moved out of state. It was not a problem for Massachusetts to update their regulations. All state health departments have regulations for reportable diseases, and they had the authority but it was not explicit for ALS. Therefore, they thought it would be clear to all of the physicians if it was made to be explicit. All states have a process for doing this. It was not that involved for Massachusetts, so this could be considered as a longer term plan. Ms. Wagner agreed that this would help.

Dr. Brooks pointed out that based on pharmaceutical databases, as high as 45% of patients are not seen in centers so these ranges are important. The 2% Not ALS is low compared with Carolinas Medical Center's experience in terms of people who are referred to them with questioned ALS. This seemed too good to be true, which he thought should be kept in mind moving forward.

Ms. Wagner replied that because all of the data are not in, this may vary some. This is based on what was received through May 31, 2012.

Dr. Muravov asked what percentage of cases has been verified at this point by the neurologist. He understood that the project is using a single neurologist for the verification, Dr. Sorenson.

Dr. Kaye responded that Dr. Sorenson has verified 447, of which 10 were deemed not to be cases.

Dr. Sorenson reminded everyone that the cases were classified as Definite, Probable, Possible based on the El Escorial criteria. The cutoff is what proportion would be expected if all possible cases are included. If all possible cases were included here, the numbers would look somewhat better.

Dr. Kaye clarified that they did not quibble. If the center said it was definite and Dr. Sorenson said it was only possible, those were not counted as not verified. Only the ones for which he said he did not believe it was ALS were not counted.

Dr. Sorenson added that the 10 cases were obvious cases of "Not ALS." These were clearly cases that were incorrectly classified.

Ms. Wagner noted that some offices may have used billing data and reported cases by the ICD code, but sometimes they did not seem like ALS and those were verified. An attempt was made to verify at least one case from each practice, so this should represent the overall practices from which cases were ascertained.

Mr. Gibson noted that while Dr. Knorr indicated that revising the regulations to include mandatory reporting for ALS was a very easy process for Massachusetts, unfortunately all states are not like Massachusetts. In states like Texas and Oklahoma, members of Congress were adamant that this not become reportable. Surprisingly, a number of patients were upset when the Massachusetts legislation was passed because many had not told their employers, families, and so forth. This issue should be thoroughly assessed and discussed before future plans move forward.

Ms. Wagner found that many patients had not consulted their families when she was doing case ascertainment for ALS and MS, so they were very careful not to divulge information.

Mr. Kingon indicated that he spent 18 years in sexually transmitted disease (STD) control at CDC, and they had to be very careful in terms of confidentiality with regard to reportable diseases. There were always physicians and patients who did not want to be reported. He was curious about whether Massachusetts worked with the state epidemiologist, and noted that the Council of State and Territorial Epidemiologists (CSTE) meet frequently to consider which diseases should or should not be included.

Dr. Knorr replied that it was through their infectious disease regulations. A section was added on environmentally related infectious diseases. There is a legal process that they had to go through.

## Updates from Registry Partners

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### Northeast ALS Consortium

**James Berry, MD**  
**Neurology Clinical Trials Unit**  
**Massachusetts General Hospital**  
**Northeast ALS Consortium**

Dr. Berry reported that the Northeast ALS Consortium (NEALS) was founded in 1995 with 9 centers. There are now over 100 sites nationally. There is also a coordination center for data management and a monitoring center for outcomes monitoring. The goal of NEALS is to translate breakthroughs in basic science into clinical research / trials rapidly and effectively. NEALS aims to support young investigators, allow resource sharing, ensure reliable trial results, attract biotech companies to the field of ALS to increase the amount of research, and provide patients with information about becoming involved in clinical trials. The NEALS website, with the help of ALSA, has been revamped and there is a very good search feature so that patients can find research for which they may qualify, which is synergistic with the capability of the National ALS Registry to send patients who are interested information about trials for which they may qualify without them having to search for these.

A number of ALS clinical trials are being conducted through NEALS and with partners. There are NEALS-led trials, partially NEALS-led trials with participating centers, and then some gray area in between. NEALS-led trials are trials in which the principal investigator is a NEALS investigator, but the coordination center and data monitoring center are running the trial and NEALS sites are participating. There are a number of trials which are partially NEALS-led and in which there is NEALS site participation. A list of these follows:

#### NEALS-Led Trials

- ☐ Ceftriaxone for the Treatment of ALS
- ☐ Creatine and Tamoxifen for the Treatment of ALS – A Selection Design Trial
- ☐ Arimoclomol for the Treatment of superoxide dismutase 1 (SOD1)-Mediated ALS

#### Partially NEALS-Led Participating in Trials

- ☐ Human Spinal Cord-Derived Stem Cells for the Treatment of ALS
- ☐ ISIS 333611 Antisense Oligonucleotide for the Treatment of SOD1-Mediated ALS

#### NEALS Site Participation

- ☐ Dexpramipexole for the Treatment of ALS
- ☐ CK357 for the Treatment of ALS-Induced Weakness
- ☐ NP001 for the Treatment of ALS

#### Upcoming NEALS Trials

- ☐ Fingolimod
- ☐ Mexillettine
- ☐ Mesenchymal Stem Cells Secreting Neurotrophic Factors

There are a few non-drug intervention trials that are being led by NEALS investigators, including the following:

#### Exercise Study

- ☐ Compares usual daily exercise with a prescribed exercise program
- ☐ We do not have data to guide us about best exercise regimens
- ☐ Now enrolling

#### Diaphragm Pacer Study (being planned)

- ☐ Pacer currently has Humanitarian Exemption from FDA based on safety data
- ☐ Study will aim to determine efficacy
- ☐ In planning phases

#### Nutrition Study

- ☐ Testing high fat/high calorie diet versus routine diet
- ☐ In patients with gastrostomy tube
- ☐ Enrolling

There are also a number of biomarker discovery and biobanking efforts underway. The biofluid banking can support biomarker research by allowing ready access to high quality samples and clinical information. Biomarker discovery has numerous potential benefits. It could certainly lead to early diagnosis and study entry, could provide surrogate endpoints for clinical trials, inform research in ALS pathophysiology, and identify novel therapeutic targets. The biobanking efforts at NEALS began with a large study with 4 groups: those with ALS, those with perilymph fistula (PLF) upper or lower motor neuron disease, disease mimics, and healthy controls. There

was a medication washout for non-essential medications, and clinical data and biological specimens were collected. For those with motor neuron disease, there were follow-up visits at 6, 12 and 18 months for serum plasma collection and ALSFRS. That study has been completed.

There is now a Longitudinal Biomarker Collaboration at NEALS that is enrolling only patients with ALS. It is very broadly enrolling patients who have an FVC of over 50% to ensure that more than one or two samples can be collected from participants. The idea is to collect detailed clinical information, as well as biofluid specimens from patients every 4 months for up to 3 years. The standard operating procedures (SOPs) are similar in the hope of building the biobank that exists at NEALS. That study has presented a number of challenges. What they have found at NEALS is that biomarker studies are slower to get up and running through the IRB than are trials, by and large. There is always a concern about enrollment in biomarker studies, and all the necessary elements of a virtual repository must be created. That is, not all of the samples are stored together. Some of them are stored offsite at each of the participating centers. Nevertheless, there have been successes. Enrollment is on-going, with 27 participants enrolled in the study. The hope is to expand this. Follow-up visits are underway, the virtual repository is up and running, RNA analysis is underway, sample quality appears to be high, and SOPs are working well.

The statistical advantage to using longitudinal data is that with as few as 5 patients, it can be shown that a biomarker may be tracking with disease progression. The reason for the null hypothesis in a biomarker study is that there is no change in the biomarker over time. So if the assumption is made that a biomarker is at least as good as ALSFRS-R, with as few as 5 patients it can be statistically demonstrated that disease is progressing. The reason for that is because this compares the difference between the null hypothesis with no change to the change observed assuming the parameters of the ALSFRS-R. This is different from a clinical trial where a much smaller change due to a treatment is being sought, say 30%, rather than the null hypothesis with no change over time. The use of longitudinal data and the collection of longitudinal biomarker samples in this context can be incredibly powerful. The hope is to find a biomarker that is much more reliable than the ALSFRS-R that could be used as a surrogate outcome. The caveat is that this is for targeted analysis. Untargeted analysis reduces power because of multiple comparisons.

There are a number of other initiatives on which NEALS investigators are interested in working. Clinical databases are important for standardizing the collection and capture of clinical data across NEALS sites, allow natural history studies, and could complement epidemiologic data from ALS Registry. There has been discussion about creating a NEALS tissue bank, and there is increasing discussion about using telemedicine, much of which is being demonstrated or considered in the National Biorepository effort. Many of NEALS' efforts are complementary to the work being done by ATSDR. One of the exciting things that NEALS investigators are recognizing about the National ALS Registry is the ability to use it as a recruitment tool. This is filtering down to investigators, and there are opportunities to explain this better so that people understand the potential benefits.

### **Discussion Points**

Dr. Horton inquired as to what recruiting mechanism is being used currently.

Dr. Berry replied that recruitment is done in a number of ways. Much of the recruitment is done in clinics. If a center is participating in a trial, they typically will talk to their clinic patients about

it. The trials are listed at [clinicaltrials.gov](http://clinicaltrials.gov), and the hope is that the ALSA / NEALS website will help patients who are proactive about searching for trials in which they may be able to participate. NEALS also looks to partners like the MDA and ALSA to advertise for them. However, NEALS does not have targeted, direct advertising in the way that they could with the Registry.

Dr. Horton said he hoped that NEALS would keep in mind that the National ALS Registry is a great mechanism for recruitment, and that ATSDR is happy to work with NEALS.

Dr. Boylan said it was true that from a practical standpoint a lot of recruitment for clinical trials is local. There is much in the way of the research team at the individual sites determining who among the folks they are seeing may be good candidates for trials, for a range of reasons that are not entirely physical, and then selecting from that pool. One thing that is missing is that there is a population of patients who do not go to those centers who may be interested and who may be very good candidates for these studies. Those are the people who are being lost with traditional methods of recruitment. Efforts like the Registry Notification System can potentially make a difference in this area.

Mr. Wiebe noted that many clinical trials have follow-up criteria and people need to be located near a center. He wondered whether researchers could identify a particular geographic area in which to conduct outreach.

Dr. Horton responded that data can be filtered by geographic region, state, sex, et cetera. Again, everything relates to promotion and letting people know that this system exists.

Dr. Muravov mentioned that during the second day of the meeting, there would be presentations on the research notification component of the Registry.

### **American Academy of Neurology**

**Karolina Craft, MA**  
**Senior Policy Analyst**  
**American Academy of Neurology**

Ms. Craft indicated that in addition to being a Senior Policy Analyst, she also serves as a Staff Liaison to the Registry Task Force, which recommended that the AAN support registries of neurologic conditions, including the National ALS Registry. She said that they were very lucky to have Dr. Brooks on the Registry Task Force. The AAN is a professional association of nearly 25,000 neurologists. Its mission is to promote the highest quality patient-centered neurologic care.

The AAN recognizes that the National ALS Registry is a groundbreaking effort. In an effort to support the Registry, in 2011 AAN posted promotional materials in sections of its web pages, including the Movement Disorders, Neuromuscular, Spine, and General Neurology sections. These materials were also sent to the Executive Committees of those sections, and promotional materials were disseminated during the AAN annual meeting. This year, AAN posted promotional materials on the AAN Homepage under the title, "Encourage Your Patients who Have ALS to Enroll in the National ALS Registry." These promotional materials included a letter explaining what the National ALS Registry is and what patients should know about it, a guide for providers, and a link to the Registry website. This information was also posted on the section

web pages and was shared through AAN's social media (e.g., Twitter, Facebook). This week, members will receive an e-newsletter from AAN that will also encourage neurologists to discuss participation in the ALS registry with their patients who have ALS.

As noted, the Registry Task Force recognizes that the AAN actively supports registries of neurologic conditions, and the Registry Task Force recommendations were submitted and evaluated earlier in June. AAN is in the process of developing an official dissemination process that will help to evaluate how effective AAN promotion is, and identify ways to improve communication with AAN members about the Registry. Hopefully this year, with the cooperation of the National ALS Registry, AAN plans to conduct a survey among neurologists in the US to collect their comments about the National ALS Registry. AAN looks forward to future opportunities to collaborate with the National ALS Registry to increase participation. There are plans to publish information in AAN news in August 2012 about opportunities for neurologists with the National ALS Registry. Looking at Dr. Kaye's maps illustrating participation, Ms. Craft thought AAN could engage its state advocacies to promote the National ALS Registry during state neurological society meetings.

### **Discussion Points**

Dr. Horton said he saw the recent posting on the AAN website about encouraging people to enroll, and ATSDR really appreciates that. It is one thing to say it one time, but he wondered whether AAN planned recurring efforts periodically so that the message does not get lost. Obviously, new neurologists come on board and others retire, so it is important to continue to get the message out.

Ms. Craft responded that AAN could do more. When she said they were in the process of developing promotional materials, that is what she meant by that. They will have an official way of sending this information periodically to members, and will also try to track the effectiveness of that communication.

Dr. Horton inquired as to whether AAN uses social media as well.

Ms. Craft responded that they recently published a piece on Twitter and Facebook, and it is still on Facebook.

Dr. Horton indicated that ATSDR would be happy to work with AAN on a piece describing the National ALS Registry.

Ms. Craft said that perhaps AAN toolkits could be utilized as well, and once the tablets are made available to the ALSA chapters, AAN can inform neurologists that this is available and that they can refer people. There are many potential future collaborative efforts.

Dr. Horton inquired as to what other registries AAN promotes.

Ms. Craft replied that another registry is the National Parkinson's Registry. There are various reasons why AAN looks into registries. For the National Parkinson's Registry, AAN is considering the possibility of publishing quality measures for reporting purposes to CMS.

Dr. Weisskopf suggested not only placing an advertisement in *Neurology Today Magazine*, but also potentially writing an article about the National ALS Registry.

Ms. Craft said she thought this was a good idea, but she could not commit to anything at that point because all of the AAN publications are separate from the academy, but she will reach out to the publications.

Dr. Horton emphasized that ATSDR considers the AAN to be another valuable partner, with constituents ATSDR wishes to reach.

## Biorepository for ALS Specimens

**Wendy E. Kaye, PhD**  
**Senior Epidemiologist**  
**McKing Consulting Corporation**

Dr. Kaye extended Dr. Gwinn's regrets for being unable to attend due to being double-booked, and presented on her behalf. She reported that a meeting was convened in March 2012. The following questions were posed with regard to developing a biorepository:

- ☐ How many people have ALS?
- ☐ What are the underlying genetic and environmental causes, if any?
- ☐ How can understanding these causes lead to prevention and treatment?
- ☐ What biomarkers are useful for predicting disease progression and treatment response?
- ☐ Epidemiologic, clinical, and basic research findings need to be combined into one location tool to conduct research.

A biorepository is a collection of biological specimens (e.g., blood, urine, and tissues) stored for future use by researchers. Consideration was given to how biorepositories have been used in ALS research. There have been some gene association studies and related clinical trials, and there are some registries related to environmental causes. An ALS biorepository could be used in the future to validate biomarkers (exposures, diagnosis), classify ALS subtypes (prognosis, treatment), and discover underlying pathobiology. Thinking about all of this and trying to design a biorepository that would allow for all of these activities was the focus of the discussion during the March 2012 meeting.

Examples of potential biomarkers for proposed ALS environmental risk factors are listed below:

**Examples of potential biomarkers  
for proposed environmental ALS risk factors**



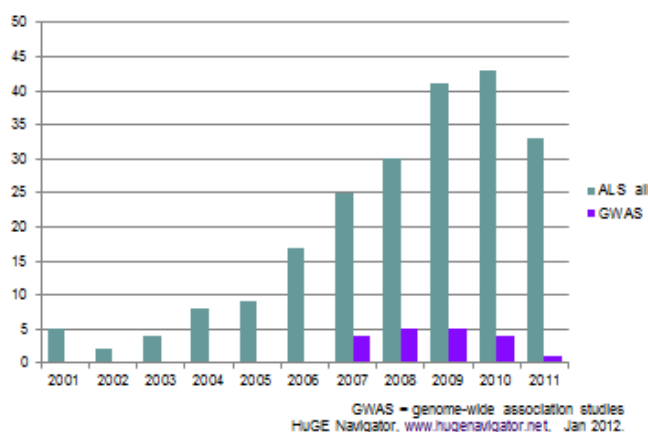
Proposed risk factor	Example / potential biomarkers
Infectious agents	enterovirus PCR for enterovirus RNA in CSF, brain or spinal cord
Pesticides	organophosphates paraoxonase enzyme activity, <i>PON1</i> genotype (blood)
Metals	lead, mercury brain, blood, CSF levels of metals and organic compounds
Drugs, chemicals	formaldehyde cytogenetic biomarkers
Injury	head trauma A-beta protein deposition in neurons, <i>APOE</i> genotype



Consideration was given to what type of materials should be collected and stored in order to evaluate some of these potential risk factors.

There has been an explosion of genetic association studies over the last 10 years, including

### Genetic association studies of sporadic ALS by year, 2001-2011




genome-wide association studies and studies focused specifically on ALS. It is important for the biorepository to be able to accommodate those types of projects as well. Two clinical repositories are in place, NEALS and the National Institute for Neurologic Diseases and Stroke (NINDS, NIH). NEALS collects serum, plasma, CSF, whole blood, extracted DNA, and urine. There are 5 clinical trials and 7 biomarker studies, each enrolling approximately 30 to 300 participants, with on-going open enrollment underway. NINDS has collected DNA and cells, and has 2021 participants. The National Registry of Veterans with ALS is a population-based biorepository that collects DNA (blood 85%, saliva 15%), and has enrolled over 1200 participants. There are two brain banks, the VA Biorepository (VAB) Brain Bank and the MRC London Brain Bank for Neurodegenerative Diseases. The VAB collects brain tissue. The MRC London Brain Bank for Neurodegenerative Diseases collects fixed and frozen human brain tissue and spinal cord, frozen CSF, and extracted DNA/RNA and has enrolled 189 persons with motor neuron disease.

