U.S. FOOD & DRUG ADMINISTRATION

Action Plan for Rare Neurodegenerative Diseases including Amyotrophic Lateral Sclerosis

A five-year action plan developed to meet requirements under Section 4 of the Accelerating Access to Critical Therapies for ALS Act.

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Introduction

The U.S. Food and Drug Administration (FDA or the Agency) protects and promotes public health by helping to ensure that safe and effective medical products are available to improve the health of people in the United States. The ecosystem in which FDA fulfills this role is rapidly evolving, with therapeutic innovation on an unprecedented scale, clinical trial designs of increasing complexity, and expanding availability of drug[1] development tools.

FDA proactively fosters medical product development by providing scientific vision and direction. This action plan[2] is a five-year FDA plan to advance innovation that promotes and accelerates medical product development for the treatment of rare neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS). This action plan has been developed consistent with provisions in the Accelerating Access to Critical Therapies for ALS Act and may evolve over time.

Accelerating Access to Critical Therapies for ALS Act
On December 23, 2021, the President signed into law, the "Accelerating Access to Critical Therapies for ALS Act,"[3] (hereafter, the ACT for ALS) which directs the Department of Health and Human Services (HHS) to take a number of actions, including, as required under section 4 of the ACT for ALS, to develop an action plan to facilitate the development of and access to drugs for ALS and other rare neurodegenerative diseases. Specifically, section 4 notes that within six months of the enactment of the ACT for ALS, FDA shall publish on its website an action plan describing actions the FDA intends to take during the five-year period following publication of the plan with respect to program enhancements, policy development, regulatory science initiatives, and other appropriate initiatives to:

- Foster the development of safe and effective drugs that improve or extend, or both, the lives of people living with ALS and other rare neurodegenerative diseases; and

- Facilitate access to investigational drugs for ALS and other rare neurodegenerative diseases.

Additionally, section 4 states that the action plan will identify appropriate representation from within FDA to be responsible for implementation and include elements to facilitate:

- Interactions and collaboration between FDA and stakeholders (including patients, sponsors, and external biomedical research community);

- Consideration of cross-cutting clinical and regulatory policy issues, including consistency of regulatory advice and decision making;

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[1] For the purposes of this document, all references to drugs include both human drugs and biological products.

[2] This action plan has been prepared by the Office of New Drugs in the Center for Drug Evaluation and Research (CDER) in cooperation with CDER's Office of Translational Sciences and the Center for Biologics Evaluation and Research (CBER) at the FDA.

[3] Public Law No. 117-79.

- Identification of key regulatory science and policy issues critical to advancing development of safe and effective drugs; and

- Enhancement of collaboration and engagement across FDA and with other operating divisions within HHS, the Public-Private Partnership for Rare Neurodegenerative Diseases, and the broader neurodegenerative disease community.

The ACT for ALS also directs HHS to:

- Award grants to participating entities for scientific research using data from expanded access to investigational drugs, for individuals who are not otherwise eligible for clinical trials for the prevention, diagnosis, mitigation, treatment, or cure of ALS (section 2);

- Establish and implement a Public-Private Partnership for Rare Neurodegenerative Diseases between the National Institutes of Health (NIH), the FDA, and one or more eligible entities for the purpose of advancing the understanding of neurodegenerative diseases and fostering the development of treatments for ALS and other rare neurodegenerative diseases (section 3); and

- Award grants and contracts to public and private entities to cover the costs of research on, and the development of interventions intended to prevent, diagnose, mitigate, treat, or cure, ALS and other rare neurodegenerative diseases in adults and children, including the costs of development and critical evaluation of tools, methods, and processes to:

  – Characterize such neurodegenerative diseases and their natural history;
  – Identify molecular targets for such neurodegenerative diseases; and
  – Increase the efficiency and productivity of clinical development of therapies, including through the use of master protocols and adaptive and add-on clinical trial designs and efforts to establish new or leverage existing clinical trial networks (section 5).

