

2018 National ALS Registry Annual Meeting Executive Summary

The cause(s) of ALS (Amyotrophic Lateral Sclerosis) remain unknown for 90-95 percent of those diagnosed with the disease and there is still no cure.

The Agency for Toxic Substances and Disease Registry (ATSDR) established the National ALS Registry to determine how many people in the US are living with ALS, to describe the demographics of ALS patients, and most importantly to examine the risk factors for ALS. Although the Registry's primary purpose is to capture cases of ALS, the Registry does a lot more than just count cases. The Registry is also:

- Funding ALS research,
- Collecting specimens from Registry enrollees through the National ALS Biorepository,
- Connecting patients with researchers recruiting for ALS clinical trials or epidemiological studies,
- Obtaining etiologic data from Registry enrollees through 17 different online risk factor modules such as occupational history, military history, residential history, history of traumatic brain injury (TBI),
- Providing data and biospecimens to scientists to further ALS research.

The National ALS Registry Annual Meeting was held in Atlanta on August 7-8, 2018. There were 51 attendees, including persons living with ALS, neurologists, researchers, representatives of national ALS organizations, representatives of pharmaceutical companies, Registry staff, and other ALS experts.

Background, Methodology, and State of the Registry

Because ALS is a non-notifiable condition, CDC does not receive reports from states of the occurrence of ALS, as it does for most communicable diseases. The novel methodology developed by ATSDR for identifying newly diagnosed ALS cases uses data from national administrative databases (i.e., Medicare and the Veterans Administration) in addition to the information entered into the online Registry web portal by persons living with ALS.

Improvements and accomplishments during the last year:

- Published the third *Morbidity and Mortality Weekly Report (MMWR)* report on February 23
- Collected hundreds of additional biospecimens via the National ALS Biorepository
- Biospecimens can now be paired with epidemiological and risk factor survey data already collected by the Registry
- Redesigned the Registry website with a responsive design, enabling access by hand held devices
- Published over one dozen peer-reviewed articles/abstracts from Registry staff and research partners
- Published a Notice of Funding Opportunity and funded 1 R01 and 4 new grants awarded in Fall 2018
- Initiated the development of a new Spanish Registry website
- Targeted 56 percent of Registry funding to supporting ALS research
- Created new digital assets including graphics, videos, and infographics
- Launched an outreach project with partners in selected states
- Implemented a Customer Satisfaction Survey that focuses on Registry enrollment to better inform us about how people are learning about the Registry and to improve promotion and outreach.

Research

The National ALS Registry released the third prevalence report in February 2018 for persons living with ALS in the US. ALS prevalence was estimated to be 5 cases/100,000 for 2014. The total case count was 15,927, including cases from the national databases and the Registry online portal. This is a slight increase over the previous report. ALS continues to be more common in whites, males, and persons 60-69 years of age. The lowest number of ALS cases was among persons 18-39 years of age and > 80 years of age. Males continue to have a higher prevalence than females across all data sources.

Data from the Registry indicate that completion of the risk factor surveys is steadily increasing. Over 76,000 risk factor surveys have been completed to date. Approximately 65,000 had been completed last year at this point. The Research Notification System has also proven to be quite successful, with approximately 95% of registered persons with ALS opting in to participate in research notifications. Over 35 institutions, including pharmaceutical companies, domestically and abroad, have used the Registry to recruit for their clinical trials and epidemiological studies.

National ALS Biorepository

The National ALS Registry now includes a Biorepository. People taking part in the Registry are eligible to participate in the National ALS Biorepository. From those interested, participants are selected to be geographically representative of the US. Blood and urine specimens are collected in the person's home. These biospecimens can now be paired with epidemiological and risk factor survey data already collected by the Registry for use by scientists in their research. Registry participants may also donate tissues postmortem. Postmortem samples consist of brain, spinal cord, cerebrospinal fluid (CSF), bone, muscle, and skin. Persons with ALS can take part in the Registry and Biorepository even if they have donated specimens to other biorepositories and studies. Biospecimens have been collected from over 500 participants, including over 30 postmortem collections to-date. There are now thousands of aliquoted samples available for researchers to use that include bone, blood, brain tissue, cerebrospinal fluid (CSF), fingernails, and hair.