In terms of what a biorepository could add to the National ALS Registry, it could help to correlate biomarkers with the extensive amount of epidemiologic data being collected by the National ALS Registry. It would also allow for the enrollment of a nationally representative, population-based sample of participants not selected by geographic area, exposure, or clinical characteristics. In addition, it would increase the number of biological specimens available for research on ALS. People have to be participants in the National ALS Registry in order to participate in the biorepository. The biorepository will be developed as an add-on to the National ALS Registry, with the thought that if it went forward, right now to conduct the pilot, those who have agreed to be in research will have to be contacted to determine whether they are interested in participating. If it were to go forward, people could consent at the time that

they agreed to be in the Registry if they were interested in this portion as well, which would somewhat simplify the process of the feasibility study. The goal of the National ALS Registry Biorepository Pilot Study is to pilot methods for collecting and banking biological specimens from participants in the National ALS Registry, and assess the potential for developing a comprehensive, national research resource. The objectives are to maximize scientific potential, given the National ALS Registry parameters; maximize cost-efficiency; make recommendations for long-term sustainability; and recommend a process for providing access to researchers. Within the 4-year timeline of this project, guidelines will also be developed for access to samples and the process for that, which will be presented to ATSDR.

Participants in the March 2012 meeting included experts in ALS, biorepositories, and biomarkers. The outcome of the meeting was that input was provided into the draft ALS biorepository pilot study protocol in terms of sample size and follow-up, specimens to be collected, and potential research uses. The original protocol called for 150 participants in the blood and urine portion, not the brain banking portion. Research considerations are that the biospecimens collected from participants should complement registry epidemiologic data, allow for comparisons with other studies, maximize the scientific utility within National ALS Registry constraints, and be “future-proof” (e.g., amenable to emerging technologies and research priorities).

The following table began from a paper by Otto that assessed the characteristics of biomarkers and how well they measured the activity [Otto et al, *Amyotrophic Lateral Sclerosis*. 2012 Jan;13(1):1-10]. The meeting participants engaged in a session in which consideration was given to how easy various specimens would be to collect, and how practical they would be for a national biorepository:

<div> <div>The National ALS Registry Biorepository Pilot Study: Specimen Considerations</div>  </div>						
Characteristic	Blood	CSF	Urine	Saliva	Skin	Muscle
Proximity to CNS pathology	++	+++	+	+	+	+
Less molecular complexity	+	+	++	+++	++	++
Less invasive	++	+	+++	+++	+	+
Practicality of sampling	+++	++	+++	++	+	+
Ease of handling for storage	++	+	++	+	+	+
Resistance to exogenous drug contamination	+	+++	+	++	++	++
Candidate molecules to date	++	+++	+	+	+	+
Potential for DNA/RNA analysis	+++	+	+	++	+++	+++
+++ high; ++ moderate; + weak						

From: Otto et al, *Amyotrophic Lateral Sclerosis*. 2012 Jan;13(1):1-10.

For example, CSF received a high mark with respect to proximity to the central nervous system pathology, but received a low mark for invasiveness and handling. Everyone was given 4 votes to rate all of the various biomaterials that might be collected, and then they engaged in a group discussion. Consideration also had to be given to current laboratory methods for environmental

chemicals, genotyping, gene expression, epigenetics, micro ribonucleic acid (miRNA), metabolomics, and proteomics. In consultation with laboratory experts, the order in which the tubes have to be collected in order not to impact other analyses negatively was determined. Approximately 30 to 35 mls of blood will be collected in the order depicted in the following table:

The National ALS Registry Biorepository Pilot Study: in-home collection					
Priority	Sample preservative	# tubes	ml / tube	Fractions	Potential analyses (examples)
<b>Blood</b>					
1	K <sub>2</sub> EDTA	1	10	White cells, red cells, plasma	DNA, proteins, red cell lipids
2	K <sub>2</sub> EDTA	1	4	Whole blood	Lead, other metals
3	Plain	1	10	Serum	Clinical biochemistries, metabolic products, other small molecules
4	PAXgene RNA	2	2.5	RNA-stabilized whole blood	Intracellular RNA
<b>Urine</b>			9	--	Electrolytes, environmental chemicals, metabolic products, gut microbiome
<b>Nail clippings</b>			--	--	Metals
<b>Hair clippings</b>			--	--	Metals
<b>Saliva*</b>			2	--	DNA

\*saliva samples will be self-collected only when blood collection fails.

Although the K<sub>2</sub>EDTA test was originally listed as the fourth priority in terms of what researchers wanted, the PAXgene RNA tube must be last according to the manufacturer. The K<sub>2</sub>EDTA has to be done second with lead-free tubes in order not to contaminate the sample. Saliva is a back-up in the event that a blood specimen cannot be drawn; however, it will not be collected if a blood specimen is collected. This is an opportunity for someone to provide a DNA sample if a blood specimen cannot be drawn at any given time, or if there is a catastrophic event like loss of tubes in shipment, untimely delivery of the specimens to the lab, or dropping a tube. Urine, hair, and nail clippings will be collected from everyone in-home. Items were removed from the initial list that were desirable, but could not be done in-home. For post-mortem collection, participants must be enrolled in the National ALS Registry with eligibility to be confirmed with the treating neurologist, and they will be followed prospectively. Specimens to be collected include brain, spinal cord, CSF, muscle, and bone. There was some discussion about collection of teeth, but this was determined not to be feasible and was eliminated from the list. This component will be done in collaboration with the VA Biorepository Brain Bank, with all of the same methods and processing to be used so that these specimens could be combined with specimens in the VA's bank, which would increase the sample size available.

In conclusion, Dr. Kaye indicated that the draft protocol has been completed and has been submitted for ATSDR's external peer review. This process requires that the protocol be submitted to three outside scientists for review and comments. Once that is completed, the protocol will be submitted to the IRB for review.

## **Discussion Points**

While she recognized that it was somewhat difficult to begin projecting timeframes, Dr. Bruijn requested whether researchers could be given access in the first year of collection or if ATSDR planned to wait until the entire collection was completed and verified.

Dr. Kaye replied that discussions on how to give access to specimens is not even slated until Year 3 of the contract.

Dr. Bruijn emphasized that this would be valuable samples of valuable information to which access should not be delayed.

Dr. Kaye responded that the problem is that as the samples are being collected, it will not be clear whether they are representative, and there will not be a representative population until they are all collected.

Dr. Traynor also advocated for early access.

Dr. Horton indicated that governance of these samples is a major component of the feasibility study, so how the samples are allocated, how often, et cetera will be assessed during the feasibility study. While he understood that researchers did not want the samples to sit there until they were all collected, they must keep in mind that this is a feasibility study. Whatever samples are collected, assuming funding is allocated by the federal government to launch a full scale bioregistry, it will already be pre-populated with the feasibility samples. The second half of the contract will be collecting samples.

Dr. Kaye expressed concern about coordination of the actual collection of samples.

Dr. Bruijn noted that the NINDS repository was populated in a few months. She emphasized that the ALS community is highly mobilized. This is very different from filling in modules. Though it is complex and multiple samples must be collected, she was confident that it could occur rapidly.

Dr. Horton pointed out that the National ALS Registry is already being opened up for researchers to use it and there is not even a completed dataset. Perhaps if that same model is followed, the biorepository could be opened up as well. However, this has to be taken step-by-step in order to hear researchers' thoughts and make a uniform decision.

Dr. Traynor emphasized how important this biorepository is. The frontotemporal degeneration (FTD) field is so far ahead of the ALS field in terms of understanding the causes of their disease, given that they concentrated from a very early stage on the pathology of the condition with a classification system. They now can show that the different types FTD according to neuropathology relate to different genetic mutations. Particularly collection of brains and making them available immediately is absolutely crucial. To put this into perspective, the largest collection of ALS brains that he knows of is less than 100. ATSDR has an opportunity to lead the field. In addition to the post-mortem collection, it would be very useful to collect skin biopsies for the purpose of fibroblast culture and induced pluripotent stem (iPS) cell lines. Using iPS cell lines is going to be a coming wave in the ALS field, so any opportunity to collect those would be beneficial.

Dr. Kaye responded that this was discussed during the meeting in March, but it was determined that this could not be done post-mortem. The way they were going to be processed and the fact that they were going to be post-mortem specimens was going to render them not useful for fibroblast and iPS cell lines, but skin biopsies in people's homes was deemed to be impractical.

Dr. Sorenson seconded Dr. Traynor's comments about the skin biopsies, because they are no more invasive than a blood draw and they cause less bruising. These are not that difficult to obtain, and there is tremendous potential in collecting skin biopsies.

Dr. Traynor indicated that there is an existing collection of fibroblasts in part in the Coriell repository that they may want to tap into.

Dr. Horton inquired as to whether they were going to highly recommend to people who take part in the biorepository that they should complete the survey modules in the National ALS Registry, and whether it would be a contingency.

Dr. Kaye responded that it would not be a contingency, though it will be recommended. The only one that is critical to complete is the ALS Functional Rating Scale for the post-mortem specimens, because the VA does that as well.

Dr. Sowell wondered whether there was a way to give preference to those who complete the modules, especially if there are overwhelming numbers of volunteers.

Dr. Kaye saw no reason why they could not do this. Because of how the Registry was set up, the initial email inviting people to participate will be from ATSDR, while subsequent emails will be from McKing for follow-up. Preference could be given to those who have completed the most data.

Mr. Wiebe indicated that MDA frequently receives questions from people who want to donate post-mortem. Different centers collect samples, but it is pretty difficult if an individual is being followed at a certain center to be able to coordinate. He presumed ATSDR would take more all-comers than individual centers would. He wondered whether Dr. Kaye could estimate the timeline for beginning to collect samples.

Dr. Kaye replied that they anticipate that sometime after the first of 2013 that all of the clearances will be received. The non-post-mortem specimens will probably begin first, because people will be given the option to donate all of the specimen types, including post-mortem. An attempt will be made to try to target the requests to people for post-mortem for people who have been in the Registry longer and whose disease may have progressed further. A national diener group will be used so that people do not have to be within a facility. They will do their best to take all-comers and not turn anyone away because they are not associated with a particular referral center.

Mr. Handsfield pointed out that the Emory neurology clinic is already doing a lot of this work. In terms of post-mortem studies, there is only one brain and one spinal column per person. He wondered whether any thought had been given to a meta-database component for those who are in the Registry who have already committed post-mortem specimens so that there could be sharing of specimens.

Dr. Kaye said she knew a lot of processing must go into the specimens that would easily be available versus actual pieces of tissue that people want for experiments.

Dr. Brady indicated that the primary stumbling block would be the consent form that was signed for the post-mortem collection in terms of whether it could be shared with others. Other issues would pertain to technical and privacy factors. The first step would be to assess the ICF document that each center has to determine how open they are in terms of sharing samples.

Dr. Kaye noted that another issue is that ALS patients are very generous in donating specimens, and if specimens were obtained from multiple biorepositories, there could be duplicates. Consideration needs to be given to how to de-duplicate specimens acquired from multiple locations.

Mr. Handsfield said he thought he remembered from serving on an IRB that those who have died do not have privacy rights. He wondered how that would affect the bioregistry.

Dr. Kaye responded that this is dependent upon the state. It is complicated, but people will be consented before they die. The consent forms will have to be clear about what types of information and specimens can be shared. The next-of-kin will also be consented prior to death, and they will be consulted again prior to the collection.

Mr. Handsfield stressed that for those in the Registry who have already consented to some other program, perhaps their registry participation can be added to the use of those tissues. For example, someone may be giving their brain and spinal column to Emory, but the National ALS Registry might negotiate a way to have access to those tissues and data from those tissues.

Dr. Kaye replied that the new clinical module that will go live soon asks if people are participating in projects, but it does not ask specifics about them. Knowing this would make coordination easier, so perhaps this is something to add.

Dr. Horton inquired as to whether this would have to go to OMB.

Dr. Kaye indicated that no questionnaire data will be collected as part of this project. All of the questionnaire data is being collected as part of the National ALS Registry, which has OMB clearance. Under the old rules, that would not have needed OMB clearance, but there has been some reinterpretation by OMB. For example, previously if a medical record was abstracted, no OMB clearance was needed but now it is. OMB has to do with burden on the participants. Under the old rules, the collection of specimens without a questionnaire would not have required OMB clearance. The only questions that have to be asked are for processing, such as when people drank fluids last, when they ate last, and whether they are wearing nail polish or the polish was removed. Those types of questions usually qualify for clinical exemption, but with changing rules they will need to apply and see what happens.

Dr. Muravov pointed out that in many cases, even if there is a signed consent from the PAL, after death consent would have to be acquired from the family.

Dr. Kaye clarified that consent does not have anything to do with whether questions are being asked. The protocol is designed such that during the initial consent process, the family member must be involved in the post-mortem collection decision and they also agree. The family will not have to sign a formal consent form after the person has died, but the next-of-kin designated will be consulted to make sure that they are still okay with the donation. If they are not, the collection will not be done.

Dr. Sowell pointed out that when someone dies, it requires the next-of-kin calling whoever is going to be making arrangements for collection of the post-mortem specimens. That serves as a type of consent in and of itself.

Dr. Bradley noted that one of the challenges is that the next-of-kin may give a different answer from what the patient would have said. This may be a point for an educational section when the subjects register. He suggested having something on the website when they register that indicates that there are no costs.

Dr. Kaye replied that they will do this. She recalled that the VA Brain Bank only had a few post-mortem samples that were not collected because the next-of-kin changed their minds. They have learned from the VA's experience that if the next-of-kin are included up front, there is buy-in. Some are likely to be missed because someone changed their mind or notification is not made in enough time to collect the specimen within the window. Given that this will be done throughout the country, it is going to be difficult to get samples from some places. Based on the transit time, Hawaii and perhaps Alaska may have to be left out.

Dr. Sorenson asked Dr. Brady how many of the people the VA signed up remembered to call at the time of death, and how long there was to harvest the tissue following death. They tried to set this up at the Mayo Clinic's center, and people would sign up, be consented, and everything would be in place, and then the family would forget about notification. The pathologist required harvesting within 24 hours to ensure that the tissue would be usable.

Dr. Brady replied that much of the VA's success comes from regular contact with its cohorts quarterly or semi-annually. Perhaps 4 or 5 decided not to do this. There are a couple of approaches. If the next-of-kin are engaged early in the process, it is possible to get a sense of whether there is going to be hesitancy. With respect to the 24-hour window versus other windows, the VA's upper limit is probably 48 hours. They have found in the analyses they have been conducting that the primary driver of tissue quality is the agonal state and tissue pH at the time of death. Approximately 90% of the VA cases have RNA integrity numbers (RIN values: a measure of tissue RNA quality for genetic research) greater than 4 which is acceptable for at least some types of molecular studies. They have been notified in the 48-hour range, have gone ahead and done the recovery, and the tissue has been usable. There are many factors with respect to what drives tissue quality. While the aim is always to have it done as quickly as possible within 24 hours, if someone wants to make a donation and the VA feels that the recovery will result in research grade tissue, they will go ahead. Beyond 48 hours, the VA would probably not pursue it.

Dr. Kowall emphasized that there is a relationship that is built between the participants in the Registry and the staff. Staff are all very clinically savvy and participants are obviously very motivated, so he thinks that is why they do not lose them. They have a relationship with them, everything is in place, and when the time comes so far they have not been surprised. The next-of-kin are very motivated to complete the process that they have already invested in, often for an extended period of time.

Dr. Traynor noted that it is not the patient who gives consent. It is actually the relatives, so they do have the right to say "no."

Dr. Kowall replied that this may vary from state-to-state. Certainly in Massachusetts, once someone dies, their body becomes the property of the next-of-kin. That is why the next-of-kin

and patients are engaged at the outset. Generally, most people will follow the wishes of the patient. Having them both on board from the beginning makes a difference.

Mr. Handsfield added that this can be done somewhat through legal channels with advanced directives and durable powers of attorney.

It was noted that it is a national law that the next-of-kin have the right to the body.

## **PALS' Perspective on the Registry**

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### **Rob Tison Person with ALS**

During this session, Mr. Tison presented general PALS feedback, the results of a registry awareness survey, and improvement recommendations.

The following list reflects general PALS feedback with regard to the National ALS Registry:

- 1) The required password reset frequency is still 60 days, even though it has been reportedly extended to 180
- 2) Risk modules are lacking, though most are unaware of additional pending modules
- 3) There is no concept of millions in appropriations each year versus actual spending
- 4) No tangible results have been presented thus far, yet ALS patients are a time-constrained group
- 5) The "Homepage" is too busy and confusing, making simple registry a challenge
- 6) The "Change Password" screen gives no visible confirmation once the password is changed

Mr. Tison reported that a Registry Awareness Survey was administrated online at SurveyMonkey.com. There were 216 total respondents, but only 201 completed all of the questions. This represents nearly a 2% sample of the ALS prevalence group, based on 4 per 100,000 population. The survey was given just over one month from May 11, 2012 through June 17, 2012. The primary goals of the survey were to: 1) assess PALS' awareness of the voluntary self-registration portion, risk factor surveys, every-6-months disease progression survey, and registration by newly diagnosed PALS; and 2) to determine the method(s) of PALS becoming aware of the active registry. The secondary goal of the survey was to determine the percentage of survey respondent PALS enrolled in the Registry, enrolled in Medicare, and receiving ALS benefits from the VA. Survey eligibility was simple. It was open to American PALS (or CALS on their behalf); and excluded CALS of PALS who died before October 2010, since they could not enroll. Eligible participants were invited regardless of whether they were enrolled in the Registry. The survey drew volunteers from forums like PatientsLikeMe.com, ALS Therapy Development Institute's (ALSTDI) forum, ALS Forums, Facebook, and even mass emails from the Catfish Hunter ALS Association Chapter and the Indiana ALS Association Chapter.

