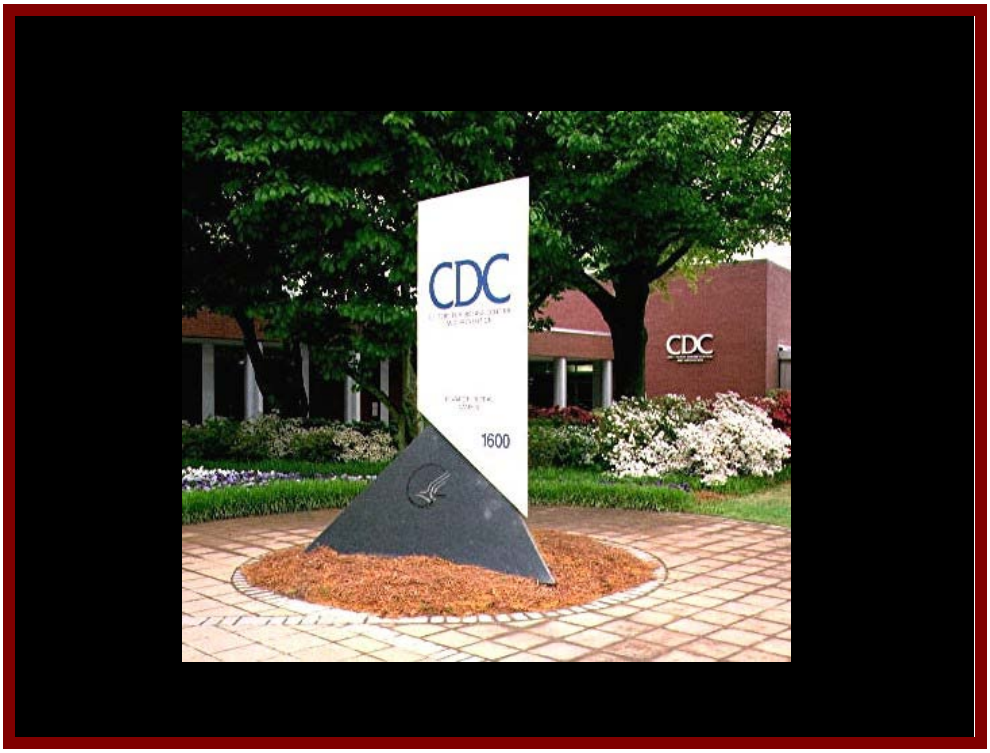
Centers for Disease Control and Prevention (CDC)
Agency for Toxic Substances and Disease Registry (ATSDR)



Summary Report: March 13-14, 2006
Workgroup on Multiple Sclerosis (MS) and Amyotrophic Lateral Sclerosis (ALS) Surveillance

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.

I. Welcome and Announcements

March 13, 2006

Dhelia Williamson, PhD, MS
Division of Health Studies
Agency for Toxic Substances and Disease Registry (ATSDR)

Dr. Dhelia Williamson called the group to order at 8:30 a.m. on Monday, March 13, 2006. After welcoming them and thanking them for their attendance, she led them in brief introductions.

G. David Williamson, PhD
Director, Division of Health Studies
Agency for Toxic Substances and Disease Registry (ATSDR)

Dr. David Williamson is the Director of the Division of Health Studies at the Agency for Toxic Substances and Disease Registry (ATSDR). He welcomed the group to this critical meeting and noted that CDC staff members hoped to facilitate their work during the meeting and in the field. ATSDR has been interested in the neurological and autoimmune diseases for the past few years. They have worked with state health departments to capture baseline information such as the prevalence of multiple sclerosis (MS) and Amyotrophic Lateral Sclerosis (ALS) in certain areas. Workshops on the surveillance of those diseases were held in 2002, and this meeting represented a "natural next step." He indicated that each participant came from a different background and area of expertise, and that their recommendations would help to fill current gaps in MS and ALS surveillance.

Sharon Campolucci, RN
Deputy Director, Division of Health Studies
Agency for Toxic Substances and Disease Registry (ATSDR)

Ms. Campolucci said that most of ATSDR's past work has focused on MS. When this workshop was planned, its focus was intended to be MS. Congress has asked that ATSDR address ALS and provide a report in a year. This workshop provided a good opportunity to "jump start" the process of including ALS in ATSDR's work. Congressional legislation authorized $900,000 for ALS; however, that money was not actually appropriated. Funds that are now devoted to ALS work come from other areas in the CDC budget.

Ms. Campolucci clarified the differences between *authorized*, *appropriated*, and *allocated* funds. Programs can be authorized through Congress without funds being appropriated for them. The ALS program is *authorized*, but no funds were *appropriated* for it. Therefore, the $900,000 for ALS work comes from CDC's allocated budget. She emphasized that the funding for this meeting did not come from the $900,000, but from funds that were already in the pipeline.

II. Overview of the Project and Goals

Dhelia Williamson, PhD, MS
Division of Health Studies
Agency for Toxic Substances and Disease Registry (ATSDR)

Dr. Dhelia Williamson offered a brief overview of ATSDR's involvement with MS and ALS. Over 22 million Americans are affected with an autoimmune or neurologic disease. Although these diseases cause significant morbidity and disability, little or no information is available on many of them. Some of the diseases are caused not by a single gene disorder, but by environmental components combined with genetic components.

ATSDR works in communities that are concerned about exposures to hazardous substances and where notable numbers of people in the communities have an autoimmune or neurological disease. ATSDR funded different investigations to address community concerns regarding possible increases in these diseases. ATSDR conducted a cluster investigation of MS in El Paso, Texas. A lead smelter has operated in that community for 100 years, and 25 people who attended the same elementary school reported having MS. Biological data were available on the affected persons because CDC had conducted lead testing in the area, and some of the families had kept hair samples. No baseline prevalence estimates existed, so it was impossible to determine whether there was an excess of MS in the community.

ATSDR then funded several studies to determine a baseline prevalence of MS. These studies were conducted in Loraine County, Ohio; the cities of Sugar Creek and Independence, Missouri; and Lubbock, Texas. Communities in Ohio and Missouri were concerned about MS rates and hazardous waste sites. There were no MS-related concerns at the Texas site. The studies are complete, and they did show a latitude gradient with MS. There was a lower prevalence in Texas, and prevalence increased farther north. ATSDR is conducting a case-control study in those three areas of individuals who were identified with MS. Participants complete a questionnaire regarding different environmental exposures and provide a blood sample for genetic analysis. The blood sample is also used for metabolic analysis, which has been done for ALS, but not MS. ATSDR has expanded its prevalence studies to five additional areas and to include ALS. They expect reports from these sites to be available at the end of the year.

ATSDR is ready to "take the next step." The goal of this meeting was to discuss a national surveillance strategy for select autoimmune and neurologic diseases. This effort would provide national prevalence estimates and identify people to participate in follow-up epidemiological studies. The meeting included discussions of current efforts, strengths and limitations, and hopes for the future.

III. Participant Presentations

III.1 National Multiple Sclerosis Society

Nicholas G. LaRocca, PhD
Director, Health Care Delivery and Policy Research
National Multiple Sclerosis Society

Dr. LaRocca presented ways in which a database or mailing list from a voluntary health organization could play a role in studying prevalence rates. He also presented the National MS Society's efforts in this area.

There are a number of different sources for case ascertainment in MS, including:

- Neurologists
- MS organizations
- Physician inquiries
- Hospital discharge data
- Others

Historically, certain sources are more productive than others. The most productive sources appear to be neurologists, followed by MS organizations. Eliminating overlap, these sources can capture 90 to 95 percent of MS cases in a given geographic area.

The National MS Society has 342,000 members in its database who are coded as persons with MS. This large number could be a pool for studies. These databases, however, tend to be mailing lists rather than scientifically-formulated databases, so they have limitations. About one percent of the Society's database is duplicates due to coding and other errors. Close to four percent of people on the list are likely to be deceased, and the database has not been updated to reflect those changes. Nearly 11 percent do not have MS because they were miscoded. And, the database tends to under-represent those who are less disabled, those who live in rural areas or the South, and those with lower incomes. While this database is a rich resource, it should be utilized with great care. The National MS Society has used its database for several studies and national surveys addressing health-promoting and preventive measures, healthcare delivery in rural areas, insurance issues, and the Sonya Slifka Longitudinal Multiple Sclerosis Study. The Sonya Slifka study is a prospective, longitudinal study using a national sample that is largely representative of people with MS. Determining representativeness is challenging because there is no "gold standard." The study goals are to:

- Explore clues to prognosis;
- Explore clues to the etiology and pathogenesis of MS;
- Examine the long-term economic effects of MS;
- Examine the impact of MS on quality of life over time;

- Consider the cost effectiveness of treatment; and
- Examine access to specialists and to disease-modifying agents.

2156 people with MS participated in the study, including 482 recently-diagnosed people. The sample was randomly selected from the National MS Society database. The study actively recruited recently-diagnosed participants through a variety of methods. The data collection schedule includes a baseline telephone interview and interviews every six months for 54 months. The study collects comprehensive data, from demographic information to healthcare utilization and family history. Over 800 physicians were also contacted. Physicians reported clinical data and practice patterns. Case ascertainment begins with a telephone interview, which determines self-diagnosis, and progresses to physician confirmation. Of the 842 participants for which diagnosis was confirmed by physicians or medical records, most had either clinical or laboratory-supported diagnosis. The patients who could not be confirmed using the Poser criteria were confirmed with longstanding characteristics and symptoms over the course of the disease. In the absence of physician confirmation, the expert panel developed a set of proxy criteria:

- Whether the individual had used an MS disease-modifying drug; and
- Whether the person showed two out of three of the following:
  - reporting the month and year of diagnosis,
  - identifying the course of their disease, and
  - three of six typical MS symptoms.

The information has been used to address scientific questions, for advocacy efforts, for strategic planning for the Society, to answer statistical questions, and for outside investigator access. In particular, characteristics of the over-65 MS population have been examined. This group tends to have lower median family incomes and significant differences in health insurance coverage and disease symptoms. The National MS Society captures the largest number of MS patients of any single source in the United States, and despite issues with outdated records and difficulties in coding, the database is a useful research tool.

Discussion Points:

- An inquiry was posed regarding whether anyone in the sub-sample of recently-diagnosed patients did not meet the proxy criteria for MS. Dr. LaRocca replied that all participants met the proxy criteria.

III.2 Accelerated Cure Project for Multiple Sclerosis

Hollie Schmidt, MS, DS/MS
Vice President, Scientific Operations
Accelerated Cure Project for Multiple Sclerosis

Ms. Schmidt introduced the group to her nonprofit organization, the Accelerated Cure Project for Multiple Sclerosis. The organization was funded in 2001 by Art Mellor, a high-tech entrepreneur who was diagnosed with MS in 2000. The group aims to cure MS by determining its causes. Their goals include: 1) Removing obstacles to research; and 2) Accelerating the

determination of the causes, triggers, and pathways that lead to MS. The organization administers two scientific programs. The "Cure Map" is a comprehensive analysis of what is currently known and not known about how MS develops. It divides the causes of disease into five major areas:

- Genetic
- Pathogens
- Nutrition
- Toxic agents
- Trauma

These factors, singly or in combination with each other, cause most human diseases. MS is a complex disease and a great deal of information is needed about it, so the program can help to focus research efforts. Analyses and databases are accessible on their website.

The Accelerated Cure Project's other project is a large-scale repository for samples and data from people with MS and related diseases and controls. This effort emerged from the Cure Map, which indicated that MS research requires the application of large amounts of data. MS may not be a single disease, but a collection of diseases with similar manifestations and different causes. Traditional studies are not likely to have impact on this multifactorial disease. Large studies are expensive and difficult, so the Accelerated Cure Project initiated a pilot to lead to a large-scale longitudinal project of 10,000 subjects, including cases and controls. The study will be multidisciplinary and collect a variety of sample types. Detailed data on each participant are collected. Researchers who use samples from the repository will be required to submit their results to a database, so studies on the same subjects can be correlated. Access to the data and samples is open to the field, upon review. Four sites will participate in the effort, which will begin enrolling subjects in the spring of 2006.

