ALS ASSOCIATION

Global Research. Nationwide Advocacy. Local Care.

December 13, 2022

United States Department of Health and Human Services
National Institutes of Health
National Institute of Neurological Disorders and Stroke

Attention: National Advisory Neurological Disorders and Stroke Council and Council Working Group

RE: The ALS Association's Public Comments on the National Institute of Neurological Disorders and Stroke (NINDS) Draft ALS Strategic Plan

We are deeply grateful to the National Institute of Neurological Disorders and Stroke (NINDS) staff and volunteers who devoted so much time developing this thoughtful plan. Overall, we are excited by the focus on ALS and offer some broader comments to frame the strategy of the plan. Detailed comments follow.

First, although this plan was inclusive in its development, it could accomplish more by keeping people living with ALS central in its focus. For example, statements like the ones of page 18, *"The most significant advances in the field of ALS over the last 30 years have come from the identification of pathogenic mutations in a large number of genes that cause motor neuron disease and FTD,"* reflect a common and regrettable bias of research funders to focus on academic questions (in this case, work that has not yet led to any approved treatments), and not the state of people living with the disease under study.

To keep more focus on people living with ALS, National Institutes of Health (NIH) should consider the timescales of different research efforts and contrast them with the timescales of people living with ALS. Like any large investment portfolio, NIH research should be explicitly managing the time to potential impact of various research efforts. There are many questions about the fundamental biology of ALS that need to be studied and will take decades to answer. Many of those questions are addressed in this plan. As that work continues, we urge NIH to increase its focus on studies that can offer meaningful improvements for people living with ALS much more quickly, such as testing new treatments and refining the application of existing ones to improve quality of care.

NIH also needs to carefully consider the workforce and infrastructure that underlie ALS science. Freely available research resources will not be used unless we have multidisciplinary research teams with the funding to study them. Clinical research will advance at a snail's pace if we concentrate trial and treatment resources in a handful of centers.

To further focus on people living with ALS, we implore NIH to use science to improve the effectiveness and delivery of ALS care in the real world. The October meeting highlighted some of the challenges people with ALS face in accessing treatment and NIH has helped address systemic bias in other disease spaces. People with ALS suffer from two dysfunctional systems; the neuromuscular system and the American health system. Even now, only about half of people with ALS are getting life-extending, evidence-based standards for multidisciplinary care. If we only focus on one system and ignore the other, the impacts of this plan will have an artificially low ceiling. We cannot imagine anyone involved in this planning process wanting to see the benefits of their work existing only in research journals.

This focus on quality of care and how to deliver it needs greater emphasis in this plan. We would like to see funding to optimize the delivery of ALS treatment in the real world, including studies on optimizing combinations of treatments for different forms of ALS. We also have evidence showing multidisciplinary care and respiratory therapy can increase length and quality of life. We need to understand how to expand the utilization of these services and continue to refine these models as other technology advances. ALS causes painful and life-threatening complications like falls, pneumonia, social isolation, and poverty, and we would like NIH to invest in science and the workforce to reduce these risks. NIH can offer tremendous benefit to the lives of people living with ALS today by simply focusing more research funding on these topics.

Finally, we appreciate the statement about ALS research on page 29, *"That progress occurred on three dimensions – bringing new investigators and technologies into the field; new discoveries of the genetic and biological pathways that cause motor neurons to die; and engagement on the part of the biotech and pharmaceutical industries. Much of that was catalyzed by a greater degree of collaboration and effective partnerships."* We want to add that these improvements were driven by a tremendous increase in spending from NIH, the United States Department of Defense (DOD), and philanthropic groups like The ALS Association. Research investment works, and the power of increased research spending on ALS will be critical to the success of this plan.

To turn this plan from a concept into an actual research agenda, NIH will need to make explicit decisions about the level of investments into projects, people, and infrastructure, and continually curate its portfolio over time. The existing momentum in the ALS space must be capitalized on, nurtured, and channeled towards quantifiable improvements in health. NIH's funding, along with the leadership of this plan, can play a huge role in making ALS a livable disease. The Association looks forward to working with NIH to make that happen.

The ALS Association and Our Strategic Priorities:

The ALS Association leads the way in funding global research, providing assistance to over 20,000 Americans with ALS and their families, coordinating multidisciplinary care through over 90 certified clinical care centers, partnering with stakeholders on the research and development of novel therapies, fostering government partnerships and elevating the voice of the ALS community in public policy. Our goal is to do whatever it takes to cure ALS, and until we can, to transform the quality of life of people with ALS to make it livable. The urgency of the ALS patient community necessitates an extremely aggressive timeline – speed matters!