The Registry Awareness Survey questions were as follows:

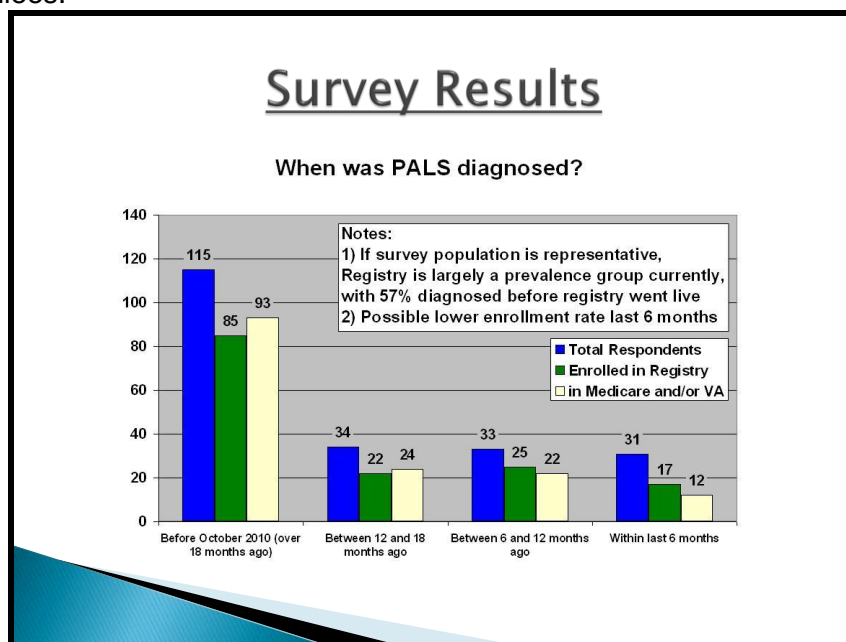
- 1) **Which best describes you?**  
☐ PALS (person with ALS)



- ☐ CALS (caregiver) answering survey for PALS living as of October 2010 - No duplicate PALS/CALS!
  - ☐ Person with another form of Motor Neuron Disease (e.g., PLS, PMA)
- 2) Is PALS a resident or citizen of the United States of America?**
- ☐ Yes
  - ☐ No (no need to continue survey)
- 3) When was PALS diagnosed?**
- ☐ A) Before October 2010 (over 18 months ago)
  - ☐ B) Between 12 and 18 months ago
  - ☐ C) More than 6 months, up to 12 months ago
  - ☐ D) More than 3 months, up to 6 months ago
  - ☐ E) Within last 3 months
- 4) How did you become aware of the active US National ALS Registry?**
- ☐ Still unaware
  - ☐ ALS Clinic visit
  - ☐ Neurologist or Physician (unassociated with specialized ALS clinic)
  - ☐ ALS organization email, website, or other media (e.g. ALS Association, MDA, ALS-TDI)
  - ☐ ALS forum (e.g. PatientsLikeMe, ALS Forums, etc.)
  - ☐ ALS support group
- 5) Are you aware of the voluntary self registration component of the Registry?**
- ☐ Yes
  - ☐ No
- 6) Has PALS self-enrolled in the National ALS Registry?**
- ☐ Yes
  - ☐ No
  - ☐ No, but plan to do so
  - ☐ No, non-ALS disease variant excluded
- 7) Are you aware of the 6 one-time risk factor surveys?**
- ☐ Yes
  - ☐ No
- 8) Are you aware of the every-six-months quality of life survey?**
- ☐ Yes
  - ☐ No
- 9) Is PALS enrolled in Medicare?**
- ☐ Yes
  - ☐ No
- 10) Does PALS receive ALS benefits from the Veterans Affairs?**
- ☐ Yes
  - ☐ No

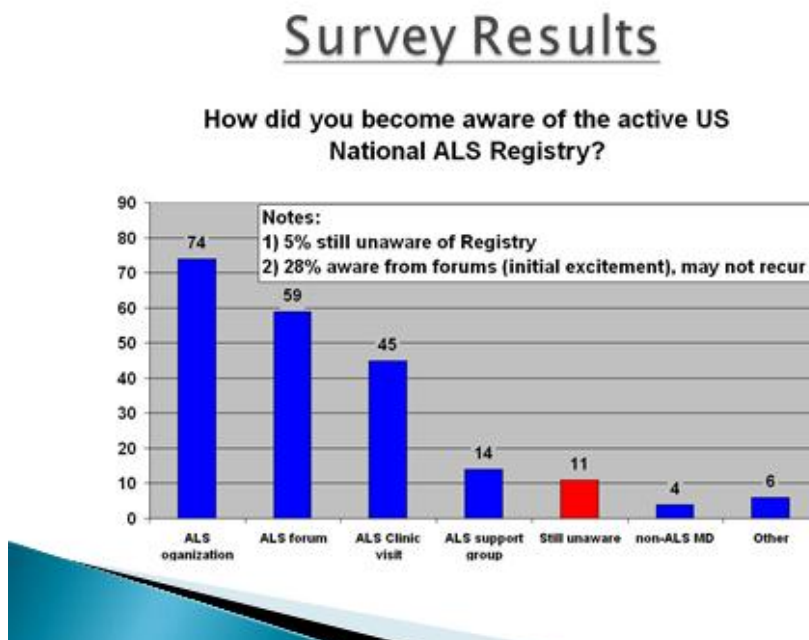
In terms of the first question regarding which category best-described participants, there were 149 PALS, 56 CALS, and 8 with Other MNDs. In regard to the question pertaining to when

PALS were diagnosed, but overlays other answers, including registry enrollees and national database enrollees:



If the survey population is representative, the Registry is largely a prevalence group currently, with 57% diagnosed before the Registry went live. There is a possible lower registry enrollment rate during the last 6 months. For example, 74% of those diagnosed over 18 months ago registered. However, only 55% of those diagnosed within 6 months registered. Is registration slowing?

The results of the survey question pertaining to how participants became aware of the Registry are presented below.

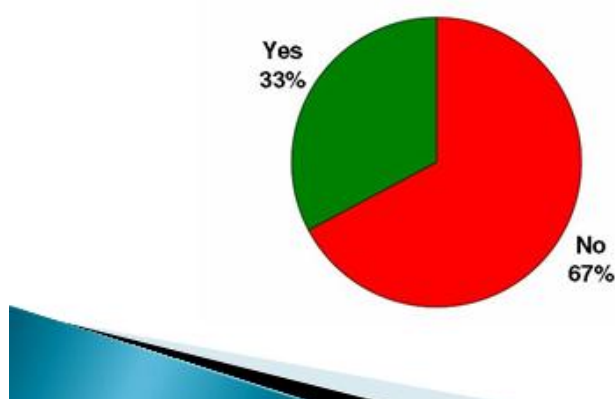


Five percent of the respondents were still unaware of the Registry and 28% aware from forums (initial excitement that may not recur).

In terms of self-enrolled, 74% of participants indicated that they self-enrolled, 25% indicated that they did not self-enroll, and 1% had not self-enrolled because they have a non-ALS disease variant and were excluded. Of the participants for this survey, 33% were aware of the 6 one-time risk factor surveys and 67% were not. If enrolled in the National ALS Registry, 42% of

## Survey Results

Aware of the 6 one-time risk factor surveys?



respondents indicated that they were aware of the 6 one-time risk factor surveys and 58% said they were not. Note the small, disappointing change. Per Dr. Horton, 39% to 46% of individuals completed specific modules as of January 25, 2012. Mr. Tison said it was his strong opinion that non-completers are simply unaware. He wondered whether a new name might help, such as the National ALS Registry and Risk Factor Data Repository. Of the respondents, 28% were aware and 72% were unaware of the every-six-months quality of life or disease progression survey. Of those enrolled in the National ALS Registry, 36% were aware and 64% were not aware of the every-six-months quality of life survey. Of PALS, 73% indicated that they are and 27% indicated that they are not enrolled in Medicare. Of note, 25% are enrolled in neither Medicare nor VA, 12% are enrolled in both Medicare and VA, and 42% of non-enrollees are enrolled in neither Medicare nor VA. Of the respondents, 14% indicated that they do and 86% indicated that they do not receive ALS benefits from the Veterans Affairs.

In conclusion, Mr. Tison presented the following recommendations for improvement from a PALS perspective:

- ☐ Rename the Registry to reflect that it is more than a list of names
- ☐ Include greater registry button promotion on all ALS sites and forums
- ☐ Have dedicated computers at clinics
- ☐ Have dedicated volunteers at clinics (like for lunch help)
- ☐ Chapter semiannual dedicated email blasts
- ☐ Simplify the "Homepage" to be more focused on enrollment and survey completion

## **Discussion Points**

Dr. Horton thanked Mr. Tison; pointing out that he did all of this on his own and that it spoke volumes about his passion for trying to determine the risk factors for ALS. He invited everyone to join him in a round of applause for Mr. Tison. Regarding the password issue, the time is supposed to have changed from 60 to 180 days. However, Mr. Tison was hearing from PALS that this may not be the case. This is a major issue from PALS, and he has been told by some PALS that they are not going to participate in the Registry anymore because it is so burdensome.

Mr. Johnson added that all of the parameters have been changed in the database from 60 to 180 days. If an account is inactive or gets locked, the password has to be reset. That may be one reason some people have had to reset it in 60 days. There are rules and regulations that have been instituted by CDC. While they would love for this system to be comparable to Medicare and Medicaid where the password does not have to be changed, CDC requires that a number of security parameters be in place. Approval was received to extend the timeframe to 180 days, which was a major challenge, but efforts continue to try to impress upon the CDC security team that this system needs to be as simplified and easy for ALS patients as possible. Email communications are monitored regularly, and this was the first time he had heard that people were still being asked to change their passwords in 60 days. He indicated that he would look into this to ensure that it is working as it is supposed to. For security reasons, it has not been communicated to PALS that the policy has been changed. The security team does not want the information to be made public, because it would be a hacker's dream.

Mr. Tison indicated that his own account was locked out two weeks prior to this meeting after resetting it in April.

Mr. Johnson indicated that if the account is locked, people are asked to reset their password at that point because a lot of people do not remember their password after their account is locked. Dr. Sorenson emphasized that Mr. Tison had identified a potentially important tool with this survey that could be used by the agency to keep the registrants engaged in the survey. The issues identified by Mr. Tison are eye-opening. He wondered whether ATSDR had given any thought to using surveys such as this.

Dr. Horton responded that any question ATSDR designs must go through IRB and OMB. This does not prevent others from doing this, although ATSDR cannot tell others to do it on the agency's behalf. To a certain degree, ALSA did this on their Listening Tour as well. Some of the themes seem to be common, especially the password issue.

Mr. Gibson responded that during the Listening Tour, the primary audience was the chapters. However, the chapters have been encouraged to obtain feedback from people with ALS about their experiences with the Registry so that ALSA can provide the feedback to Dr. Horton.

Mr. Handsfield indicated that the second generation of BioSense program is no longer housed at CDC, it is in the Amazon cloud. This has allowed a lot more flexibility, so consideration could be given to moving the Registry database into a cloud environment.

Dr. Horton replied that they would still be facing IRB / OMB issues.

Mr. Handsfield said that while it would not change the IRB / OMB issues, it would give the agency more flexibility about how the security requirements are applied.

Dr. Brooks applauded Mr. Tison for this great effort. Carolinas Medical Center recently completed a survey of a comparable sample size at a clinic visit where many of their patients indicated that they were locked out. This is a major issue that ATSDR's team needs to address. The second issue is that there is not any re-contact. They heard earlier about the algorithm for defining whether someone died if they do not answer emails, which is not going to work. He suggested that ATSDR work with Mr. Tison on the development of a quality improvement module. Anything like this is going to be very important for getting patient involvement in the system.

Ms. Sanchez indicated that the National Death Index data will determine whether someone has died if they have not communicated through the web portal. Once someone has been identified through the National Death Index, emails will no longer be sent to them. No one will be assumed to have died just because they have made no contact in 6 months or a year.

Dr. Sorenson thought it was a concern that almost two-thirds of the people who are registered are not aware of the risk factor modules.

Dr. Horton said that to a certain degree, ATSDR's data shows the same thing. It is known that people are enrolling, but they are not taking the extra step to complete the survey modules.

Dr. Bruijn suggested that perhaps insufficient attention was being called to the modules at the outset. While there is a lot on the homepage about registering, the importance of taking the surveys is not emphasized as much.

Dr. Antao responded that the flow of the website was recently changed. First, people would register and go directly to the main webpage. When they noticed that people were not taking the surveys, they changed this. After someone registers, there is now a screen that offers them the possibility of taking the survey. That would be the next natural step after registration, so it is expected that this will improve the number of people taking the surveys.

Mr. Wildman stressed the importance of making sure that this is not simply a database of names of people with the disease. Efforts have been made to get this point across to Congress, but a better job must be done of letting people know that the surveys are critically important and are the Registry. More education is needed in terms of branding, follow-up, et cetera. A lot of the efforts ALSA has planned are designed to keep interest going.

Dr. Gubitz thought it would be a motivating factor for patients if they are told when they enroll in the Registry that they can also be active participants in ALS research. That message needs to be up front. If it already is, then based on what they learned from Mr. Tison, perhaps it needs to be further enhanced.

Dr. Weisskopf emphasized that as soon as people register, it should be apparent from the website that the risk factor surveys are critical to complete. He wondered how often people revisit the site once they have registered and completed all of the modules, and how that meshed with the length of time before they are locked out.

Mr. Johnson replied that accounts are locked out if someone forgets their password. If an account is not used for more than 180 days, the account becomes inactive at that point.

Dr. Traynor inquired as to whether there had been attempts to hack the site.

There have been some attempts to hack the site simply because it is a government website. He can trace specific attempts that failed. Some may have been registrants who forgot their passwords, but security would probably say that it is 60 / 40 hackers trying to get into the website because it is a government website.

Dr. Kaye added that she was told by security that CDC has 10,000 hacking attempts per day, and Mr. Hansfield said it was closer to a million.

Mr. Wiebe stressed that it is vital for people to be able to return to use the Registry, and thought it was great that the password requirement had been extended to 6 months. However, people will only return to complete surveys every 6 months. Even in an ideal setting, they will have to reset their password every time they return to the surveys.

Mr. Johnson replied that this was taken into consideration. During the last meeting, PALS were asked and they said that 180 days would be feasible. This number was not arbitrarily determined.

Dr. Horton added that they are trying to make it easy for people so that they do not have to check back every week or every other week. That is the reason for the auto-generated emails about the surveys. Mr. Johnson staffs the phones from 8 to 5 Monday through Friday dealing with people who are locked out. Constituents having password issues can contact Mr. Johnson.

Regarding some of the other issues raised by PALS that Mr. Tison highlighted, Dr. Horton stressed that they are constrained by OMB in terms of the number of questions that are permitted. If it were up to ATSDR, they would ask as many questions as they could. However, they cannot burden the public in terms of the number of questions asked. By design, they have to keep the surveys fairly succinct. Hopefully, the new open-ended module will be beneficial because PALS will be able to speak their minds. This would be the appropriate place to discuss questions that have not been asked in the modules. Through the feedback mechanisms, they receive many emails in which people suggest particular topics that should be considered. Consideration is given to all of the suggestions that are received. ATSDR agrees about the issue regarding no results being reported to date. This process takes time, and ATSDR has no control over the Medicare and Medicaid lag. To a great extent, they are at the mercy of other agencies. He had not previously heard that the website is too busy. ATSDR thought it was better to place "How To" guides and information about how data are being secured on the homepage to give people peace of mind, but if it does seem too busy, perhaps some of that information can be moved from the homepage to a resource link.

Dr. Muravov indicated that one of the options would be to keep titles but remove subtitles. They could have a list of resources, but it would not necessarily have to be on the front page.

Regarding whether registration is slowing, Dr. Horton indicated that when the Registry was initially deployed in October 2010, huge numbers of people were enrolling every day. That was largely people who were watching for the Registry to be deployed. After a certain point, a steady state was reached and has continued. It is important to continue to promote the Registry and to increase awareness that the Registry exists, especially among newly diagnosed people. Consideration has not previously been given to changing the name of the Registry, and Dr. Horton did not know whether this would be possible or feasible. His initial concern would be that it has already been branded as the National ALS Registry. Modifying the name could be problematic.

Dr. Sowell said that while they could change it, it is easy to remember this way. Rather than changing the name to include "Risk Factor Surveys" they need to do a better job of promoting and increasing awareness of the risk factor surveys rather than just the ALS registry. Perhaps if people were more aware of the risk factor surveys, they might be more willing to join the Registry because they would perceive more value to enrolling in the Registry than just giving their names as persons with ALS.

Dr. Muravov added that ATSDR is discussing how to make the Registry useful even before approval is received to release information. Hopefully, doing this will increase interest and motivation for PALS to enroll and to see an actual link between spending time entering information in the Registry and seeing some results. He thanked Mr. Tison again for his efforts.

Dr. Sorenson pointed out that reaching a steady state is to be expected. Once prevalent cases are cleared out and steady state is reached, this should offer an idea of incident cases. He wondered if Dr. Horton could share any numbers at this point.