Learning more about the prevalence of MS will lead to better understanding of clusters, triggers, and possible links. The registry, especially subpopulations of interest, could be useful to the research community. The organization is also interested in standardizing data across studies and registries to combine them and increase the power of studies and analyses.

Discussion Points:

- An inquiry was posed about establishing a control population early in the process. Ms. Schmidt replied that they are collecting controls. They have a list of priority order, from identical twins to first degree relatives. They are also asking subjects with MS to bring unrelated controls.

- It was noted that different circumstances and factors might require different controls; for instance, an identical twin would not be appropriate in the genetics area.

- A question was asked regarding whether the repository would include pediatric patients. Ms. Schmidt replied that pediatric patients are not presently included in the study, but acknowledged that pediatric MS is important and could be added later.

- A panelist asked whether the registry was paper-based or web-based, and whether focusing on four centers would yield a group that could be generalized to the MS population. Ms. Schmidt replied that their study would be electronic, but that their pilot was paper-based. While they are beginning with four sites, they intend to broaden their representation in other regions.

III.3 North American Research Consortium on Multiple Sclerosis Registry (NARCOMS)

Tuula Tyry, PhD, MAED
NARCOMS Program Manager
Barrow Neurological Institute

Dr. Tyry explained that NARCOMS is a project of the Consortium of Multiple Sclerosis Centers (CMSC), a nonprofit organization of over 200 member centers representing over 4000 health care professionals worldwide. NARCOMS began in 1993, and its purpose was to expedite and facilitate recruitment for clinical trials by creating a registry that could match clinical researchers and sites to subjects throughout the nation. The mission of the project has changed and expanded to include epidemiological studies. The NARCOMS database includes over 30,000 people, 18,000 of whom actively respond to surveys. The database allows both cross-sectional and longitudinal studies.

The NARCOMS database is based on self-reported data. Participants enroll voluntarily and submit updates every six months. The questionnaires are detailed, and the response rate varies between 40 and 60 percent. The questions cover demographic information, birthplace, education, socioeconomic status, insurance coverage, and disease characteristics, including age of diagnosis and symptom onset and relatives with MS. The questionnaire asks about characteristics of the disease rather than about specific groupings. Treatment status in the past and present and quality of life issues are assessed. The update surveys include extra questions that reflect current research interests. The database began in1993 at Yale University on a limited budget. At the time, the user interface made it difficult to update the database. Since they hoped to make the database accessible to researchers around the world, in 2003, the database moved to the Barrow Neurological Institute in Phoenix, Arizona. They contracted with an outside company which has helped them to develop the database to make it simpler to work with. A "virtual desktop" allows the database to be accessed via the Internet. On-line updates are available almost immediately.

Enrollment is between 1000 and 2000 every year. Their focus has not been on increasing enrollment, but in retaining members, given that they have had problems with attrition. Of the overall enrollment, 23 percent have not responded to surveys for the last two years. They can still be contacted, but are not included in analyses. About half of the persons who enrolled ten years ago are still involved in the database. The majority of enrollees come from the National MS Society, from the Internet, and via word of mouth. They have not yet systematically approached physicians or clinics to enroll participants. A Spanish version of the enrollment form is ready. The number of update surveys has increased from 8,000 to about 10,000. It is important to plan for growth from the beginning of any project. Maintenance of the database is

important, and IRB rules can change. Further, it is important to stay in touch with the people who use the data to ensure that the data are relevant. The online survey has been completed by persons in Canada and in 50 other countries in addition to the United States.

NARCOMS has learned the following lessons: 1) It is important to plan for growth from the beginning of any project. Maintenance of the database is important, and IRB rules can change; and 2) Is important to stay in touch with the people who use the data to ensure that the data are relevant.

Discussion Points:

- An inquiry was posed regarding how they confirm diagnosis. Dr. Tyry answered that they do not routinely confirm diagnosis, as the database is self-reported. They do ask whether a patient has been diagnosed or has had an MRI. They are completing a validation study to examine this issue, and medical record reviews and physician interviews indicate high validity from this self-reported data.

- A question was asked about ease of finding the website on the Internet. Dr. Tyry said that their access is good, but that there is room for improvement. They have worked through MS Center websites to link to their searches. They also work with the Centers for Excellence.

- Clarification was requested regarding the relationships between the organizations, with the hope expressed that they could see each other not as competitors, but as collaborators. ATSDR can facilitate further collaborative work. Dr. LaRocca agreed that the groups see themselves as collaborators and focus on the general mission.

III.4 Multiple Sclerosis-Computed Stored Ambulatory Record (MS-COSTAR)

Helen Tremlett, PhD
Assistant Professor, Department of Medicine
Division of Neurology
University of British Columbia Hospital

Dr. Tremlett explained that the University of British Columbia in Vancouver has housed MS-COSTAR. They call it the "British Columbia-Wide" database. British Columbia is in southwest Canada. The population is about four million. The prevalence of MS is high, perhaps more than one per thousand. Until 2005, there were four MS clinics in British Columbia. They are linked in the database. Another MS clinic has opened in Vancouver, with which they hope to link.

The database was established in 1980 and is population-based and longitudinal. It is estimated that 80 percent of the MS population in British Columbia is included in the database. It records all of the licensed disease-modifying therapies for MS. Until 2005, Canadians who needed these drugs had to acquire them through an MS clinic. Over 6000 MS patients have been followed through the database for up to 25 years. Recent natural history studies revealed that patients are seen regularly. The neurologists have been consistent over the database's history.

The database used to be called COSTAR and was complicated. A data manager had to retrieve data for researchers. Core data came from neurologists who complete forms on patients who come into the clinics. Data included typical identifiers as well as the entire neurological examination. Peripheral data such as other drugs being taken were not captured well. The Vancouver MS clinic hosted the database, and when its founder passed away in 2004, it became clear that the database was too expensive to maintain in that form. Now, it has moved to the Brain Research Center in Vancouver and operates under the umbrella of the Neurosciences Database. The database is now in Access format, and they are considering redesigning their data entry sheets. Originally, COSTAR was a scheduling system for clinic visits. It provided, and still provides, a record for physicians, but does not have instant access. It is still used by clinical trials for potential recruitment and other research such as natural history studies. Patients at the clinic sign a consent form for inclusion in the database, and few people decline to participate.

Dr. Tremlett commented that the database was "too ambitious" and tried to collect too much data, which contributed to "data collection fatigue" and a lack of consistently collected peripheral data. Any data other than core data should be collected over a limited timeframe, or else neurologists will not fill out the forms. Further, forms must be unambiguous. A manual and data dictionary should explain each question, even if it seems obvious. Data entry personnel must be trained well, and the interface must be user-friendly. Neurologists should be able to access the information directly. With this capability, they may be more motivated to complete the forms thoroughly. MS-COSTAR now has a good system for policing access to the database. It requires requesters to submit a form stating the use for the data. A long-term budget is also a key to success. Further, an efficient method for obtaining missing data should be created.

MS-COSTAR has limitations. It does not include information regarding MRIs, it does not include tissue samples on all patients, and it is not 100 percent population-based. The database is not an accurate mortality registry, although they do collect that information and attempt to collect outcome data on patients. The database is not shared with other clinics in British Columbia and cannot be accessed by neurologists. At present, it is not linked to other databases, but they hope to link to a cancer registry.

Regarding a minimum dataset, Dr. Tremlett felt that its aim should be clear. The minimum dataset for prevalence and incidence studies should include:

- A unique identifier so that patients can be updated and to allow linkage to other databases;
- Typical identifiers, including contact information;
- Date of onset;
- Diagnosis, which may have to include levels of certainty; and
- Race and/or ethnicity.

If the dataset is meant to recruit patients into a research project, then the level one data as well as disease cause may need to be included. Clinical trials will require a disease date and a disability measure. Ideally, relapses will be included, but its definition is problematic. Other items include onset symptoms and birthplace, depending on the study. If the study will include policy and

health planning, then details such as hospital admission data, co-morbidities, and drug usage will be warranted. Finally, prevention and control issues will require a host of other details.

III.5 Mayo Clinic

Brian Weinshenker, MD
Department of Neurology
Mayo Clinic College of Medicine

Dr. Weinshenker described the Rochester Epidemiology Project, which has no specific dataset. The work that comes from the Mayo Clinic involves cross-sectional, and sometimes longitudinal, evaluation of existing resources, typically medical records. The Rochester Epidemiology Project is closer to a philosophy or an infrastructure than to a database.

Variations in incidence and prevalence can occur as artifacts in epidemiologic studies due to differences in ascertainment. Incidence and prevalence studies are classified based on means of ascertainment. In active studies, investigators go to a community and either conduct a cross-sectional survey or stay there to monitor the incidence and prevalence of a disease over a period of time. Work over a period of time allows for prospective ascertainment, whereas cross-sectional studies rely on asking patients when their symptoms began, which is difficult to determine in MS. The Rochester community uses "the spider" approach, which allows for ongoing and consistent mechanisms of ascertainment. Artificial variations in incidence and prevalence estimates can occur when case-finding studies are launched in communities. The Mayo Clinic's processes and efforts have remained consistent in Rochester since 1910. The size of the community surveyed will change the means of the survey. Large surveys with uniform methods of ascertainment allow for regional differences and can yield useful numbers, but there are difficulties with quality and certainty of diagnosis. This is less problematic in surveys of small communities with institutions highly committed to accurate diagnosis.

Diagnosis is a major problem for MS. There are no cardinal symptoms of MS, and the symptoms are very heterogeneous. The diagnostic criteria rely on the presence of relapses and remissions of neurological dysfunction, but this applies to many neurological diseases, including inflammatory, vascular and metabolic disorders; furthermore, approximately 15% of patients with MS have not had any relapses (primary progressive MS). The diagnostic tests that do exist are non-specific for MS. There tends to be a large reservoir of mild cases in the community who may not come to medical attention. This group can vary according to access to healthcare. The ability to detect MS has been affected by technological advances. For instance, the use of MRI has led to an over-diagnosis of MS in this country. Variations in population structure and age distribution across the country will lead to variation in the incidence and prevalence of MS. Another confounder is the proportion of the population that is of Northern European extraction.

The Rochester Epidemiology Project has its roots in the efforts of Dr. Henry Plummer, an internist at the Mayo Clinic who created a central records repository. In 1910, he and his secretary developed the first medical diagnostic index, which led to a series of studies on the epidemiology of several diseases. In 1950, the first survey of MS in any community was published from the Mayo Clinic (Maclean et al. Res Public Assoc Res Ment Dis 28: 25-27,

1950). In 1966, Dr. Len Kurland started the Rochester Epidemiology Project and received National Institutes of Health (NIH) funding for an infrastructure to retrieve patient information for epidemiological projects. This led to incidence and prevalence studies of many diseases in Olmsted County.

Patients who reside in Olmsted County have their diseases tracked and indexed. These records can be mined for various research questions. The philosophy is to establish an infrastructure with high diagnostic accuracy based on a standard of care at the Mayo Clinic. Records are indexed for easy retrieval, and all tissues and radiological studies are preserved indefinitely. Projects are based on periodic cross-sectional review of data. Physicians with diverse interests are trained in epidemiologic methods so that they can take advantages of the resource.

Incidence and prevalence studies of MS have been performed. The most recent were reported in 1990 and 2000. The spectrum of MS-related disability in Olmsted County has also been studied. Special groups, such as those with benign MS, have been identified and studied. Predicting the patients who may not suffer disability due to MS has great impact given the current availability of expensive and partially effective drugs, who some feel should be used selectively. Analytic epidemiologic studies have exploited the historical cohort strategy. A 2003 update of MS incidence in Olmsted County reveals that approximately 60 patients per 100,000 population per decade have been identified with MS since 1965; thus, the incidence of MS has not changed since the advent of MRI in Olmsted County.

III.6 University of Maryland, Veterans' Administration Multiple Sclerosis Surveillance

William J. Culpepper II, MA
Baltimore Veterans Affairs Medical Center

Mr. Culpepper said that in 2002, MS Centers of Excellence were established based on a Paralyzed Veterans of America (PVA) report showing great disparity across the Veterans' Administration (VA) system in how MS patients were treated. The centers are located in Baltimore and in Seattle/Portland. The Centers were charged with creating registries to track the MS population through the VA system and to assess their care. Further, the registries would access participants for research projects and help provide updates on the characteristics of the population and their healthcare utilization patterns.