The ALS Association is intently focused on ensuring people with ALS live longer and their loved ones are prevented from getting ALS. To achieve these goals, the Association's research plan is based upon investments within three key pillars: 1) Finding new treatments and cures, 2) Optimizing current care and 3) Preventing or delaying the harms of ALS.

Under the first pillar, our focus is on increasing research funding, increasing the number of clinical trials for new ALS therapies (including by funding preclinical drug development and programs aimed at increasing clinical trial capacity) and improving regulatory science for ALS (biomarkers and clinical study endpoints, in particular). We are placing these objectives above the fundamental science needed to better understand ALS, because our priority is to improve the health of people with ALS as quickly as possible. There are numerous risk factors, pathways and genes that have been identified as playing a role in ALS, and we can find more effective treatments faster if we place greater emphasis on testing their treatment potential quickly. As new treatments come to clinics, the ALS community needs the capacity to rapidly test their effectiveness in the real world, and in combination with other treatments taken by people with ALS.

Under the second pillar, our focus is on optimizing the use of assistive technologies (including developing and validating innovative technologies), reducing complications from ALS (including identifying and disseminating best practices for care) and increasing access to high quality care/ services.

Sadly, a diagnosis of ALS often means more trips to the emergency room for falls, more hospital stays for infections, more pain, and tremendous isolation and poverty. Family members face behavioral health risks, physical injuries, and choosing between paying for care for their loved ones and their long-term financial security (link for results from the Caregiver needs survey, https://www.als.org/ research/als-focus/survey-results/survey-3-results). These issues are well understood but poorly documented. NIH can use research techniques to better understand these issues, develop interventions, and improve the health of people with ALS, and those that love them, while the search for disease modifying treatments continues.

Under the third pillar, our focus includes treating ALS as early as possible, including leveraging the use of genetic counseling and testing. Additionally, it envisions identifying risk factors for development of ALS and then using that knowledge to advance changes in policies, programs, and practice that will reduce the incidence of the disease. Finally, we can develop new preventive approaches by validating more ALS-associated genes and then finding ways to prevent the disease from emerging.

Our ultimate objective is to develop interventions that can prevent cases of ALS in people, whether those interventions be pharmaceutical, behavioral or via policy. This has never been done before and requires the ALS community to overcome both scientific and organizational obstacles. The NIH, especially NIEHS and NINDS, is well-suited to fund the translation pipeline – from population-based association of ALS risk factors to clinical intervention on those factors – that can ultimately reduce incidence. We have seen ALS devastate multiple members of the same family, and it needs to stop.

Specific Comments in Reference to the NINDS Strategic Plan:

Accelerating Research on the Biology Behind ALS

Studies of the basic biology of ALS are important and NIH has a strong record of investing in this type of basic and pre-clinical science. However, many of these efforts will take decades to yield clinical benefit, and we have not seen evidence that such efforts are underinvested relative to other aspects of this plan. We encourage NIH to increase investment in studies that can offer meaningful improvements for people living with ALS today, such as testing new treatments and refining existing ones, while maintaining its investments in biology and other science with a longer time to impact.

Page 15: *"What are the modifiable genetic and environmental risk factors, including epigenetic factors and those influencing genomic instability? Studies grounded in human-based epidemiology studies with the collection of samples from people living with ALS as well as their family members are needed to identify genetic and environmental risk factors."*

Despite the plethora of potential risk factors, some of which have been identified years ago, we have no practical guidance or interventions to reduce the risk of ALS.

There are many identified potential risk factors. For example,

- Nowicka N, Juranek J, Juranek JK, Wojtkiewicz J. Risk Factors and Emerging Therapies in Amyotrophic Lateral Sclerosis. Int J Mol Sci. 2019 May 28;20(11):2616. doi: 10.3390/ijms20112616.
- Longinetti E, Fang F. Epidemiology of amyotrophic lateral sclerosis: an update of recent literature. Curr Opin Neurol. 2019 Oct;32(5):771-776. doi: 10.1097/WCO.0000000000000730.
- Belbasis L, Bellou V, Evangelou E. Environmental Risk Factors and Amyotrophic Lateral Sclerosis: An Umbrella Review and Critical Assessment of Current Evidence from Systematic Reviews and Meta-Analyses of Observational Studies. Neuroepidemiology. 2016;46(2):96-105. doi: 10.1159/000443146.