Dr. Horton replied that until they are able to demonstrate that the data are representative, numbers cannot be shared. They are asked this question at every conference they attend, but they are not at this point yet.

## End of the Day Questions Session

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**Robert Kingon, MPA, Facilitator**  
**Carter Consulting, Inc.**

During this session, Dr. Kingon called for any additional comments, questions, and / or suggestions.

### **Discussion Points**

Dr. Horton requested that they revisit the placing of advertisements in clinical journals in terms of whether this would result in a return on investment. It has been emphasized to him that many patients read ALS-specific magazines, so it seems like that would be a good place to continue taking out advertisements, but he remained uncertain about clinical journals.

Dr. Berry thought ATSDR would be better off putting its efforts into publishing about the creation of the Registry. True articles that explain what is being done are more likely to appeal to clinicians and gain their trust. Clinicians and researchers really operate by evaluating an entire effort.

Dr. Horton replied that ATSDR is currently placing advertisements in patient magazines, and has placed an on-line advertisement in MDA's patient magazine website. They could probably get some traction out of this, but it sounded to him like placing advertisements in clinical journals would not be as beneficial.

Dr. Bruijn asked whether ATSDR planned to present data at the upcoming ALS / MND workshop in Chicago. It would be beneficial to have perhaps a platform presentation.

Dr. Horton responded that he did not know whether consideration had been given to presenting during that meeting.

Ms. Sanchez added that they have presented the 2001 through 2005 data in a few conferences, and she thought they presented it in a poster presentation during the ALS / MND meeting in Florida. It has taken a while to reach the publishing stage, but the NDI have not been presented at the ALS / MND symposium so they can look into doing so. NDI data have not been presented anywhere yet. A presentation is planned for the American Public Health Association (APHA) meeting in October 2012, which will be the first time that the NDI data will be presented.

Dr. Bruijn emphasized that it would be good to generate excitement among researchers by presenting real data. She thought the more they presented real data, the more feedback and interest they would receive.

Dr. Brooks endorsed Dr. Bruijn's comments. He suggested presenting a paper that describes the difficulties they have had in presenting the data. Perhaps the APHA poster could be presented in Chicago. The presentation has to be of substance. He agreed that doctors do not read advertisements.

Dr. Horton indicated that Dr. Kaye is writing a paper on the pilot efforts as well. ATSDR is beginning to work on publications, and he agreed that they need to at least let people know the methodologies. Once the data become available, there will be much to review and publish.

Now that the AAN supports the Registry efforts, Dr. Gibson wondered whether they could have a session or part of a session to focus on the Registry rather than just doing another poster session.

Ms. Craft responded that she did not know because she is not involved in organizing the conference and there are strict criteria for how sessions are selected, but she will check into the possibilities.

Dr. Brooks suggested contacting Walter Rocca at Mayo who is looking for presentations for next year's meeting.

Dr. Gubitz pointed out that since the launch of the Registry, many advancements and enhancements have been implemented and not everybody may be aware of these. Now is the time to show how responsive ATSDR has been and how the Registry has been improved. This is very exciting and is something to be proud of.

*With no further business posed or comments / questions raised, the meeting was adjourned.*

## Day 2

### Research Notification Component

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#### Overview

**Oleg I. Muravov, MD, PhD**



**Principal Investigator, National ALS Registry Program  
Environmental Health Surveillance Branch, DTHHS  
Agency for Toxic Substances and Disease Registry**

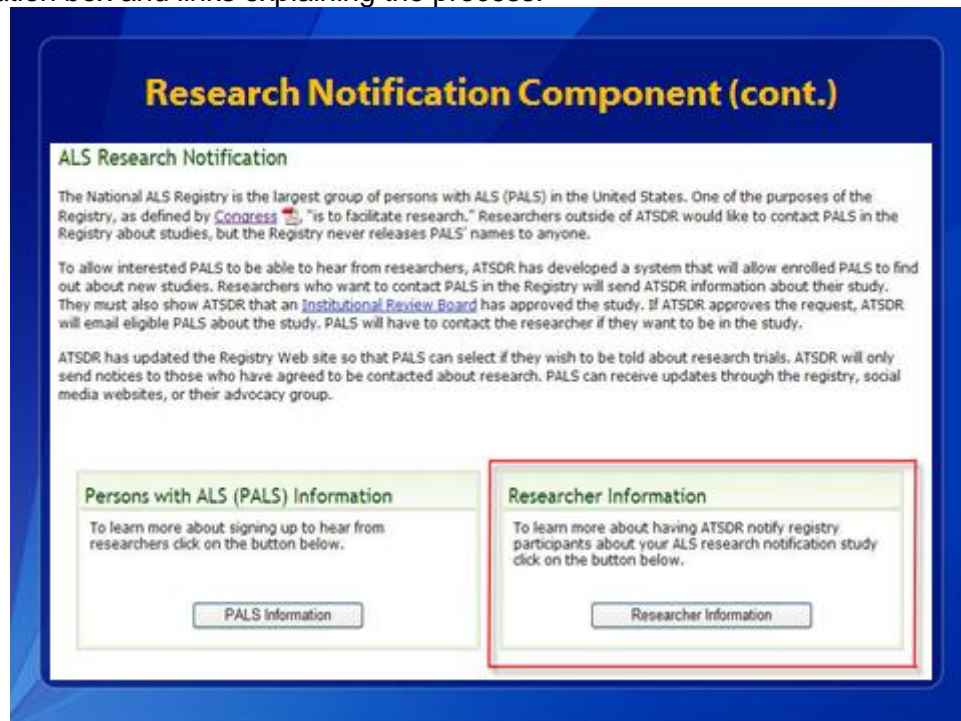
Dr. Muravov reported that the National ALS Registry has the largest group of PALS in the US. ATSDR hears from researchers who would like to contact PALS in the Registry regarding their studies, and the agency hears from some PALS that they would like to know about research for which they might be eligible to participate. In response to these requests and to follow the language of the public law, one of the purposes of the National ALS registry is that it allows enrolled PALS to find out about new clinical trials and other studies for which they may be eligible. This potentially increases PALS enrollment into new ALS studies by providing researchers with one more source of ALS cases.

ATSDR developed the Research Notification Component, which is a mechanism to notify registrants about clinical trials and other research studies. In terms of how the new Research Notification Component works, a researcher completes an application with the study criteria and



submits it to ATSDR, the application is submitted to an external panel for research evaluation, upon approval ATSDR identifies registry enrollees who meet eligibility criteria, and ATSDR contacts enrollees via email who gave contact consent and provides study and researcher contact information. PALS are responsible for following-up with the researcher. The tool went live in May 2012. PALS are notified of studies / trials for which they are eligible. New registrants have been able to sign up for clinical research notices since August 2011. At that time, the webpage was modified to include a check box to ask registrants if they are interested in receiving notifications about research. Existing registrants were notified and able to sign up for notices beginning in December 2011. No personal identifying information from PALS is given to researchers.

Dr. Muravov showed screenshots of the Research Notification Component webpage showing the notification box and links explaining the process.



The minimum information researchers must submit includes the following:

- ☐ Who is conducting the study
- ☐ Who is sponsoring the study
- ☐ The study objectives, procedures, and protocol
- ☐ IRB-approved recruitment materials
- ☐ Proof of IRB approval (e.g., an IRB approval letter)

The variables available on everyone to search for eligible enrollees include the following:

- ☐ Sex
- ☐ Date of birth (month, year)
- ☐ Date of diagnosis (year)
- ☐ Current address (Country, State / Province, City)

Current risk factor surveys include the following:

- ☐ Socio demographic Characteristics
- ☐ Occupational History (for most recent, longest held jobs)
- ☐ Military History
- ☐ Smoking History
- ☐ Alcohol Consumption History
- ☐ Physical Activity
- ☐ Family History of Neurodegenerative Diseases (parents, biological siblings and offspring)
- ☐ Disease Progression

New risk factor surveys anticipated being available in 2012 and early 2013 include the following:

- ☐ Clinical information
- ☐ Open-ended questions

New risk factor surveys anticipated to be available in 2014 include the following:

- ☐ Residential History (all residences of > 6 months)
- ☐ Residential Pesticide Exposure
- ☐ Occupations Involving Toxicant Exposures
- ☐ Hobbies Involving Toxicant Exposures
- ☐ Traumatic Brain Injury
- ☐ Electrical Injuries
- ☐ Caffeine Consumption
- ☐ Reproductive History for Women
- ☐ Health Care Insurance

### **Discussion Points**

Dr. Bradley inquired as to whether any pilot grant funding programs were being planned through the Registry for investigators to develop new modules. If not, it would be good to plan some pilot grant funding in ATSDR's budget for next year.

Dr. Muravov replied that they do not have such a program at this point, but they are open to new ideas. Because there is a limit on the amount of information that can be asked of registrants, ATSDR has to include as much as possible with absolute minimum information. If they were to add a module, they would probably have to remove something else to keep it under 45 to 50 minutes overall.

Dr. Horton added that ATSDR is happy to hear any ideas in which investigators are interested, and they can assess it from there. Nothing is off of the table.

It sounded to Dr. Boylan as if saturation will be reached with the number of modules or amount of materials in the Registry, or will soon be reached with the new modules that are coming out. He asked for clarification about this.

Dr. Horton replied that they are approaching the upper limit of the burden ceiling established by OMB. If anything is added above and beyond what Dr. Muravov listed, consideration will have to be given to the burden in terms of the total number of minutes a person would need to take all of the modules.

Mr. Wildman inquired as to what percent of existing registrants have consented.

Mr. Johnson indicated that approximately 95% of new enrollees have consented for clinical research notifications.

### **Demonstration**

**Greco Johnson**  
**Business Analyst**  
**Emergint**

Mr. Johnson led participants through a demonstration of the National ALS Registry Research Notification Component. He indicated that on the National ALS Registry homepage, there is a section called "ALS Research Notification". This page provides a quick start guide for researchers or applicants to guide them through the process of completing the clinical research notification application. This is a 1.5 page step-by-step document that indicates the requirements. There is also a link on the homepage to a brief overview of ATSDR's plan for a clinical research notification tool. There is also a section for PALS, who can update their account information to sign up for clinical research notification through this link. New registrants can also go through this link to create an account, enroll in the Registry, take surveys, and sign up for clinical research notification as part of the registration process. ATSDR collects information about the date an application is submitted, the title of the study or project, the principal investigator / director, the applicant's organization, any co-principal investigators, contact information, the funding source, any conflicts of interests, a brief summary of the proposed study and project activities, background, specific aims, methods, population, measures, and analyses. Information is also collected about the federal assurance number, IRB approval dates, plans for the use of data, specific age range, time periods (i.e. diagnosis), sex, city and state of residence. These are basically the study parameters. After the application is completed, there is a research notification form on which additional information is collected and a request is made to attach all application materials. All application materials are required to be in PDF format. Once completed and submitted, the applicant will receive an acknowledgement that will include a tracking number. A system-generated email will also be sent with the tracking number. The status of the application process can be checked through the site from the beginning to the end of the application process.

### **Discussion Points**

Dr. Horton indicated that for an approved application, ATSDR would then query the system based on the parameters of interest indicated in the application.

Dr. Traynor asked whether a query could be done based on family history.

Dr. Horton replied that they should be able to query on family history.

Dr. Kaye added that while they can query on family history, it was important to keep in mind that less than one third of the people who are in the Registry answered that question.

Dr. Muravov indicated that more people have completed the demographics module, and that family history has the lowest response rate of approximately 39%.

Dr. Horton noted that investigators also have the option to have the information sent to all registry enrollees, and there is a check box for that as well.

With respect to distribution of this information, Dr. Brooks asked whether he was correct in understanding that a PALS will enter his or her account number and ask to search for trials with respect to zip code, for example, or if they could search for any clinical trials.

Dr. Horton responded that they can search for any clinical trials. The clinicaltrials.gov link will still be on the main page. The purpose of this is to take them out of the equation, and ATSDR would notify enrollees based on the study a researcher who has submitted an application is conducting to let them know that they are eligible for a specific study. The goal is to make it as easy as possible so that PALS do not have to search.

Dr. Brooks noted that this is a “push out” kind of mechanism.

Dr. Muravov added that when PALS sign up, they do not have to indicate the types of studies or locations in which they are interested. They sign up to receive any notification, and it would be up to them to decide whether they want to participate based on what they receive.

Dr. Weisskopf asked whether there was a possibility to include in the email that PALS with a family history are being recruited, so that even if they have not answered the survey, they would know the focus of the study.

Dr. Muravov replied that this would be part of the recruiting materials.

Dr. Sowell clarified if the investigator's IRB has approved an email or flyer that states this, ATSDR would send it out.

Dr. Horton replied that the way he views this is that ATSDR is the “middle man” trying to link researchers directly with PALS, such that PALS can ultimately contact researchers directly if they wish to participate in a study.

Dr. Muravov indicated that the process from the submission date through approval takes up to approximately 60 business days.

Dr. Horton indicated that the application number makes it easy for researchers to see where their application is in the process, so that they do not have to keep sending emails and calling ATSDR for updates.

Mr. Gibson thought this was a great tool when it is used, but wondered how to get the word out. Until people are working on this, it will just sit there.

Dr. Horton replied that ATSDR is in the process of creating a tri-fold or some type of brochure that various groups can send out (e.g., ALSA, MDA, AAN, et cetera). The quick start guide is already on the site and it steps people through the process.

Dr. Muravov added that as Ms. Craft mentioned the previous day, the AAN Registry Task Force is willing to promote the National ALS Registry and the new initiative, so he thought this valuable piece could be included in their future notifications to their members and others.

Dr. Horton suggested that perhaps ATSDR could conduct a webinar from time to time to ensure that people know the Research Notification Component is in place. ATSDR is happy to work with others to increase awareness of this component.

Dr. Bruijn pointed out that if ATSDR promotes this, but researchers are not aware of the gaps, they may request something very specific. Her suggestion would be to send requests to everyone in the Registry at this point because of all of the gaps. This should be clarified.

Dr. Horton replied that this information could be included in the tri-fold or brochure.

Dr. Kaye added that researchers who are interested in sub-setting the data are going to have to talk to someone on the team first in order to discuss the limitations. That way, investigators can weigh the pros and cons.

Dr. Sorenson suggested disseminating information to increase awareness that this is now an option. By disseminating information through MDA, ALSA, Amyotrophic Lateral Sclerosis Research Group (ALSRG), and NEALS, approximately 90% plus of ALS researchers in the country would be canvassed. This could be done with a simple email indicating where to find the link.

Mr. Handsfield noted that this part of the Registry is directed to a different audience than the rest of the site. All of the discussion about advertising the day before was directed to PALS to encourage them to join the Registry. In the case of researchers, it may be wise to put a direct link to this application in the professional side of ALSA and other groups who want to promote this.

Dr. Sorenson replied that it would be on the ALSRG website by the next day.

Dr. Horton noticed in checking social media that ALSA promotes a lot about NEALS clinical trials. This would be another tool to promote the Research Notification Component.

Ms. Craft indicated that she recently wrote an article that includes this information that is going to appear in the August 2012 issue of *AAN News*.

Dr. Horton pointed out that the goal for this session was to ensure that everyone in attendance had a clear understanding of this component of the National ALS Registry. He invited feedback about whether people thought this would be well-received. Although the anticipated fall/winter 2013 date for the first dataset from the Registry is a while away, there is no reason why they cannot take advantage of what is in the system already immediately for purposes such as this.

## Creation of a Review Group for Data Requests

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**Vinicius C. Antao, MD, MSc, PhD**  
**Lead, Registries Team**  
**Environmental Health Surveillance Branch, DTHHS**  
**Agency for Toxic Substances and Disease Registry**

Dr. Antao led the participants in a discussion regarding the establishment of a Data Access Committee. The Amyotrophic Lateral Sclerosis (ALS) Act specifies in its paragraph (d)(1)(B) that the National ALS Registry should provide for research access to ALS data:

“SEC. 399R (d)(1)(B) provide for research access to ALS data as recommended by the Advisory Committee established in subsection (b) to the extent permitted by applicable statutes and regulations and in a manner that protects personal privacy consistent with applicable privacy statutes and regulations.”

As ATSDR continues to collect ALS data from administrative databases and through the web portal, the agency would like to put in place a Data Access Committee. The committee would initially be charged with developing standard operating procedures for data sharing and later with reviewing and approving of data submissions. In preparation for the Annual ALS Meeting, the following questions were posed to participants for discussion during this session:

**Data Access Committee**

- ☐ What is the ideal size of the Committee?
- ☐ What expertise should be considered in the Committee composition?
- ☐ What is the ideal time commitment for participants?
- ☐ How should conflicts of interest be dealt with?
- ☐ Are there other aspects for consideration?

**Standard Operating Procedures**

- ☐ What data request procedures should be in place?
- ☐ What criteria should be used to review protocols?
- ☐ What would be the ideal mode of data access/delivery?
- ☐ Are there specific criteria that should be considered for creation of data sets?
- ☐ How about quality control procedures?
- ☐ What measures have to be taken to assure confidentiality of participants?
- ☐ What publication requirements should be in place?
- ☐ Are there other aspects for consideration?

Examples of other data release panels and procedures can be found in the links below:

National Database for Autism Research (NDAR)

<http://ndar.nih.gov/ndarpublicweb/policies.go#AccessCommittee>

CDC's Research Data Center (RDC)

<http://www.cdc.gov/rdc/index.htm>

**Discussion Points**

Dr. Horton clarified that this effort was being undertaken now in preparation of anticipated data availability in fall/winter 2013. It is important to set forth procedures about how access to these data will be granted. A similar activity is underway just for the research proposals. An internal / external panel will review the applications received through the Research Notification Component of the National ALS Registry. Internally there has been discussion regarding whether there should be one panel that reviews research proposals and data requests, or if two separate panels should be established, one to review proposals and the other to review data requests.

