Frequently Asked Questions

ACT for ALS

A grant program at the National Institutes of Health (NIH) should be in line with the NIH mission of advancing research. What research value do Expanded Access Programs (EAPs) offer?

- EAPs do not offer the benefit of a placebo control, the recognized gold standard in clinical research, but EAPs **can** and **do** generate meaningful data by utilizing other comparison groups, such as natural history, synthetic controls[1], even potential AI forecasting[2], to learn about a treatment. They also are a valuable source of real world data (RWD) that can support clinical trial findings[3].
- Platform trials, which have been commonly used in oncology, but which are only beginning to emerge in the ALS field, offer another source of information. For example, the HEALEY ALS Platform Trial, run by leading ALS neurologists Dr. Sabrina Paganoni and Dr. Merit Cudkowicz, includes an Expanded Access Program that offers those living with ALS access to one of multiple drugs, providing comparison groups without employing a placebo control.
- If designed properly, EAPs can generate data on drug interactions, pharmacokinetics and dosing. EAP data can supplement clinical trial data in support of new drug applications. The FDA itself advocates for drug sponsors to employ EAPs to collect real world data in support of drug applications[4]. For example, EAP data can:
    - Support safety and efficacy of a **primary drug approval** application.
    - Build evidence for a **label expansion** to include subpopulations of people that were not included or eligible for the clinical trial.
    - Support positive **coverage determinations** by payors.
    - Inform future **clinical trial design**.
- EAP data may be especially important in rare diseases, like ALS, where, in the words of the FDA's Center for Biologics Evaluation & Research Director, Peter Marks, data from "every patient counts."[4]

[1] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7218288/
[2] https://www.nature.com/articles/s41598-019-49656-2
[3] https://bpspubs.onlinelibrary.wiley.com/doi/pdf/10.1111/bcp.14284?fbclid=IwAR3mTq1iY4ESuyf4e-VPMSK7GaC6oGNkguWLoHLpV3tJzTjmig8yfqDUUxQ
[4] https://pink.pharmaintelligence.informa.com/PS124296/Expanded-Access-Data-Can-Support-Approval-Decisions-US-FDA-Says

- Importantly, **EAPs are the only mechanism to learn about ALS in people who are further along in their disease progression**. The vast majority of clinical trials limit eligibility to patients within 24 months or less of symptom onset. This means that we are not collecting data about the disease or possible treatments in a majority of ALS patients. Building an EAP research program at NIH would help fill that gap in knowledge.

Would increasing Expanded Access Programs (EAPs) lead to investigational therapies negatively impacting clinical trial recruitment?

- ALS progresses too quickly for "prior use of an investigational drug" to be a major problem in clinical trial recruitment. Most people living with ALS, who on average live 2 to 5 years past diagnosis. will only have *time* for one trial.
- By the FDA's own definition[5], those who are eligible for a clinical trial are NOT eligible for expanded access programs. Therefore, promoting EAPs would NOT affect recruitment or retention in other clinical trials because they serve entirely different populations of people. Also, see this factsheet for more information on EAPs.
- The vast majority of ALS clinical trials limit eligibility to people whose symptoms began 18-24 months prior to recruitment. Most people living with ALS (estimated between 50% and 90%) do not meet this basic eligibility requirement, meaning they have no chance of gaining access to an investigational therapy if not for EAPs.
- The argument that ALS clinical trials would be harmed by EAPs was directly contradicted by two of the world's leading ALS clinicians during a hearing[6] before Congress on July 29, 2021.
- In summary, it is highly unlikely that someone who is eligible for an EAP would ever be eligible for a future clinical trial, because they would be excluded by their advanced disease progression.

How would an Expanded Access Program (EAP) grant program at NIH relate to the existing EAP program at the Food and Drug Administration (FDA)?

- The FDA EAP program is designed to provide an approval pathway for drug sponsors to offer an investigational treatment to people living with ALS on their own dime. The EAPs in this program may not be designed to provide high-quality research, because that is not the purpose of the program.
- A primary impediment to providing investigational treatments under expanded access is a drug manufacturer's willingness or ability to assume the costs necessary to make the treatment safely available to more patients.

[5] https://www.fda.gov/news-events/public-health-focus/expanded-access
[6] https://www.youtube.com/watch?v=nKXboU90z_E

- The proposed NIH grant program for EAPs would do two things: 1) make it possible for small drug developers to fund large expanded access programs for promising therapies and 2) incentivize drug developers to design EAPs that conduct rigorous research about later-stage treatment performance and/or ALS disease progression.
- Though the programs are distinct, it is likely that there will need to be substantial coordination between NIH and FDA to select and administer the grants under ACT for ALS section 2.
- This is an opportunity for INNOVATION -- something that is severely needed in ALS research.

Are there any concerns around the federal government paying for investigational drugs through Expanded Access Programs (EAPs)?

- The federal government pays for the development and delivery of investigational therapeutics all the time, particularly for rare diseases. Examples of federal funding for investigational therapies:
    - Operation Warp Speed and the COVID-19 vaccines.
    - The FDA's Orphan Products Grants Program[7].
    - Multiple NIH clinical research programs collectively spend over 10 million federal dollars each year.
- There is precedent for the federal government providing grants to small businesses for the purpose of developing biotechnology. NIH's Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs allow US-owned and operated small businesses to engage in federal research and development that has a strong potential for commercialization[8].
- Funding EAPs is in line with existing US government policies and guidelines, particularly the following:
    - FDA's own 2019 guidance on ALS drug development[9].
    - The Right to Try Act[10].
- The ALS community expects recipients of the EAP grant program to undergo a full and rigorous peer review process. The goal is NOT to get ALL experimental drugs on the street, the goal is to meaningfully expand access to the most promising treatments for this 100% fatal disease.

[7] https://www.fda.gov/industry/developing-products-rare-diseases-conditions/orphan-products-grants-program
[8] https://sbir.nih.gov/
[9] https://www.fda.gov/media/130964/download
[10] https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/right-try

What are the companies that are doing exciting work on ALS that would be eligible for the grant? Are there enough that this isn't just an earmark in disguise?

- Most of the big pharmaceutical companies have gotten out of ALS drug development, and most of the treatments currently in the pipeline are being developed by smaller companies with less cash on hand to fund large expanded access programs.
- There are more than 100 companies working on potential ALS therapies currently, most of which are small businesses. Some examples include:
    - Amylyx -- recently announced it will submit a new drug application to the FDA for AMX0035.
    - BrainStorm -- wanted to offer expanded access to its investigational therapy, NurOwn, but was unable to host an EAP due to cost.
    - Prilenia therapeutics -- neuroprotective drug Pridopidine is currently in Phase 2/3 trials.

Why aren't companies doing Expanded Access Programs (EAPs) today? What makes us confident that it is cost -- rather than manufacturing capacity -- that is the more significant barrier to bigger EAPs?

- The current FDA EAP program provides approval for drug sponsors to offer an investigational treatment to people at their own expense.
- Based on our conversations with sponsors, the primary impediment to providing investigational therapies under expanded access is the cost associated with safely administering it to a larger population.
- While certain therapies (e.g. stem cell based therapies like NurOwn) may have a longer production timeline, we have not heard any manufacturing or supply chain challenges that could not be remedied with additional funding.
- Feasibility of production would need to be considered on a case-by-case basis as part of the grant application and review process.
- The grant mechanism may even be designed to assist with timely manufacturing.