For the purposes of carrying out the ACT for ALS, the legislation authorizes the appropriation of $100,000,000 for each of fiscal years (FYs) 2022 to 2026. FDA's ability to execute this action plan is contingent on the appropriation and distribution of these funds to FDA. FDA continues to collaborate and cooperate with its partners within HHS, including the NIH, to implement the legislation. This action plan, and its publication, addresses the requirements of section 4 of the ACT for ALS.

Rare Neurodegenerative Diseases

Overview of Rare Neurodegenerative Diseases
Neurodegenerative disease is an overarching term for a variety of progressive conditions that affect the neurons of the nervous system, resulting in damage to, and ultimately the death of, those cells. Although rare neurodegenerative diseases are particularly challenging from both research and drug development perspectives, there has been encouraging progress in drug development for a number of such diseases. For example, patients suffering from neuromyelitis optica spectrum disorder, a rare autoimmune disease affecting the brain and optic nerve, had no FDA-approved treatments available to them until 2019, when the Agency approved Soliris (eculizumab). With several subsequently approved therapies, treatment of this disease has dramatically advanced. As another example, spinal muscular atrophy (SMA) is a rare neurodegenerative disease that affects nerves and muscles and is characterized by progressive muscle weakness. Between 2016 and 2020, FDA approved two drugs for use in adults and children with SMA, and a gene therapy product for children younger than two years of age with the most severe form of the disease. Unfortunately, most rare neurodegenerative diseases still do not have an FDA-approved treatment, particularly treatments that arrest or reverse disease progression.

Although there has been much progress in basic and preclinical research on rare neurodegenerative diseases, scientists have yet to identify the key underlying molecular mechanisms that give rise to many of these diseases. Identifying such mechanisms could lead to precise targets for the development of novel treatments. Further, compared to many other areas of drug development, translational animal models or easily measured biomarkers of treatment response that could help prioritize promising treatments for clinical development are less advanced. These factors and others have resulted in a challenging clinical trial experience in this arena and many failed trials.

This situation reflects the limitations and reality of drug development when the mechanisms precipitating the disease and pathways leading to disease progression are not well understood. Addressing these knowledge gaps will be a critical step in overcoming some of the current challenges faced in clinical drug development of new therapies targeting rare neurodegenerative diseases. The scientific community is working to better understand the pathogenesis of rare neurodegenerative diseases, which could lead to better drug targets, along with the discovery of prognostic and diagnostic markers, all of which would facilitate drug development in this area. We can leverage these efforts together with advances in clinical trial methodologies to accelerate the development of new treatments.

Advancing Science and Innovation for Rare Neurodegenerative Diseases
FDA will engage in the following activities to advance science and promote innovation for rare neurodegenerative diseases.

Establish the FDA Rare Neurodegenerative Diseases Task Force (FY 22)
In May 2022, the Accelerating Rare disease Cures (ARC) Program was established to drive scientific and regulatory innovation and engagement to accelerate the availability of treatments for patients with rare diseases. FDA will leverage the ARC Program's infrastructure, expertise, and strategic leadership to establish an inter-center Rare Neurodegenerative Diseases Task Force.
The task force will ensure a strategic cross-cutting Agency approach to advance the development

of medical products to address rare neurodegenerative diseases. It will build on the work of the ARC Program and in particular the collaborative efforts of the medical product centers by facilitating and expanding ongoing engagement and collaboration with subject matter experts across FDA. This task force will ensure cohesion in FDA's approach to, and its coordinated efforts towards, advancing science and drug development for rare neurodegenerative diseases. This interdisciplinary task force will also foster external engagement with the rare neurodegenerative disease communities.

The FDA Rare Neurodegenerative Diseases Task Force will include representatives from the Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), Center for Devices and Radiological Health (CDRH), the Office of the Commissioner, including the Office of Orphan Products Development, and other FDA Centers and/or Offices as needed. The task force will be co-led by senior representatives from CBER and CDER, in coordination with a senior official from the Immediate Office of the Commissioner. The task force will establish working groups, as needed, to consider cross-cutting issues.