Dr. Knorr was not clear what the difference would be, and what type of data someone would request that ATSDR would want a panel to consider. Sometimes aggregate data are readily available on a website so that researchers can have access.

Dr. Antao indicated that no data are currently available due to OMB's restriction that ATSDR must demonstrate that the dataset is stable. Once this is demonstrated, they will be able to release data to external researchers. ATSDR envisions that this may occur in late 2013, so they want to take into consideration now how to release these data once they are available. The mechanism now is for researchers to contact ALS patients to participate directly in research. The idea of the proposed panel(s) would be to provide data from the Registry to researchers to conduct their own analysis.

Dr. Bruijn thought one committee would be sufficient. Having one committee to evaluate whether proposed research is reasonable and represents an important priority should be sufficient. It is very difficult to organize these meetings, and to ensure that there is a quorum.

Dr. Antao asked for feedback regarding who should be on the committee. Currently, the committee has neurologists, researchers, a bioethicist, and ATSDR representatives.

Dr. Buijn thought having a statistician would be important, and that there should be participation from organizations (e.g., ALSA, MDA, and NIH).

Dr. Bradley raised the opposite point of view. The current research committee is designed to be an IRB with regard to the Registry and protecting patients rather than having the spread of disciplines and expertise needed on a research committee that is considering access to data that is already in the Registry. The current research committee does not evaluate the proposals in any depth. While he agreed that it is much simpler to have one committee, there are compelling reasons to have two committees.

Dr. Traynor disagreed. He would recommend zero committees. He wondered what the bias of the committee would be. He would argue strongly that there should be a very low threshold toward sharing the data. They want these data that they have gone to so much trouble to collect to be used by as many people as possible as long as it is ethical. He was not advocating for access to the data without IRB approval. He was saying they should share the data if there is IRB approval and no ethics laws are being violated. Some theories may be tested and refuted based on this, but it is good to test theories with real data to determine what the results are. The issue here is gaining access to the data, and he cautioned ATSDR against putting up barriers to this.

Dr. Bradley wondered about obtaining OMB approval for the data to be put on line so that people could search it in real time.

Dr. Horton replied that this is not out of the question. Any dataset that ATSDR releases would be de-identified. They are exploring a number of ways to make these data available. One mechanism is through CDC's Research Data Center (RDC), which is an online repository. It is secure and requires that an account be set up. It would allow people to download the data and subset it however they wish for whatever purpose they want. His branch operates a surveillance system that tracks chemical spills throughout the country, and it has a public use dataset that is directly on the website. People can fill out information about who they are, their affiliation, and their intended use of the data. At least ATSDR has a way of tracking the data. It is good for ATSDR because it allows them to tell Congress how many people the data have been shared with. Having something like this for the National ALS Registry is not out of the question, but consideration must be given to how to govern that.

Dr. Knorr indicated that Massachusetts plans to put their de-identified data up on the National Environmental Public Health Tracking Network (Tracking Network), which is another CDC program that has a public portal and a secure portal for researchers. Anyone can query the data, look at it in different ways, and download it. The secure portal data are generally de-identified and it is web-based access with a password, but unsuppressed status. It can be identified and there can be small cells, so an IRB would not want it to be generally releasable except under consent. Then there is a third level because these data are at the individual level, and this includes names and addresses. Formal requests for these data go through the IRB committee. He suggested using a format similar to the Tracking Network public portal so that anybody can request information without a password required. He thought a lot of people would see the type of data they wanted to see, and it would be readily accessible to everybody. But there would also be a mechanism for researchers to acquire more information if they choose. It is very important to determine what the charge of the committee(s) will be. The Massachusetts



IRB Committee is comprised of a large group that includes community representation, but they get bogged down in terms of biases and whether proposed research is what they really want or like. When they receive projects that have already gone through an NIH IRB and received approval, it seems like they are interfering with the research practice. If they clearly state that the goal of the committee is to protect the privacy of the data, the committee can focus on that and can try to avoid getting enmeshed in biases that are going to be inevitable.

Dr. Horton indicated that Dr. Portier is strongly advocating exploration of Environmental Tracking for displaying these data. They have engaged in conversations with the Environmental Tracking group. He inquired if there is a tracking mechanism that permits Massachusetts to determine how many people have downloaded the data, their affiliations, and how they are using the data.

Dr. Knorr replied that this is one of the requirements of Environmental Tracking that CDC places on them, because they want Massachusetts to be able to assess whether they are getting unique hits, for what purpose, what page they are going to, what type of data they are obtaining, et cetera.

Dr. Horton asked whether there had ever been a case in which someone wanted to download data, but they were prohibited from doing it because their aims or objectives were thought to be unscientific.

Dr. Knorr responded that the formally stated purpose of the IRB is to protect privacy, and to ensure that studies have the purpose of improving morbidity and mortality in Massachusetts. If a study is not well-designed such that it cannot answer that question, it would be denied.

Dr. Horton asked whether the Massachusetts data were already on the portal, and whether the process was such that when someone wanted to download the data, CDC would notify Massachusetts first so they could review who is requesting access to the data.

Dr. Knorr responded that it is not, but they expect to put it up in the spring. The public portal has cell suppression rules for minimum sizes of variables. Because the focus is environmental, the portal is map-centric, so someone can look at cases geographically but can also look by age, sex, and other variables. If the cells meet the minimum size guidelines, anyone can view and download the data on their own and Massachusetts does not get involved beyond ensuring that the minimum cell size is met. If a researcher wants to see the suppressed data, they have to submit an IRB request that may go through CDC to Massachusetts or may come directly to Massachusetts. Then it goes through Massachusetts's IRB.

Dr. Horton asked whether Massachusetts gets a monthly report for the public portal that tells them how many people have accessed their data.

Dr. Knorr said that while he was not sure how it worked, Massachusetts has control of that process and can evaluate that at any time.

Dr. Brooks said he could imagine that at some level, they might want to relate GPS data at the residence level to a particular survey.

Dr. Knorr added that the map-centric function has the capacity to add other data layers and link with environmental datasets (e.g., air pollution, water pollution, et cetera).

Mr. Wildman emphasized that public access is vital because people with ALS, their families, and survivors want access to the data. They have been hearing this since before the Registry was created, and it is a motivating factor for people to enroll. Obviously, it is necessary to deal with confidentiality, privacy, and de-identifying the data, but anything that makes it easier for people who are affected to find out this information is important.

Dr. Horton indicated that one of the original intents was to put up a US map that could be “moused” over by state to see case counts, prevalence rates, et cetera. That may satisfy patients who want to get a sense of how common the disease is, but for other details, people will have to request the data, download it, and conduct analyses that address their objective.

Mr. Handsfield pointed out that standards have already been established by the National Center for Health Statistics (NCHS) in terms of what has to be considered for public use data that can be downloaded. There are other requirements for more protected data, and there are even situations in which it is legitimate to request personal identifier information as well.

Dr. Antao clarified that CDC provides access to identifiable data as long as the researcher goes through the RDC. It can never leave the building, but they can match their data in the RDC.

Mr. Handsfield indicated that other processes are in the works as well. As far as CDC having these data, that is covered under the Privacy Act System of Records Notice (SORN) 0136. The RDC protects data that way, but there are other ways to store data in a protected way that is fully secure that does not have to be in the RDC.

Dr. Sorenson strongly encouraged ATSDR to work with Dr. Knorr and his group, given that their system sounds exactly like what ATSDR wants to accomplish.

Dr. Horton indicated that Environmental Tracking has a long history doing this. They have a series of disparate datasets (environmental data, disease data, et cetera), and people can query the data and cross-reference it. This is definitely an option that is being explored.

Mr. Gibson indicated that one of the intentions for creating language for the Registry in the very beginning was to not deviate from it being a research tool. One of the top priorities for other disease groups like MS and Parkinson's is to determine how many people have those diseases. That really was never the goal of the National ALS Registry. ALS does not have a powerful research tool, so the idea was for researchers to be able to use this and move forward. While he did not want to hide information, it could possibly come out that there are not 30,000 people with ALS and that it is much lower. There would be a lot of negative connotation about what this all means if there is a map with people in each state. He could hear appropriators and Congressman saying, “You only have 2 people in the whole State of Texas who have this disease?” He thought it was very important that consideration be given to everything in terms of research projects, because the intention was never to figure out the number of people who have the disease. If incidence is higher in one state, that is important. While they should not hide information, they should also not be distributing information that could be damaging to the research tool they wanted to create, particularly in a budget-conscious environment. That could hurt the overall goal of finding a treatment and cure.

Dr. Bruijn was concerned that there might be publications of a large number in a particular state, but if it is not a well-controlled study, it might be an alarm that is not really legitimate. They must be cautious of that kind of data being readily available and the numbers being somewhat misrepresented.

Dr. Kaye said that as a person who answered cancer cluster calls for a large portion of her career at CDC, she concurred with the idea that they do not want to create an illusion that there is an excess in an area when there really is not. Regarding the issue of access, she recently had a call from someone who had heard about the release and was interested in conducting a study. The person had no research experience and knew a little about an IRB, but did not think IRB approval was needed if the study was not a clinical trial. While everyone in the room was qualified, she emphasized that they must be prepared to receive requests from people who everyone would agree do not have the necessary qualifications. It is not that they are trying to limit the research, but it must be balanced.

Dr. Antao heard suggestions for a range in the number of committees from 0 to 2, and it seemed like a compromise would be to have 0 for some types of data and a more formal committee for other levels of data complexity. In terms of moving forward, he requested more feedback about how ATSDR should proceed in terms of setting this up following this meeting. For example, should they convene a task force or just get a sense of the agreement in terms of moving forward.

Dr. Traynor thought they could come up with a rough idea during this meeting about who should be on the committee, and then it could be circulated to the wider community. He thought that Drs. Bidichandani and Bruijn certainly should be on the committee because they are representative of the primary charitable organizations.

Dr. Brooks thought that in order to get a clear vision of what they should do, they should have a clearer vision of what they want to do. He looks at ATSDR as having a certain role historically looking at clusters of ALS. He looks at the Department of Defense (DoD) and the VA as identifying that there is an environmental factor affecting the military. The larger goal should be from the point of view of causation. This is a relatively rare disease, but there is a potential link. He thought as they looked through all of the databases, they should probably be working with DoD, the Navy, the Air Force, et cetera to determine how to integrate some of these data bases to address the larger question. The Data Committee will be more complex than they think if the true vision is evaluated more precisely.

Dr. Bruijn pointed out that establishing a task force would mean more meetings. She thought ATSDR could develop a list of a core group who could be the beginning point of dialogue and refining it further that would be the core of people willing to be on the committee.

Dr. Antao responded that that was more or less how they proceeded with the Research Notification Committee. They called a handful of people who were very helpful in developing procedures. They could follow the same procedure, even asking some people who are already on the committee and adding others with different expertise.

Dr. Knorr thought it might facilitate the process if ATSDR could draft review criteria so that those who are on the committee could react to it rather than spending time to develop something from scratch.

Dr. Bruijn thought it would be helpful to have some liaison with the two committees (research and data) because there might be a reason to understand the process in both.

Dr. Antao clarified that the idea would be that some people on the existing committee could participate in the other one to help get it started, and maybe even participate in it on a rotational

basis. For the Research Notification Committee, the term is 2 years. He wondered whether that would be acceptable for the Data Committee as well.

Mr. Handsfield commented that he had not really heard the roles of the committees defined yet, and he thought they had to be careful not to create another IRB. One critical role could be having those with expertise in data content help assist researchers in how to best use the data. Perhaps an investigator could contact the committee before they prepare the protocol for an IRB. A lot of the use of these data will be a 2-stage use. The first one will be to identify likely subjects for further research, and then through the mechanisms to send notices to registrants to determine whether they want to participate in the studies. These multiple phases need to be considered.

It seemed to Dr. Horton that a research committee is needed, because they need to ensure that studies being proposed are appropriate. He liked the suggestion that the threshold be kept low for data access, because they do want as many people as possible to use the data and not create yet another barrier. It seems that they could keep the existing committee, and have a mechanism like Tracking or RDC where people can access the data that has minimum criteria that people would have to satisfy. He is all for not having a committee if possible. People are too busy, and this means yet another call or meeting. He wants to be able to demonstrate to Congress that these data are being used, and that barriers are not being put up.

Dr. Antao mentioned that the other side of the spectrum is if there are almost no requirements, there may be publication issues. He worries that someone may obtain the data and start publishing information that could be misleading or incorrect.

Mr. Tison suggested that PALS representation always be included.

Dr. Sowell expressed concern about putting all of the data out for anybody to use. NCHS and many other places have some fairly tight controls over their data usage to ensure that the data are not used beyond the limitations of it—that the interpretations are consistent with where the data can go. Having seen papers that stretch data and laboratory analyses way beyond what can be done with the data is very concerning. People with agendas could obtain the data from the Registry and misuse it to make a conclusion that is not justified, whether it is by intent or because of lack of experience. It serves no good to science and it misuses the efforts the PALS have put into sharing their data, so she would prefer some sort of control over how the data are used.

Dr. Horton indicated that ATSDR was instrumental in setting up the World Trade Center (WTC) Registry post-911. They have a research proposal / data committee, which Dr. Antao sits on. He asked Dr. Antao to speak about this and to indicate how data are released.

Dr. Antao added that the way this works is that if anyone wants access to WTC data, they have to submit a brief proposal that goes to a committee that will analyze the proposal. Datasets are provided on a CD or other means depending upon the size. This committee meets every month or on an ad hoc basis as needed.

Dr. Weisskopf said he was sensitive to avoiding “junk science,” but there are other settings in which data are quite open, even within the government. NCHS certainly has restrictions on some data, but they have National Health and Nutrition Examination Survey (NHANES) that he could get on his desktop immediately and on which he could run analysis. Of course, they do not share everything. For example, they will not give data on those over age 85 because the

numbers are too small. He wondered why WTC decided to have an extra level rather than allowing a certain amount of data to be totally open. He was hesitant to require someone to send publications through CDC, given that it would slow the process tremendously. There is peer review in general for publication, so he favored allowing people who are approved to handle their own publication efforts. There are obviously models for the various levels, so they should leverage those rather than "reinventing the wheel."

Dr. Sorenson thought that there would be a low risk of papers that stretch the data being published in peer-reviewed journals.

Dr. Gubitx mentioned that a possible parallel, although the data are very different, is how genome-wide association datasets can be accessed. The process is that a researcher must complete a data request form. It includes a very short section, like a letter of intent, for the researcher to explain the intended use of the data. A team of program staff with relevant expertise at NINDS reviews the data request form. There is a two-week turnaround, and there is an email system. She is notified through a SharePoint email site that a request has been received and that she has to review it. It is a fairly fast and smooth process rather than a burdensome committee process that allows them to track the types of research projects the data are being used for, and to determine whether requests are legitimate. This system also allows them to know how many times the data are requested, which is very beneficial as future investment needs are planned.

Dr. Antao thought that sounded like a good model and ATSDR certainly wants to streamline the process as possible. They have a desire for things to move faster.

Dr. Horton asked how many people review the NINDS data requests.

Dr. Gubitx replied that a review team includes 4-5 NINDS program directors, which is determined by the diseases that are covered in the studies that are currently housed at a website called the Database of Genotypes and Phenotypes (dbGaP) that is managed by National Center for Biotechnology Information (NCBI), which is part of NIH. If there were more diseases, the teams would probably be bigger, but right now dbGaP houses datasets from only a few genetic studies in neurological disorders. It is therefore not a lot of work.

Dr. Horton asked whether consensus was required, and what would happen if two reviewers thought the application was great and the other two thought it was "junk."

Dr. Gubitx responded that they would discuss it, but it is rare that there is disagreement.

Dr. Boylan asked whether there were any external reviewers.

Dr. Gubitx replied that there are not. For data requests, reviews are done in-house. The epidemiological data that the National ALS Registry is collecting is a different type of data, and she thinks it is a good idea to have subject matter experts involved and not just government agency staff. She just wanted to report how they do this for genome-wide association studies.

In the interest of trying to streamline the data release, Dr. Boylan indicated that the Mayo Clinic IRB is centralized and covers three different sites. It is electronic and takes a stratified approach to its review process, which has some conceptual parallels with what conceivably would work with something like this. For example, for personnel changes to protocols it is entirely electronic and is automatic; if individuals being moved in or moved out meet the pre-

established criteria in the electronic IRB system it is done without any input at all. It just happens internally in the system as an overnight review and reset and does not require formal review. Research that is considered to be minimal risk is sent in the system through a set of criteria that IRB staff checks through to determine whether their proposed study is minimal risk. There is a very streamlined process with a subcommittee of people from the main IRB who review it so that they can fast track through the system very quickly. A higher risk project would require a much more involved and formalized process. This process allows requests to move through the system at different speeds based on the level of complexity involved and level of review required, and it meets all of the requirements as far as level of scrutiny, patient protection, and all other issues that have to be considered. That type of approach could allow some levels of data from the National ALS Registry to be made available without much delay or manpower on the part of ATSDR, and could allow more time and effort to be devoted to the more detailed reviews that may be required for other projects.

Dr. Nelson pointed out that development of data requests procedures and development of protocol review criteria will take a lot of work by ATSDR scientific staff and the members of the committee to anticipate the types of requests they will receive and to ensure that they have appropriate data request procedures and review criteria for those. She imagined a committee that would be very dedicated and spend a lot of time early on, but as time goes on, the process could be expedited for less complicated requests and more time could be taken for more complex requests.

