

Collaboration Roadmap to Advance Drug Development in ALS

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Author's Note (October 2022): This roadmap was developed following the private workshop held in January 2021 and presents targeted recommendations for all stakeholders in ALS drug development put forward at that time. The roadmap was delivered to FDA in September 2021 and is not reflective of recent developments in this disease area in the past year. In keeping with Duke-Margolis's commitment to public transparency, this roadmap is being released now as a public record of the output from the private workshop. The Center is pleased to see progress being made in this space and continues to support the recommendations in this roadmap as providing a path to advance of drug development to address ALS.

Background

Amyotrophic lateral sclerosis (ALS) is a rare but fatal motor neuron disease; most cases of ALS are sporadic with no known cause or cure. Approximately 5,000 people are diagnosed with ALS each year.¹ The disease is generally characterized by progressive muscle weakness with death occurring, on average, three to five years after disease onset due to ventilatory failure.²

The onset and progression of ALS is still not well understood and may vary among patients. The diagnosis of the disease is challenging, and clinicians must rely on the exclusion of other diagnostic possibilities and the presentation of characteristic symptoms and signs. About 25 percent of patients have bulbar onset ALS, where they first experience the symptoms of difficulty swallowing or speaking, while the remaining 75 percent of patients first present with weakness in their arms and legs. In all forms of ALS, patients experience degeneration of the upper and lower motor neurons. ALS is a multisystem neurodegenerative disorder, meaning the disease progression can include behavioral and cognitive changes in addition to muscle weakness.³

ALS is heterogenous in nature – it can be classified as either genetic or sporadic. Most patients (90 percent or more) are diagnosed with sporadic ALS, meaning the disease seems to occur at random without clear risk factors or family history. Some researchers even theorize that what is currently diagnosed as ALS could be a combination of separate, similar diseases.⁴ Research has linked genetic mutations to ALS in approximately 10 percent of cases. Therapeutics are being developed to target and treat ALS in patients with certain types of genetic ALS.^{5,6}

Despite more than two decades of multimillion-dollar clinical trials, there are currently only two approved drugs for ALS on the market: riluzole and edaravone. Both drugs have been approved as safe and effective by the US Food and Drug Administration (FDA) but provide modest benefit and do not halt or reverse symptoms. Current standard of care for most patients is comprised of symptom management and respiratory support via a multidisciplinary care team.^{7,8} There is a large unmet medical need for more therapies that can slow or even reverse progression of ALS.

Researchers in the preclinical and clinical space are working to identify and study potential drug candidates that can address this unmet need. However, there are numerous scientific and operational challenges to developing pharmaceutical treatments for patients with ALS including:

- gaps in disease characterization and heterogeneity within the ALS patient population
- need for biomarker identification and validation (this will result from improved scientific understanding of the disease)
- developing and validating additional clinically meaningful endpoints
- limited number of researchers working in the field
- barriers to patient trial access and enrollment
- designing trials that decrease time to results as well as patient and caregiver burden
- lack of standardization in how data is collected and shared from clinical trials and other studies
- hurdles to accessing data and databases across the research community and industry

The Project and Workshop

To facilitate a discussion on ways to accelerate drug development for ALS, the Robert J. Margolis, MD, Center for Health Policy at Duke University (Duke-Margolis), in conjunction with the FDA, hosted a private workshop on January 27 and 28, 2021. The workshop included a wide array of stakeholders, including: researchers from academic, nonprofit, and government institutions; clinicians; industry representatives; patients; and patient advocacy stakeholders. This workshop explored topics and considerations related to:

- priorities for basic, preclinical, and clinical research
- challenges and scientific considerations associated with clinical trial design
- applicability and feasibility of innovative trial designs
- understanding and integrating patient experience data in clinical development programs
- research infrastructure and data sharing among researchers

This document builds on the discussion from the private workshop, as well as listening sessions that were held individually with key stakeholders.

The objective of this document is to provide multi-stakeholder recommendations for increased collaboration within the ALS research community to improve and accelerate therapeutic development.

ALS Research Landscape

There is a growing pipeline of investigative treatments being researched and developed. A brief overview of some of the leading candidates in the pipeline can help to understand the current landscape for ALS research and development and to understand where there is a need for further research.