Establish the Public-Private Partnership for Rare Neurodegenerative Diseases (FY 22)
FDA will establish a Public-Private Partnership for Rare Neurodegenerative Diseases between the NIH, the FDA, and one or more other eligible entities for the purpose of advancing the understanding of and fostering the development of treatments for rare neurodegenerative diseases including ALS.[4] The public-private partnership will facilitate and support research and innovation (e.g., advances in drug development tools) among other activities. FDA experts will provide scientific and regulatory knowledge and direction.

Develop Disease-Specific Science Strategies (FY 22 – FY 26)
FDA will develop multi-year, disease-specific science strategies (strategic plans) to address substantive issues in drug development for rare neurodegenerative diseases. To develop these science strategies, FDA will systematically assess unmet medical needs, evaluate the state of clinical development, and identify challenges to drug development by disease area. After an assessment, FDA can develop multi-year, disease-specific science strategies to address the identified gaps and challenges.

To illustrate this strategic approach, this action plan includes a science strategy developed for ALS. The ALS Science Strategy outlines activities that FDA will conduct over the next five years (June 2022 to June 2027) to address current challenges to ALS drug development. In addition to a multi-year, sequenced roadmap, the ALS Science Strategy describes how the strategy will be implemented and leveraged more broadly for rare neurodegenerative diseases.

In the near term, FDA will begin implementing the ALS Science Strategy and, subject to the availability of resources, conduct a needs assessment to identify other rare neurodegenerative diseases that would benefit from heightened coordination across the Agency. In the longer-term, FDA will assess the impact of the ALS Science Strategy on the ALS drug development landscape and, subject to the availability of resources, determine whether to systematically develop disease-specific science strategies for other rare neurodegenerative disease areas.

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[4] The Agency is establishing this public-private partnership in accordance with requirements under Section 3 of the ACT for ALS.

Leverage Ongoing FDA Regulatory Science Efforts

In addition to the activities listed above, FDA has ongoing efforts that support regulatory science and innovation across areas of unmet medical need such as rare neurodegenerative diseases. These FDA efforts include (but are not limited to):

- Accelerating Rare disease Cures (ARC) Program – advances rare disease regulatory science and focuses on novel tools and approaches that can support rare disease product development;

- Complex Innovative Trial Design Meeting Program – advances the science used to support novel approaches, such as the use of complex adaptive designs and Bayesian models, and promotes their adoption in drug development programs to advance innovation;

- Critical Path Innovation Meetings (CPIM) – creates a forum for stakeholders (industry, non-profit, academia, other government agencies, patient advocacy groups, consortia, etc.) to communicate directly with FDA subject matter experts and have an open scientific discussion and exchange of ideas with a common goal of improving efficiency and success in drug development;

- Fit-for-Purpose Initiative – provides a pathway for regulatory acceptance of dynamic tools for use in drug development programs to enhance the understanding of disease progression, to inform patient selection, and to optimize clinical trial design in specific disease areas;

- Model-Informed Drug Development Paired Meeting Pilot Program – promotes the development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources to enhance understanding of disease progression, improve clinical trial efficiency, and optimize drug dosing/therapeutic individualization;

- Patient-Focused Drug Development Program – ensures that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation;

- Rare Disease Cures Accelerator - Data and Analytics Platform (RDCA-DAP) – provides a centralized and standardized infrastructure for patient-level data to accelerate rare disease characterization; and

- Real-World Evidence Program – explores the potential use of real-world data (RWD) and real-world evidence (RWE) to support regulatory decision making, including the approval of new drug indications or post-approval study requirements for approved drugs.

Science Strategy for Amyotrophic Lateral Sclerosis

Overview of Amyotrophic Lateral Sclerosis

ALS is a progressive neurodegenerative disease that primarily affects motor neurons in the cerebral motor cortex, brainstem, and spinal cord. This leads to loss of voluntary movement; difficulty in swallowing, speaking, and breathing; and a shortened life expectancy. ALS is a heterogeneous disease characterized by the degeneration of both upper and lower motor neurons. Most individuals with ALS die from respiratory failure, usually within three to five years from when symptoms first appear. Approximately 5,000 individuals in the United States are diagnosed with ALS annually, and approximately 20,000 Americans are currently living with the disease. ALS is diagnosed by identifying its characteristic clinical symptoms and signs and excluding other possible diagnoses. Most cases of ALS are sporadic; however, in a small minority of individuals ALS has a clear familial inheritance pattern that may be associated with an identified gene. In addition, genetic variants have been detected in some sporadic ALS cases.

