Frequently Asked Questions (FAQ) about Our Research Program, Experimental Therapies, and More

To help provide more information about our research program, our spending decisions, our approach to certain experimental therapies, and other matters, we have put together the below Frequently Asked Questions.

OUR RESEARCH PROGRAM

Can you describe the Association's approach to research?

The ALS Association funds the best research taking place, anywhere in the world. We are the world's largest private funder of ALS research and have funded hundreds of research projects and investigators and dozens of research collaborations. We are not limited to one lab – the world is our lab.

As much as we spend, though, the government and the private sector spend much more. This is why our advocacy efforts are so critical – to help secure significant amounts of funding for ALS research. Further, we use Association funds to complement and leverage other research funders and advance federal research spending through our advocacy program. For example, since the ALS Ice Bucket Challenge, the $40 million that we have invested in completed research projects directly generated more than $120 million in follow-on research grants from other funders. We have also invested in infrastructure, like programs to share scientific data and clinical samples, that have helped ALS investigators work together.

This leverage shows on a macro level as well. The National Institutes of Health spends five times more than we do on ALS research, and their spending on ALS has grown 82% since the ALS Ice Bucket Challenge through the end of Fiscal Year 2019. We work with Congress, the Centers for Disease Control and Prevention and the Department of Defense to dedicate additional research dollars to ALS and successfully helped to grow these funding sources by more than 30% compared to pre-ALS Ice Bucket Challenge levels. And, as in all disease spaces, we rely on pharmaceutical companies to fund the expensive final clinical trials needed to bring drugs to market.

How does the Association decide which research projects to fund?

We issue broad calls for research applications (RFAs) on specific topics and entertain applications from a diverse set of stakeholders including academia, industry and other nonprofit institutions. Each

application received by The ALS Association typically undergoes two stages of review. First stage is the letter of intent (LOI) stage where short preproposals are vetted by Association staff and advisors for novelty, feasibility and whether the idea is suitable for the RFA. Selected preproposal ideas are then invited to the second stage to submit full proposals, which are lengthier and more detailed. These full proposals are thoroughly vetted by an ad hoc review committee, which is a panel of scientists selected based on the expertise required for reviewing that particular RFA and who do not present a direct conflict of interest with regard to the investigator, institution or the scientific idea itself.

Each application is typically reviewed, scored and critiqued by two to three reviewers and are evaluated based on criteria that illustrate impact on ALS research, rationale/background for the proposed work, research strategy, operational feasibility and the team expertise/collaboration. The review committee makes funding recommendations based on our research budget to the ALS staff who then work with a committee of our Board of Trustees to select and approve projects for funding. It is important to note that there might be some projects where our funding is enough to cover the entire project idea, whereas others may receive funding that will cover partial costs and is expected to leverage our funding to obtain additional funding. It is also common for the Association to work with other ALS nonprofits to jointly fund research projects. Reviews and critiques are shared with awardees to make any revisions to the research plan based on recommendations from the review committee. Similarly, reviews and critiques are also shared with applicants whose projects were not prioritized for funding. This provides context for our funding decision and includes guidance on improving their proposal ideas for future re-submission. Once the funded projects are contracted, funding announcements are made to the community through various methods, such as listed on the Association website, social media, press releases and blog.

Why did the Association choose not to fund a certain research project?
There are four possible reasons why we would not fund a request:

1. It is not among the best projects we could afford to fund when the application was submitted;
2. It is a great project, but too expensive, and there is not a coalition of funding partners to make it work (The ALS Association works hard to find other funding partners to complement and accelerate ALS research);
3. It is out of scope (for example, we would decline requests to fund ALS treatment in foreign countries where the findings would not be relevant to Americans with ALS);
4. A researcher has not formally applied for funding.

Why doesn't the Association fund experimental treatments (such as NurOwn) for people living with ALS?
Drugs that are being tested in clinical trials are experimental. Because they are experimental, it is still unclear if they work or will cause additional harm to people with ALS. The entire trial process takes many years and usually totals more than $1 billion. We are committed to help improve the clinical trials process (see question below). Because of the time and expense, the scientific community has broken the clinical trial process into three discrete phases, with each phase being larger, more expensive and more difficult than the one before it. If a drug shows poor results in an early phase, we avoid the time, expense, and burden of a later phase trial. To get to the next phase, a drug must show promising results in the previous phase.