Registry Enrollment

This session included discussions on the Registry enrollment, demographics, and completion of the risk factor surveys. Registry enrollment increased rapidly during the first months immediately following the launch of the Registry in October 2010, then there was a slight uptick in enrollment in 2013 and 2014, probably due to the Ice Bucket Challenge, and there has been a slow decline since then. Approximately 40% of Registry participants are female and 60% are male. The percentage of ALS patients enrolled in the US by region is highest in the Midwest (31%) compared with only 17% in the Northeast. ATSDR is currently working on outreach activities with its partners to increase enrollment.

In addition to registering, persons with ALS are encouraged to take the risk factor surveys available on the Registry. The completion rate for the surveys is about 60% compared to 70% to 80% for other national surveys including the NHIS – Household Module, NHANES – Conditional Exam, and the NIS – Landline Response Rates. The risk factor survey data provide information to researchers to assist in discovering other ALS risk factors and etiology, allows patients to tell their stories, and optionally link biospecimen data for more robust studies.

Evaluating the Completeness of the National ALS Registry

Evaluating the completeness of the National ALS Registry is important because ALS is not a reportable disease. Physicians and other health care providers are required to report diseases designated as reportable. Although no surveillance system is able to identify 100% of the cases, because ALS is not reportable, non-traditional case ascertainment is used making evaluation of the completeness of the Registry even more important. ATSDR used two different methods to evaluate the completeness of the

Registry: state and metropolitan area surveillance data and capture-recapture methodology. The State/Metro Surveillance Project involved intense case ascertainment in three states (New Jersey, Florida, and Texas) and eight metropolitan areas (Atlanta, Baltimore, Chicago, Detroit, Las Vegas, Los Angeles, Philadelphia, and San Francisco). Patients identified by the state/metro surveillance project were compared with those in the Registry. The findings showed that the Registry was more likely to miss people who were non-white, Hispanic, living in the Western US, not using Medicare for insurance, and less than 65 years of age.

Capture/Recapture methodology uses probability analysis to estimate the number of cases that might be missed. Both methods showed remarkably similar results. Both methods identified non-whites and those less than 65 years of age as under-represented in the Registry. Both methods identified Medicare as an important source for case identification. Men were found to be under-represented in the Registry using capture-recapture methodology, but not in the comparison of state and metropolitan surveillance data. The comparison of state and metropolitan area surveillance data identified Hispanics and those from Western states as under-represented, but this was not assessed using capture-recapture methodology.

ATSDR is working to increase outreach to populations shown to be under-represented in the Registry by creating a Registry website in Spanish and by placing articles in local papers that target African Americans and rural communities. ATSDR is also planning to use the estimated underreporting findings from these methodologies to adjust ALS prevalence estimates.

Communication & Outreach

One of the most important objectives of the meeting is to discuss the barriers, challenges, and successes the Registry has experienced and to receive recommendations on how to address these issues. Some of the issues were that the Registry could do a better job of communicating all that it is doing and the Registry website is difficult to navigate. ATSDR is currently working with its partners, the ALS Association, the Muscular Dystrophy Association, the Les Turner ALS Foundation, and with Brunet Garcia to address these challenges to increase awareness of the Registry and to improve registration and completion of the risk factor surveys.

Some of the ways these issues are being addressed are as follows:

- ATSDR created a new award winning video titled "[Hope](#)" to show the value of the registry.
- All of the Registry materials, including [videos](#), social media, and [printed materials](#) are available for use by the partner organizations and others.
- The Registry website has been reorganized to make it easier to navigate. They are continuing to find ways to improve the website and welcome feedback from everyone.
- The Registry team is also trying to reach people who are underrepresented in the Registry. One of the partnerships they engaged in this year was with BlackDoctors.org, which is a very popular health-related website primarily aimed at African American communities. They ran an article to raise awareness about ALS and the Registry, which has been well received.
- Articles written by ATSDR were released this year for which they pay a minimal amount for placement, and then local journalists pick them up. As of July 2018, this generated 3672 news articles and these get picked up continuously online.
- A collaboration with Medscape produced a very nice article targeting neurologists in rural areas.

Under-Enrolled States Outreach Project Update

The goals of the Under-Enrolled States Outreach Project are to focus on six states where enrollment in the Registry is less than expected and to identify health districts within those states which could benefit from increased Registry outreach. The six states participating in this project are Hawaii, Mississippi, New York, West Virginia, Utah, and Wyoming. The Registry and the ALS Association and MDA are working collaboratively to compare data to identify the health districts in each state that are under-enrolled. Outreach plans were developed and are being implemented during July 1-December 31, 2018. ATSDR will review and assess the findings to determine the effectiveness of the project. If the project is effective in raising enrollment levels, the plan is to expand the project to other selected under-enrolled states.