There is no cure for ALS and the current treatment options are limited. Over the last four decades, numerous clinical trials have been conducted for ALS, yet only two drugs, Edaravone and Riluzole, which provide limited benefit, have been approved by the FDA for the treatment of this disease. Individuals with ALS often use supportive measures that do not alter the rate of progression or treat the underlying cause of the disease. As symptoms progress, individuals become increasingly or totally dependent on others for care. There is a critical unmet need for additional safe and effective therapies for individuals with ALS.

Recent and Ongoing FDA Activities to Support Drug Development for ALS

FDA has and is continuing to work closely with individuals with ALS, their caregivers, researchers, drug developers, and other stakeholders on efforts to accelerate the development of new therapies for ALS while helping to ensure that they are safe and effective. In 2019, FDA issued the guidance for industry *Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment*.[5] The guidance sets out the Agency's current thinking regarding the clinical development program and clinical trial designs for drugs to support an indication for the treatment of ALS. In 2021, FDA issued the draft guidance for industry *Human Gene Therapy for Neurodegenerative Diseases*,[6] which conveys the Agency's draft recommendations on developing human gene-therapy products for neurodegenerative diseases affecting adult and pediatric patients. In addition to these guidances, FDA provides direction to developers at the very early stages in drug development, and its expedited development and review programs[7] facilitate drug development for ALS.

In 2020, in cooperation with the Duke Margolis Center for Health Policy, FDA organized a workshop series to explore the state of science for ALS.[8] These workshops brought together ALS experts from the patient, scientific, clinical, industry, and regulatory communities; highlighted recent progress in basic and clinical ALS research; and identified opportunities to advance the development of medical products that will benefit individuals with ALS.

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[5] FDA Guidance for Industry: Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment

[6] FDA Draft Guidance for Industry: Human Gene Therapy for Neurodegenerative Diseases. When finalized, this guidance will represent FDA's thinking on this issue.

[7] FDA Guidance for Industry: Expedited Progras for Serious Conditions – Drugs and Biologics

[8] For more information on the Advancing Therapeutic Development for ALS workshop series, visit: https://healthpolicy.duke.edu/projects/duke-margolis-center-health-policy-and-us-food-and-drug-administration-workshop-series

Overview of the Science Strategy Planning Process
The ALS Science Strategy is disease-specific and builds on current science and research to support drug development for ALS. It also provides a strategic vision and direction for ongoing and future FDA activities. To inform the development of this science strategy, FDA subject matter experts:

- Assessed areas of unmet medical need and the current state of clinical development;
- Identified challenges to drug development; and
- Explored opportunities for purposeful FDA scientific leadership.

Central to FDA's development of the ALS Science Strategy are the perspectives of individuals with ALS and their caregivers. The Agency shares the ALS community's desire for a cure or therapies that slow the progression of symptoms as well as therapies such as assistive devices and digital health technologies that can help manage and mitigate symptoms. Through FDA's engagement with the community, we heard the need for advances in science, improved research, faster clinical trials, expedited drug reviews, and increased patient access to investigational products. In the ALS Science Strategy, FDA is committing to engaging in activities to identify, promote, and support advances that could have a significant positive impact on the development of therapies for ALS.

The National Institute of Neurological Disorders and Stroke (NINDS) is also administering a strategic planning process for ALS.[9] As the NINDS finalizes its research priorities, the ALS Science Strategy may be updated to encompass other promising research opportunities. FDA will engage with NINDS to inform consideration of such updates to FDA's ALS Science Strategy.

Overview of the ALS Science Strategy
The ALS Science Strategy outlines activities that FDA will conduct over the next five years (June 2022 to June 2027) to address current barriers and challenges to ALS drug development. These activities include coordination and collaborations across FDA, with other federal agencies such as the NIH, and with external stakeholders.