We need a prevention strategy focused on risk factor validation and translation, not focused identification. A strategic plan should advance ALS science across disciplines, from epidemiology and genetics, to target validation, development of experimental models, human studies, and eventually real-world intervention. That movement seems missing here.

Page 15: *"Funding strategies should emphasize the importance of building teams with individuals from various disciplines and broad perspectives."*

Excellent! This is exactly what the field needs!

Page 16: *"A fundamental principle is that access to all data, samples, and other resources should be equally available to researchers in academia and industry as it will take both groups working together to successfully translate fundamental research into therapeutics."*

We strongly agree with this principle, but that does not mean that making data available will result in its use, or that data collection strategies should be centrally directed. The questionable assumption that increasing and improving research resource supply will improve resource utilization comes up throughout the plan. We believe, instead, that resource utilization should be actively supported.

Centers of Excellence, Page 16-17
"NIA-funded Alzheimer's Disease Research Centers (ADRCs), the NINDS-funded Morris K. Udall Centers of Excellence in Parkinson's Disease Research, and the Paul D. Wellstone Muscular Dystrophy Specialized Research Centers (MDSRCs)."

We do not find the rationale for the center model compelling, and we have strong concerns about this approach. The sample centers cited are not a good model for the ALS community in two ways.

First, its concerning to us that only one of these diseases, Multiple Sclerosis, offers treatment options that can significantly improve course of illness and quality of life, and yet all three are highlighted for their success on process measures like collaboration and repositories. We need impacts as quickly as possible, not processes. The center approach would be more reassuring if a direct line could be drawn from center funding to clinical benefit.

Second, all three of the cited center programs serve more prevalent diseases, making it easier to run clinical trials in specific geographic areas. Geographic access to high quality ALS care and clinical trials was a major theme brought up during the October meeting. *"Enhanc[ing] the clinical trial infrastructure of each Center"* does nothing to address these issues and takes NIH funding away from new clinics and trial sites. Center funding for clinical trials would make high quality care and clinical trials less accessible to people with ALS in most parts of the country.

The ALS space is already relatively centralized. The most likely outcome of the center model is that the extant well-funded ALS research institutions will get the center grants. NIH can deliberately increase the scientific and geographic diversity of ALS research worldwide through workforce and capacity grants and guide the field through focused RFAs.

We also recognize that the R funding mechanism is slow, and a key advantage of center funding is that it can support smaller projects and trainees much faster. Slow funding processes are not a good reason to focus funding to specific institutions and slow the growth of geographic and scientific diversity of the ALS field. We instead encourage NIH to explore other fast funding approaches, perhaps through public private partnerships.

However, Center grants might be useful if they can be targeted to specifically increase research capacity in the ALS space for research where geographic access for patients is less of a concern. Creating centers to encourage NEW collaborations within a center, for example between Schools of Medicine and Engineering for assistive technology, or Medicine and Social Work to address social isolation, could bring new thinking into the ALS space.

Page 18: *"The most significant advances in the field of ALS over the last 30 years have come from the identification of pathogenic mutations in a large number of genes that cause motor neuron disease and FTD."*

We strongly disagree with this statement and point out the most significant advances in the field of ALS are the approval of disease modifying treatments like riluzole, edaravone and Relyvrio, and life extending evidence-based standards of multidisciplinary care. This lack of focus on patient impacts is troubling. This plan needs to focus on people with ALS.

We appreciate NIH being willing to support the ongoing costs of large scale repositories and the commitment to make them open. Especially noting that more than one repository is necessary to maintain the diversity in collection procedures that are necessary in a poorly understood disease. However, it is unrealistic to think that these complex resources will be fully used by the current ALS scientific workforce. These data and resources will likely require multidisciplinary research teams, and unless funds are made available to use them, the ALS community will not take full advantage of any freely available resources.

For example, the Agency for Toxic Substances and Disease Registry (ATSDR) ALS National Registry maintains a specimen repository and reported in 2022, *"Since samples became available in 2017, more than 25 researchers inquired about sample procurement and availability; of those, 15 researchers completed an application."* Is that low or high? What is the level of resource utilization expected from this investment? Overinvesting in resources and underinvesting in people will also result in low utilization of shared resources.

Rechtman L, Brenner S, Wright M, Ritsick M, Rahman F, Han M, Raymond J, Larson T, Horton DK, Mehta P. Impact of the National Amyotrophic Lateral Sclerosis Registry: Analysis of Registry-funded Research. Ann Clin Transl Neurol. 2022 Nov;9(11):1692-1701. doi: 10.1002/acn3.51660.