That means every experimental drug in a clinical trial has shown promising results in the previous trial. It also means the clinical benefit of that drug for people with ALS is still unknown. What we do know is that most drugs fail the clinical trial process at some point and may not achieve the clinical benefit we hope.

Because the odds of success of any single drug are poor, we work to ensure there are as many drugs being tested as possible. It would be irresponsible for the Association to divert funds away from scientific testing or care services to provide access to experimental drugs as if they were not proven treatments.

Why doesn't the Association fund Phase 3 trials?
The Association has never funded Phase 3 trials, the last and most expensive phase of clinical trial before approval. The costs and risks of such trials are too enormous. Once a trial reaches Phase 3, it is traditionally funded by pharmaceutical companies or organizations with greater resources (such as the National Institutes of Health) that can bear the impact if a trial fails or there are other costs, such as lawsuits. That is why virtually no patient advocacy organizations fund Phase 3 trials.

If The ALS Association were to spend a large portion of its assets on a Phase 3 trial, that expense would prevent us from funding research on many other smaller trials. If the Phase 3 trial fails (as is often the case), or even if it succeeds but does not result in a full cure for everyone with ALS, all the treatments that could have been tested would have been behind schedule, and people would have to wait even longer for an effective treatment. The ALS Association is best placed to seed fund many smaller trials and research initiatives to have more chances of one or two therapeutic approaches being successful. When these smaller trials show good results, we work with investors, drug companies, and regulators to make sure the testing process continues.

The Association funds projects across the research pipeline from basic science to better understand what causes ALS to drug development and biomarker studies and continues into funding Phase 1 and Phase 2 clinical trials. We are also open to funding Phase 4 (or post-market trials) after drug approval to gather real world evidence of drug efficacy and combination therapies. At the same time, the Association is focused on funding research that is aimed at improving the lives of people with ALS more immediately, such as assistive technology and caregiver/patient burden.

But didn't the Association fund a Phase 3 trial run by Cytokinetics?
No. We apologize for the confusion we created with an erroneous headline of a press release (which we have since corrected). In 2015, The ALS Association awarded $1.5 million to Cytokinetics for the collection of clinical data and plasma samples to advance the discovery of biomarkers in ALS in VITALITY-ALS, a Phase 3 clinical trial of tirasemtiv in patients with ALS. This is not Phase 3 funding, as the purpose of the grant was to enable plasma samples collected from patients enrolled in a Phase 3 clinical trial to be added to The Northeastern ALS Consortium (NEALS) Repository, an open resource for the scientific community to identify biomarkers that may help to assess disease progression and underlying disease mechanisms in ALS. This funding of add-on projects to already existing Phase 3 trials could help benefit not only that particular trial but future trials, as well.

SPECIFIC EXPERIMENTAL THERAPIES

Why doesn't the Association fund NurOwn, T-regs, and CuATSM right now?
These three experimental therapies are promising, but they are still experimental. As of Aug. 1, 2019, there are more than 30 experimental treatments in clinical trials. While some therapies may show benefit in certain individuals, we cannot be certain that these benefits are due to the treatment, or are likely to occur for others, until the testing is complete. It is critical that we fund as many treatments as possible to advance them through the clinical trials process, rather than risking most of our resources on individual therapies.

Why did The ALS Association previously not fund NurOwn?
BrainStorm initially applied for funding in 2012, and its clinical trial proposal was peer-reviewed by a panel of experts in the field of ALS and related disorders. The committee did not select the project for funding in that cycle due to competing trials which were prioritized.

Why isn't the Association supporting BrainStorm now?
We certainly support BrainStorm applying to the FDA to expedite bringing NurOwn to market, whenever BrainStorm thinks it is ready. We hope that BrainStorm's NurOwn trial is successful and that thousands of people living with ALS, and those in the future, will benefit. We continue to have discussions with the leadership of BrainStorm, as well as conversations with the FDA around NurOwn and other treatments.