The activities in the ALS Science Strategy are framed around four focus areas. Along with the activities in these areas, FDA will establish and/or enhance structures and processes to ensure coordinated efforts in and outside the Agency to drive the development of safe and effective drugs for ALS. The four focus areas of the ALS Science Strategy are:

- Improve characterization of disease pathogenesis and natural history – the greatest challenge in developing drugs for ALS is the lack of a clear understanding of its pathophysiology. To address this, we need increased focus on natural history, including quantifying disease progression; predictive and prognostic biomarkers; and efficient translation and implementation of basic science discovery.

[9] More information about NINDS's ALS Strategic Plan is available here: https://www.ninds.nih.gov/About-NINDS/Strategic-Plans-Evaluations/Strategic-Plans/Amyotrophic-Lateral-Sclerosis-ALS

- Facilitate access to investigational new drugs[10] – approaches to increasing patient access to investigational new drugs whenever possible through greater participation in clinical trials should be explored and prioritized. Currently there are barriers to, and burdens associated with, participation in clinical trials. To address these issues, and improve the diversity of participants, use of digital health technologies and decentralized trial designs will be explored to facilitate the collection of data from participants where they live and, when appropriate, ensuring mechanisms for expanded access (generally outside of a clinical trial) are appropriately integrated into development programs.

- Enhance clinical trial infrastructure and agility – rethinking approaches to clinical trials can enable early selection of promising therapeutic candidates for further development, optimize clinical trial design, improve access to the trials, streamline clinical trial operations, and reduce the time and cost of drug development.

Near-term Activities (FY 22)
Near-term activities will focus on setting up the infrastructure needed to implement the ALS Science Strategy, engaging with internal and external stakeholders, and stimulating scientific research. Although initiated in the near term, these activities will continue throughout this five-year period of the ALS Science Strategy.

Establish FDA Rare Neurodegenerative Diseases Task Force's ALS Working Group
The FDA Rare Neurodegenerative Diseases Task Force will establish an ALS Working Group to ensure a strategic cross-cutting Agency approach to advance the development of medical products to address ALS. The ALS Working Group will build on CDER's new ARC Program and the collaborative efforts of the medical product centers by facilitating and expanding ongoing engagement and collaboration with subject matter experts across FDA. The working group will ensure cohesion in FDA's approach to, and its concerted and coordinated efforts towards, advancing science and drug development for ALS. This will include considering cross-cutting clinical and regulatory policy issues. This interdisciplinary group will also foster engagement with external stakeholders who work with the ALS community.

In line with this scope and remit, the working group will support the implementation of the ALS Science Strategy. Specifically, the working group will ensure that the ALS Science Strategy is implemented in a manner consistent with its goals, available resources, and evolving scientific understanding and public health needs. From time to time, and as appropriate, the ALS Working Group will consider, revise, and update the ALS Science Strategy.

Support Translational Science Research
Through the Public-Private Partnership for Rare Neurodegenerative Diseases, FDA experts will provide scientific knowledge in support of research that could be leveraged for drug development. Areas of ALS research where FDA experts could provide input include (but are not limited to):

- Understanding of disease natural history (e.g., genotype-phenotype relationships, large datasets of placebo-controlled patient data to look at predictors of deterioration);

- Understanding of disease pathophysiology and development of animal models, in vitro models, and other models that may be most useful for pharmacological pre-clinical proof of concept;

[10] Investigational new drug means a new drug or biological drug that is used in a clinical investigation. See 21 CFR 312.3(b).

- Biospecimen sharing across sponsors;
- Identification, development, and validation of biomarkers and potential surrogate endpoints that could be used in clinical development programs;
- Development of fit-for-purpose, model-informed tools for use in clinical development programs; and
- Enhancing clinical trial design and infrastructure.

Medium-term Activities (FY 23 to FY 24)
Medium-term activities will concentrate on areas such as patient-focused drug development, encouraging data sharing, developing study data standards, and exploring the use of digital health technologies.

Explore Gaps in Understanding of ALS Natural History
FDA will review its experience with hereditary ALS and rare neurodegenerative disease applications to identify common gaps in the natural histories of ALS and rare neurodegenerative disorders. FDA will use this experience to inform our recommendations on additional natural history studies, with the goal of improving subsequent clinical trial designs, and to facilitate bringing new products to market.