ALS Association

The ALS Association is working exclusively on ALS and is the largest national non-governmental funder of ALS research. They are very supportive of the Registry, working with 39 chapters, two territories, and over 130 clinical partners nationwide. There are 62 Centers of Excellence, which also participate in research. The ALS Association promotes the Registry during their events, meetings and conferences, through social media, on their website, as well as encouraging their chapters to also promote the Registry.

The ALS Association is working closely with the Registry and has identified challenges and opportunities. Challenges include an ALS community that does not have the best impression about what the Registry is and may not have a clear understanding of why the Registry is important. They pointed out the need for the Registry to provide feedback to the ALS community on their research and other activities. There is also the challenge of under-counting. However, the work that the Registry is doing to better understand the under-counting seems to be very important to identifying the solution, which will help in the allocation of resources. They also underscored the value of the Registry in supporting the type of research to address the very important question of why some people get ALS and others do not.

Muscular Dystrophy Association

The Muscular Dystrophy Association continues its efforts to improve and expand their ability to support the National ALS Registry. MDA supports research, support services, Care Centers, education, and the Resource Center. More than 12,000 individuals with ALS have access to nearly 50 designated MDA ALS Care Centers across the US and a Network of Care Centers at over 150 top institutions and affiliates. MDA promotes the National ALS Registry through social media, online publications, outreach phone calls, community events, MDA Care centers, the MDA website that houses information on the National ALS Registry, ALS support groups, the National Resource Center, educational conferences and seminars, and print materials.

Some of the highlights of MDA's 2018 National ALS Registry outreach efforts include an ATSDR breakout session and information booth during the MDA Clinical Conference in March 2018, incorporating MDA Engage Events on the ALS Registry into regional MDA Engage Events as far as data, information, and print materials, posting weekly Registry messages to the MDA national social media pages and monthly to MDA's local district level social media pages, and providing a link to the National ALS Registry on MDA.org.

Les Turner ALS Foundation

The Les Turner ALS Foundation provides comprehensive ALS care in Chicagoland through individualized care, local community support, and scientific research at the Les Turner ALS Center at Northwestern Medicine. The support services team works directly with persons living with ALS and their families and others. Their promotional efforts for the National ALS Registry and Biorepository include home and clinic visits, support groups, a National ALS Registry Associate, print newsletters, e-news and website, Annual Education Meeting, education for medical professionals, Annual Research Symposium on ALS and NeuroRepair, community education and expos, and social media.

A unique feature of the Les Turner ALS Foundation is the National ALS Registry Associate. She meets every person who presents to the clinic, provided they are willing to meet with her. She provides personal assistance for anyone who is interested in being in the Registry or who may need assistance with completing the risk factor modules. They have estimated that between her support and assistance at the clinic, 80% of individuals served by the Turner Foundation are currently enrolled in the Registry.

Brunet-Garcia

Brunet-Garcia is working with the National ALS Registry on strengthening communications and outreach efforts. Their objectives are to raise awareness and engagement of the Registry, provide value to persons with ALS with simpler access to updates from the ALS Registry and stakeholders, and to coordinate efforts of partners and others to promote the Registry and support persons with ALS.

Brunet-Garcia has developed improved messaging and branding including articles, testimonial quotes, social media, fact sheets, and posters. All of the materials are shared with the partners. Marketing materials were also created to show the value of the Registry including fact sheets and a new retractable display for use at conferences and other events. They are also working with the Registry and the partners to assess feedback to ensure the best products in terms of content and design.

Update from Pharma

Cytokinetics, Inc.

Cytokinetics, Inc. is working on developing drugs for muscles. Cytokinetics targets compounds that bind to the proteins that make up the sarcomere, which is the fundamental contractile unit of the muscle. They presented an update on their clinical trials in ALS for *tirasemtiv* and *reldesemtiv*, compounds that target troponin, one of the fundamental proteins that make up the contractile unit of the muscle. The compounds are known as fast skeletal muscle troponin activators (FSTAs). The methodology and results of Cytokinetics' Phase 3 clinical trial of *tirasemtiv* were presented. Unfortunately, *tirasemtiv* was not well-tolerated and dose reductions and discontinuations were common. Therefore, *tirasemtiv* was discontinued in terms of its development. However, because patients who tolerated the drug and received benefit, Cytokinetics is continuing to make *tirasemtiv* available to the patients in the trial whose physicians deem that they are benefitting.