How much funding has The ALS Association given to the T-regs project? Will there be additional funding?
We are proud to have supported Dr. Stan Appel's T-regs immunotherapy project, which started out as a mouse model experiment and has since advanced to Phase 2 trials in humans. The ALS Association has so far provided over $1.4 million to T-Regs trials, both at Dr. Appel's clinic and at other sites. We have funded him in partnership with ALS Finding a Cure and MDA, who have contributed additional resources.

How much funding has The ALS Association given to the CUATSM project? Will there be additional funding?
Dr. Joseph Beckman at Oregon State University conducted the initial studies of the impact of CuATSM in an ALS SOD1 mouse model. The ALS Association funded this study in 2016 for $300,000 with support from the Oregon and Washington Chapter. They found compelling results showing that administration of CuATSM significantly slowed the progression of ALS in these mice allowing the mice to reach their normal lifespan. Normally the mice would die within two weeks without treatment. With treatment, some mice survived more than 650 days.

The company Collaborative Medicinal Development (CMD) is planning to launch a Phase 2 randomized, placebo-controlled clinical trial for CuATSM to confirm these results in Australia later this year. This trial will involve a larger number of participants and to further test safety and efficacy. We are not aware of plans to expand the study outside of Australia into the United States, Canada and/or Europe.

Currently, the Association is not funding the Phase 2 trial, but CMD is welcome to apply for funding through the Association's research program.

ALS ICE BUCKET CHALLENGE IMPACT

Why hasn't the Association spent all the ALS Ice Bucket Challenge money?
We have spent or committed all the funds that were raised through the ALS Ice Bucket Challenge. The Challenge generated $115 million for the national office of The ALS Association in 2014. Since 2014, we have spent and committed more than $131 million toward our mission, including more than $89 million committed to fund worldwide research collaborations. We have leveraged the awareness raised by the Challenge to raise even greater revenues since then. We currently are spending more money than we are taking in.

In the four years prior to ALS Ice Bucket Challenge, the Association's national office raised an average of $20.2 million per year in revenue while spending $17.5 million per year, including $12.3 million in program expenses. By contrast, in the four years since the Challenge (not including the actual year of the Challenge) the national office has averaged $28.4 million in revenue while spending an average of $35.7

million, including nearly $29 million on program expenses. This means the national office is spending almost 2.5 times what we previously spent per year on our mission. The Association has devoted a page on our website to provide a list of how those funds are being spent. You can view those investments here.

What was the result of all that ALS Ice Bucket Challenge spending?

The ALS Ice Bucket Challenge was transformative for us and other ALS organizations. It spurred a massive increase in the Association's capacity to invest in promising research, the development of assistive technologies, and increased access to care and services for people with ALS. We previously spent between $4-6 million per year on research, and we now invest between $17-19 million per year.

Since the Challenge, we're also assisting more people with ALS. The number of people with ALS served by our chapters has increased 28% from 15,731 in fiscal year 2015 to 20,101 people served in fiscal year 2018. In addition, The ALS Association has established more Certified Centers of Excellence and Recognized Treatment Centers.

Some research highlights:

- Association-funded researchers have identified five new genes linked to ALS, including KIP5A, C21orf2, NEK1, TBK1, and TUBA4A (Nicolas et al., 2018; The ALS Association, 2018). [https://www.scientificamerican.com/article/ice-bucket-challenge-credited-with-als-breakthrough]

- The Association funded The Neuro Collaborative, which developed new "antisense" drug therapies that target two common ALS genes and are being tested in clinical trials (The ALS Association, 2018; Washington University School of Medicine, 2018).

- Three other clinical trials acknowledging sponsorship from the Association have been registered on ClinicalTrials.gov, including trials for two additional drug therapies (Barrow Neurological Institute, 2018; Wainger, 2018) and an e-Health program promoting healthy weight in ALS patients (Massachusetts General Hospital, 2018).