Collect Patient Perspectives on Clinical Trial Participation
FDA will gather input from patients and their caregivers on the challenges and barriers to participation in clinical trials. FDA is particularly interested in hearing from individuals with rare neurodegenerative diseases who participated in decentralized clinical trials during the coronavirus disease 2019 (COVID-19) pandemic. Decentralized trials have several potential benefits including reduced patient and caregiver burden, increased enrollment, and enhanced retention of a more diverse population. Patient and caregiver perspectives and experiences on this topic will strengthen FDA's understanding of the opportunities and challenges related to participation in decentralized clinical trials and inform future activities in the ALS Science Strategy.

Facilitate and Encourage Data Sharing
FDA will continue to facilitate and encourage data sharing and standardization through RDCA-DAP and the new Public-Private Partnership for Rare Neurodegenerative Diseases. Collecting and sharing individual-level data, as appropriate, including sponsor-contributed clinical trial data, with researchers and drug developers will enhance understanding of disease progression and promote the development of drug development tools such as clinical outcome measures and biomarkers.

Support the Development of Study Data Standards for ALS
FDA will support the development of study data[11] standards for ALS, such as a Clinical Data Interchange Standards Consortium (CDISC)[12] Therapeutic Area User Guidance for ALS. ALS-specific study data standards can describe the most common biomedical concepts relevant to studies of ALS and how to consistently represent such data.

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[11] Study data is information about a clinical trial participant. It includes demographic information, details of medical treatment, descriptions of the participant's progress, and other relevant information.

[12] To learn more about the Clinical Data Interchange Standards Consortium (CDISC), visit: https://www.cdisc.org/.

Cell and Gene Therapies Safety Project

FDA will review its experience with applications for ALS and rare neurodegenerative disorder treatments to identify cross-application safety signals, with a focus on factors such as the specific type of product (e.g., gene therapy, cell therapy, vector), route of administration, and study population (e.g., age, disease severity, clinical manifestations). FDA will use this safety information to inform the design of subsequent clinical trials for the use of cell and gene therapies to treat ALS and other neurodegenerative diseases.

Explore the Use of Fit-for-Purpose[13] Digital Health Technologies[14]

FDA will encourage exploring the use of digital health technologies to potentially improve understanding of the disease and increase access to investigational drugs through more accessible clinical trials. Using digital health technologies may enhance use of decentralized trial approaches that can increase trial participation and reduce the burden of trial participation on individuals with ALS and their caregivers. For example, digital health technologies may reduce the need for travel to study sites. These technologies may also be used to increase ability to monitor and assess drug response by providing a more comprehensive assessment of the rate of decline in the range of functional capabilities affected by ALS.

FDA will consider the available digital health technologies that can help facilitate decentralized trials, how these technologies can be implemented in a decentralized clinical trial setting, and when entirely decentralized trials using digital health technologies and telemedicine approaches might be appropriate. FDA will also encourage efforts to increase awareness among sponsors, clinical trial investigators, and clinical research personnel of digital health technologies and their use in clinical research.

Encourage the Incorporation of Expanded Access into Clinical Development Programs

FDA will explore approaches to encourage sponsors to consider and incorporate strategies related to expanded access early in their clinical development programs. Whenever possible, an investigational drug should be used as part of a clinical trial. However, if patient enrollment is not possible (e.g., patient ineligibility), enrollment in a clinical trial is not feasible (e.g., distance to a trial precludes access), or, there are no available clinical trials open for enrollment (e.g., between the completion of clinical trials and regulatory approval or commercial availability), expanded access offers a possible route for gaining access to an investigational drug. It is important that sponsors have mechanisms to manage any expanded access programs they have in place, as appropriate, and potentially integrate these expanded access programs into their development program.[15]

Promoting Successful Translation from Bench to Bedside

FDA will encourage efforts to increase the awareness of and educate academic investigators and clinical research personnel on the regulatory aspects of drug development. Specifically, FDA will aim to improve their familiarity and understanding of federal regulations, guidance documents, and approaches for high-quality rare disease clinical trials.