Dr. Sorenson pointed out that data requests may be received in the planning stages of projects. For example, Dr. Traynor was asking about family history. An investigator may ask how many patients are in the database with a family history of ALS that they could access. That may be used as part of their planning process for a grant, so there may be requests about data and numbers of cases even before a formal IRB-approved project is submitted for review. Consideration should be given to how this type of request will be handled.

When talking about the anticipated data release date of fall/winter of 2013, when the committee review analysis article is written, and there is a forecasted real date for public data availability, Mr. Tison would like to be alive.

Dr. Horton replied that it was a fair question and Mr. Tison was not the only one saying that. While he would like to be able to state a hard date, there are external issues. If ATSDR can obtain data from Medicare and Medicaid, they can start processing it immediately. It is really dependent upon when those data are received, so he did not want to venture a month or timeframe other than fall/winter 2013. While he knew that was not a good answer, there are factors beyond what ATSDR can control.

## Current and Proposed NIH ALS Research

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### Session Introduction

**D. Kevin Horton, DrPH, MSPH**  
**Chief, Environmental Health Surveillance Branch**  
**Division of Toxicology and Human Health Sciences**  
**Agency for Toxic Substances and Disease Registry**

Dr. Horton emphasized how this registry is really a collaboration and ATSDR cannot do this without its partners (e.g., MDA, ALSA, AAN, and neurologists). It makes sense to continue that collaboration with other groups as well, including other federal partners. This session highlights this collaborative effort, especially with the potential establishment of a bioregistry.

Consideration must be given to what can be done with a bioregistry in terms of the types of analyses that can be done. ATSDR is excited to work with its various partners to help move the National ALS Registry forward.

### **NIH-Sponsored Research on ALS Risk Factors**

**Amelie Gubitz, PhD**

**Program Director, Neurodegeneration**

**National Institute of Neurological Disorders and Stroke**

**National Institutes of Health**

Dr. Gubitz reported that ATSDR and NIH have formed a partnership to advance ALS research. She explained that when she talks about ALS research at NIH, she always emphasizes that ALS research is a shared mission across multiple Institutes and Centers at NIH. NIH is a very large agency with 27 different Institutes/centers, at least 11 of which are invested in ALS research. Dollar wise, NINDS is the lead Institute for ALS research at NIH with 75% of the funding. Nevertheless, the contributions by the other Institutes are very important. During this session, Dr. Gubitz specifically highlighted the contributions of the National Institute of Environmental Health Sciences (NIEHS) and the National Institute on Aging (NIA). Both NIEHS and NIA have proven themselves to be excellent partners for NINDS in terms of ALS research. The research portfolios for these three Institutes are very nicely complementary, and on occasion they co-fund some of the more expensive awards. In addition, NIEHS and NIA have very active intramural research programs that conduct ALS research. Dr. Traynor's laboratory at NIA is an example, as is Freya Kamel's and Dale Sandler's group at NIEHS. In fiscal year 2011, NIH invested \$44 million in ALS research. About 90% of this amount is allocated to research laboratories across the US.

NIEHS, NIA, and NINDS support ALS risk factors research, but each Institute has a different emphasis. NIEHS is primarily interested in supporting research that explores environmental risk factors for sporadic ALS and that investigates the role of gene-environment interactions in the disease. NIA primarily supports genetic risk factor research in sporadic ALS. NINDS supports research focused on genetic risk factors, environmental risk factors, and the role of gene-environment interactions. This is only a smaller slice of NINDS overall research portfolio. The majority of its funding is allocated toward research that investigates the cellular and molecular pathogenesis of the disease, as well as clinical trials in ALS and preclinical therapeutic development.

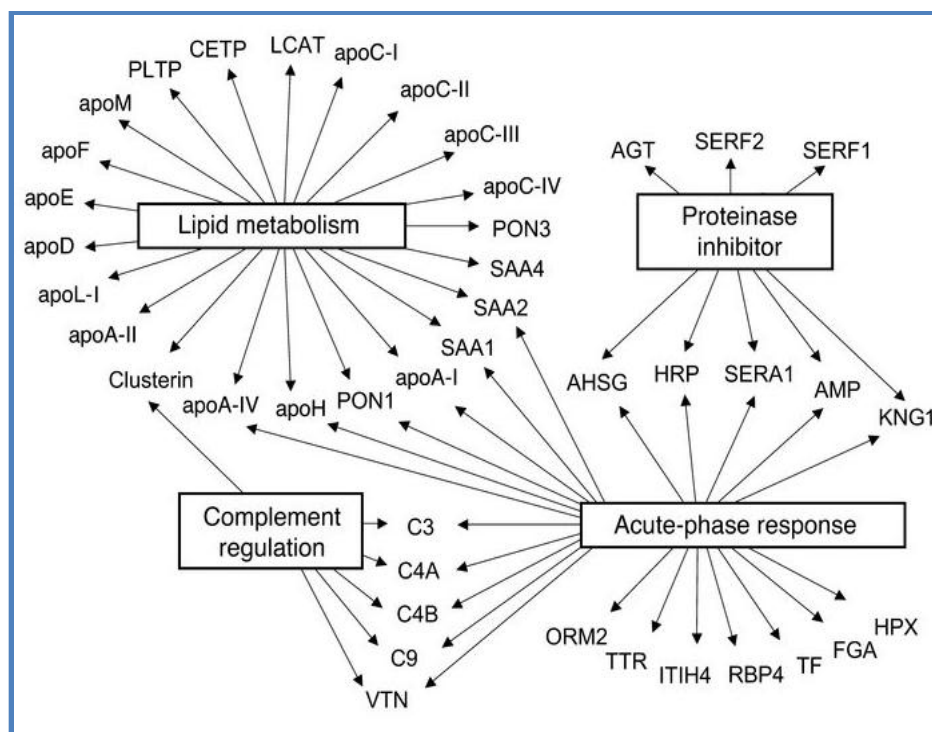
Regarding the goals of the National ALS Registry, Dr. Gubitz emphasized that in addition to determining better estimates of the incidence and prevalence of the disease in the US, data that have been collected by the Registry will also inform the understanding of the risk factors of sporadic ALS. The Registry is collecting data on environmental and occupational factors, and the question of the causation of sporadic ALS is a shared research interest between ATSDR and NIH and has formed the basis for the agencies' recent partnership. Through this collaboration, ATSDR is planning to provide one year of funding for three NIH projects that explore risk factors of the sporadic form of the disease. The scientific staff of ATSDR and NIH met to discuss which projects would be most appropriate for this collaboration. NIH assessed its pipeline to identify projects that are highly meritorious, which means they already went to a

study section or through NIH's intramural vetting process and received very good scores but are still pending funding. It was also agreed that it would be appropriate to select projects that approach this research question from different directions. By design, the following projects were selected:

- ❑ The role of gene-environment interactions in sporadic ALS (Teepu Siddique, Northwestern University, Feinberg School of Medicine: Association of ALS with gene-environment mediated changes in HDL proteins)
- ❑ Non-genetic risk factors (occupation, toxins, behavioral) of sporadic ALS (Marc Weisskopf, Environmental Health and Epidemiology, Harvard School of Public Health: Environmental risk factors for ALS in a representative sample of the US population)
- ❑ Genetic risk factors of sporadic ALS (Bryan Traynor, Laboratory of Neurogenetics, National Institute on Aging, Intramural Research Program: Large genome-wide association study in ALS)

Dr. Gubitz briefly summarized the overall gist of Dr. Teepu Siddique's one-year research endeavor that ATSDR is hoping to support. The hypothesis that underlies Dr. Siddique's project is that the risk for sporadic ALS is elevated in certain populations by changes in environmentally-sensitive proteins. Specifically, Dr. Siddique will analyze the entire proteome of high-density lipoprotein (HDL) particles that are found in the plasma and cerebrospinal fluid (CSF) in sporadic ALS in humans compared to normal control subjects to screen for changes corresponding to detoxification (e.g., of pesticides or pathogens) or oxidative stress. Dr. Siddique is focusing on HDL particles because they are known to contain enzymes and proteins that respond to environmental challenges, such as infections by pathogens or exposure to pesticides or oxidative stress. The following figure illustrates that HDL particles are more than a cholesterol transporter, which is the function for which these particles are most famous:





Vaisar et al., 2007

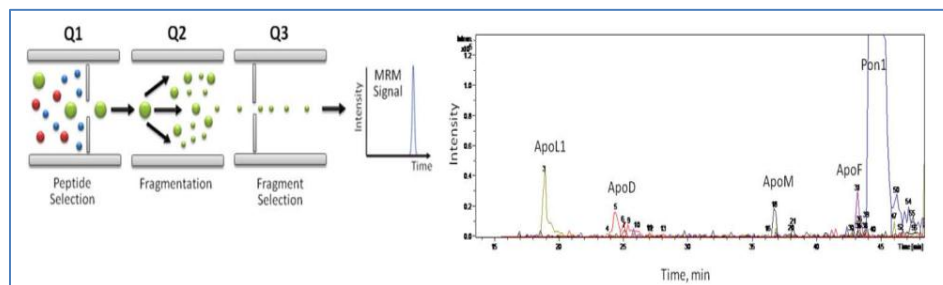
In fact, HDL particles contain a full array of proteins and enzymes that are involved in lipid metabolism and that have regulatory roles in the complement system, which is part of innate immunity, which in turn can be recruited by the adaptive immune system to protect or clear pathogens from an organism. These particles also contain proteins that are involved in the acute-phase response to inflammation, and several other proteins that function as proteinase inhibitors.

Dr. Siddique is going to analyze all of these proteins within the HDL particles, but there are three candidate proteins in which he is particularly interested, including the following:

- ☐ Apolipoprotein L1 (APOL1), which is known to play an important role in host defense and cellular homeostasis
- ☐ Paraoxonase enzymes (PON1 and PON3), which are known to be involved in detoxifying organophosphate pesticides, as well as protecting lipoproteins from oxidative damage.

The data that support the relevance of these three proteins to sporadic ALS is that Dr. Siddique found that the levels of PON1, PON3, and APOL1 levels are increased in sera of sporadic ALS patients. This proposal contains very nice data in this regard, and he now hopes to extend these data to a larger number of samples from sporadic ALS patients. Also in previous work, Dr. Siddique and other investigators have found that there seems to be a genetic association between specific polymorphisms in PON1 and PON3 and sporadic ALS. There is conflicting data on this in the public literature, but Dr. Siddique maintains that the association is real in specific populations. Much more recently, he found evidence for a similar association between polymorphisms in the APOL1 gene and sporadic ALS (these data are not yet published).

The approach that Dr. Siddique is going to take entails mass spectrometry-based quantitative measurements of peptides derived from HDL proteins. The method he is using is traditional mass spectrometry, but there is a novel twist. This novel twist is based on liposorbption and site selection by fragmentation. This method is referred to as multiple reaction monitoring, and it will allow him to very sensitively quantify these proteins in the HDL particles. The following illustration is a typical chromatogram for the identification and quantification of apolipoproteins and PON1 in plasma from a normal control subject:



The project deliverable for this one-year research endeavor is quantitative data of the entire protein “cargo” of these HDL particles in plasma and CSF for several hundred sporadic ALS patients. Fortunately, Dr. Siddique already has a very large and rich human biospecimens collection that he is going to use for the study. Throughout the year, he is planning to add additional samples. This type of research really underscores the value of high-quality human biospecimens collection, and of course, this is the key mission of the ALS Bioregistry that ATSDR is currently piloting. In terms of the expected outcome, the data are expected to support or refute the hypothesis that changes in specific environmentally-sensitive proteins in HDL particles contribute to ALS risk. This will direct future research efforts.

### **Discussion Points**

Dr. Nelson inquired as to who the control population is.

Dr. Gubitz replied that she would find out and would email Dr. Nelson with the information.

### **Environmental Risk Factors for ALS in a Representative Sample of the US**

**Marc Weisskopf, PhD, ScD**

**Associate Professor, Departments of Environmental Health and Epidemiology  
Harvard School of Public Health**

Dr. Weisskopf emphasized that there is little information on established risk factors for ALS other than age and perhaps being male. Evidence for other non-genetic risk factors is unfortunately not very strong. However, several types of exposures have received interest in ALS research from an epidemiological perspective, although evidence is still somewhat conflicting. Cigarette smoking has received quite a bit of attention. There are various reports suggesting that it is, in fact, related to ALS. Dr. Weisskopf's own take on this is that this remains unclear. The data are not very clean, and there may be differences in this risk factor between men and women. Some studies observe the risk factor in women and not in men, while other studies see it in both. Where it is observed, there often is not a very clean dose-response. Thus, cigarette smoking is not a totally worked out risk factor at this stage, at least in Dr. Weisskopf's mind. Another potential risk factor is military service. There were the original

studies on the Gulf War that were followed up by several others suggesting increased risk in those who were deployed to the gulf. There is one general paper published by Dr. Weisskopf several years ago, which remains to date the only study that has evaluated a wider spectrum of military service. In fact, the Institute of Medicine (IOM) raised that as an issue when considering the evidence that there is really only one paper that looked generally at military service. Another potential risk factor that has received attention is lead exposure. Lead has been a potential suspect as a risk factor for ALS for a while. A lot of the early studies were relatively small, but there was some suggestion that lead may be involved. Two recent studies using biomarkers, either blood lead or bone lead, seemed to suggest an association with lead. But again, the associations were not as clean as preferred. There was some association with occupational history and associations with blood lead, but not quite as obvious for bone lead, which is an odd pattern to find given what is known about those biomarkers. While intriguing, whether lead is a risk factor is not settled by any means.

The hypothesis that Dr. Weisskopf proposes to address is that ALS risk may be elevated among people who smoke cigarettes, serve in the military, or have higher exposure to lead. The

## Hypotheses

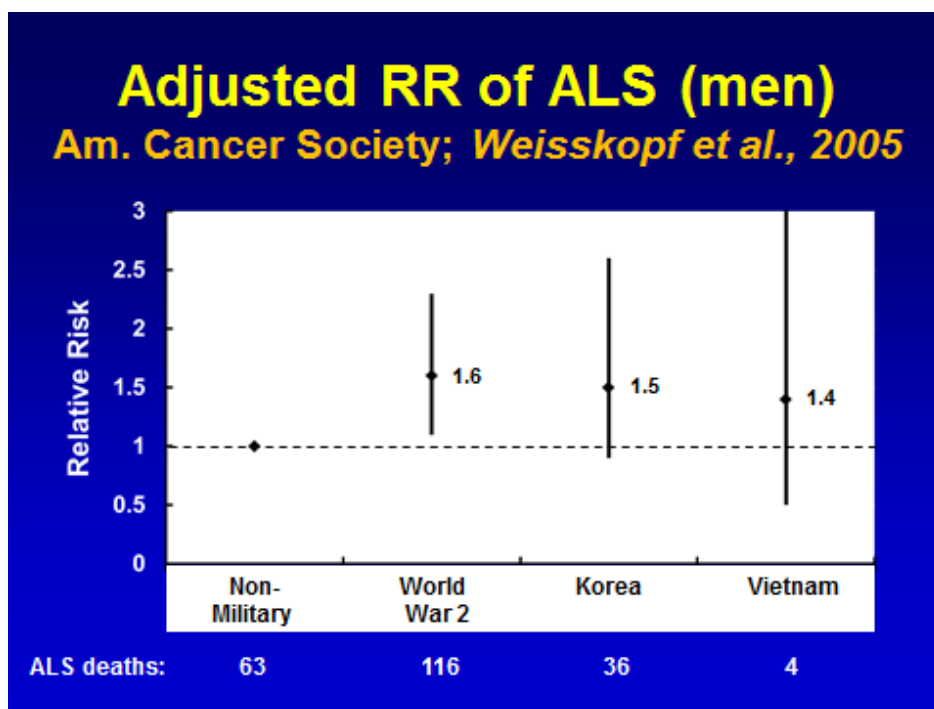
- **ALS risk is elevated among people who:**
  - ▶ **Smoke cigarettes**
  - ▶ **Serve in the military**
  - ▶ **Have higher exposure to lead**
- **Approach**
  - ▶ **US population based prospective cohort study**

approach he proposes to take is a US population-based prospective cohort study. The study population is based on Current Population Surveys (CPS) that are administered by the US Census Bureau and US Bureau of Labor Statistics. While these are typically known for their use regarding labor statistics, the National Cancer Institute (NCI) began linking these data to mortality data through the NDI. Each CPS is a national stratified cluster sample of US households with participants from every state, including Puerto Rico and DC. These are meant to be representative of the US civilian non-institutionalized population, and they have a very high response rate of approximately 96%. Those questionnaire data have been linked to the National Longitudinal Mortality Study (NLMS), with linkage of CPS with National Death Index (NDI). ALS deaths can be identified from the NDI information using ICD-9 335.2 through 1998 and ICD-10 G12.2 after 1998 as the underlying or contributing cause. Cox proportional hazards methods will be used to assess follow-up from baseline to the end of follow-up or to death. The CPS began in 1973 and was conducted in 1978 and 1979, and has been conducted yearly since then with a few additional ones at certain intervals. The NDI has been electronic since

1979, so before that no one can be linked. Who died can be determined through the Social Security Administration; however, the cause of death is not available.

Based on preliminary assessment that has been done of the NLMS, overall there is a total of 2.4 million people. While it is weighted toward the younger side because the ages were at baseline when people answered their CPS questionnaires, there is a healthy distribution across the age ranges for men and women. The preliminary ALS death rate based on NLMS has also been assessed by age and sex. Dr. Weisskopf already has over 700 cases and anticipates more with further follow-up and searching. ALS death rates for men total 381 per 100,000 population, and 332 per 100,000 for women. This is generally what might be expected in the US population, with the numbers more or less relating. Data on cigarette smoking includes current and former status, the age smoking was started, frequency of smoking, and the average number of cigarettes. The military service data includes period of service and conflict. The lead exposure data includes occupational exposure using job-exposure matrixes to link occupations to potential lead exposures based on other data from industrial hygienists and the like about which jobs had higher lead exposure. There are also data on covariates from NLMS, including age, sex, education, race / ethnicity, and socioeconomic status (e.g., Income, dwelling, type of health insurance).

