

2020 National ALS Registry Annual Meeting Executive Summary

The National ALS Registry meeting was held in Atlanta on August 4-5, 2020.

National ALS Registry Update: Goals, Methodology, and Achievements

The goals of the National Amyotrophic Lateral Sclerosis (ALS) Registry are to determine the incidence, prevalence, demographics, and risk factors for ALS in the United States (US). Because ALS is a non-notifiable condition in the US, Agency for Toxic Substances Disease Registry (ATSDR) uses a two-pronged approach to ascertaining ALS cases including (1) online registration by ALS patients via the web portal and (2) identifying ALS cases from large national databases (i.e. Medicare and the Veterans Administration). Persons with ALS can also provide information about risk factors for ALS by completing one or more of the Registry's 17 online surveys.

The Registry does more than just count cases, it is also:

- Funding investigator-initiated research for ALS epidemiological studies and clinical trials,
- Collecting biospecimens including tissue, hair, nails, and blood and post-mortem samples (brains, spinal cords, and other specimens), through the National ALS Biorepository,
- Connecting patients with researchers recruiting for ALS clinical trials or epidemiological studies,
- Gathering etiologic data from Registry enrollees via online risk factor modules such as, occupational history, military history, residential history and history of traumatic brain injury (TBI),
- Providing data and biospecimens to scientists to further ALS research.

Registry accomplishments since the last meeting include:

- ATSDR funded 17 research studies to date, with 2-3 new studies funded in Fall 2020, depending on the availability of funds.
- Assisted over 50 institutions (e.g., pharmaceutical companies and academia) with their clinical trials and epidemiological studies resulting in over 3000 patients recruited to date.
- The National ALS Biorepository has received blood and saliva samples from over 1300 participants and over 50 post-mortem collections.
- ATSDR staff attended 20 conferences and ALS patient symposiums to present findings over the past year.
- ATSDR launched a new user-friendly Registry website.
- Change in password component of Registry made to define password expiration period (6 month, 1 year, or indefinite)
- A new Spanish Registry website was launched on July 22, 2019.
- New social media, graphics, and other digital assets have been created to enhance the Registry communications and outreach efforts.
- Over 76 peer-reviewed publications/abstracts from Registry staff and research partners (over ½ dozen more since last year) have been published. There were 10 publications in 2019 and 4 in 2020.
- A Google outreach campaign was completed in July 2020 in states with high proportions of minorities such as Texas, Florida, and California
- ATSDR also has received Office of Management and Budget (OMB) approval for a new survey, Survey 18 (S18), that soon will be launched for the Registry. This survey is based upon specific sports in order to evaluate the role of traumatic brain injury (TBI) in sports in terms of sports played, duration, level (e.g., high school, collegiate, professional, et cetera).
- Targeted 56 percent of Registry funding to supporting ALS research.

2020 Coronavirus Pandemic Impact

2020 saw the unprecedented event of the COVID-19 pandemic causing rippling effects on healthcare worldwide.

- Publication of the MMWR of prevalence for 2016 will be delayed until fall or winter.
- In home collection of blood for the National ALS Biorepository was suspended to prevent phlebotomists and patients from being exposed to COVID-19
- ATSDR's colleagues at the NIH have been impacted by COVID-19 as well in terms of genetic testing and whole genome sequencing (WGS) and are awaiting their laboratories to be back up and operational

COVID-19 attack rate among patients with ALS was measured against the attack rate of other neurological disorders. COVID-19 rates in cohorts of ALS patients was comparable with those observed in European and US cohorts of Parkinson's and Multiple sclerosis. Incidence rates of COVID-19 ALS cases did not seem to be affected by treatment with or without riluzole, edaravone or both together.

Partner organizations have also been dramatically affected by the ongoing pandemic. The ALS Association, which relies on face-to-face engagement with patients about the Registry at their 90 multidisciplinary clinics across the country, had to modify how they work in lieu of in person engagement events. The Muscular Dystrophy Association has seen new opportunities arise in the virtual space: creation of a new COVID-19 landing page on mda.org, shifting over to telehealth services at their many MDA Care Centers, and launching a series of Facebook Live Events focusing on supporting the neuromuscular community through these trying times. The Les Turner ALS Foundation has also had to adapt from in-person programming in the Chicagoland area to primarily virtual and phone programming; they have also set up a new COVID-19 website to handle questions about the pandemic and ALS.

Research Update

The most recent findings from the Registry indicate that in 2015, there were 16,583 persons identified in the US as definite ALS cases through the national databases and the Registry portal. This equates to a prevalence estimate of 5.2 cases of ALS per 100,000 persons, representing a slight increase since 2014. ALS continues to be more common in whites, males, and persons aged from 60-69 years of age.