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[13] In the context of use of a digital health technology in a clinical investigation, fit-for-purpose means a conclusion that the level of validation associated with a digital health technology is sufficient to support its context of use.

[14] FDA Draft Guidance for Industry: Digital Health Technologies for Remote Data Acquisition in Clinical Investigations. When final, this guidance will represent FDA's current thinking on this issue.

[15] Section 561A of the Federal Food, Drug, and Cosmetic Act (FD&C Act), requires a manufacturer or distributor of one or more investigational drugs for the diagnosis, monitoring, or treatment of one or more serious diseases or conditions to make its policy for evaluating and responding to expanded access requests submitted under section 561(b) of the FD&C Act both public and readily available, such as by posting the policy on a publicly available website. Information on expanded access availability for applicable drug clinical trials are required to be submitted to www.ClinicalTrials.gov under 42 CFR §11.28(a)(2)(ii)(H) or 42 CFR § 11.28(c).

Longer-term Activities (FY 25 to FY 26)
Longer-term activities will incorporate the insights and knowledge gained from earlier activities in the ALS Science Strategy and focus on enhancing the design and conduct of clinical trials.

Explore Innovative Trial Designs
FDA will explore approaches to optimizing the design of clinical trials, including the use of adaptive designs, enrichment strategies, master protocols (which use a single infrastructure, trial design, and protocol), model-informed drug development approaches, and novel statistical approaches for small populations. These trial design strategies may be able to be applied to expedite ALS trials, reduce the need for exposure to placebo when appropriate, and enhance overall trial performance, including improving the quality of the evidence generated.

Enhancing Clinical Trial Infrastructure and Agility
FDA will continue to explore platforms and paradigms to enhance use of decentralized trials, building on previous activities in the ALS Science Strategy.

Through the Public-Private Partnership for Rare Neurodegenerative Diseases, FDA will also encourage innovative approaches to support the conduct of clinical trials for ALS therapies, including practical steps and successful approaches to start up, implement, and sustain clinical trials and/or clinical trial networks. There may be opportunities to leverage and/or complement an existing clinical trial network(s).

Implementation of the ALS Science Strategy
FDA will adopt a multifaceted approach to implement the ALS Science Strategy. It will involve patient engagement, public workshops, research projects, coordination across FDA centers and offices, collaboration with the NIH, and public-private partnerships.

The FDA ALS and Rare Neurodegenerative Diseases Task Force and its ALS Working Group will ensure that the implementation of the ALS Science Strategy is consistent with its goals, available resources, and evolving scientific understanding and public health needs. The task force and its ALS Working Group will work closely with the new Public-Private Partnership for Rare Neurodegenerative Diseases, which will include the NIH, the FDA, and one or more eligible entities for the purpose of advancing the understanding of and fostering the development of treatments for rare neurodegenerative diseases including ALS.

The implementation of the ALS Science Strategy is dependent on receiving consistent funding over the next five years, starting in FY22. The resources needed to implement the ALS Science Strategy include (but are not limited to):

- Cross-disciplinary subject matter experts to provide input across activities;
- Funding to support exploratory research projects in the forms of grants, public workshops, and/or research fellowships; and
- Program staff to coordinate and track activities.

FDA recognizes the importance of obtaining external input in helping ensure that all perspectives are considered. FDA will continue to communicate with the ALS community to engage their support and expertise and partner with them on our efforts as possible. The ALS Science Strategy will be periodically reviewed and updated, as appropriate, to ensure that FDA is supporting activities that will advance the scientific understanding of and the development of drugs for ALS.

Leveraging Scientific Advancements Across Rare Neurodegenerative Diseases

It is critical to leverage scientific advancements across rare neurodegenerative diseases to speed innovation and avoid duplicative efforts. In addition to supporting research and development of ALS therapies, FDA anticipates that the ALS Science Strategy will advance science and innovation for other rare neurodegenerative diseases that are in need of more effective therapies. For example, FDA could translate learnings in methodological approach or the development of biomarkers, clinical outcome measures, digital health technologies, and modeling and simulation tools in ALS to advance drug development for other rare neurodegenerative diseases.