There are two FDA approved treatments for ALS, riluzole and edaravone. Riluzole was approved in 1995, while edaravone was approved more recently in 2017. While these treatments now comprise the standard of care for patients with ALS, neither of these treatments are known to halt or reverse disease progression.⁴

Overview of the Current Research and Development for ALS

Researchers are exploring different therapeutic approaches for ALS, including stem cell approaches

Rilutek (riluzole):

administered orally as either a tablet, liquid, or oral film; marketed by Sanofi; unknown mechanism of action

Radicava (edaravone):

administered intravenously; marketed by Mitsubishi Tanabe Pharma America; relieves effects of oxidative stress which may be related to death of motor neurons

(such as regeneration or neuroprotection of nerve cells via direct injection); delivering protective factors to motor neurons; improving the glial (support) cells surrounding the motor neurons; improving nerve and muscle coordination; and targeting gene mutations. There are several potential candidates currently in clinical development, including both cell and gene-directed therapies.

One late-stage therapy in the pipeline is Amylyx Pharmaceuticals' AMX0035, a combination therapy that aims to minimize cellular mechanisms linked to cell death in ALS. Results were released from a phase 2/3 trial, called CENTAUR, in late September 2020.⁹ The trial showed that there was a modest but statistically significant decrease in the disease progression of patients in the treatment group compared to the placebo as measured by the ALS Functional Rating Scale-Revised (ALSFRS-R) – a test used to measure patients' physical function over time. FDA has expressed interest in receiving data from

a Phase 3 trial before considering the drug for approval. Amylyx is slated to begin a global Phase 3 trial with participants in both Europe and the United States in mid-2021. Amylyx is also seeking approval for the drug in Canada and the European Union.^{10,11} An example of a late-stage gene-directed therapy in development is Biogen's tofersen (BIIB067). Research on treatments targeting mutations in one specific gene – SOD1, which is responsible for 12-20 percent of genetic ALS cases – have shown early promise. Tofersen specifically targets this genetic form of ALS (SOD1-ALS). Currently, the drug candidate is in phase 3 clinical trials, with an expanded access program that began in the summer of 2021 for participants with a confirmed SOD1 mutation.^{12,13}

Innovations in ALS Clinical Trials and Research

In addition to innovative drugs in the pipeline, there are also innovative trial designs being utilized to assess therapeutic safety and efficacy. For instance, the HEALEY platform trial, which opened in 2020, is the first platform trial in ALS research. A platform trial shares a master protocol across multiple treatment arms running simultaneously.¹⁴ One benefit of platform trials is the ability to test multiple drugs and delivery routes at the same time, decreasing the overall cost and burden of research and expediting definitive answers on therapeutic safety and effectiveness.¹⁵ Platform trials with adaptive features show promise in both addressing operational challenges in conducting clinical trials for patients with ALS and accelerating the advancement of promising drug candidates.

ⁱ Author's note (October 2022): since the writing of this paper in September 2020, Amylyx has since received approval for their drug AMX005 in the US and Canada.

Innovative Trial Design: The HEALEY Platform Trial

The HEALEY Center for ALS is conducting the first platform trial for ALS which is being run out of Massachusetts General Hospital in partnership with the Northeast ALS Consortium (NEALS), Berry Consultants, and five industry partners. The platform trial design allows the researchers to increase efficiency by decreasing the time needed to conduct a trial by 50 percent and reducing the total cost of research by 30 percent. Currently there are four drugs being studied with the goal of adding two-three new regimens each year.

The HEALEY trial is perpetually enrolling participants into the double-blind study. Each treatment arm shares a single placebo group, minimizing the number of patients that will receive a placebo. Additionally, patients will be offered the drug in the treatment arm through open-label extension – a program that gives participants, including those in the placebo arm of the trial, access to the investigational product after the trial has ended. The primary endpoint for the HEALEY trial is change in disease severity utilizing the ALS Functional Rating Scale-Revised (ALSFRRS-R).

Source:

<https://www.massgeneral.org/neurology/als/research/platform-trial>

Another innovation in ALS trial design is the use of digital tools to assist in data collection and the assessment of exploratory endpoints. The use of these technologies reduces the burden on patients to come into a clinic for monitoring. Such technologies were widely utilized during the COVID-19 pandemic when patients were unable to attend their appointments in-person. This demonstrated the feasibility of using digital tools for remote data collection during clinical trials. Each of these examples of innovative design approaches exemplify how the clinical trial process is being updated to ensure the patient experience and perspective is incorporated.