Page 19, Proposal 3. Increase the biotherapeutic pipeline by enabling clinical trials and fostering academic/industry collaboration

We strongly encourage significant increases in investment in this space relative to the other priorities in this plan, especially given that clinical research is generally far more expensive than basic research. We also strongly support funding for clinical trials, but that funding will not be effective if trials are highly concentrated in a handful of centers with limited populations. Given how rare ALS is, we need to increase diversity in clinical trials, and access to state of the art care, throughout the country.

Page 21: Principles for a large, comprehensive ALS natural history study

We support the idea of additional natural history studies, but note these studies can be very expensive and take years to generate findings. Thus, such studies should only be undertaken if they have the intent and ability to address a specific scientific gap. For example, FDA has committed to evaluate its use of data from ALS natural history studies and the results of that evaluation may reveal gaps to be targeted by new natural history studies. NIH should increase its focus on studies that offer meaningful improvements for people living with ALS today, such as testing new treatments and refining existing ones. NIH has the capacity to fund both.

Page 23: *"Determining how to detect the earliest manifestations of ALS and whether they are confined to the motor system is important for identifying individuals early in disease when treatments may be most effective. Currently, people are diagnosed approximately 12 months after first symptom onset, meaning that we are intervening with treatments late in the disease process."*

We appreciate the focus on early manifestation, diagnosis, and treatment. It is worth noting that this statement makes it clear that we have the technology to diagnose people earlier now but are not. Therefore, this statement also makes it clear that people with ALS suffer from two dysfunctional systems; the neuromuscular system and the American health system. Developing better tools for detection will have limited benefit since our health system cannot effectively use the tools it has now. The October meeting highlighted some of the challenges people with ALS face in accessing treatment. NIH could serve people with ALS better if it also funded research to help our health system identify and treat people with ALS sooner.

Page 25: Quality of life *"for people living with ALS is often underestimated by others and should be assessed by people living with ALS themselves."*

Thank you for recognizing this fact. It is a significant problem in both research and access to care.

Page 26: *"Improve our understanding of how physical, psychological, cognitive, and behavioral symptoms impact QOL in people living with ALS and their caregivers to facilitate the development of meaningful pharmacological and non-pharmacological management approaches."*

This is an excellent set of research recommendations, but it is unclear if there are sufficient skilled scientists in this space to do the work. NIH may need to invest in career development or find ways to engage more social scientists into this space.

Also, we request NIH take efforts to ensure any measures and assessments developed be accessible to all scientists and clinicians without charge.

Page 27, 3. Identify evidence-based best practices and resources for the care of people living with ALS by caregivers, people living with ALS themselves, clinicians, allied professionals, and researchers.

There appears to be some confusion between information dissemination and service provision in this section. Some best practices can only be delivered by specialists or teams of specialists which are not physically accessible to everyone with ALS. This is not just a training issue, but a workforce, capacity and reimbursement issue. Some caregiver best practices, like patient transfer, require some in-person instruction and cannot be reliably taught via video or brochure. It would be easy to create or translate materials that offer no benefit. NIH needs to clearly define the expected impact for each intervention and have a realistic theory of how it will be achieved.

Page 29, *"Over the past decade, there has been dramatic progress in accelerating ALS research into clinical trials, in stark contrast to the prior 140 years since the disease was discovered. That progress occurred on three dimensions – bringing new investigators and technologies into the field; new discoveries of the genetic and biological pathways that cause motor neurons to die; and engagement on the part of the biotech and pharmaceutical industries. Much of that was catalyzed by a greater degree of collaboration and effective partnerships among all the constituencies that are necessary to bring effective treatments to patients, including academia, industry, venture capital, ALS non-profits, clinicians, patients, and government."*

We appreciate and agree with that comment and would add that that the tremendous increase in spending from NIH and philanthropy played a critical role. Research investment works, and the power of total spending on ALS should not be underestimated

Page 29, Establish multi-modal data platform to include multi-dimensional clinical data

This is a worthwhile thought but will take a long time. Some of this work is already funded though the FDA and other consortia, as pointed out in the plan, so any further efforts should seek to include best practices from and, ideally backwards compatibility with, extant work. The slowness of this work does suggest it should get a lower priority.

Page 31, 3. Establish a framework for ALS research collaboration across academic, industry, government and organizations for people affected by ALS that will ensure all ongoing and future collaborative efforts emphasize diversity, equity, and inclusion with a goal to accelerate research and authorization for effective treatments.

We appreciate these goals and emphasis on outcome and speed. Thank you.

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