The FDA Rare Neurodegenerative Diseases Task Force will provide a forum for the dissemination of insights and knowledge derived from the ALS Science Strategy. The task force will consolidate these insights and learnings in real-time with relevant work in other rare disease and regulatory science initiatives. The task force will also assess the impact of the ALS Science Strategy on the ALS drug development landscape and determine whether to systematically develop and publish disease-specific science strategies for other rare neurodegenerative disease areas.

Recognizing the promise that cell and gene therapy products may hold for treating rare neurodegenerative diseases, including hereditary forms of ALS, CBER will create a center-wide core team, called the CBER NEUrodegenerative Rare disease Operation (NEURO) Team, as part of the Agency's efforts to implement the ACT for ALS, including this Action Plan and the ALS Science Strategy. The CBER NEURO Team will routinely communicate and collaborate within CBER and across the Agency to advance development of cell and gene therapies for rare neurodegenerative diseases. The CBER NEURO Team's activities will include outreach to relevant stakeholder communities and identification of projects to advance product development.

The FDA Rare Neurodegenerative Diseases Task Force will work in partnership with FDA Center programs, such as the CBER NEURO Team and CDER's ARC Program, to share knowledge across FDA review staff and other relevant external stakeholders. The task force will also leverage the strengthened partnerships and expertise fostered by the ALS Science Strategy to work toward a greater understanding of disease pathophysiology and natural history for other rare neurodegenerative diseases. This is critical to advance drug development programs for rare neurodegenerative diseases.

FDA will coordinate across the Agency and leverage other comprehensive programs, including new efforts specified in the goals letter in anticipation of the Prescription Drug User Fee Amendments reauthorization for FYs 2023 to 2027,[16] to advance rare neurodegenerative research, including (but not limited to):

- Advancing Real-World Evidence (RWE) Program – seeks to improve the quality and acceptability of RWE-based approaches to support regulatory decision making, including approval of new indications of approved medical products or to satisfy post-approval study requirements.

[16] PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 through 2027. Congress is currently considering legislation to reauthorize the Prescription Drug User Fee Amendments.

- CBER Rare Disease Program – facilitates advancing development of CBER-regulated biological products for rare diseases through supportive activities and active collaboration with rare disease partners across the Agency.

- CDER Rare Diseases Team (RDT) – facilitates advancing development of CDER-regulated drug and biologic products by coordinating CDER rare disease policy, procedures, and training for the review of treatments for rare diseases and collaborating with external and internal rare disease stakeholders. The RDT serves as the program management office for the ARC Program.

- FDA Digital Health Center of Excellence – provides regulatory advice and support to the FDA's regulatory review of digital health technology.

- FDA Office of Orphan Products Development's Grant Programs – awards grants and contracts to clinical investigators to support the development of safe and effective medical products for patients with rare diseases. This Office is responsible for the activities under section 5 of the ACT for ALS.

- Rare Disease Endpoint Advancement (RDEA) Pilot Program – advances rare disease drug development programs by providing a mechanism for sponsors to collaborate with FDA throughout the development of efficacy endpoints.

FDA will use these programs and the knowledge accumulated from them to provide strategic direction on the challenges and solutions related to drug development for rare neurodegenerative diseases. FDA will also encourage stakeholders to leverage the accumulated knowledge by engaging in effective collaborations and robust communications.

Conclusion

FDA provides scientific leadership to advance and protect the public health. This action plan outlines the efforts FDA will engage in over the next five years to address the unmet medical needs of individuals with rare neurodegenerative diseases including ALS. Executing the ALS Science Strategy within this action plan will enhance FDA's ability to address substantive issues in ALS drug development, deepen its scientific expertise to enhance regulatory decision-making, and promote its collaboration with external stakeholders. The ALS Science Strategy will serve as an example for how FDA can systematically and strategically foster and advance drug development for rare neurodegenerative diseases.

FDA looks forward to continuing to engage with the rare neurodegenerative disease communities to facilitate the development and approval of therapies to treat these devastating diseases.