Current Data Sharing Efforts

There are various existing databases for ALS research including endeavors by the NIH, the CDC's ALS Registry, and privately funded databases such as AnswerALS, NeuroBANK™, and the ALS/MND Natural History Consortium. These databases contain pertinent information from preclinical and clinical research which can be used to support innovation and efficiency in trial design and to inform targeted patient

recruitment. Expanded contribution to such centralized shared data resources can support better understanding and documentation of disease progression and response to treatment with a reduced investment of resources.¹⁶

In addition to these databases, several options have emerged to help researchers link data, including samples from patients with ALS.¹⁷ NIH NINDS has a database of common data elements for ALS research developed in 2011.¹⁸ Resources such as the ALS/MND Natural History Consortium in conjunction with unique patient identifiers such as NeuroGUID™ (Neurological Global Unique Patient Identifier) and NeuroSTAmP (System-specific Transactional Anonymous PIN) facilitate this exchange of information.^{19–21} A patient may have multiple NeuroSTAmPs which link back to one NeuroGUID™. The benefits of these technological advances allow researchers to gather data on specific patients, even if they did not collect the data themselves. NeuroGUID™ specifically allows patients' research and clinical data to be linked across both clinical visits and research projects longitudinally – making databases and efforts such as the ALS/MND Natural History Consortium possible.

During the Duke-Margolis/FDA private workshop, stakeholders pointed to the need for further linkages among the various tools outlined above. Even within NIH multiple platforms have been created to collect and analyze data, but a leading standard has not yet emerged. Other stakeholders noted that while there are a number of databases available to assist in ALS research, there needs to be a concerted effort to ensure that the databases are linked.

Key Challenges

Key challenges in therapeutic development for ALS can be categorized broadly into scientific and operational challenges. Scientific challenges can be defined as those related to the disease pathophysiology and our understanding of disease natural history. Operational challenges are those related to clinical trial design and conduct and related resources. The challenges described here are drawn from discussion in the private workshop held in January 2021.

Scientific Challenges

Gaps in disease characterization, the heterogeneity of the ALS patient population, and a lack of fit-for-purpose biomarkers all create significant scientific challenges across all clinical phases of drug development.

Although progress has been made, studies indicate that the drug development enterprise is underperforming with respect to the generation of effective ALS therapeutics.^{2,22} Poor disease characterization of ALS is the root cause of many of these challenges – both scientific and operational. The lack of understanding of disease etiology paired with the high variability in disease presentation makes it challenging for researchers to identify potential drug candidates and design clinical trials.

Disease heterogeneity and gaps in knowledge about the genetic mutations associated with different ALS phenotypes impact the predictive validity of disease models, impeding overall ability to test investigational therapeutics. Disease heterogeneity, including differences in onset and progression, can complicate the process of defining inclusion and exclusion criteria for clinical trials and make it difficult for clinicians to determine whether a drug will work across the entire ALS patient population or merely a subset of that population. Such differences among patients may also result in varied responses to treatments. This can make it challenging to determine common characteristics among patients who improved during a trial despite the treatment proving unsuccessful among a broader cohort.

A lack of identified and validated biomarkers remains a challenge for pre-symptomatic and early-stage disease diagnosis. Researchers are continuing their work to develop and validate more sensitive diagnostic and prognostic biomarkers in an attempt to support better characterization of the disease and its causes.² The lack of identified and validated biomarkers also impacts the predictive validity of preclinical disease models, which have historically not aligned well with clinical outcomes, and impacts patient screening and enrollment in clinical trials. Barriers to the identification of biomarkers to support therapeutic development include disease heterogeneity (sporadic vs. genetic) and confounding variables (e.g., gender, age, and ethnicity) which make it difficult to link markers to clinically relevant measures of disease presence or severity. Improved diagnostic biomarkers would be helpful to identify ALS patients earlier in disease progression. Improved predictive biomarkers would be helpful in stratifying patients for clinical trials based on disease progression.²²

Researchers also face challenges in the development and validation of innovative, clinically meaningful endpoints that reflect the patient experiences. There has been an increased focus on the need for measures of therapeutic benefit beyond mortality endpoints in clinical trials for ALS—for instance, measuring improvements in the functional status of patients as characterized by patient-reported outcomes. It is important to also incorporate the patient perspective on what classifies as meaningful outcome measures to them. Patients would like endpoints to address the challenges they face in day-to-day life such as breathing, swallowing, and feeding themselves. Patients and clinicians alike have also expressed dissatisfaction with the standard functional rating scale for outcome measurement in ALS, the ALSFR-S, and how it measures disease progression for different patients.²³ For example, measures of strength and other measures of functional status identified as important by patients are not directly measured in the scale.