The VA is a rich source of data. The project's first step was to examine ICD-9 codes. Mr. Culpepper was surprised to see that ICD-9 codes only have a single three-digit value to capture all MS cases. They pulled all cases with an inpatient or outpatient MS diagnosis code from 1998 to 2002. They also examined outpatient pharmacy records and pulled patients who were prescribed one of the four primary disease-modifying therapies (DMTs). This approach yielded 25,712 unique veterans, a number that was larger than anticipated.

It was clear that their registry would not be precise if it relied solely on ICD-9 codes. Since the diagnosis is made clinically, it was necessary to use an alternative case finding method to narrow the group down. If a veteran sustains an injury or contracts a disease while on active duty which could have been related to military service, he or she may receive a disability award. In order to

receive the award, a thorough medical evaluation and workup is required to document the condition. This information is available through the Veteran Benefits Administration, and is a source for identifying definite MS cases. Another good source was the outpatient pharmacy. These two strategies yielded 9506 cases, about 5000 of which were service-connected.

Their next challenge was to identify true MS cases that were not service-connected and have not resulted in the prescription of DMTs. They conducted a chart review of the 680 cases that were identified at the VA Medical Centers in their region. They calculated the number of healthcare encounters in which MS was listed as a primary diagnosis. They hoped to eliminate the non-MS cases, but they would rather adopt a conservative strategy and perhaps initially include false negatives that could be ruled out later. The algorithm combined the ascertainment methods and enrolled persons in the MS cohort who had service-connected disability, were prescribed DMTs, or if a patient had more than one healthcare encounter per year in which MS was the primary diagnosis. This cohort is classified as "possible MS" or MS.

It was possible to compare the statistical algorithm to the chart review, which was based upon the McDonald criteria. If there were disagreements among clinicians in the chart review, the cases were classified as MS or "possible MS." They used 680 cases to compare the statistical algorithm to the chart review. The overall agreement was 91 percent. They have used the algorithm with some national data sets as well. The findings indicate that the statistical algorithm is a reliable method for identifying cases. The algorithm noted that 46 percent of the cases did not have MS, which will save a great deal of time. Applying the algorithm to national data yields 14,533 cases with a high probability of MS or possible MS. Their next task is to include clinical aspects such as subtype and other items that are not in the extant data. They hope to create templates that will be incorporated into the VA's medical records system.

Discussion Points:

- A question was raised regarding whether all of the cases had received a 340 code on multiple visits. Mr. Culpepper replied that the cases were required to have more than one visit per year. The VA system mandates that patients be seen annually in order to maintain their eligibility for benefits. Patients in the VA system who have MS would have at least one visit per year, and that visit should have MS as the primary diagnosis. Patients with fewer visits were not included in the group. He added that they have not addressed care and epidemiological issues without the clinical information that they need.

III.7 Amyotrophic Lateral Sclerosis Association (ALSA)

Edward J. Dougherty
Senior Vice President, B&D Consulting

Mr. Dougherty noted that in many ways, ALS surveillance is not as robust as MS surveillance; however, the work in ALS has been significant. ALSA has driven ALS research as the group is involved in supporting work at the National Institute for Neurological Disorders and Stroke (NINDS) repository at the National Institutes of Health (NIH). ALSA has also worked to help identify the minimum data set required for ALS research and surveillance. ALSA looks forward

to developing the research agenda for the ALS Registry. They hope that this work will link with other, ongoing projects.

ALSA's annual advocacy conference two years ago focused on registries and surveillance activities in ALS. The transcript from that meeting led to the language for the appropriations that resulted in the allocations for the ALS Registry. A great deal of collaborative work has resulted in this effort.

ALSA has also supported the ongoing work of the VA Registry. This initiative is bringing them closer to gathering and identifying data elements for ALS. ALSA is involved in a number of national and international partnerships. Collaborations among various organizations drives the research agenda, as no one organization or research center can do the work alone. CDC's leadership will maximize the importance of a variety of research projects. ALSA also works with the Agency for Healthcare Research and Quality (AHRQ) to identify the framework of a research agenda for registries and surveillance projects, including such issues as privacy.

III.8 Muscular Dystrophy Association (MDA)

Valerie A. Cwik, MD
Medical Director
Muscular Dystrophy Association

Dr. Cwik addressed the group via conference call. MDA is excited about CDC's increased efforts in ALS and is pleased to be involved in the ALS surveillance project. MDA was founded in 1950 and added additional neuromuscular diseases, including ALS, to its programs shortly after its founding. The mission of MDA is to identify causes and cures of neuromuscular diseases. Their programs are three-pronged:

- Healthcare services, including a network of 240 clinics nationwide, 36 of which are specialized MD/ALS Centers;
- Research programs; and
- An educational mission, including publications, a website, and public and professional seminars and support groups.

MDA has provided more than $170 million in funding for research and healthcare services in ALS. MDA does not perform research and does not maintain a database, but it funds research around the world. The organization has committed about a quarter of its research budget, or $8 million, to ALS work. About 50 projects are currently funded in ALS. These projects include:

- The ALS Connection;
- A structured interview of potential genetic and environmental risk factors for ALS; and
- A project looking at cholesterol-lowering medication as risk and prognostic factors for ALS.

Traditionally, MDA funds research in the basic or clinical sciences. Recently, however, they have developed an ALS translational research program to bridge the gaps between basic science

and clinical trials. A number of registries and databases are maintained by clinicians around the country. Some of these resources are extensive and have been in place for a number of years. These databases include systematic collections of data that have been important in the development of clinical trials and therapies for ALS.

ALS Connection, led by Dr. Robert Miller and his colleagues at California Pacific Medical Center, is a newly launched, web-based ALS registry. Individuals with ALS can access it from the Internet. This registry is patient-driven and physician-confirmed, which reduces the burden on physicians while still allowing them to participate. All individuals with ALS are welcomed to participate, but the project targets patients who are not attending large ALS clinics. The purposes of ALS Connection are to:

- Identify ways to improve the quality of care for patients with ALS;
- Learn about disease evolution;
- Provide long-term follow-up about quality of life and outcomes of patients with ALS;
- Provide information back to participants and healthcare providers involved in the study; and
- Provide data for ALS research.

Planned outcome studies include studies to examine disease onset sites and the rate of spread to other body regions. Information about demographics and the diagnostic process will be gathered, and outcome studies on disease severity are planned. Studies on quality of life measures, therapeutic interventions, and patient satisfaction will result as well. The database has launched, and about 100 patients have been enrolled to date. The project is designed to accommodate additional modules and has methodologies and goals that are similar to the ALS CARE Database.

MDA is excited about the opportunities that will result from CDC's national surveillance project. It is important that the goals are well-defined, and they expect that the project will contribute to the understanding of ALS. Dr. Cwik speculated about how this project will interface with the multiple existing registries. MDA anticipates participating in this effort via their nationwide network of clinics and clinic directors, in disseminating information, and in funding. While MDA has not yet collaborated with CDC, they have provided supplemental funding to NIH projects.

Discussion Points:

- Dr. Miller thanked Dr. Cwik for her presentation. He emphasized that the ALS CARE Database parallels the web-based ALS Connection. ALS Connection focuses on patients who do not have access to large care centers, where the ALS CARE Database comes from those large specialized clinics. He hopes to compare the care, risk factors, outcomes, and demographics of these patients.

III.9 Amyotrophic Lateral Sclerosis Patient CARE Database

Fred Anderson, PhD
Research Professor of Surgery
Director, Center for Outcomes Research
University of Massachusetts Medical School

Dr. Anderson echoed Dr. Miller's comments, adding that ALS CARE has received support and collaboration from a number of organizations and individuals. ALS CARE intends to improve the quality of care and health outcomes for ALS patients and their caregivers. It was envisioned as a database or registry of clinical practices and outcomes that would be open to all United States and Canadian neurologists, and through those providers, to patients with ALS. Sanofi-Aventis Pharmaceuticals, the manufacturer of the only FDA-approved medication for ALS, has supported the database through an unrestricted educational grant. ALS CARE has received support from ALSA over the years, as well as from the World Federation of Neurology.

Dr. Anderson stressed that while ALS CARE is funded by a pharmaceutical company, this funding is purely pro bono. The database is designed to give physicians perspective on the quality of care that they are providing to ALS patients as well as to learn the perspectives of the patients themselves. Scientific goals and publications come from an independent advisory board that includes clinical scientists, neurologists, nurses, and patient advocates. ALS CARE is an observational cohort study with data from physicians, patients, and caregivers. It uses standard data collection instruments and has broad participation, but most of the participants are neurologists at ALS specialty clinics who see a number of patients. There is relatively little participation from physicians or neurologists who only see one or two ALS patients. For this reason, ALS CARE and ALS Connection are a good "match." Data are collected during routine visits, and confidential reports are sent to participating neurologists on a quarterly basis.

The database is not population-based and is not designed to look for the causes of ALS. Patients must enroll through a participating neurologist. Further, neurologists volunteer to participate, and there is no evidence to indicate whether they are representative of all neurologists in the United States. ALS CARE is representative of neurologists in large specialty clinics, however. Study coordination is based at the University of Massachusetts Medical School and can receive data either on paper or over the Internet. They provide scientific support for the analysis of data for scientific publications. The database focuses on North American practices and outcomes. They use coded physician and clinic identification numbers, and physicians' names are kept in a separate database to protect their confidentiality. The sites assign protected identification numbers for patients. They could access the patients for enrollment in a study, but ALS CARE does not hold patient names.

Physician-reported data includes the type of ALS, diagnostic criteria, features, and regions affected. The database includes the ALS Functional Rating Score, capacity, details about other conditions, and other therapies. The patient provides personal information and health status questions, including satisfaction with care. The caregiver, whether a family member or a paid caregiver, provides information about his or her health status and other issues. The end of life

data includes the date of death, use of hospice, whether directives were in place and followed, and information regarding the level of distress at the end of life.

ALS CARE is observational; therefore, there is no control group, and it has a number of limitations. Data come from academic-based practices at large clinics. There are no data on pathological confirmation. They have attempted to follow up with patients every six months, but as with any voluntary effort, data decreases over time. In recent years, about 500 new patients per year are recruited from about 30 ALS Centers. There is good geographic distribution in the centers. Follow-up is more difficult because funds to compensate clinics for their efforts are not available. They wish they could have more longitudinal data. ALS CARE maintains a website, which includes copies of the data collection forms and other information about the study. The study has captured trends in physician practices and in patient characteristics at enrollment. It has end of life data on almost 2000 of the 6000 patients in the database. There is strong synergy between the project and neurologists, thanks to the quarterly reports, and the adoption by the American Academy of Neurology of an ALS practice parameter. Over the last four years, data from the ALS CARE database have demonstrated that there have been trends of improved practices at the ALS Centers.

III.10 Veterans' Administration Amyotrophic Lateral Sclerosis Registry

Edward J. Kasarskis, MD, PhD
Co-Principal Investigator, VA ALS Registry
VA Neurology Service

Dr. Kasarskis has a joint appointment at the University of Kentucky and has given direction to the VA ALS Registry, which is funded through the VA Cooperative Studies Program. The Registry was created because of the Gulf War study with Ron Horner, which was an opportunity to study the "outbreak" of ALS in veterans who were deployed to the first Gulf War. The risk ratio is approximately twofold higher for this population of young people. Rates were consistently higher in those who served the Air Force. An increase in ALS was later found among many veterans. These threads supported the idea of a national registry for veterans. The goals of the VA ALS Registry are to:

- Identify as completely as possible all living veterans with ALS;
- Track the longitudinal evolution of the disease and how it affects these individuals;
- Collect clinical data and eventually to bank DNA to match clinical phenotypes; and
- Interest and involve veteran in ALS-related research.

The VA launched the Cooperative Study Program at the closure of surveillance of veterans of the Gulf War. Subjects began to be enrolled in the VA Registry in 2003. The recruitment methods are similar to efforts to recruit for MS surveillance. The VA maintains an electronic medical record that is uniform across the country, which allows for rapid identification of individuals who have been coded correctly. The first "data sweep" was in the broad category for motor neuron diseases. A more refined search of that subset looked specifically at the designated code for ALS. National publicity with ALS associations and organizations and MDA has helped their efforts, drawing more veterans to register.