Unfortunately, information about cigarette smoking was not asked on every CPS, so it is a much smaller group that has information on cigarette smoking. It is anticipated that with additional follow-up, there will be at least an additional 200 ALS cases in that group, and probably more depending upon how much follow-up can be accomplished. Data based on a publication on cigarette smoking and lung cancer and chronic obstructive pulmonary disease (COPD) rates within NLMS show that cigarette smoking is extremely strongly related to lung cancer and COPD, as would be expected [Adapted from Lewis et al., *Int J Tuberc Lung Dis* . 2009]. In Dr. Weisskopf's original study using the American Cancer Society's (ACS) Cancer Prevention Study II (CPS-II) about general military service and risk of ALS, he found about a 50% to 60%



increased risk of ALS. The breakdown by period of service suggested that there was little difference by service, but there were very few ALS deaths from people who served in Vietnam (N=4). It was a population heavily weighted toward World War 2 (WW2). From the NLMS, only data from men were used because very few women served in the military. The population was weighted much more away from WW2 and closer to Vietnam, so hopefully there will also be sufficient information to explore Vietnam service more within this dataset. In terms of lead exposure, there is a much larger dataset, but a much smaller fraction of it is publically available. A study conducted on the dataset that is publically available used a job-exposure matrix to assign lead level exposures to different people, and assessed the incidence of brain cancer mortality. At least with brain cancer, this study found a rather strong dose-response association with lead exposure [van Wijngaarden et al., 2006, based on a subset of the NLMS]. Dr. Weisskopf's proposal is to use a similar job-exposure matrix to explore the risk of ALS. There are other job-exposure matrixes that may potentially be explored as well.

The project deliverable is analysis of the association between three potential ALS risk factors in a nationally representative US-based prospective cohort. The original military study was conducted using the CPS-II, which was really a volunteer cohort and has been criticized for that in some cases. The proposed study would be in a nationally representative population, which is nice. The expected outcome is that the results of the study will support or refute the hypothesis that the studied risk factors contribute to ALS risk.

### **Discussion Points**

Dr. Bradley inquired as to whether Dr. Weisskopf has residential geographical data from the surveys.

Dr. Weisskopf replied that he was not entirely sure. If it is there, he can obtain it. He is just not certain at what level they have these data. They have region and state, but he did not know beyond that.

Dr. Bradley said he thought the death data base included the address at death, so they might be able to approach at least the ALS cases in that way.

Dr. Horton asked whether ATSDR should consider assessing the CPS and labor data in terms of another dataset for the National ALS Registry.

Dr. Weisskopf did not think so, because the only way ALS is identified is through NDI. The CPS data does not include any ALS information.

Dr. Brooks asked why Dr. Weisskopf's preliminary analysis showed nearly twice the rate of ALS, and whether it was because he was getting people at the high range of his 95% confidence limits. The Wisconsin data shows about 2 per 100,000 for that age group. He wondered whether NLMS had a pool with a higher rate of ALS.

Dr. Weisskopf replied that this was because he was excluding the very young. A typical number of about 2 per 100,000 would represent the entire population. The pool is nationally representative. While he reported by age, if everyone is included the range is 1.5 to 2.

Mr. Tison asked whether, in Dr. Weisskopf's opinion, if about 35% of registry enrollees completed the smoking risk factor survey it would be useful not knowing any selection biases.

Dr. Weisskopf replied that this is definitely a problem. It is certainly still useful, but they would really like to know the differences between the people who did and did not complete that survey. In terms of the issue of the response rate of the surveys, even if something is completed, comparisons can be made with statistical techniques to assess those who did answer the smoking survey versus those who did not. He asked Mr. Tison to clarify whether he was talking about the Registry or the proposed study.

Mr. Tison clarified that he was talking about the National ALS Registry.

Dr. Weisskopf indicated that he had a similar issue in terms of the proposed study in that not everybody was asked about smoking, so he will have to deal with that by trying to compare people who did and did not receive the questionnaire. There are statistical techniques that can be used, but they are based on having other information about the people who did not respond to the information. It is still useful, but the more they can get even something, even if someone does not complete every survey, that alone can help with missing data on other variables.

Dr. Kaye requested clarification regarding whether 335.2 or 335.20 was used for the death data, and how they would deal with the disease in G12.2 that is not an NMD.

Dr. Weisskopf responded that he would have to check on the answer to the 335.2 / 335.20 question, and that they are stuck with having to use the G12.2 category that is not an NMD. There is clearly an increase when switching to ICD-10, but it is not so much of an issue unless the risk factor being assessed happens to vary by whether they are getting ICD-9 or ICD-10 data. That may be the case, because there may be secular trends. They will have to make some adjustments depending upon whether they are looking at ICD-9 or ICD-10.

Dr. Kaye inquired as to whether they have the actual written text. She is getting the codes and the hard copy. Being able to see the hard copy is beneficial. They can screen for words in addition to using the code. It is amazing because they get some that clearly say "ALS" but for some reason did not get coded, and some that are coded as "ALS" that do not say that in the text.

Dr. Weisskopf responded that the unfortunate limitation of the data he will be using is that it includes 2.4 million people, so he will not be able to do this.

Regarding prevalence of ALS among military service and the Gulf War, Dr. Muravov said he knew about Dr. Weisskopf's paper on general military service and ALS. He wondered what his personal take was on what actually caused that link with ALS among soldiers in the first Gulf War.

Dr. Weisskopf replied that this is tricky. There were numerous editorials about that data, and one of the complaints was that the Gulf War soldiers were exposed to so many things, they would never find out what it actually was. The problem is that given the confidence limits, it is not totally clear to him yet that those who served in the first Gulf War are necessarily different from the larger population he was investigating. They may in fact have a higher risk, which is what the actual point estimate might suggest. Taking that from another angle, his analysis of the general military population suggests that it is not something specific to the first Gulf War. There may have been something in the first Gulf War that further exacerbated the risk, and that is why they were getting numbers closer to 2. It is really hard to say what that is, and there are many theories. It was intriguing to him when he observed it in the larger population, because that actually limits the realm of factors upon which they may want to focus, because then it has

to be exposures that are really common across different factors such as head trauma, possibly lead exposure, and maybe some types of infections. In terms of the Gulf War, Dr. Weisskopf does not feel like he has a good idea of what that element could be.

Dr. Sorenson noted that the risk has gradually increased between Vietnam, Korea, and WWII. A lot of that could be accounted for by age. He wondered whether Dr. Weisskopf adjusted for age in his reference population.

Dr. Weisskopf replied that the rates are all age-adjusted.

### **Large Scale Genome-Wide Association Study of ALS**

**Bryan Traynor, MD**

**Assistant Clinical Investigator**

**Neuromuscular Diseases Research Group**

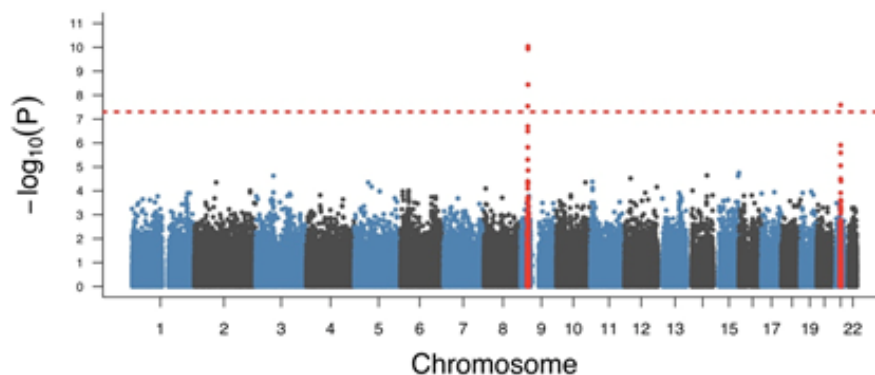
**National Institutes of Health**

In terms of the current understanding of the pathogenesis of ALS, Dr. Traynor indicated that ALS has to be divided into two categories: Familial ALS, which accounts for about 10%, and the rest, which is sporadic ALS because there is no apparent family history or it appears to occur sporadically throughout the community. It is fairly safe to say that the genetic component of familial ALS is understood for about two-thirds of familial ALS. About 11% is understood for sporadic ALS. While that is a tremendous amount of progress over the last three years, it is clear that there are many other genes to find for familial and sporadic ALS. The proposed project is aimed at trying to achieve this.

The Genome-Wide Association Study (GWAS) has been remarkably successful in ALS to date because it has been instrumental in unraveling Chromosome 9 Open Reading Frame 72 (C9ORF72). One of the criticisms made about the Genome-Wide Association Studies in general is that they tend not to find genes. Found instead are areas within the genome that appear to be associated with altered risk of a particular disease. ALS is one of the rare instances in Genome-Wide Association Studies in which that is not the case, given that they have been able to bring it forward from finding a strong association signal toward finding the actual underlying variant in the underlying gene. The following Manhattan Plot shows the chromosomes and the strength of the association signal, with each dot representing a single nucleotide polymorphism (SNP) or marker that has been genotyped across the genome. The reason there are so many dots is that about a million markers are genotyped in most GWAS. Oftentimes, as many as 7 million markers will be genotyped across the genome. In the illustration, highlighted in red are two spots that represent the association signal. It is called a Manhattan Plot because it is supposed to look like downtown Manhattan. This is the Manhattan Plot for the Finnish GWAS. Prior to that, all of the GWAS that were done were more like Dublin Plots because there were really no skyscrapers. This Manhattan Plot allowed investigators to hone in on Chromosome 9 and assess what was occurring:



## GWAS in ALS has been amazing successful in unraveling C9ORF72



The overall aim of Dr. Traynor's Large Scale Genome-Wide Association Study of ALS is to perform a GWAS of 10,000 ALS patients and a similar number of control individuals. Dr. Traynor emphasized that GWAS is a numbers game. Investigators were very lucky with Finland because it was a conserved population, but for populations in the US and Europe, it is a numbers game. To put this into perspective, Parkinson's disease started more or less in the same realm as ALS with a couple of hundred samples and did not really see anything. After a couple of thousand, they began to see some signals, but it was not really until there were 7000 to 10,000 samples that the frosted glass dropped away and the association signal started to come in. Currently, a meta-mega analysis is being conducted with Parkinson's disease that involves about 20,000 cases and about 9000 controls. In terms of the current literature, ALS is at the level of about 4000 cases and 5000 controls. The idea behind the Large Scale Genome-Wide Association Study of ALS is to go much further to genotype about 10,000 ALS cases and a similar number of controls. This should allow for sufficient power to identify several new genetic loci. The reason this has not been done previously but is being proposed now is because the cost of genotyping has decreased dramatically. To put it into perspective, the initial GWAS study cost about \$1,000 to genotype each sample. The cost quoted for the proposed study is about \$57 per sample.

Two important aspects of GWAS are samples and the chip that will be used. Because NIH is based in America, they like to collect as many ALS samples as possible from the US. The hope for the proposed study is to collect approximately 4000 samples from the US. Italy is being particularly targeted because Dr. Traynor has a longstanding collaboration with an excellent neurologist there, Dr. Adriano Chiò, who is an expert in ALS. In addition to being an excellent neurologist, Dr. Chiò is also a really good diplomat because he has managed to put together about 43 centers across the entire peninsula of Italy that have all collected ALS samples totaling about 3000. Though the genetic cause of the majority of cases in Finland has been essentially worked out, there is still value in including those 500 cases and 500 controls onto the chip because Dr. Traynor believes there are still additional data that can be pulled out. They are



also very fortunate to work with Dr. Michael Sendtner at the Universität Würzburg in Germany who has collected a large cohort, as well as John Hardy and others in the UK who have also collected a large cohort of samples. Dr. Traynor also believes that it is worthwhile to include samples from Australia. The original family where transactivation response DNA binding protein-43 (TDP-43) mutations were found was an Australian family that Garth Nicholson and Ian P. Blair have worked on.

With regard to chips, the previous chips were designed to select markers typically with a frequency of greater than 5% in the general population, all across the genome. It was really equidistant markers across the genome. The new Exome chip is designed to specifically take the rare variants that have been found through Exome sequencing and whole genome sequencing in the 1000 Genomes Project and interrogate the coding regions within the genes. In contrast to the previous chip, this is a very gene-centric platform. There are two main hypotheses within genetics, which are the Common Disease – Common Variant (CD-CV) hypothesis and the Common Disease-Rare Variant (CD-RV) hypothesis. Essentially, the previous GWAS have looked at the CD-CV hypothesis, and this will look at the CD-RV, which is going in the opposite direction. CD-CV really applies to diabetes and heart disease, something that is very common in the population. The incidence of ALS is quite rare, so maybe this paradigm is more appropriate in terms of understanding a rare disease such as ALS. In addition to getting the 700,000 variants specifically within the genes, Illumina has offered an add-on custom content of about 5000 SNPs at a very low price. Basically, the investigators can tell Illumina what they want, so they decided to use that ability to select SNPs to customize this chip to test some of the variants found in previous GWAS studies. About 1500 most associated SNPs from previous GWAS are being included. So this is a Large Scale Stage 2 Genome-Wide Association Study of ALS. In terms of what to use the rest of the markers for, it turns out that in Parkinson's disease, many of the association signals that have been seen actually lie in genes that have been implicated in familial Parkinson's disease. With that in mind, the investigators decided to deeply interrogate all of the known genes for ALS, including assessing the haplotypes across known genes.

In terms of resources, most of the DNA samples are in hand. They have been collected and are in the NIH laboratory or other laboratories, and the necessary equipment is in place (e.g., Tecan robot, iScan system, NIH biowulf cluster). They can basically run about 2000 samples per week in terms of genotyping and processing, given that they have been funded by various charitable organizations and the intramural program of NIH to purchase this rather expensive equipment that allows them to go through this very quickly. They also have access to a fairly sizable computer cluster that will allow them to analyze the data. Their secret weapon is Mike Nalls, who is the statistical geneticist who is a guru with respect to analyzing these data. Regarding the deliverables, Dr. Traynor said that he honestly believes they will find new genetic loci. Importantly, he believes that they will identify mutations samples that carry known mutations. The raw genotype data will be made publicly available on dbGAP so that researchers with approved IRBs can access it very simply. All of the genome data from previous GWAS have been made available in dpGAP. There is a counter on the website about how many times those data have been accessed and downloaded. At this point, data has been downloaded 84 times. All of the GWASs that have been published on ALS have included the data that were initially published in 2007. Researchers can acquire these data for free, and essentially it is a mechanism for improving power.

Obviously, the purpose of this meeting was to discuss the National ALS Registry. He thought it was important to take a moment to talk about how the proposed study would tie into the National ALS Registry and leverage resources. The chip they are designing, called the

Neurochip, is going to be on the shelf at Illumina and anyone who wishes to purchase it can. It is being designed to be open and publically available, which means that when the samples in the bioregistry become available, they too can be run on the Neurochip in exactly the same way. That would give information about the potential mutations in these particular samples at a very cheap price. As mentioned earlier, this is a numbers game in that the numbers always need to be increased. Using the National ALS Registry to go to all of the patients in order to collect their samples represents a way in which the numbers can be increased. It highlights the CDC efforts with respect to the Registry. In terms of the discussion earlier about disclaimers with respect to CDC and publications, actually the other side of that coin is equally important; that is, making sure that the people who download the data and subsequently publish on that data acknowledge that it came from CDC and include the appropriate numbers.

### **Discussion Points**

An inquiry was posed regarding the timeframe. Dr. Traynor replied that on the application he said 12 months, but he hopes to complete the project before that in 6 months. What tends to happen in his laboratory is that when they have a project, they work rapidly to get it done.

One participant found this to be very exciting. In terms of describing the chip as gene-centric, he inquired as to whether intronic associations would be found. For instance, would it find C9ORF72 as easily as it was found with the genome-wide non-specific chip?

Dr. Traynor replied that one of the things they will do with these data is imputations. About 750,000 SNPs will be measured across the genome, and they will be within genes. Because the haplotype structure within the normal human genome is known from the 1000 Genomes dataset and from other datasets, they can compute for free except for computer processing time up to 7 million. Even though these SNPs are going to be very much based within the genes, they can impute nearby SNPs which tend to be within the introns. The same issue applies with all GWAS, in that this is never known until the experiment is actually conducted.

### **OMB Submission**

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**Wendy E. Kaye, PhD**  
**Senior Epidemiologist**  
**McKing Consulting Corporation**

Dr. Kaye reported that this data collection was approved in July 2010 and will expire July 31, 2013. This means that between now and July 2013, an application must be submitted to OMB to continue data collection. An application to continue is basically the same as the initial application. It asks for progress and is as long and as complicated as the original application. Therefore, the process must begin about a year out. They will soon begin to think about what will need to be sent and any changes they want to make for the next 3-year time period. For example, the additional risk factor modules they would like to include will be addressed in the request for continuation of the project. In the interim, they are asking to process a non-substantive change to the application for the clinical module and the open-ended question so that those can go up before August 2013. If they were in the new application, they would not be approved until that time. There is a little lag from when OMB approves the application and when it is implemented, given that it also has to go through computer security clearance because this is a web-based application. The order of approvals is IRB, OMB, and computer

security. Dr. Kaye is in the process of writing the request for the non-substantive change to add the short modules. She will probably begin in September in earnest to work on the continuation application in order to submit it in plenty of time.

### **Discussion Points**

Dr. Horton requested confirmation about whether the clinical and open-ended question modules had already been IRB-approved.