Cytokinetics also described their clinical trial with *reldesemtiv*, a similar compound to *tirasemtiv*, but with a completely different chemical structure, which does not have the side-effects seen with *tirasemtiv*. *Reldesemtiv* has greater pharmacodynamic effect at lower plasma concentrations, was designed to minimize crossing of the blood brain barrier (BBB), has no known drug-drug interaction with riluzole that *tirasemtiv* did, and has demonstrated tolerability in healthy subjects.

Cytokinetics used the National ALS Registry's notification tool for both clinical trials and reported that the tool works very well and recommends its use for all studies.

Mitsubishi Tanabe Pharma America

Mitsubishi Tanabe Pharma America reported on the Edaravone Biomarker Study they hope to implement by the end of 2018. Edaravone, a drug which slows the loss of physical function, was introduced approximately one year before this meeting and since then over 3000 patients have been placed on the drug. However, many payers placed restrictions on access to edaravone and many questions were raised about which patient populations were appropriate to receive the drug and what the optimal timing was to initiate therapy, in addition to questions about the clinical development program. In the first Phase 3 trial, the drug did not meet its primary endpoint.

A second Phase 3 trial used an enrichment strategy that was gleaned from the first trial. This examined a population that was high-functioning, but rapidly progressing. In the second trial, the drug did meet its primary endpoint.

However, there are questions remaining that Mitsubishi Tanabe hopes this biomarker study will begin to answer regarding the drug's mechanism of action, identification of a quantifiable biologic measure for the effects of edaravone on ALS, help in determining the feasibility and validity of specific biomarkers in patients undergoing edaravone therapy, and provide guidance regarding more frequent dosing at higher strengths. Findings of the biomarker study may be released as early as June 2019.

Mitsubishi Tanabe Pharma America is also using the National ALS Registry notification system to recruit participants for this study.

NEALS Update

The Northeast ALS Consortium (NEALS) functions as an international academic research consortium, a contracted research organization, and a resource for the ALS community at large. NEALS' mission is to translate scientific advances into new treatments for people with ALS and MND as rapidly as possible. Members are working on therapeutic developmental drugs for ALS, advocacy, and other activities which further ALS care.

NEALS provides resources for the ALS research community including training site managers, coordinators, evaluators, and site and project PIs. NEALS has also created the Pooled Resource Open-Access ALS Clinical Trials Database (PRO-ACT), a repository of data from placebo and treatment patients. There also is the NeuroBANK, which is a powerful natural history database. NEALS also maintains a Biorepository/Living Library and coordinates monthly webinars for persons living with ALS, caregivers, and the ALS community.

The number of NEALS research trials and persons participating in the trials were presented by year from 1999 through 2017, which show the dramatic increase in NEALS-associated research studies.

The National ALS Registry is working with NEALS to assist in recruiting patients for their clinical trials and studies through the Registry's Research Notification System and serves on their committee for recruitment.

ATSDR-Funded Research Update

ATSDR provides funding to support ALS research studies to help the ALS community learn more about the disease and to also help prioritize new risk factor modules for the Registry. Principle investigators presented updates of nine ATSDR-funded studies on environmental and genetic risk factors.

Persons Living with ALS Perspective and Next Steps

These sessions provided critically important feedback from the ALS patient community on the value of the Registry, what is going well and where we need to do better. Meeting participants also shared their observations and insights regarding the top priorities for the Registry and the Biorepository for the coming year.

National ALS Registry Action Items for 2018/19:

The National ALS Registry is not just an ATSDR initiative. We recognize that the success of the Registry depends on the collaboration of all the stakeholders. During the coming year we will continue to work collaboratively with the partner organizations and other stakeholders to achieve the following:

1. Send semiannual newsletter to inform ALS community of Registry activities on new research, research results, biorepository, ATSDR-funded studies, risk factor surveys
2. Redesign Registry website to make information for patients and caregivers more engaging and easier to find
3. Analyze data to determine activity that improves enrollment in the Registry, e.g., social media, promotional material, clinical staff suggestions
4. Increase researcher awareness of data and specimen availability
5. Provide enrollment statistics at smaller level than state e.g., health district
6. Provide an estimate of ALS prevalence that adjusts for under-ascertainment
7. Analyze risk factor survey completeness by year to look for improvements, e.g., how many enrolled, how many surveys were completed
8. Track status of recommendations from the annual meeting and provide an update at 6 months and present progress at the next annual meeting
9. Focus messaging about completion of surveys where data is most needed
10. Discuss research opportunities with representatives of pharmaceutical companies