The telephone screener is a powerful tool for sharpening the accuracy of diagnoses. The group gets verbal consent from the subjects to collect medical records. The first question posed to the proxy or to the patient is, "Have you ever been told by a health professional that you might have ALS or Lou Gehrig's Disease?" Another key question is, "have you ever had progression in muscle weakness?" These two questions are strong filters. The survey collects demographic information for future contact and details about military service, including the branch served and the facilities where the patient was stationed. When a patient is enrolled, Registry staff obtains medical records from the medical providers. Not all patients receive their services through the VA system. Many receive care from the private sector, so records from both sources are needed. A team of individuals abstract the data and flag certain elements, such as co-morbidities, family history, and points pertaining to the diagnosis. The flagged material is reviewed by a single neurologist with expertise in ALS. Individuals are categorized according to diagnostic certainty. Dr. Kasarskis reviews the records for quality control and agreement. Then, telephone follow-up interviews capture the ALS Functional Rating Scale and survival data as well as medication use and use of other assistive devices.

5600 individuals have been recognized. The phone screener has been applied to 3000 of those, and 2000 individuals have screened "eligible." The majority have agreed to participate. The Registry has completed nearly 1500 chart reviews, and only 35 of those have been labeled as "not ALS." Relying only on ICD-9 codes resulted in a high rate of false positives. The phone script only had a two percent false positive rate, based on subsequent chart review.

The VA ALS Registry has learned a number of lessons. Patients appear to be enthusiastic about participation. ICD-9 codes are not an accurate means for gathering subjects. The medical record review process represents a major time and cost burden. Among the individuals who self-report an ALS diagnosis, 98 percent have a confirmed diagnosis from medical record review. All individuals are asked to participate in the DNA bank. This effort is not immortalized DNA, but one-time banking. One of the Registry's successful tactics has been to go directly to the veteran's home to take blood. It took time to find a national home health nurse agency to go the veterans to draw blood or to do a mouth swab, but it has been beneficial not to ask subjects to go to their healthcare providers to provide samples. Only nine percent of participants have refused to contribute DNA, which further indicates enthusiasm from the patient community. The chart abstractors focused not on medicines listed in the VA pharmacy, but on other medicines not on the VA formulary.

If subjects do not participate, it is often because they feel too sick or debilitated to do so. Collecting samples at their homes helps to address this problem. The Registry costs approximately $485,000 a year to support, which translates to $400 per banked sample.

III.11 Amyotrophic Lateral Sclerosis Consortium of Epidemiologic Studies (ACES)

Lorene Nelson, PhD
Associate Professor and Chief, Division of Epidemiology
Department of Health Research and Policy
Stanford University School of Medicine

Dr. Nelson said that while the ALS Consortium for Epidemiologic Studies (ACES) is based at Stanford University, it is intended to be a nationwide and worldwide resource for researchers who investigate risk factors for ALS, particularly sporadic ALS. The Consortium began last year, was funded by ALSA, and will continue for three years. ACES is not a database, but a methodological resource for researchers launching epidemiologic studies of ALS, especially, but not limited to, case-controlled or association studies. The Consortium came about as a result of an effort by ALSA to encourage new funding sources for ALS epidemiologic research to investigate environmental risk factors for ALS. Its broad objectives are to:

- Form an epidemiology consortium as a methodologic resource for investigators who would like to conduct research on the environmental, lifestyle, and genetic factors associated with ALS;
- Lay groundwork for future research collaborations so that risk factor data can be pooled across studies in the future. Given that ALS is relatively rare, is it important to provide an infrastructure for researchers to use common instruments for their research questions;
- Develop a Consortium website where investigators can obtain information on methodological approaches, risk factor modules, data dictionaries, data quality control protocols, and an "epidemiologic toolbox."

ACES aims to:

- Develop a consensus on standard data elements to collect in epidemiologic studies through coordinated meetings with ALS researchers;
- Develop standardized data collection instruments for assessing risk factors for ALS so that when investigators finish collecting data, it can be pooled;
- Use a modular format so that investigators can tailor the instruments to suit their research questions;
- Build in flexibility so that data items can be added; and
- Foster collaboration among investigators.

They are developing Access database data collection forms that can be used with the risk factors modules. They have a method for tracking data elements across studies to enable later collaborations. The benefits of multi-site studies include the increased sample size. Collecting data using standardized questionnaires will allow the data to be combined and analyzed, resulting in increased statistical power. Larger sample sizes also allow for division into distinct subgroups.

ACES has more than 50 members. Cross-discipline "fertilization" is another benefit of the Consortium, as it includes neurologists, epidemiologists, geneticists, statisticians, toxicologists, basic clinicians, and others. The Consortium emphasizes precisely defining biologically relevant research questions, and the combination of disciplines allows basic science to inform epidemiology, and vice versa.

The ACES website includes a comprehensive, "state of the disease" literature review as well as a comprehensive review of analytic epidemiology studies to date. It includes a registry of past and ongoing studies, links to funding resources and other research groups, and access to the expertise of other ACES members. Consultation regarding study design and methodologic issues is available for new investigators. Instrument development and standardization will be included on the website, as will study tools and data management tools.

Consortium members and investigators have discussed the data elements that should be collected in long-form modules; that is, studies that examine risk factors for ALS. These elements include socio-demographic characteristics, a lifetime occupational history, military history, residential history, residential exposures, trauma, anthropometric characteristics, chronic medical conditions, medications, reproductive factors, hormone use, and family history of neurodegenerative diseases. Lifestyle factors of interest include physical activity, tobacco use, alcohol consumption, caffeine intake, recreational drugs, diet, and vitamin and mineral supplementation. Each of these domains will have a shorter version.

Last year, the ALS research group defined elements that are necessary for an ALS registry, which include the following:

- Name and contact/locator information
- Social Security Number, which may not be possible to collect
- Sex
- Date of birth
- Race/ethnicity
- Physician information
- Data necessary to support the El Escorial diagnostic criteria and to assign a degree of certainty
- A means to allow for multiple dates for clinical information to enter the process, as a definite diagnosis might not be possible at initial onset of symptoms
- Methods by which ALS was confirmed
- Family history of ALS.

III.12 Agency of Toxic Substance and Disease Registry Prevalence Projects

Laurie Wagner
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Environmental and Injury Epidemiologic and Toxicology Branch
Texas Department of State Health Services

Ms. Wagner explained that ATSDR has funded work to estimate MS and ALS prevalence through cooperative agreements. The initial MS prevalence studies were conducted in Ohio, Missouri, and Texas. At the time, no states had baseline rates of MS. In order to be counted, a case had to: 1) reside within the study area, which was determined by zip code; 2) had to have a physician visit during the study period; and, 3) a diagnosis of MS that was confirmed by a consulting neurologist by review of abstracted medical records. Case ascertainment primarily consisted of visits to neurologist's offices and clinics. Secondary sources included nursing homes, death certificates, and hospital discharge data. Death certificates were not enlightening, as verification from doctor's offices was still required. Hospital discharge data were not enlightening either because states do not include identifiers on hospital discharge data.

The initial study used ICD-9 codes for MS, transverse myelitis, other demyelinating diseases, and optic neuritis because the consulting neurologists for the study, as it was suspected that these would turn into MS cases. However, this was not the case during the three-year study period. Descriptive data, demographics, diagnosis data, laboratory data, MRIs, and attack histories were summarized so that the consulting neurologists could assess whether the cases were "definite", "probable", "possible", or "not MS" according to the Poser and MacDonald criteria. In Texas, the prevalence of MS was 43 cases per 100,000 population while in Missouri the prevalence was 88 per 100,000, and in Ohio the prevalence was 112 cases per 100,000. Prevalence increased in locations farther north.

It became clear from the initial prevalence study that the detailed forms took too long to abstract. Diagnoses were not able to be confirmed for many cases because information was not available from the medical record, even though medication prescribed and office visits made it clear that the patient was being treated for MS. Because a small percentage of the cases of the other diseases were actually MS, and secondary data sources provided little information, it was decided that the next study would focus on clinics and neurologists' offices and only include the ICD-9 code for MS.

The current prevalence study is an expansion of the first study. It adds years to the study period and also adds ALS. Since they were working in neurologists' offices, it seemed logical to capture ALS records as well. The current study includes Massachusetts, Illinois, Washington, Missouri, and Texas. They will only pull specific ICD-9 codes for MS and ALS. They will not include every record on the long abstraction form. If a neurologist is treating a case as MS or ALS, then the survey will accept those cases. The study is in a one-year, no-cost extension and will end in September of 2006. Three of the states have completed their data collection. Health Insurance Portability and Accountability Act (HIPAA) requirements and IRB restrictions have delayed the study in some places.

As a result of the study, it is possible to provide prevalence estimates for MS and ALS at the state level for small communities with environmental concerns. The study has provided insight into conducting surveillance on neurological diseases and has shed light on autoimmune diseases as well. It is essential to use state and local health departments to get into neurologists' offices, and even with this help, the neurologists can, and do, refuse to allow entrance. There is under-ascertainment of cases. Many offices are not computerized and cannot find all of their cases. It is sometimes difficult to gain entrance to the offices and medical facilities. All information on MS diagnoses is not always found in the medical records, so some cases are not counted. The work is staff and resource intensive, as well as time-consuming.

Discussion Points:

- A question was asked regarding whether the prevalence rates were corrected to account for the clinics and offices that did not allow the study to access their records. Ms. Wagner replied that in the initial study, all offices allowed access. The current study encountered refusals, and the numbers will reflect that.

- An inquiry was posed about why an office might refuse access. Ms. Wagner said that she tries to set appointments with offices, but they do not always call her back, so she relies on "drop-in" visits. One office that refused to share information stated that the neurologists were not interested in participating. Ms. Wagner had supplied them with HIPAA and state health and safety code information, but ultimately, access is determined by the office managers more than the doctors.

- It was noted that neurologists may value the results of research, but they are not research scientists and do not have the time and resources to participate in the effort. They may see the researchers as disruptive. For the VA registry, they did not ask the offices to make judgments about what information should be included. The offices sent all of their records, and Registry staff read through them to find pertinent data elements. Ms. Wagner said that the offices only have to identify records of patients with MS. Study staff abstract, pull records, and re-file them.

- It was indicated that the VA Registry has the benefit of specific identifiers for patients. They specify that they are working for patient care, not for research.

- A panel member recalled that an apparent excess of cases was one of the incentives for the study, and inquired as to whether vital statistics data from the communities surveyed were available to correct for differences in the population structure. Ms. Wagner replied that they had this information for each area.

- It was pointed out that physician-to-physician contact could be more helpful than working through an office manager. Many offices do not have a research nurse. If a state health department physician were to make initial contact with the physician, access might be granted. Ms. Wagner agreed that the approach could be helpful. In Lubbock, their consulting neurologist was part of the community and could meet with the area physicians.

- It noted that neurologists will sometimes meet with them, but then access will still be refused. Ms. Wagner responded that the neurologists can agree, but they are not the persons who work to pull the records, so refusal is still possible.

- A panel member asked for an estimate of the percentage of non-responders. Ms. Wagner replied that she does not know how many patients are seen by the physicians who are not cooperating. She knows that she is missing some, though.

IV. Presentation of ATSDR Proposal

Wendy Kaye, PhD
Senior Epidemiologist
McKing Consulting Corporation

Dr. Kaye thanked the group for attending the meeting and expressed her appreciation for their efforts. She then described ATSDR's efforts so far and explained the goals for the rest of the meeting, explaining that the project began as an effort to create a national surveillance system for selected neurological and autoimmune diseases. The first step was to identify the existing registries and databases on a large number of conditions. Based on that information, the next step was to select a disease or diseases to consider for surveillance and to develop and test the methodology. A large number of MS databases exist in the United States, Canada, and abroad. Some databases were designed for particular studies, but those data are not always accessible. A number of databases for ALS exist as well. She also considered Alzheimer's and Parkinson's disease registries.