Operational Challenges

There are various operational challenges impeding drug development for ALS, including issues with inadequate sharing of data, data interoperability, competition for limited funding, planning for expanded access programs early in the clinical trial planning process, patient access to clinical trials, and lack of adequate clinical trial staff and trained researchers in the field of ALS.

As with many other diseases, ALS research efforts can operate independently of one another, and with their own separate standards for data collection. This can create hurdles in data sharing which can slow down research and limit researchers' ability to compare or analyze data from different trials.²⁴ Another challenge in data sharing is the timeline of communicating key research findings. Researchers often have to wait until publication to learn about successes and failures of clinical trials (and often failures are not published at all), which can lead to duplication or researchers unwittingly conducting dead-end research. Journal submissions are required to undergo the peer review process, which while crucial for validation of research findings, can result in numerous re-writes that will not change the core results. Sharing these findings more rapidly can help the ALS research community to more efficiently identify what are promising pathways for research. If the article is not accepted for publication at all, then researchers need to seek out other methods in which to communicate their results.

There is only a limited amount of funding available for ALS research and many organizations compete for these funds. This contributes to the research community's reluctance to collaborate or share data. For example, in 2020, the National Institutes of Health (NIH) allocated approximately \$4 billion dollars for research into neurodegenerative diseases; of those funds, \$107 million dollars was for ALS research.²⁵ For comparison, in the same year NIH allocated more than \$7 billion dollars on cancer, and \$788 million on breast cancer alone.²⁵ In addition to the NIH, the Department of Defense funds ALS research through the ALS Research Program established by Congress in 2007 and the CDC maintains the ALS registry.

Many ALS patients are eager and willing to join clinical trials because of the limited treatment options available; however, it can be difficult for many patients to access these trials. Patients who are not located near one of the research centers where clinical trials are taking place may be unable to participate. Traveling to research centers can be costly and challenging for patients given the nature of the disease and its impact on mobility. Even for patients conveniently located near a research center, regular monitoring visits can be burdensome. Clinical trial researchers are exploring novel approaches to

address these issues. Examples of such approaches include decentralized trials and remote monitoring with digital tools to reduce the need for travel.

Further, patients enrolled in trials, including those in the placebo arm, often want the option to continue the treatment after the trial ends, but it can be challenging and expensive for sponsors to offer this if they did not consider it early in the planning process. Some patient groups have proposed that all clinical trials incorporate an option for expanded access or open label extensions. Open-label extension studies can be offered following the completion of randomized trials to allow access to investigational treatments to all trial participants, including those who were placed in a placebo arm. Industry, regulatory, and other stakeholders may also consider pathways outside of clinical trials for increasing patient access to investigational products, including through existing regulatory pathways such as FDA's expanded access pathway (also known as compassionate use).

The lack of trained researchers and staff also presents a challenge for accelerating and continuing ALS research and drug development long term. For example, while patient enrollment remains a challenge for some clinical trials, the HEALEY platform trial is experiencing another problem—trial enrollment is limited due to a lack of staff able to enroll the unusually large numbers of patients who have expressed interest. It is important to continue to increase the cadre of ALS researchers, clinical trial specialists, trial coordinators, and other positions.

Roadmap for Improving Collaboration and Coordination in the ALS Research Community

Despite the scientific and operational challenges in ALS drug development described above, creating greater linkages among stakeholders in the ALS community could enable more efficient and productive approaches to overcoming them. First, it is important to understand who the stakeholder groups are involved in ALS drug development.

Stakeholder Landscape in ALS Research

The ALS research community is comprised of numerous stakeholders including: regulators (such as the FDA); researchers; funders; sponsors; payers; and patients with ALS and advocacy groups who represent them.