Dr. Kaye affirmed that these have been IRB-approved, and they anticipate submitting these to OMB without substantive change by the end of July. It is drafted and just needs to be sent in.

Dr. Horton indicated that they frequently receive questions about when the next series of modules will be coming out, and they try not to bore people with IRB and OMB issues, but these are necessary obstacles that the agency has to overcome. It is not as straightforward as it seems, and they do try to push things through as quickly as possible.

Dr. Traynor requested confirmation regarding whether IRB and OMB approval must be sought for the biorepository as well.

Dr. Kaye responded that they definitely will have to go through IRB, but for OMB they will most likely be able to obtain what is called a "Clinical Exemption" because the only information collected is the information necessary to process the specimens (e.g., when people had something to drink, when they had caffeine, when the specimen was collected, et cetera). No additional risk factor questions will be asked. For that information, participants will be funneled back through the Registry and will be encouraged to complete that information. They have to be registered in the National ALS Registry to be eligible for the bioregistry, so they do not want to duplicate the effort by asking participants to complete the same information more than once in the same project.

Dr. Traynor wondered whether it was better for ATSDR to get everything right the first time, or if it was simpler to submit a protocol and then amend it later. He said he raised this issue because of the skin biopsies.

Dr. Kaye replied that in her experience with CDC's IRB and OMB, it is better to get it right the first time. She clarified that OMB does not have a hard and fast rule about times. It is more of a general rule about what a reasonable amount of burden will be for people. ATSDR said that given this population, they wanted to keep the overall burden an hour or less if someone wanted to register and complete all of the surveys from start to finish all at once. This is based on common sense. NHANES takes over 4 hours, so it is not a hard number. In terms of the biorepository, an outside peer review is required for ATSDR on any research process. They could make some revisions at that time. The issue with skin samples is that there is no money in the contract for processing specimens. If it can be put in a vial and placed on a shelf, and it can be used 5 years from now, that is fine. The only money in the contract for processing is to spin down the blood, aliquot it, and freeze it and for the brain specimens that the VA will be grossing. Otherwise, the muscle sample is going in a vial of formalin, the bone is being dropped in something, the hair and nails are going into lead-free containers and it is all being put on the shelf. Anything that can be dropped in a bottle, put on a shelf, and does not need processing can be considered.

Dr. Traynor pointed out that this might be an opportunity to work with NIH in terms of the Coriell repository, because they do accept fibroblasts. It does require funds, but perhaps that would be something to discuss with Dr. Gubitz.

Dr. Gubitz indicated that they could discuss this offline.

Mr. Gibson inquired as to whether they could have a visual to help illustrate the timelines in terms of being transparent to the group, and that would allow them to share with others what challenges there are.

Dr. Kaye responded that once a package leaves her desk, it is out of their control. It goes to an office above them, to an office in CDC, to HHS, to OMB.

Mr. Gibson clarified that he meant a list of what the general process is, and include approximate dates like a year from July it has to be submitted to OMB.

Dr. Kaye said she could provide a list of the different types of approval that are required, but she could only give broad timeframes.

Dr. Sowell added that the problem with OMB is that it is really variable. Sometimes approval occurs within 8 months of when it is submitted, which is the projected estimate. Sometimes it may take 3 years, and there does not seem to be a really good pattern of what takes how long. ATSDR can estimate how long it may take, but once it is submitted to OMB, it is up to them.

Mr. Gibson clarified that that was not what he was asking. For example, Dr. Kaye gave a date earlier of July 2013 with regard to the continuation application.

Dr. Kaye responded that she could give a list that the first step is IRB approval, followed by OMB clearance, followed by computer security and each one of these takes an estimated amount of time. By 2013, the continuation application has to be approved, so it needs to be submitted by a minimum of 6 months ahead of time to ensure that there are no lapses. Renewals do not take the prolonged time that initial applications take, and she always allows time to write the application, submit it to ATSDR and CDC, allow time for their questions, and submit it to OMB in ample time to avoid overlaps.

Mr. Wildman thought she presented a similar timeline between 2008 and the launch of the National ALS Registry.

Dr. Kaye said she would look at that, and could redo it.

Dr. Boylan asked whether the content of the clinical module had changed at all in the process of passing through the review process.

Dr. Kaye responded that the content had not changed, but it looks much prettier now. It has been somewhat reorganized to make it similar to the other modules. Dr. Kaye grouped things together in a more formal format, and Dr. Nelson made it look like all of the other modules so that it will be easy to implement.

Dr. Horton indicated that within the clinical module, consideration is being given to adding a body that a person can click on to show where they first noticed symptoms, similar to what PatientsLikeMe does.

Mr. Kingon pointed out that if there is a Republican Administration in 2013, the change in administration could create complications as well.

Dr. Kaye agreed that changes in administration do sometimes tend to complicate things.

## **Next Steps and Strategies for Enhancing the National ALS Registry for all End-Users: Open Discussion**

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**Robert Kingon, MPA, Facilitator**  
**Carter Consulting, Inc.**

During this session, Mr. Kingon called for an open discussion of next steps and strategies for the National ALS Registry for all end-users. He particularly suggested sharing ideas and recommendations about efforts that could be implemented immediately to improve the Registry.

### **Discussion Points**

Dr. Nelson noted that increased participation in the modules had been a common theme during this meeting. When they conduct population-based studies in Western Washington State and Northern California, they are presumably ascertaining most ALS patients. They typically have a response rate of over 90% for two-hour interviews, blood draws, and so forth. People with ALS are highly motivated to do this, and people are already in the Registry, so ATSDR should be able to improve on that. The National ATSDR Registry website is beautiful. It is very rich, but it is very busy, so she could imagine clicking around and losing track of the goal of completing the risk factor modules. She wondered whether there was a way to communicate to registrants what their progress has been. Perhaps there could be a temperature gage that shows the completeness of their information on risk factors. Some people may think they have completed all of the modules, but maybe they disregarded the smoking modules because they are a non-smoker. Some type of gage would continually reinforce the need to collect complete data on all aspects that there are questions about, and they would have the satisfaction of seeing that they are registered and counted with respect to the risk factor modules.

Dr. Horton indicated that they received approval from IRB to contact patients via email who have not completed the surveys, which they began doing in May. Given what is known about patient lock-outs, there is a frustration factor for those who receive an email but then find themselves to be locked out. He thought Dr. Nelson's suggestion about some type of gage on the website was interesting, and could be taken into consideration.

Dr. Nelson indicated that she participated in 23andMe where she submitted her DNA. They have a huge number of risk factor modules, which number about 3 times as many as the National ALS Registry. She continually receives requests to complete the 23andMe modules, so there are constant reminders.

Dr. Kaye asked for clarification about whether Dr. Nelson was envisioning something like the thermometers that are used in campaigns. She also noted that the surveys are just numbered and do not have descriptors on them, with the hope that people will not pick and choose. They have discovered that the system is quirky in that once someone completes a survey, the data may be sitting there not submitted. This was done so that if people grew tired they would not have to complete the whole thing, but at some point they have to click the last submit button.

They found that a number of people completed all six surveys and answered every question, but their data had not been submitted because they did not click submit. ATSDR asked the IRB for permission to move those into the completed status instead of an in-progress status. The next tutorial video will discuss surveys, how to take a survey, and this quirk in the system.

Dr. Nelson confirmed that this was what she meant, and it would show what they completed, what they had not completed, and maybe make the point someplace that even if they had never been a smoker, it is still critical for them to complete the smoking module. She asked whether there was a place on the website that shows the current status of the person, for example, if they have elected to be informed about research.

Dr. Kaye replied that when registrants go into their accounts, they can see what they have agreed to do and can change those if they want to. They can also go to the survey page and can see which ones they have completed, which ones are in-progress, and which ones are new.

Dr. Nelson suggested putting a link on the homepage for "My Status" or "Log-In to Find My Status on the Registry."

Mr. Tison suggested mailing a t-shirt when completed.

Dr. Kaye responded that ALSA has been working on giving stickers to people who attend events that say, "I've registered." Perhaps they could think of things like "I've done my surveys. Have you?" to remind people that the surveys are available.

Dr. Brooks noted that they heard the day before that lock-out occurs at 6 months, and the first follow-up survey of the ALSFSR occurs at 6 months. He wondered whether the ALSFSR could be switched to 4 months so that three sets of data could be collected in a year. He proposed as the rationale for this that they really need to be able to see if they can segregate out rapid progressive acute leukemias from chronic leukemias. The scientific justification for this is very good, and this issue of locking out people at the same time that they are going to try to complete a follow-up survey has to be addressed in a more rational way.

Dr. Kaye indicated that during a previous meeting, the potential of completing the ALSFSR at 3 months, 6 months, 1 year, and every 6 months thereafter was suggested. She asked whether that would work.

Dr. Brooks thought that would be fine. It is important to assess the issue of drop-out. There is a finite rate of drop-out, and this has to be assessed in terms of acute and chronic patients.

Dr. Bradley noted that the patients who are taking part in registering themselves are getting the feeling that they are doing something for research, and to advance the possibility of achieving a cure and so forth. That is a long-term goal and they do not receive any feedback. When the on-line version of the ALS-CARE Database was done, the goal was very much to provide immediate feedback to people. It is a difficult problem. There is the data access problem that must be dealt with in terms of the IRB, but if they could strategize how to give patients immediate feedback as they are registering, perhaps in terms of how they stand compared to others who have entered material on the website. This would be a great stimulus for people to take part in this.

Dr. Horton responded that they would have to think about the types of immediate feedback they could provide, but he totally agreed that feedback is probably important.

Mr. Kingon noted that when he orders something on Amazon, he receives immediate feedback thanking him for his order. Feedback could be something as simple as that.

Mr. Gibson suggested including something that says, "Congratulations. You have completed X percent of your surveys" when people log off. That way it is a percentage.

Dr. Horton indicated that one goal, as they get closer to a complete dataset, is to bring new articles on line such as Ms. Sanchez's data and Dr. Kaye's pilot data. While that is not the complete registry data, it starts laying the foundation that they are heading toward publications. Thought can be given to other information that can be shared with people, but in the absence of data, it is difficult.

Mr. Gibson suggested including some of the ATSDR studies conducted about ALS prior to the Registry and including them on the National ALS Registry website.

Dr. Horton responded that they are starting to fold some of those publications onto the website now. There is a publications link. Recently there was a publication from Texas from a project ATSDR funded, and this was included in the publication link either in full or at least in abstract form.

Mr. Kingon emphasized that he worked in the Office of the Director at CDC for 8 years, and he knows that if center directors keep pushing, the CDC director will go to whomever necessary to get something fixed. The lockout issue should be on Dr. Portier's list to take to Dr. Frieden, because that is key to making improvements.

Dr. Horton replied that they could definitely do that.

Mr. Kingon noted that this was the third or fourth time that he had worked with many of the meeting participants. He found this to be a tremendous project with a great group, and it was great to see such movement so quickly by a government agency.

## Closing Remarks

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**D. Kevin Horton, DrPH, MSPH**  
**Chief, Environmental Health Surveillance Branch**  
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**Agency for Toxic Substances and Disease Registry**

Dr. Horton expressed ATSDR's appreciation for everyone's attendance. It is great for everyone to be able to come together, and for the group to give ATSDR candid feedback. The Agency may think that it has all of the answers, but when they convene a group such as this, it is quickly obvious that it does not. He encouraged everyone to continue to send their comments via email, through the feedback link, or by calling. They want to hear about anything that may help enhance the Registry. The past couple of years, ATSDR has laid out its plans, but he would like to think this year and next year, they are really starting to turn the corner with the Registry. It takes time to build a registry regardless of the Registry. It does not just happen overnight. It takes a lot of work behind the scenes. In the meantime, ATSDR has launched several new initiatives that he believes will enhance and strengthen the Registry. Judging from the reaction from some of the participants and participants at other conferences they attend, there is a high

level of excitement for some of these endeavors. ATSDR will keep pushing forward, will do the best they can, and will accept comments, criticisms, and feedback from anyone willing to offer it.

Regarding the CME training module, it is critical for physicians and neurologists to serve as “mouthpieces” for the Registry. This is why ATSDR attends conferences around the country to let physicians and neurologists know that the National ATSDR Registry exists and to describe the aims of the Registry. He encouraged everyone to discuss the importance of the Registry with their colleagues, especially if they are neurologists and physicians, and how they can be spokespersons for the Registry. Tools like the tutorial that Ms. Cadore presented could be used to promote the Registry. The two words that sum up this registry in Dr. Horton’s mind are “collaboration” and “promotion.” Certainly, the tutorial video will help to reach people who maybe do not know about the Registry, or they know about it but are not exactly sure how it works. He encouraged MDA, ALSA, and AAN to help ATSDR promote the Registry by posting videos, fact sheets, et cetera on their respective websites. Other promotional videos are under consideration, such as one focused on how to take a survey. Anything that will make it clear to patients and caregivers about how they can take part in the Registry will be helpful. The Registry is only as good as the number of people who enroll and take the surveys. People are enrolling, but they are not necessarily taking the surveys. As much as everyone can help to spread that word as well, it will help. The data that are collected are not just for ATSDR. It is for everyone. The more people enrolled and who take the survey, the better.

The State- / Metro-Based Surveillance Study is very important in terms of evaluating the completeness of the Registry. There has been some confusion, at least anecdotally, regarding why ATSDR is doing state- and metro-based registries. It would be very beneficial for MDA, ALSA, and AAN to let people know that this is being done to test the completeness of the National ALS Registry. There are a number of registries, so as much as it can be clarified that ATSDR has the National ALS Registry, the better. ATSDR is very happy to be collaborating with groups such as NEALS. It is not ATSDR’s intent with respect to the bioregistry to “step on toes,” but Dr. Horton thinks they owe it to patients and their families to pilot test whether it makes sense to have a national bioregistry. The agency really appreciates being able to tap into the expertise from groups such as NEALS and ALSRG. AAN is certainly a welcomed additional partner to the National ALS Registry. ATSDR hopes to tap into AAN’s large distribution of neurologists throughout the country, and use AAN to help spread the word about the Registry.

Dr. Horton expressed his gratitude to Mr. Tison for his update, and said that he could not thank him enough for taking the time to do this when no one asked him to do it or paid him to do it. He just did this out of the goodness of his heart. He also extended his thanks to Mr. Tison’s son who helped him with the PowerPoint presentation, and to his wife for assisting him as well. It was a great effort and spoke volumes about PALS. Mr. Tison is a great example of a person with ALS participating. It is always a pleasure for Dr. Horton to meet PALS and caregivers, because ATSDR does not necessarily get this type of reception when they do community work on other types of projects. Sometimes they actually get the opposite response and are run off with pitchforks and torches because ATSDR is part of the federal government. It is a pleasure to work with such a good group of people on ALS, including researchers, patients, and caregivers. This is definitely one of his favorite projects at ATSDR.

The Research Notification Component is a tool that can be very useful for the scientific community at large, but Dr. Horton stressed that if people do not know about it, they will not come to it. He is looking forward to working with ALSA, MDA, and AAN on whatever efforts are needed to tell people about this new mechanism. How this mechanism will work, the timeframe,



and so forth will become clearer once three or four applications have been received and panel evaluations have been conducted. It is anticipated to be a tremendous resource for researchers. As indicated, the projected timeframe for data release is Fall/Winter 2013. While that seems far away, in reality it is not. Therefore, a decision must be made about whether and what type of panel to establish for assessing data requests. He thought the discussion earlier was very good, and ATSDR will continue this discussion offline with participants.

With respect to federal partners, it only serves ATSDR well to partner with NIH, NIEHS, and other federal groups that all have the same goal. The National ALS Registry follows the model of leveraging existing resources, where possible. In these economic times, the budget is uncertain and in any given year anything can occur. With regard to the ALS budget, a crystal ball is needed, but ATSDR has not been given any indication that funding is going to be pulled. Therefore, ATSDR will move forward with the best science possible and will control what they can and will not worry about what they cannot control.

In conclusion, Dr. Horton thanked everyone for attending and expressed his hope that they found the meeting to be useful, especially those who did not know a lot about the Registry before attending. With that, he bid everyone safe travels.

### **Discussion Points**

Dr. Brooks said that for the first time since he has been coming to these meetings, he has begun to realize the difference between mortality datasets and what ATSDR is trying to do, and that should be emphasized more. The other issue closer to ATSDR's own purpose is environmental tracking. In competing with potential outcome registries or registries that are formulated as part of organizations that have an interest in knowing how many patients have ALS, ATSDR must emphasize that the only way to understand the underlying cause of this disease is through entry into the National ALS Registry. This will create a dataset that no other registry is creating. Patients do not realize this, so a stronger message is needed from CDC about the National ALS Registry.

Dr. Horton agreed, and recognized that there had been efforts by other organizations trying to collect similar data. He was happy to see that ALSA recently disseminated a letter stating that the National ALS Registry is the one it fully supports. While ATSDR is not trying to discourage persons from participating in other registries, which is their right, it is imperative to get the word out that this is the only congressionally mandated population-based registry and to emphasize why it is critical for patients to enroll in this registry.

Mr. Gibson agreed that the challenge in talking to patients is that they do not fully understand what ATSDR is trying to do. It is difficult because when people are newly diagnosed, they have to deal with Medicare, their insurance, and many other things. Adding the second layer of completing the registry is challenging. However, once families understand the importance of the Registry, they are motivated to complete all of the paperwork. He thanked Dr. Horton and his team. This group has been coming together 5 to 6 years, and much progress has been made. Having once worked for the federal government, he was aware that they do not receive the accolades and applause for helping. He thanked them for continuing to do this, and everyone applauded.

*With no further business posed or questions and comments raised, the Annual ALS Surveillance Meeting was adjourned.*

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