It is logical to begin where the most work has already been done and to build on that work. It might be possible to coordinate the extant groups and create a larger database, rather than to start from scratch. Different groups identify people through different methods, such as: 1) Physician and healthcare reporting; 2) Administrative and clinical databases; and / or 3) Self-identification. Each method has strengths and limitations. For instance, physician reporting has good case verification and access to clinical data, but it is time-consuming and expensive. Self-identification is less expensive, but there are issues of verification. ATSDR hopes to do this work efficiently, feasibly, cost effectively, and accurately. They wonder if it is possible to identify people using administrative databases such as Medicare, Medicaid, the VA, and health insurance databases, and then to build on that data. Accuracy depends on the condition, as there are variations in the way physicians categorize their patients. In general, accuracy of diagnosis of neurological conditions ranges from 80 to 91 percent. If using administrative data sets is a reasonable way to begin the process, then the accuracy of identification should be increased. It might be possible to use multiple data sets from different sources and by using "capture-recapture" techniques estimate the number of cases missed. An algorithm using multiple years of data could add to accuracy, assessing multiple doctor visits and treatments.

Dr. Kaye clarified the following definitions:

- **Surveillance** is the ongoing, systematic collection, analysis, and interpretation of data. It is used for planning, implementation, and evaluating public health practice.

- A **registry** is a system for collecting and maintaining, in a structured record, information on specific people in a defined population. Unlike surveillance, a registry aims to achieve complete ascertainment. Registries are sometimes used for surveillance.

- **Longitudinal studies** involve the repeated observation of a number of people in a specific population over time. A number of the MS and ALS databases are longitudinal studies, or a combination of a registry and a longitudinal study. These databases follow people over time and also add to the cohort over time.

At the outset of this effort, ATSDR aims for a combination of surveillance and a registry, working with a minimal data set that could be collected using data sets that are available, including identifying information, demographic information, date of diagnosis and symptom onset, the type of provider, and the database from which the information was received. Clinical data is important to add for longitudinal follow-up and natural history, but that data will be added later. ATSDR has discussed how to pilot the methodology, using a national dataset for comparison, and to learn where "holes" might be. The pilot projects would be different for MS and ALS because different databases are available. New York (MS) and South Carolina (ALS) both have data systems that could be useful. They will think about other data to collect in the future, how to standardize those data items to be collected, and how the data could be used in the registry to identify individuals for research studies. ATSDR hopes that the registry will be used for surveillance and also be available for researchers to access.

Dr. Kaye opened the floor for discussion. She asked the group to keep their comments specific to MS or ALS, but recognized that it might be difficult to do that.

IV.1 Questions generated by the ATSDR Proposal

Several questions arose from the panel based on ATSDR's draft proposal, not all of which have been settled:

- **<u>What is the product of the project, and in what timeframe should it be produced?</u>**

  - The ultimate goal is a national surveillance system that is cost-effective, efficient, and accurate. However, these discussions should not be limited based on cost concerns.

- **<u>Where will this registry be housed?</u>**

- **<u>To whom will the registry answer?</u>**

- **Where and how will the information be disseminated?**

  - The registry will be housed at CDC. Outside entities might be hired to maintain the database and to help with access.

  - It is important that an unbiased source host the registry so that all can use the system.

  - Resources are limited, and a pilot will indicate what will work and the resources that will be necessary to execute the project.

  - It would be powerful to reach broad consensus from the major players in the field regarding collection, standardization, and the important features of the project.

- **Assuming that the pilot efforts go well, where will this effort lead?**

  - If the MS and ALS pilot effort is successful, then the next step will be to expand the registry.

  - The long-term goal of the entire project is to apply the methodology to other neurological and autoimmune conditions. If Medicare and Medicaid data are obtained and manipulated for one set of diseases or conditions, it makes sense to use the data for other diseases and conditions as well.

  - A possibility would be not to create a national system, but to create a system such as Surveillance Epidemiology and End Results (SEER) in the Cancer Registry, designating a population base that is representative of the United States and working to capture 100 percent of that smaller subset.

- **Would taking the registry to a larger scale include expanding into different types of data sources or expanding into multiple sites nationally or regionally?**

  - If the pilots work, then the effort will expand to be representative of the entire United States population, and then expand to include other conditions.

- **Does ATSDR envision an effort with a strict definition of surveillance; that is, a resource for public health planning?**

  - Ideally, the registry will eventually be both a surveillance system and a resource for people who are doing research to be able to identify populations to participate in projects. The initial list of variables is modest because the questions and information will change. ATSDR hopes to identify people successfully and then move to the next step.

- The project's first goal is to gather true cases in the population to determine public health implications rather than to create a platform for driving other research activities.

- Each of the different databases that exist for MS and ALS came from a different research emphasis. These goals might be different from the technical definition of surveillance.

- **What is the threshold for false positives and false negatives in the data set?**

  - No surveillance system is 100 percent complete and accurate.

  - Questions persist about the basic epidemiology of MS and ALS.

  - It may not be possible to ascertain incidence of MS, but it might be possible to have prevalence data that is not regionally isolated.

  - Some misclassification will have to be tolerated, but if cases are missed at the beginning, then they may be captured as part of the ongoing process.

  - As years go by, subjects might move from a "possible" category to a "definite" category. The surveillance system will get as accurate a count as possible with basic information and then allow research questions to drive additional information that might be gathered from the national, population-based sample.

- **Have algorithms been used with Medicare and Medicaid databases to identify cases of other chronic diseases?**

  - Most of this work has been done with diabetes. The only non-infectious disease with national surveillance is cancer.

  - Surveying conditions for which there is no definite pathology or diagnosis can be problematic. Research has been done in Canada, but their healthcare system is more unified than the United States.

- **Does ATSDR have public health prevention or intervention goals in mind? This question pertains to the sensitivity and specificity of the application.**

  - Those goals can emerge as the project is planned, although the issues of quality of care, access to care, and access to therapies have been raised.

  - The method being discussed has the potential to miss people in the early stages of MS or with mild MS.

- **Is MRI result data available through Medicaid or Medicare?**

  - The data only reflect whether an MRI was performed. The algorithm will have to be built on another factor, such as consistency of procedures related to one of these conditions being performed or visits to a pulmonologist. These factors, rather than clinical signs, will classify cases as "definite" or "probable."

- **Should ATSDR consider other means for identification other than administrative data sets?**

  - Many advocacy groups have offered or suggested mailing lists and other ways of identifying people.

  - The VA captures volunteers.

  - The VA includes a large number of regular users, and Medicare includes about 40 million people. The Medicaid population is the least stable of these, as the system includes people who are under-served, and their eligibility changes. There are about 40 million persons in this system, and the population is weighted toward women and children. None of these sources is representative of the United States population, however.

  - A recent study showed that case ascertainment through neurologists' offices and MS organizations captures between 90 and 95 percent of patients. This approach might be more beneficial and less problematic than using insurance, Medicare, and Medicaid data sets. The voluntary health organizations would be likely to cooperate with the effort.

  - Services for ALS are not available in the entire country, so this approach might not be as appropriate for ALS as for MS.

- **How would the system reach privately insured patients, since there are so many insurers and since third-party brokers are not an option, as they have no identifiers?**

  - Realistically, CDC could only access the larger companies.

  - They will not access all patients who are privately insured.

  - Using a third-party broker that employs constructed, unique identifiers for people across data sets should be explored. Some MS patients have private insurance as well as Medicare coverage.

- **Should certain clinical information be part of the core data that is gathered?**
  - Most existing data sets do not include clinical information, so this aspect of the work will have to be added and retrieved from clinics.
- **What is the timeframe for this effort? Will the pilot projects be proposed and executed at a certain time?**
  - The pilot projects will be completed within the next two years, and the information from them will move the effort forward.
- **How fast can Medicare and Medicaid information be acquired?**
  - Medicare can pull data based on an ICD-9 code, and the cost is the same to pull data for all neurological diseases or for a specific disease. This data is clean and is purchased in yearly increments.
  - Medicaid data is less sophisticated, in that it is purchased by state and is not manipulated.
- **Does ATSDR have a notion of which states might host a pilot test?**
  - ATSDR has identified good and likely locations, but they are open to suggestions.
  - South Carolina is a historically strong partner, and that state has experience with registries. They already have the data sets that are linkable and permission to do so.
- **$900,000 has been appropriated for ALS: Where does the MS money come from?**
  - That money comes from a general "surveillance" budget. Neurological and autoimmune diseases are a major concern for surveillance.
  - There are no additional monies in the budget for these diseases, so it will be important to partner with other groups to accomplish a larger product.

IV.2 General Discussion Regarding the ATSDR Proposal

Coding

- Using the ALS code number to identify persons with ALS who are on Medicare may be difficult. In 2000, Congress waived the waiting period for people with ALS, and since then, a number of neurologists may assign an ALS code to a patient with a different disease so that the patient can receive this waiver. The drug benefit has led to a number of diseases lobbying for waivers.

- In ALS, the main reported figure is incidence rates; for MS, prevalence rates are reported more often. Any algorithm will have difficulty in distinguishing between new and prevalent cases.

Data Sources

- The National MS Society funded two economic studies that used claims data to identify MS patients using the 340 code. The investigator found that in order to capture all of the cases, it was important to examine claims data for two to three years, whether the data came from private health insurance or from Medicare and Medicaid. Generating "prevalence" from insurance data based on the denominator of total persons covered results in an unrealistic figure.

- The HMO Research Network is a potential source.

- Groups that work with the Northern California Kaiser System developed an algorithm for detecting a possible case. A neurologist reviews full records and applies a case definition. This System has a wealth of information, from inpatient data to pharmacy and test findings. HMOs are defined populations and would allow for a registry approach.

- Using only Medicare and Medicaid populations will eliminate cases under private insurance, which is a large segment of the general population, especially of young people. However, it was also noted that under-insuring is rarely a problem in MS.

- The amount of data available through private insurance providers varies greatly. South Carolina, for instance, has access to Blue Cross and Blue Shield data.

- Symmetry markets software to insurers. This company did a study for Biogen, which included 45 million covered persons. Symmetry claims to have access to over 200 million people, since most private insurers use one of their procedures. However, these data do not include identifiers.

- Obtaining claims data is less of a concern than working with them. It is not possible to compare these data to data gathered from a clinic.

- It would be ideal to merge the Medicare, Medicaid, and VA databases, but this effort would require a unique identifier, and HIPAA requirements will make it difficult.

- The listed data sets are not representative, and so it will be important to include other sources, such as private insurance, particularly managed care organizations. Access to personal identifiers will likely be very problematic and there will be difficulty in linking data sets unless effort is made to work through Offices of Epidemiology at state health departments. ATSDR should consider whether it would be useful to encourage the Council of State and Territorial Epidemiologists (CSTE) and other groups to make these conditions reportable. This change would create the possibility of working through state departments, which can facilitate the collection of this administrative data with personal

identifiers. CSTE lobbies state boards of health and state legislatures to make conditions reportable. The economic impact of making a condition reportable depends on whether the data collected are existing, computerized data, in which case the impact is negligible, or whether active collection and abstracting of data is needed. It would seem that reporting MS and ALS would involve reporting data that has already been gathered, such as outpatient clinic data from larger health providers, ED data, and hospital discharge data.

- Sets of data that are completed by state are more satisfying and more representative of the general population than Medicare or Medicaid data. The National Hospital Discharge Data Survey and others are based on information shared from state health departments.

- Specialized clinics that provide high-level services for ALS are small in number, but neurologists are diagnosing ALS broadly around the country. The uninsured population, which is substantial, is in danger of being missed.

- Based on CDC's experience, going directly to neurology offices may not be an appropriate strategy. It is time-consuming and only yields estimates for pockets of the country. Those funds could be used to gather more accurate data in broader areas by using existing databases.

- It was suggested that working directly through neurologists' offices be attempted again, with the support of the three major MS organization as well as some of the newer voices in the field. Marketing the effort as a crucial step for the care of MS patients will increase buy-in. Any other approach will also be fraught with problems and have uncertain outcomes.

- Some neurologists' offices were unable to generate a list of MS patients. Some were able to generate lists from billing codes. Many offices generated lists based on the recall of office managers. There is more support in some areas than in others. Perhaps a neurologist should present the effort to increase interest and participation.

- Electronic medical record usage is increasing rapidly, and electronic retrieval could be much easier in as soon as two years. It is likely that smaller practices will be able to retrieve records by ICD-9 codes. Many offices are making the transition from paper to electronic records. These increases should be factored into the plans to that the system can take advantage of them in the future.