U.S. Food and Drug Administration

The FDA is responsible for assessing the safety and efficacy of drugs for market approval in the United States. As a gold-standard regulatory authority, the FDA expects robust scientific evidence from sponsors to ensure the drug demonstrates a benefit to patients without causing harm. For serious diseases where treatments are urgently needed, the FDA has several pathways to ensure that safe and effective drugs are made available to patients as rapidly as possible. Those pathways include accelerated approval, priority review, fast track, and breakthrough designations. The FDA coordinates with sponsors to ensure the best regulatory pathway is utilized and that the proper data is being collected to inform their decision on the drug. In 2019, the FDA issued guidance for industry on developing drugs for ALS.³

Researchers

Researchers are a broad group of stakeholders which includes those involved in all phases of research and development—from basic science to late-stage clinical trials. This broadly defined group includes lab

scientists, academics, clinicians (e.g., neurologists), and clinical trialists. Lab scientists are often working on basic science or preclinical studies focused on answering questions about disease characterization or identifying biomarkers to support drug development. Academic researchers may include lab scientists but are also those conducting epidemiological studies on the patient population to look for trends that may inform the etiology, onset, and progression of ALS. Clinicians, such as practicing neurologists, interact closely with patients and therefore understand the disease progression and patient perspective well. They will often help patients to find clinical trials to participate in and may even support clinical trial research. Clinical trialists design and conduct clinical trials for investigational therapies and work to ensure the trials and therapies are accessible to patients and that the trials are rigorous enough to establish concrete scientific conclusions. Clinical trialists may work in academia or the pharmaceutical industry.

Funders

Funders take a variety of forms and aim to support ALS research. They include government entities such as the National Institutes of Health (NIH), non-profit organizations and foundations such as the ALS Association, Project ALS, and I AM ALS as well as charities such as the Angel Fund for ALS Research. Together, funders ensure that researchers have the resources they need to address key research questions related to disease characterization and to support clinical trial research. Each funder sets their own research priorities which they direct funding towards.

Sponsors

Sponsor refers to the company or organization sponsoring a clinical trial for a specific product. The sponsor, typically a pharmaceutical company, owns the intellectual property and future marketing rights for the investigational product. The sponsor is responsible for liaising with FDA throughout the product lifecycle, paying required review fees, and collecting and submitting the data needed to move through the phases of development and approval process. The sponsor's primary goal is to demonstrate a drug's safety and efficacy in order to successfully bring a product through development and onto the market. If approved, the sponsor is also responsible for setting the price of the drug and coordinating with payers on coverage.

Payers

In the United States, payers cover a majority of the cost of drugs. Payers include commercial insurance companies and government programs such as Medicare and Medicaid. They determine the coverage of drugs for their enrollees. For all drugs, but particularly those with high price tags, payers will conduct their own assessment of clinical benefit to determine if and how it will be covered under their program. Payers will negotiate with sponsors on the price they are willing to pay for the drug.

Patients, Caregivers, and Advocacy Groups

Patients with ALS and their caregivers are at the core of the ALS research community. Patients are active in research by participating in clinical trials and providing data, including biosamples for continued use in longitudinal studies even after the initial research is complete. Patients are the individuals that have the most to gain from any potential treatment. Patient advocacy groups play a crucial role by advocating on behalf of patients and caregivers and providing a collective voice for their needs, priorities, and potential solutions to advance ALS research. Advocacy groups work hard to ensure researchers and sponsors consider the patient perspective when innovating trial designs and establishing endpoints that are

meaningful for patients in their day-to-day lives. Patient advocacy groups also host and sponsor conferences to facilitate the dissemination of information.

Roadmap for Improved Collaboration

The Duke-Margolis Center for Health Policy has developed a roadmap for increasing collaboration and coordination among stakeholders in ALS research community to tackle specific challenges across the product development lifecycle. The roadmap includes recommendations for stakeholder collaboration which aim to address challenges in drug development. We present both near-term and long-term recommendations broken down into the following four categories:

- basic and preclinical research
- clinical research and clinical trial design
- regulatory review and approval process
- post-market approval

Mapping recommendations for improved collaboration to advance drug development for ALS



Basic and Preclinical Research

Near-term recommendations:

- **Researchers** could utilize an existing data platform to assist in the circulation of pre-print data and the findings of studies that failed and were not considered for publication.
- **Funders** could collaborate on a complementary approach to strategically and efficiently allocate resources to basic and preclinical research priorities for ALS. For instance, smaller non-profits could fund under-resourced or neglected areas of research which large funders

such as NIH may not see as a priority. In this way, researchers could cover more ground, identifying unsuccessful hypotheses and promising new pathways more rapidly.