Persons with ALS can complete 18 risk factor surveys on the Registry portal, which has created a rich source of risk factor information for ALS. Data requests are being submitted from researchers for the risk factor surveys and releases have begun. Some of the institutions conducting analyses of the data include the Mayo Clinic, Rutgers University, and Columbia University.

The Research Notification System is connecting ALS patients to researchers who are recruiting for participants in their new studies and clinical trials. Approximately 95% of Registry enrollees opt in to receive notifications about opportunities to participate in these research efforts. As of the meeting date, 50 institutions have used the notification system.

ATSDR is also supporting ALS research with 61% of the Registry's funding being allocated to external research.

National ALS Biorepository

Persons with ALS who are enrolled in the National ALS Registry may also take part in the National ALS Biorepository. The Biorepository sends a phlebotomist to the patient's home to collect the biospecimens, including blood, urine, and saliva, at no charge to the patient. Postmortem specimens are also collected including brain, spinal cord, cerebral spinal fluid (CSF), bone, muscle, and skin. Biorepository participation from January 4, 2017 through June 30, 2020 resulted in consent of 931 participants for in-home blood and urine samples, 197 for saliva samples only, and 34 post-mortem samples. The number actually collected during that timeframe included 884 in-home blood and urine samples, 202 saliva only samples, and 27 postmortem samples. COVID-19 has impacted in-home collections. On March 17, 2020, all in-home collections were cancelled and have not resumed. Pre-COVID, there was an average of 20 monthly sample collections. Since COVID-19, there have been 20 saliva and 1 blood sample collections completed. Researchers can request samples for their ALS research projects. Samples can also be paired with demographic and risk factor data from the Registry. The types of specimens most likely to be requested are blood and postmortem tissue. To date, 13 researchers have been approved and more than 8,700 samples have been distributed. However, no applications have been received since COVID-19.

Research Notification System

This past year the Registry used its Research Notification System to assist academia and pharmaceutical manufacturers to help them recruit for their clinical studies <https://www.cdc.gov/als/ALSResearchNotificationClinicalTrialsStudies.html>. The system was used by Brainstorm Cell Therapeutics, Orphazyme, Orion Pharma, Amylyx Pharmaceuticals, Cytokinetics, Inc (Rudnicki), The ALS Association, Columbia University, University of Rochester Medical Center (Heatwole), Walden University, and the University of Cincinnati.

Enrollment in the Registry

In 2018, the Registry began collecting data on how participants are being referred to the Registry. The findings indicate most referrals were made by the ALS Association and doctors/neurologists. Regarding the risk factor surveys, there are now 18 surveys available on the Registry for enrollees to complete. The survey that has the highest rate of completion is the demographics survey, with nearly 60% of enrollees completing the survey in the last 3 years. As of July 9, 2020, over 90,000 surveys have been completed. Enrollment has decline 12% in early 2020 compared to early 2019, however that is most likely attributed to the ongoing effects of the COVID-19 pandemic; resulting from the suspension of in-person outreach and the impact of partner activities.

Recommendations from the 2019 Meeting

The purpose of the Registry's annual meeting is to update the ALS stakeholders on the progress of the Registry, to provide a forum to discuss challenges faced by the Registry, and to receive expert advice and discuss strategies to further enhance the Registry. In many ways, the annual meeting functions like an advisory committee to the Registry. The suggestions and recommendations that patients, caregivers, partners, and researchers provide are valuable and critical to the success of the Registry. There were 13 recommendations from 2019 that were presented in the following categories: Communications and Outreach, ALS Prevalence Estimates, Additional Analysis with Existing Data, and Miscellaneous. The activities that are being implemented to address each recommendation, the organization that is taking the lead on the recommendation, and the status of each recommendation were presented in several tables.

Communication & Outreach

ATSDR

This year, ATSDR focused on redesigning the National ALS Registry Website to improve user engagement and information utilization. They also produced a number of assets such as videos and infographics with partners to be disseminated to patients and caregivers.

ALS Association

The ALS Association is the only nationally affiliated not-for-profit health organization dedicated solely to ALS. The Association's nationwide network of 39 chapters provides comprehensive patient services and support to the ALS community. The ALS Association plays a vital role in promoting the work of the Registry through their chapters. For example, in 2020 the ALS Association saw the virtualization of the National ALS Conference, seeing over 1300 attendees across four 90 minute webinars, 260 of whom were people living with ALS. In Fall of 2020, the ALS Association was involved in a small workshop with help from the registry to develop a framework on how risk factors can be turned into guidance for people with ALS.