Identifying Cases

- The system should be piloted in areas where good cooperation from neurologists is in place. MS is more difficult to define than ALS, because MS is frequently diagnosed wrongly and because disease-modifying treatments for MS are often prescribed for patients with other diseases and conditions.

- The VA began its project with an "over-inclusive" philosophy, understanding that the initial subjects would be further screened and evaluated before they were enrolled in the registry. The process of evaluating and cleaning the data sources will be ongoing.

- The VA is developing a template for the medical record so that a 340 code that is entered will generate a reminder and a detailed checklist of data that is needed.

- There are probably regional differences in the "liberality" of MS diagnoses, which is an inherent challenge of MS.

- There are barriers in the VA system to prescribing DMTs. The system is not open to any practitioner, and sometimes the prescription must be confirmed by a designated neurologist. Using DMTs as a screen is probably more effective in the VA system than in the general community.

Partnering With Other Efforts

- The timing of this initiative is important in the ALS arena, especially given the formation of the ALS Research Group. They are in the process of designing a national database which will begin with core data from about 2000 patients with ALS who donate DNA to the NIH funded effort in collaboration with Corriel. The ALS community includes a number of different databases, but this new national effort, which includes most of the principal ALS investigators across North America, aims to form a database for research purposes. The group has a great deal of momentum and represents a great opportunity for CDC involvement to optimize the work and to bring ALS research to the next, national level.

- Part of the intent behind the legislation that authorizes CDC to do this work includes partnering between the federal government and nonprofits. Legislation that is separate from the appropriation has been proposed for an ALS registry. The House bill has 74 co-sponsors, and the Senate bill has 17 co-sponsors.

- The ALS community works together routinely, and well. The DNA banking effort is testimony to the good relationships that exist. Both the ALS and MS communities will rally around ATSDR's efforts.

- MS is more difficult to address than ALS, as many other diseases and conditions can masquerade as MS. It is possible that a system developed for ALS could be adapted for Parkinson's and Alzheimer's diseases, even though each disease has its own challenges. ALS progresses rapidly and can therefore yield information quickly.

- The National MS Society recently funded six pediatric MS Centers. The Centers have to collect data uniformly, and that data will be pooled and used for research. The pediatric population must be included in the system that ATSDR creates. Regarding MS, the pediatric population could represent cases in early stages of the disease.

General Comments

- The word "surveillance" might have negative connotations in the general population.
- Because of the difficulties in diagnosis, MS surveillance will be more difficult than ALS surveillance. A national surveillance case definition will need to be developed.

V. Discussion of MS Surveillance

The group then focused its discussion on MS surveillance, although comments regarding ALS were included as well.

Case Ascertainment:

- Medical records have limitations and should not be the sole method of ascertainment.
- Neurologists should be encouraged to report. They need to give data about outcomes, and their buy-in is crucial. Leadership in their field could encourage participation. Intensive resources are necessary to go into neurologists' offices, but those diagnoses are reliable for both MS and ALS.
- Awareness of MS has led to an increase in suspected cases and diagnoses of "potential MS."
- People could be characterized differently in the registry, perhaps using "ranges" or degrees of certainty based on the criteria that are satisfied.
- The NARCOMS validation study was based on a number of "flags." The telephone interview was quite accurate in case ascertainment. They still pulled medical records, but the extra effort might not have been necessary.
- The stated methods of ascertainment (Medicare, Medicaid, and VA) reach groups of people who are over 65, underserved populations, and people who get their care at a VA hospital, which is a subset of veterans. There was concern that these sources might not be robust.
    - These sources are the most readily accessible, and other sources will not be left out of the process.
    - Working with national organizations is an option, but those patients are not always easy to contact. The mailing lists of voluntary organizations all have problems with out-of-date contact information, miscodes, and other issues.

- Data suggest that using codes other than 340 to identify individuals with MS has not been initially fruitful.

- The ALS VA project employs trained abstractors to review the medical charts and to flag "high-value" cases. ALS experts review the abstracted, flagged records. The costs associated with this work are not high.

- A group of researchers at the Northern California Kaiser Permanente Division of Research has NIH funding to do an MS study. They have developed an algorithm and while they do not have the resources for a neurologist to review every chart, they would appreciate the opportunity to validate the algorithm. It might be possible to fund the "next step."

- In cases of MS, the entire record is often not in one location, particularly in subjects who have received treatment over a long period of time.

- The VA ALS Registry asks patients to name all of their practitioners throughout their experience. These practitioners send entire records, and Registry staff abstract them. They have found that ALS data is often not in one location, either. When asking for entire records from practitioners, they will compensate the practitioner for printing costs, if necessary.

Recruitment of Participants:

- It might be possible to identify participants and then administer a survey to them to assess whether they are eligible for the registry. This approach could lead to gathering more data that is needed, but not immediately available, such as MRI results and quality of life measures.

- HIPAA requirements for direct contact for studies can be problematic.

- The VA includes a basic questionnaire with a consent form for inclusion in the VA Surveillance Registry. Building permission for contact at the beginning of the process is crucial.

- ALS Connection collects identifiers such as Social Security numbers and other data so that it can track survival and other data. IRB approval was complicated, but it was important to be able to gather this information. This Web-based system has great potential.

- Patients often want to be in a registry because they feel that their data can help research efforts.

- The local chapters of the National MS Society would be motivated to participate in this effort and to encourage its members to join.
    - Means for contacting members of organizations depend on the study, who conducts it, how it is structured, and other issues.
    - An "opt-in" is difficult to execute, but the National MS Society has used an "opt-out" choice for its studies.
    - ALSA is a federated model, so each chapter is a separate corporation with a separate database. They may not share information, and their chapters have to opt in, or opt out.
    - The National MS Society is not federated, and its database is fed by local chapters as well as by national contacts.

Inclusion Criteria:

- There are issues with using DMTs as definite inclusion criteria. DMTs can be used as the first "cut" to create an initial "pool" for the registry. Their ultimate inclusion depends on how the subjects will be used.
- MS and ALS are challenging because there is no agreed-upon biomarker for their diagnosis. Neurologists vary widely in their experience with the diseases and in their record-keeping. In essence, the algorithm for case ascertainment is "trying to make a judgment about somebody else's judgment." The registry hopes for a higher degree of diagnostic certainty than might be present. An error rate is intrinsic.
- The date of onset and date of diagnosis is "slippery" for both MS and ALS. The VA Registry elected to capture a "boundary" of these dates.
    - If the goal is surveillance, it might be possible to put a boundary on the cases that seem to be MS or ALS, but their medical records do not include enough information for definitive inclusion. These cases could be placed in another category so that a self-report strategy with a higher error rate could be included with refinement. The cases could not be used for hard science, but could be used for planning in communities. People can also shift from one category to another as more data is gathered over the years.

- There was discussion regarding whether the type of provider giving service to the patients should be included in the database and whether this information should be factored into the certainty of diagnosis.

  - An algorithm for this factor could be developed. If other indicators do not suggest a high certainty of MS, then a diagnosis from an MS specialist might have credence.

  - Many ALS patients investigate their symptoms on their own and can "bully" their practitioners into diagnosing ALS. Diagnosis from an experienced neurologist can be crucial.

  - The diagnostic criteria for MS require a diagnosis from a specialist who is experienced and comfortable with MS, so there is precedent for it.

  - Concern was expressed concerning the definition of an "MS specialist." The majority of patients with MS receive care from a neurologist, but the neurologists have varying levels of expertise.

- There was discussion regarding how to include "certainty" in the database.

  - Mis-classification becomes more likely with additional categories.

  - An algorithm could assign subjects to certainty categories. Each category will have specific criteria, and subjects can move to different categories as time goes on. A surveillance project that finds a "cluster" of MS cases diagnosed by a physician who is not an MS specialist could raise a "red flag."

  - It could be possible to use "certainty codes" to quantify the certainty of diagnosis. The Brighton Collaboration is an international working group that is designing case definitions for vaccine-adverse events. They use levels of diagnostic certainty.

- Spinal fluid is a helpful test that is being enhanced. MRI scans yield many false positives. CSF is problematic because fewer than 50 percent of patients have a CSF test.

- The duration of follow-up is important in determining whether other conditions develop into MS.

  - Optic neuritis is the second-most common symptom of MS, and of those, half will have an abnormal MRI scan. There is a high conversion rate to MS within two years. Omitting these patients would potentially lose a population that will develop clinically definite MS; that is, they had the condition from the first symptom.

- However, the VA project concluded that only including MS diagnoses captured most cases. The VA system will capture persons who convert to MS later, though.

- This issue will likely affect incidence cases more than prevalence cases.

- Re-evaluating the newly identified cases is a possibility.

- Most adults who are diagnosed with acute disseminated encephalomyelitis are actually having a first attack of MS. This diagnosis is rare and probably more prevalent in children, but should be included.

- Transverse myelitis is complicated, and many neuromyelitis optica cases are given a diagnosis of MS.

- The frequency of neuromyelitis optica is not known, but it should be included because it is another inflammatory disease of the central nervous system that is often confused with MS.

Approaches to a Pilot Study:

- It might be possible to select states or regions that are representative of the United States as a whole and thoroughly collect data in those areas where information about baseline populations is more available.

- A good pilot for MS might assess the validity of a purely self-selected population, such as those who contact the National MS Society.

    - Often, people who say that they have been diagnosed by a physician are telling the truth.

    - Any error that occurs is likely on the part of the physician, not the patient.

- It would be interesting to determine the percentage of patients who were diagnosed with MS by a physician met the case definition for MS, based on chart review. The data from the work at the state level could be interesting. Often, there was not enough information in the chart to classify the person has having MS.

- The ease of using information from voluntary processes should be pilot-tested and information from a local chapter should be compared to a national database.

- A pilot test is needed for every source of data that will feed this registry to verify that the method is reliable.

- A recruitment strategy into a surveillance database could be defined and piloted in a region. It would yield contact information for patients and access to medical records and doctors to assign the cases to degrees of certainty of diagnosis. This process would

indicate a probability of accurate diagnoses based on expert review of medical records. This approach might be more productive than approaching the neurologists, since the physicians will be approached to provide charts of specific patients.

- ATSDR should consider more than one pilot study of the algorithm, or variations of it. A managed care organization could be instructive in showing how the algorithm works when compared to expert review of medical records, the "gold standard." Sensitivity issues can be tested with linkages to Medicare and Medicaid.

Planning for the Future:

- The initial goal of the project is surveillance, but the data should be able to be used in research. The line between surveillance and research is often blurry, but ATSDR wants to be sure that line can be crossed.

- IRB issues should be considered from the beginning.

- When planning the registry, it will be important not to weigh it down with peripheral concerns. For instance, there are many methods for recruiting patients for research that are more efficient than a registry. They must prepare the effort for the future without overloading the instrument and making it difficult to use.

General Comments:

- There is tension between conducting population-based studies that are rigorous but yield a small sample, and working with a large number of samples that might be a biased population. Large numbers are needed for research, trials, and samples. Incidence and prevalence are important, but narrow. Ideally, the registry will include subjects who have been carefully screened and are representative of the entire population. Complex genetics and risk factor analysis require large numbers. They could rely on the algorithms, which have been proven to be useful. It is possible to create a system that incorporates different parts of both approaches.

- If researchers want to use samples for case-controlled studies, the subjects will have to be of high quality and not chosen based on a limited algorithm. Compromise and realistic estimates of which elements of each approach are needed will be important. Feasibility studies will indicate whether the system works. The registry needs to be used for high-quality data as well as for national coverage.

- This effort seems to include enrolling patients in studies and accomplishing other goals, which are different from traditional CDC surveillance.

- It is important to exercise care with vocabulary and not to use language for surveillance that might be used in a different sense in diagnostic criteria. This issue could be a problem, given that there are standard terms used for surveillance.

VI. Discussion of ALS Surveillance

March 14, 2006

On Tuesday, March 14, 2006, the group reconvened and continued the previous day's discussions, steering their conversation toward issues related to ALS. Attendees from the ALS community offered to generate a synthesis document to summarize their thoughts and ideas from the meeting. This document will be shared with other ALS experts not present at the meeting for feedback.