Long-term recommendations:

- **Foundations and patient organizations** could consider establishing a collaborative group which pools a percentage of funding to investigate a group-selected research priority. This group of funders could then update the priority research area after a set time interval, such as every 1-3 years.
- The Biden Administration's proposed Advanced Research Projects Agency for Health (ARPA-H) intends to advance research in break-through, game-changing solutions that have potential to transform important areas of medicine and health that traditional research or commercial activity cannot readily accomplish. Should ARPA-H come to fruition,ⁱⁱ the **ALS research community and patient advocates** could jointly encourage the new agency to make ALS one of its disease focus areas and provide a consensus or coordinated list of initial ALS research priorities for the new agency. The stakeholders could also provide input on the consensus building for those research priorities depending upon how ARPA-H is structured and operationalized. If such a program is created, it could help overcome some of the scientific challenges in ALS drug development.

Clinical research and clinical trial design

Near-term recommendations:

- **Clinical trialists and sponsors** could identify opportunities to make more and better use of existing channels (e.g., MIDD, CID) to communicate with the FDA early and often on proposed innovative trial design, and to better explore these types of innovative designs where possible.
- **Clinical trial networks and ALS research consortiums** could join forces to develop an overarching clinical trial network, similar to the National Cancer Institute's National Clinical Trials Network (NCTN) structure for cancer research.²⁶ Bringing these networks together under one larger network dedicated to ALS research could support greater efficiency and standardization in data sharing and enhanced collaboration between consortiums.
- **Researchers** could continue to build and expand upon existing efforts to improve data sharing. Research consortiums such as the Northeast ALS Consortium (NEALS) and CReATe are crucial to this endeavor and can play a pivotal role in setting standards for data sharing. As proposed above, an overarching clinical trial network that brings these consortiums together could further support the development of standards and processes that facilitate improvements in data sharing across the whole ALS research community.

ⁱⁱ Author's note (October 2022): ARPA-H was established as part of the US Department of Health and Human Services upon the enactment of Public Law 117-03 on March 15, 2022

- **Academic researchers and pharmaceutical companies** could agree to the inclusion of a sunset clause for preclinical and clinical data in their intellectual property (IP) agreements. Such a clause may help to increase data sharing within the ALS research community. Currently, academic scientists sell their findings as IP to pharmaceutical companies who then own the findings and data in perpetuity. A sunset clause for data ownership would entail adding a clause to the IP agreement between an academic institution and a pharmaceutical company stipulating that after a fixed number of years (e.g., 5 years) the data would be part of the public domain and available via open access to researchers. Similarly, this solution could also assist FDA since the Agency has a wealth of data about the end of the pipeline it is unable to share. Such as clause could enable FDA to share this information with researchers.
- **Clinical trialists and sponsors** could utilize existing data sharing platforms or pre-print servers such as bioRxiv to share critical findings from trials more rapidly than the time needed to publish in a peer-review journal.
- **Clinical trialists and sponsors** could better and more consistently engage with and integrate patient and caregiver perspectives on meaningful outcomes and clinical trial design parameters. These design parameters include the type, frequency, duration and overall burden of data collection required by the trial protocol. Parameters could also include trial enrollment criteria, and approaches to sharing trial data with patients, caregivers, and the broader clinical research community.
- **Clinical trialists and sponsors** could utilize new tools and technology to facilitate remote participation in clinical trials to reduce the burden on patients and open trials up to more patients who may not have access to a clinical trial site. **Clinical trialists** could engage with a larger network of **clinicians and health systems** to enroll their patients in trials and allow them to use their local healthcare provider for needed in-person visits or sample collection.
- **Researchers** could submit data on exploratory endpoints to FDA to help establish and validate more primary and secondary endpoints in the future. To help facilitate more research on exploratory endpoints, **FDA and NIH** could consider aligning opportunities and priorities to match funding with data needs. There have been proposalsⁱⁱⁱ for increased collaboration between the agencies to streamline the processes between the critical research conducted at NIH and then strong ties at FDA fostering drug development.²⁷ These proposals warrant further consideration and other mechanisms or opportunities for the agencies to work together might be explored.
- **Clinical trialists** could continue to foster transparency on innovative trial designs, clinical trial challenges and solutions through published meeting readouts, recordings, blog posts, and other methods.