The 2020 COVID-19 has also had a significant impact on the ALS Association's activities. Normally relying on in-person engagement, is now exploring modifications on how to engage with patients virtually.

Muscular Dystrophy Association

The Muscular Dystrophy Association (MDA) is an umbrella organization that covers 43 neuromuscular diseases (NMDs), one of which is ALS. They offer a number of support services to the community, in addition to the research that they fund. MDA works as a partner with ATSDR to promote the Registry and in 2019 MDA has increased its social media promotion of the Registry considerably. In addition, MDA create regular online postings on their national site, including postings during ALS Awareness Month in May and the more traditional print media, such as MDA's Quest Magazine to reach a different target audience.

The 2020 COVID-19 Pandemic has also seen a significant impact on MDA. They have been able to pivot many of their programs over to virtual platforms, created a new landing page for their mda.org website, and held an ALS Facebook Live Event to answer questions from the ALS community about how COVID-19 may affect the community.

Les Turner ALS Foundation

Founded in 1977, the Les Turner ALS Foundation is one of the oldest ALS groups in the world aiming to serve persons living with ALS and their families in the Chicago area. They provide wide-ranging ALS care through patient service programs including local support groups, community educational programs and in-home consulting. In addition, the Les Turner ALS Foundation has a National ALS Registry Associate and their main objective is to meet with patients in clinics and at the comfort of their homes to provide information about the importance of the Registry and help persons living with ALS successfully enroll in the Registry. They estimate that about 85% of the individuals they serve are currently enrolled in the Registry.

In 2019, the Les Turner ALS Foundation has promoted the National ALS Registry through monthly features on their website, marketing the Registry from their social media channels, print newsletters, annual education meetings for medical professionals and more. Early 2020 saw a shift in Les Turner's

programming as the COVID-19 pandemic has compelled the organization to shift from in-person activities to virtual programming. The Les Turner ALS Foundation has also adapted by creating a new COVID-19 website that will provide support and information to families that have needs regarding ALS and COVID-19.

Update from Pharma

Mitsubishi Tanabe Pharma America, Inc. (MTPA)

Dr. Stephen Apple, Senior Medical Director, presented on the MTPA Radicava® (edaravone) development programs focused on biomarker study, oral development program, and real-world evidence plans.

MTPA, in collaboration with Massachusetts General Hospital, is conducting the Radicava®/Edaravone Findings in Biomarkers from ALS (REFINE-ALS) study to improve the understanding and application of biomarkers as an assessment of the effect of edaravone on patients with ALS.

MTPA is also looking to develop an oral formulation of edaravone for the use in people with ALS, in partnership with Mitsubishi Tanabe Pharma Corporation (MTPC) of Japan. The oral formulation is sought as an alternative to IV edaravone, in order to develop an easier to administer dosing regimen of the drug.

Finally, MTPA is pursuing a number of initiatives to bring real-world data to the ALS communities. They have outlined four objectives for assessing real-world data:

1. assess the demographics and clinical characteristics and settings in which edaravone is being initiated (e.g., home care, infusion center)
2. evaluate the economic value of edaravone, including health resource utilization and total cost of care
3. describe treatment duration, adherence, discontinuation, and survival rates
4. describe real-world effectiveness in slowing functional decline as measured by the ALSFRS-R and other clinical outcomes such as forced vital capacity (FVC) and proxy endpoints in a real-world database such as time to disability milestones.

Persons Living with ALS Perspective

An open panel including five persons with ALS provided insight into their journey living with ALS and perspective of the Registry. Each participant expressed their appreciation for the Registry and for the meeting. Participants also provided helpful insights on ways to better promote the Registry and Biorepository.

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 the following ATSDR-funded studies:

- ALS Risk in Latin Americans: A Population-Based Case-Control Comparative Study with 3 European Population-Based Cohorts
- Environmental Risk Factors for ALS: Critical Time Periods and Genetic Interactions
- Identification and Characterization of Potential Environmental Risk Factors for ALS: Using the ALS Registry Cases and a Control Population
- Novel Extracellular Vesicle and Molecular Biomarkers of Environmental Exposure and Disease Progression in ALS
- Metabolomic Signatures Linking ALS to POPs Exposures
- A Novel Innate Immunity Risk Factor for ALS

National ALS Registry Action Items for 2020/21:

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 implement the following new recommendations:

- Use residence data with other data.
- Release a draft estimate of annual MMWR report approximately 6 months ahead of MMWR report.
- Increase promotion/outreach efforts focused toward minorities to join the Registry.
- Use prevalence in terms of ranges of estimates, rather than just precise estimates.
- Include a more diversity in photos of PALS on the Registry home page.
- Use Facebook to increase targeting minorities.
- Clarify goals and develop methods to evaluate.