The Congressional Authorization:

- Mr. Gibson shared the language of the Congressional authorization. After analyzing several databases, draft legislation was drafted and introduced in both houses of Congress. The bill has not yet been passed, but reads as follows:

  "The committee recognizes that a national Amyotrophic Lateral Sclerosis (ALS) Registry may enable unprecedented progress in understanding ALS. Although several sources of ALS patient information currently exist in varying forms around the world, this information is not as comprehensive as required for the needed research. The committee provides $1 million for pilot programs to begin to gather data for a nationwide ALS registry that will estimate the incidence and prevalence of the disease, promote a better understanding of the epidemiology of the disease, and provide data that will be useful for research on improving disease management and developing standards of care. CDC should, to the extent practicable, identify and coordinate with existing data surveillance systems and registries such as state-based ALS registries, the Department of Veterans' Affairs ALS registry, and the NINDS repository."

- The report has to be approved by both houses, and it was amended to state that $900,000 should be made available to start the nationwide registry.

- It is important to generate suggestions for ways for CDC to spend the dollars, to finish the report that Congress will see at the end of the year, and to prepare for another Advocacy Day on the Hill.

- Many neurologists and patients across the country are excited about the effort and are eager for more information.

Case Ascertainment and Subject Recruitment:

- A claims-based effort could also involve a registry.
  - An initiative could throw a "broad net" and capture a large number of cases in a new way.
  - It would be novel to take a number of initiatives, including claims data, the managed care population, existing registries, and patients who are receiving certain drugs, and to mobilize neurologists at the national level to identify every patient in a certain catchment area.
  - The ALS Association in northern California has started a new initiative wherein large regions are targeted by an individual who identifies every patient with ALS in the area. This individual's goal is to bring care to the patients and help them access the larger centers.
  - This existing framework for identifying patients could be utilized.
  - The initiative begins with membership lists of national societies and moves to rolls of clinics and neurologists.
- A possible model surveillance system would rely on patient initiative.
  - ALS patients tend to want to help themselves, and then to help with research. This research focus cuts across socioeconomic status, because the patients realize that research is crucial to making progress.
  - It might be possible to validate ways to tap into this mindset to populate a surveillance instrument. This recruitment strategy could be tested.
  - When volunteers are used, though, there will always be questions regarding who is missed; therefore, other data sets must also be used and un-duplicated. Then, they can assess which patients are more interested in contributing more information than the basic data that is collected.
  - A baseline will give a good idea of the population, and other systems will provide other means for contributing information.
- There was discussion of specific codes for MS and ALS. If the United States approves ICD-10 codes, then the system will be expanded, but for now, the group should decide whether to cast a broad net for ICD-9 codes. The relevant codes are:
  - 335.2: neuromuscular diseases
  - 335.20: specific ALS
  - 335.24: primary lateral sclerosis

- 335.29: not specific, or "other"

- The VA ALS registry searched for ICD-9 codes "335.2x" to capture the entire spectrum. They encountered records with less specific diagnoses and are still working through them. They found a core group of cases that are definitely ALS, but other syndromes emerged as well. There is value in capturing all motor neuron diseases, but the workload is significant.

- The group discussed the percentage of patients who are referred to an ALS clinic through a general neurology practice with a diagnosis of a motor neuron disease who actually have another condition.

  - If the surveillance effort only considers patients from ALS clinics, then there will be less of a problem with misdiagnosis; however, if the study includes patients who are not referred to ALS clinics, other, unrelated diagnoses may confound the work.

  - About 90 percent of the patients who have second or third opinion from specialists in ALS are diagnosed with ALS. The other five to ten percent have another motor neuron syndrome. Some cases are very difficult to classify.

- The group discussed an algorithm for surveillance purposes that can be applied to cases that are not seen in an ALS clinic.

  - The DNA banking effort uses a minimum data set which requires that the clinician document the regions that have upper motor neuron signs and the regions that have lower motor neuron signs, either clinically or by EMG documentation.

  - The distribution of the signs leads to a level of diagnostic certainty according to the distribution of upper and lower motor neuron abnormalities.

  - The DNA banking form has worked well in clinical settings and could be piloted with data abstractors.

  - A large record that summarizes several years of clinic visits may have cumulative signs of disease. For instance, the first visit may include involvement in the lower extremities, and involvement may move to the upper face and tongue in later visits.

  - Abstractors are skilled at gleaning this information from medical records. It is important to note that the abstractors are not medical students or neurologists, but persons who have been trained to abstract records.

  - This approach may not be easily translated to the MS world, as MS is more difficult to understand and diagnose.

- In general, the ALS VA Registry does not "second-guess" observations from clinicians. Consistent findings are taken to be accurate, and a note from an ALS expert receives more weight than a note from a person who does not work with ALS patients often. Familiarity with the ALS field helps in making these decisions.

- The date of onset of weakness in ALS is difficult to determine.

- Regarding capturing race and ethnicity, it will be important to ask specifically whether a patient is of northern European heritage, as this question is not on the standard race/ethnicity form or medical record.

- The group discussed classifying patients based on their codes, types of services received, medications prescribed, and other claims data, in the absence of clinical information.

  - It is unlikely that a person who is taking riluzole does not have ALS: this drug is a good discriminator.

  - The 335.20 code is a good discriminator as well, as neurologists are the only physicians who use it, and they tend to be reluctant to apply it unless they are certain that the patient has ALS.

  - The extant databases capture and track many patients, and there are efforts to capture patients who are not in those databases.

  - Many of these circles overlap, but together, the likelihood of high ascertainment is good.

- Statistical techniques allow for estimates of missed cases. These methods are particularly powerful when a large number of cases are captured.

- Regarding ALS, more weight should be given to a diagnosis from certain providers versus other providers.

  - It is possible to see who assigned a code, whether it was a provider from a center with expertise in ALS, or a general clinic.

  - When a person receives a code for MS or ALS, all other claims for that person are accessible, regardless of whether the claim related to his or her MS or ALS.

  - The National MS Society created a set of criteria for MS experts for a panel for the Social Security Administration. These criteria were based on the individual, not on an institution. Relying on institutions for reliability is problematic and arbitrary. There is no Board certification to be an MS specialist.

- It was noted that the VA is a closed system. It is possible to identify the clinic or ward that was the source of the prescription, but not the individual who made the diagnosis.

- The VA ALS Gulf War study was criticized for under-ascertaining non-deployed veterans, creating an artificial effect. The study did a pharmacy database sweep for Rilutek use, and they did not identify any patients that were not already in the system via other means. The VA MS Surveillance project identified 422 patients solely on DMT use. They were taking advantage of the VA prescription drug plan, but seeking their primary and MS care in the community, not through the VA system.

- In California, diseases and conditions such as epilepsy, dementia, and Alzheimer's disease, as well as others that might impair a person's ability to operate a motor vehicle, are reportable. There was discussion regarding the process for making a disease reportable.

  - The federal government cannot require states to report conditions. The health department in each state can lobby to make diseases reportable in that state. An endorsement from CSTE is helpful in working with state legislatures.

  - Some state legislation is broad enough to include certain diseases without modifying the legislation.

  - In some states, the decision is made by the legislature, usually based on the recommendation of the state epidemiologist and the state health commissioner.

  - In other states, the authority to designate reportable conditions is delegated to the state health department.

  - The state epidemiologist can work with the state health commissioner or board of governors to make a condition reportable.

  - The Parkinson's Disease Registry Act was passed in California in late 2004, with intensive lobbying. Its implementation has been difficult because a section of the state health department has had to carry it out. The pilot project will start soon to develop a prototype for the registry. Support from other entities has made it possible. They are looking at ways to validate case ascertainment, working with the Kaiser network and with an NIH-funded researcher in rural areas.

  - This state level process requires lobbying, perhaps from the chronic disease section, environmental health section, or injury or infectious disease section. Chronic disease sections are historically interested in diabetes, cancer, heart disease, and asthma, so endorsement from the CSTE would be helpful.

- If they adopt the registry model that focuses on certain geographic areas for additional information, then it might be more feasible to lobby those locations to make the diseases reportable.

- The group discussed the reliability of reporting.

  - Cancer registry reporting and infectious disease reporting is often conducted through the pathology department of a hospital or through laboratory reporting.

  - Chronic disease reporting will rely on physicians in the community or in hospitals to do the reporting. Physician reporting, even when it is mandatory, is not always reliable.

  - Good reporting requires information from a variety of sources, including physicians, hospitals, and laboratories.

  - A reporting law alone will not be effective: it must be attached to active surveillance methods, such as contacting physician offices that are likely to see the condition.

  - Making a condition reportable removes physician concerns regarding confidentiality.

  - Simply making a disease reportable does not mean that it will be reported.

  - Epilepsy is reported for driver licensing purposes, not to state health departments.

- The group discussed using electronic medical records to link to reporting.

  - Some states in the traumatic brain injury (TBI) study modeled a system by which the primary source of reporting was administrative data from hospitals, plus mortality data.

  - California has hospital discharge records available.

  - It might be possible that reportable entities that are included on electronic records such as hospital discharge data could automatically be reported.

  - In California, the physician who sees the patient must make the report, not the hospital.

  - These factors are why successful surveillance reports rely on multiple sources. The data have to be de-duplicated, but it is more beneficial to over-capture cases to ensure that all cases are captured.

- Not all community neurologists have electronic records for patients, even if they have electronic billing records.

- In western Washington State, a study on incident, newly-diagnosed ALS included a reminder letter to physicians that suggested referring patients to the study. There was excellent case ascertainment from this approach. They must remember the "town versus gown" issue, in which community physicians may be reluctant to send their patients to a university hospital.

Data Sources:

- Because Medicaid releases data by state, it might be advantageous to work with smaller states first. However, there may be identification difficulties with a rare condition in a smaller state. Medicaid information is of great interest in the advocacy world, as there is no good system for identifying people in need.

- Medicare data is more consistent, as patients who are eligible for it, remain on it. Medicaid patients vary from year to year. Since ALS progresses, and needs associated with it continue, there may be less "back and forth" of patients.

- Dr. Thurman described his work using state data to address TBI. During the 1990's, up to 14 state health departments were funded to look at all state hospital discharge data and mortality data, extracting those with ICD-9 codes for TBI. They sampled a random proportion of those cases and reviewed them to see how many fit the actual case definition of TBI, considering their sensitivity, predictive value positive, and other parameters. The states then generated good estimates of incidence and prevalence. In a few states, this effort became a true registry, in that patients with TBI were contacted to learn about the longer-term outcomes of their injury and to examine issues such as access to care. TBI has an advantage over MS and ALS in that incident cases have separate ICD-9 codes. The study examined emergency department data, having agreed that the brain injury had to have resulted in hospitalization or a visit to the emergency department. MS and ALS face challenges in that incident cases cannot be distinguished from prevalent cases based on ICD-9 codes, and not all cases will be diagnosed in a hospital, so other venues will need to be considered.

- Physicians' electronic notes can be problematic in that many physicians "cut and paste" their observations. The same language can appear in successive notes, and inaccuracies are a problem.

- The group wondered whether CDC can influence drug companies to disclose patients who are prescribed ALS medications.

  - Would the companies divulge prescribing habits and patterns, or would that information be considered proprietary?
  - The claims data set will include pharmacy information. Schedule D is not yet part of the Medicare data, however, and it cannot be searched at this time.

- Most pharmaceutical companies use IMS Health for their sales and distribution statistics. This information is available for a fee, depending on the complexity and specificity of the information desired. Information on diagnosis is also available. IMS Health does not identify patients, but identifies who makes prescriptions and where they were filled.

- The state of Kentucky has a resource called a "Casper report" that can list persons who are prescribed controlled drugs or narcotics. Systems will vary state by state, and other drugs may not be captured, but it could be a valuable strategy.

- The Ohio State Board of Pharmacy monitors narcotic prescriptions for individuals. Information regarding controlled substances is captured, which could lead to the reporting and capturing of MS and ALS medication data. Not every patient takes riluzole, and not every physician prescribes it, but the information could still be useful in populating a denominator.

- It was noted that individual pharmacists may not be engaged at this level. However, most pharmacies are owned by larger chains with computerized records and networks. Their drug stocks have an electronic trail.