Long-term recommendations:

- Once a clinical trial network is established, ALS **clinical trialists** could then aim to achieve a consensus on utilizing standard unique identifiers for patients to ensure better data linkages

ⁱⁱⁱ Author's note (October 2022): On December 23, 2021, the Accelerating Access to Critical Therapies for ALS Act was signed into law.

across data ecosystems, such as NeuroGUID™ and NeuroSTAmP which have been implemented in some NEALS clinical trials.

- Once there is a therapeutic candidate with a strong enough anticipated treatment effect, **clinical trialists and FDA** could consider utilizing historical controls in innovative clinical trial design. Clinical trialists could also consider eliminating the placebo arm of trials if the anticipated treatment effect is large enough. Patients and patient advocates maintain that such a change is crucial to ensure that as many patients as possible have access to potentially life-altering treatments.

FDA review and approval process^{iv}

Near-term recommendations:

- **FDA** could continue to exercise appropriate regulatory flexibility in meeting the statutory requirements for expedited approval pathways as it pertains to potential treatments for ALS.
- FDA currently collaborates with the European Medicines Agency (EMA) through an initiative known as the Rare Disease Cluster.²⁸ Currently, the proceedings of this workgroup are confidential. **FDA and EMA** could consider releasing a public summary of the proceedings to foster transparency among the rare disease communities, especially if there are certain considerations for ALS or neurodegenerative diseases as a whole.
- **FDA** could consider working with researchers to study international regulatory processes and procedures and how they may be reflected in the context of US regulatory policy to bring medicines for serious and life-threatening diseases to the market rapidly and safely.

Long-term recommendations:

- As conversations continue around the historical application of and potential improvements to accelerated approval and other expedited approval pathways, **FDA along with all other stakeholders** could consider updates to these pathways or the development of a new one.^{29,30} It has been suggested that potential changes could model the EMA's conditional approval pathway which may grant a medicine conditional approval if the benefit-risk balance is positive and the patient's need is greater than risk inherent in the need for more data.³¹ Other proposals have also been made for potential new expedited pathways for serious, life-threatening diseases and conditions.³²
- As advances are made in ALS research, whether in basic science, identification of biomarkers, or other progress related to drug development for ALS, **FDA** could work with **clinical trialists and sponsors** to establish additional guidance on innovative approval pathways for ALS, building on the existing guidance, to foster additional transparency on the review process and keep pace with scientific advancements.

^{iv} Author's note (October 2022): In June 2022, U.S. Food and Drug Administration released its "Action Plan for Rare Neurodegenerative Diseases including Amyotrophic Lateral Sclerosis (ALS)"—a five-year strategy for improving and extending the lives of people living with rare, neurodegenerative diseases by advancing the development of safe and effective medical products and facilitating patient access to novel treatments.

Post-market approval

Near-term recommendations:

- Once a new product for the treatment of ALS is approved, another consideration will be access for patients, particularly affordability. Given that therapeutics in the pipeline include gene therapies and monoclonal antibodies, there will be a great deal of attention paid to the price set and subsequent consequences for coverage by payers.³³ **Patient advocacy groups, clinical trialists, and sponsors** could engage **payers** early in the development process to ensure that payer evidentiary questions can be answered quickly following a potential approval. Discussions with payers about late-stage products (e.g., AMX0035 and tofersen) could begin now to better understand what clinical evidentiary needs are required of a novel therapeutic for ALS. Similarly, these stakeholders could discuss manners in which to continue to collect post-market data.

Conclusion

ALS is a fast-moving and devastating disease, and there is a high unmet need for therapeutics that can slow or reverse its progression. Many different organizations and stakeholders are dedicated to the common goal of finding safe and effective treatments for ALS. The efforts of these groups have the potential to be enhanced by increased collaboration and coordination. In this document we described the challenges impeding drug development for ALS and provided recommendations on how to increase collaboration and coordination to overcome these challenges and accelerate research and development.

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