- Pharmacy data includes the provider. Working "backwards" will play into the strategy of finding patients through providers. A provider who prescribes this medication is likely to be an ALS specialist.

- Given that ALS is a fatal disease, and given the caveats and inconsistencies associated with using death certificate data, it is still worth considering cross-referencing with the National Death Index. These numbers will not address incidence, but could be useful for cross-validation.

Strengths and Limitations of Considering MS and ALS Together:

- Were the diseases combined to benefit from each others' experiences?

- Do the diseases have commonalities of process? In some ways, the diseases are very different.

- MS and ALS may not marry well in a registry, given that the diseases and the communities are so different.

- The registry will examine all neurological diseases, but will start with MS and ALS because a great deal of work is being done in these areas. It is hoped that this basic strategy can be applied, with adjustments, to other conditions.

- There was concern that combining disorders will lead to dilution of effort.

- There was also concern that if MS and ALS split up, then the workgroup will lose efficiency. A full research focus to the registry is preferable, as the bulk of money should be concentrated on gathering patients that are representative of the country, and other money should be devoted to gathering more information.

- While MS and ALS are quite different, the methodology for building a registry for each can be similar, and attacking both at once is efficient.

    - The approaches to their registries can be similar: validating case ascertainment, gathering subjects, and other issues.

    - The initial funding will be devoted to creating the entities that will then address the specifics.

    - Both "camps" seem to value a rigorous registry approach, with excellent case ascertainment and good application of case definitions.

    - This registry can be a basis for estimating incidence and prevalence, launching case-controlled studies, contributing biological samples, and more.

    - It might not be possible to create a national registry with this degree of rigor everywhere, but certain states could provide estimates rigorous estimates.

- ATSDR hopes to address a continuum. In order to get deeper information about the diseases, such as causes and treatments, it is important to know how many people actually have the disease. If both conditions target the same data sources, then surveillance can be done on both at once. A broad base will then exist for identifying people with the conditions, and specificity comes later. A population-based estimate of prevalence is needed before any more steps can be taken.

- MS and ALS differ in that the distribution of MS across the country varies from north to south, and sampling may cause problems with the estimate. The distribution also varies by ethnicity.

- Mortality data show a southeast to northwest gradient in ALS, although the variation is not as long-term and striking as the MS gradient.

- Representative samples of the national population for MS and ALS might not be identical, but could overlap. Population growth and migration also affect samples that attempt to be representative.

- The MS and ALS communities are "on the same page," but they may have different agendas.

Pilot Test:

- It might be advantageous to circulate a list of the co-sponsors of the Congressional bill to help decide where to pilot-test the algorithm. A system will have to work in disparate locations, from rural to urban.

- The pilot projects will be funded from the $900,000 allocation. If a pilot study focuses on surveillance, then it might be difficult to move from the surveillance to a registry.

Goals of the Registry:

- The database should be used for incidence and prevalence as well as for a potential research recruitment tool.
  - Dr. Tremlett suggested "SUSAN": Surveillance in the United States of America for Neurological Diseases, or Autoimmune Neurological Diseases.
  - This group, under the umbrella of CDC, would set up the initial database looking at prevalence and incidence.
  - The other aims, such as recruitment, would fall under a subgroup.
  - If prevention and control or collecting environmental data were areas of interest, then more subgroups could be created.
  - This approach keeps the disparate project aims separate.
- Surveillance is the key concern for CDC, but patients have different concerns.
  - When the Congressional appropriation for the registry was announced, it became clear that most patients in the ALS community want to participate in it.
  - Neurologists may have still different goals: they want to know how many people have the disease, and they want to know how to contact those people to make sure they are cared for and to identify them for studies.
  - Different stakeholders imagine the project outcome differently.
  - It was suggested that the project be broad beyond only surveillance.
- The first goal is to enumerate as much of the population as possible, as accurately and efficiently as possible. Longer-term goals include contacting those people for additional information. Further, future meetings might consider MS and ALS separately or might consider other points.

- Next steps may influence the first phase of surveillance. All of the goals should be on the table at the beginning to aid in planning.

- The ALS group has built modules for specific issues. The registry should build on minimal elements and also fit with the big picture of ALS efforts. They could then build a meaningful registry.

- There is polarity between building a registry to answer questions regarding incidence and prevalence and building a registry to serve a broad research agenda. The MS community may feel that it has other mechanisms to pursue a broad research agenda, so the registry does not need a number of other goals. The registry does not have to be the same thing for both diseases.

- It will be challenging to create a rigorous national registry in the United States, given its geography and size, but work in Europe indicates that it is possible.

- The ultimate product should sample the full extent of the known and suspected variations in the diseases.

- This effort could result in a broader understanding of how many patients live away from the major medical centers. These patients are not included in clinical trials and also may have care needs. They need a larger view of the picture of disease in the country, but they are also eager to make progress in researching the diseases.

General Comments:

- It was suggested that proceedings or an executive summary of this meeting be generated. A great deal of valuable discussion was taking place, which should be captured for current efforts and for future directions.

- The VA ALS registry is outstanding and motivated the ALS community to work for the Congressional authorization. It is not a traditional, minimal registry.

VI. Final Comments and Recommendations

The group discussed reaching a consensus about the project's primary goals. It was agreed that the goals will be different for MS and for ALS, but that the initial effort should focus on incidence and prevalence, beginning with minimal data sets. Pilot and feasibility studies in a limited number of geographic areas will lead to an expansion of the algorithm, leading to the ultimate goal of national surveillance.

VI.1 Project Goals

- It may be ambitious to expect consensus at an initial meeting, but it is useful to be able to report certain points on which there was agreement.

- One panel member expressed her belief that the registry approach is preferable to the surveillance approach; that is, they would rather not collect crude numbers in a surveillance sense, but collect data for a registry with goals to which they can all subscribe. A broader net may initially be needed to get a national picture, but a registry is the ultimate goal.

- If their goals are too lofty, then the process will not be able to proceed. An ultimate objective for all diseases is a research database, of course, but it may not be initially feasible.

- Practically, $900,000 is not enough to create a registry. The VA ALS Registry costs $2.1 million over two years for 1500 patients, which does not include the principal investigators' salaries. If the $900,000 is spent on a strong surveillance project for ALS, then it can be a tool to leverage for more funds to build an ALS registry. Most registries start with general surveillance and concentrations of resources in certain geographic areas.

- SEER selected areas to be representative of the United States and then re-inflated its numbers for the whole of the United States. This approach has limitations, as demographics shift, and MS has a north-south gradient, but a demographer can help them select areas that will provide a national picture.

- If surveillance is the appropriate path, then the ALS community must buy into it and it must be done with the understanding that it will move quickly into a registry format.

- Regardless of whether the outcome is surveillance or a registry, the initial steps are the same: case ascertainment and data sources. Additional discussions can address funding and moving the initial surveillance project to a full registry.

- This effort will operate in phases and eventually drive a research agenda for MS and ALS. The data collection will not be so minimal as to offer no patient information at all. The surveillance aspect will have value on its own and can evolve.

- It might be helpful to think of this project as a large effort that includes early surveillance activities and moves into data capture for a registry. There was concern that considering surveillance alone will be short-sighted. Some of the funds available now will set the agenda for the more detailed data capture.

- If the pilot projects are successful, then the next step will be to collect data. The group should think about the data to collect, how to standardize the elements, and whether the data come from patients, physicians, or other sources. They begin this planning process now so that they can move to the next phase smoothly and quickly.

- It will be important to prove that phase one can be done successfully before moving to phase two. Planning for later phases can occur while phase one is ongoing, however, to ensure that consistent, quality data are collected.

- The ALS community has done some of this work already, and it may not be necessary to reinvent all elements of the registry. It is important to focus on MS and ALS separately, as they have different needs.

- It is possible that the first phase of the work will work for one disease and not the other, so it may be necessary to revisit them after the pilots are completed.

- Different databases exist for each disease. They must consider how to use the data that they have and where to house it. The surveillance must be integrated with the registry from the beginning, including building blocks for sharing data, lest they have to recreate the elements later. The infrastructure will ensure that the phases will connect.

- Researchers will be interested in different data elements. Those who engage in genetic research will be interested in cases with family histories. It would not be wise to complicate the initial effort with too many details, too early in the process, or else it will become unwieldy.

- Should the group devise national surveillance case definitions for MS and for ALS so that they are all comfortable with the cases that are enrolled? It might be wise to assess the available data sets and try different algorithms before deciding on definite definitions. Eventually, they will have to set definitions.

- Another next step will involve working with groups that are dedicated to MS and ALS. These groups have expressed interest in helping with the effort and have databases and experiences that can be shared.

VI.2 Next Steps

- Each group should meet separately and have an agenda so that they can generate useful information based on their knowledge of the disease and expertise in working with it. The groups will have ideas regarding a national registry for surveillance.

- There was discussion regarding how to better publicize their efforts, perhaps by sharing information with physicians and affected persons via national association websites or other means.

- The National MS Society will disseminate information about this meeting.

- It will be productive for the disease-specific organizations to exchange ideas and information that they glean from their broader constituencies. They have learned a great deal from their ALS colleagues about new approaches. Continuing these dialogues will be useful.

- Disease-specific workgroups will meet with CDC to produce recommendations. While the two diseases can work together, each has unique details that are specific to their populations. Common strategies could work. Independent work should be done, but the larger group should still be maintained. Perhaps they could meet in conjunction with each other and split into disease-specific groups before rejoining to share experiences, data sources, and other elements that could be lost if they do not meet together.

- It seemed that most of the ALS community that works on registries and databases was represented at the meeting. The MS field may be larger, and other persons should be brought into this process. There are two national surveillance systems for MS, one in Denmark, which has been ongoing since 1948, and another that was established ten years ago in Norway. Those systems will have dealt with issues such as records and algorithms, and it would be worthwhile to contact them to learn from their relevant experiences.

- A recent meeting in Dublin convened international partners who are working on ALS databases. Countries such as Italy and Ireland have unified health systems, so their ability to detect, capture, and follow cases is uniquely simple. The challenges are significant in the United States.

- There are differences in healthcare systems, but the clinical data will be similar, so their case definitions and algorithms could be instructive.

- It will be interesting to learn how the European groups share data across locations.

- The EDMUS system is not a centralized database, but a software package used to collect standardized data on MS throughout Europe. This data can be aggregated on as-needed basis.

- The MS database in Australia is similar. Clinics that participate use software that creates and shares the minimum data set. In Australia, a university is responsible for collecting the information. The effort is voluntary by clinician.

- A registry for genomic studies has begun in the United Kingdom. This system has three hubs, which are the points for data collection. Each hub is responsible for a certain number of sites and reports to a central hub. The system is similar to the DNA collection for the ALS Research Group. When large centers gather data on individual patients, ascertainment bias can be a problem.

- The United Kingdom also has the General Practice Research Database, which is completed by primary care physicians. It covers four million people, which is a representative sample of the population. The National MS Society has funded research with this database to assess risk factors for MS, and there are problems with verifying the diagnosis, capturing cases that have an appropriate length of exposure.

- ALS has a system in place, which should be connected and centralized. There are gaps in this system, and their efforts should lie in filling those gaps. Perhaps they should build a national registry by working on the "weak spots" rather than concentrating on areas in which they are comfortable. The MS and ALS teams should be separate, as their issues are different, but they can learn from each other as they build their infrastructure. It is important to use their limited resources wisely.

- The ALS surveillance effort has been pursuing data elements and is on a different timeline from MS. Their approaches and gaps are different. There is value in examining areas where ascertainment is considered to be excellent.

- A working document will be circulated among the ALS community for reaction. The reactions will be reported to ATSDR and to the ALS Research Group meeting in San Diego. A conference call with the ALS RG leadership should be held before the meeting.

- Regarding MS, a report from this meeting will be shared with the Task Force, and a Task Force meeting will result in recommendations and details. There are other epidemiological issues to discuss, and the Task Force may not agree that this effort is their highest priority: other research questions in MS may take precedence. Next, the Senior Research Advisory Committee of the National MS Society will consider the report.

VII. Closing Remarks and Adjournment

With no further business posed, Dr. Kaye and Dr. Dhelia Williamson thanked the group for their input, discussion, and ideas. In conclusion, the group expressed interest in meeting again after the MS and ALS communities meet and work independently.

End of Report

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