- Between 2014 and 2018, the Association awarded more than 300 ALS research grants to more than 200 different scientists.

- Grantees reported that their Association funding accelerated their research productivity and enabled them to form collaborations not only with other researchers but also with clinicians and patients.

- One of the most common achievements that grantees reported was identification of new therapeutic targets. Participants also reported gene discovery, initiation or completion of one or more clinical trials, and identification of new biomarkers.

Some care services highlights:

- The number of people with ALS served by our chapters has increased 28% from 15,731 in fiscal year 2015 to 20,101 people served in fiscal year 2018.

- After the ALS Ice Bucket Challenge, the Association increased access to the highest standard of care around the country. We funded 29 new ALS Certified Treatment Centers of Excellence and 20 new Recognized Treatment Centers, raising the total number of Association clinics offering state-of- the-art care from 34 to 90, a 165% increase. Key clinicians described how the Association's clinical program grants fostered more multidisciplinary, holistic services. Clinical improvements included home visits, caregiver support, nutrition services, social services, and health navigation.

Why does the Association have $90+ million in reserves?
The ALS Association is spending far more money than it is generating, even as revenues have grown. Overall, since the ALS Ice Bucket Challenge, the national office of The ALS Association has spent nearly $160 million. Since Feb. 1, 2015, after the Challenge ended, the national office of The ALS Association has generated nearly $114 million in revenue.

We are running a deficit of several million each year, even as we have taken on multi-year commitments to clinics and research studies. We need cash reserves to ensure we can fulfill our commitments to the ALS community, even if the economy changes and we experience a loss in revenue.

Many of the research commitments we have made since the ALS Ice Bucket Challenge are multi-year commitments, meaning that we will spend the money in the future only when certain benchmarks are met. (Thus, even though we've committed over $82 million to research, some of that continues to show up on the asset line of our IRS form 990.) This enables us to ensure the most promising research continues to be funded over many years, and if those benchmarks aren't met, we're able to fund other projects.

Before the ALS Ice Bucket Challenge, you had much less in operating reserves, why do you need more now?
Because our commitments have dramatically increased. In the four years prior to ALS Ice Bucket Challenge, the Association's national office raised an average of $20.2 million per year in revenue while spending $17.5 million per year, including $12.3 million in program expenses. By contrast, in the four years since the Challenge (not including the actual year of the Challenge) the national office has averaged $28.4 million in revenue while spending an average of $35.7 million, including nearly $29 million on program expenses. This means the national office is spending almost 2.5 times what it previously spent per year on our mission.

The Association cannot fall back to expenditure levels prior to the Ice Bucket Challenge. Too many scientific projects and clinics depend on our funding. Until we reach a sustainable level of funding, we will continue to rely on deficit spending. We can't stop supporting the new clinics we helped open or do anything to slow the pace of scientific discovery until we have a world without ALS.

OUR ADVOCACY EFFORTS

What is the status of the FDA Guidance Document?
The ALS Association has led the FDA Guidance Document effort from the beginning, and we continue to request that the FDA expedite the final guidance document. Prior to the community-led guidance and the resulting draft FDA guidance on ALS Drug Development, there was no specific clarity around the FDA's expectations for companies developing ALS therapies. An FDA guidance in draft form serves this purpose even before it is finalized. The ALS Association also convened a community workshop to provide further insights on ways in which the draft FDA guidance could be strengthened. The FDA is working on a final ALS guidance and has said there is "movement" toward completion. We have requested that the FDA act more urgently and have indicated we're willing to help expedite the guidance.

What else are you doing to improve the clinical trials process?
In addition to preparing the first ever Drug Development Guidance for ALS, The ALS Association also helped to lead the development of the ALS Clinical Trial Guidelines (published in March 2019) and held a workshop in 2018 with the FDA, people living with ALS and caregivers and academic experts on ALS Therapy Development and Regulatory Pathways. The ALS Association also funds the NEALS consortium

of clinical trials which offers expert advice on trial design for anyone wanting to work on ALS in the United States.

Why doesn't the Association support an Executive Order from the President to make NurOwn (or another treatment) available?

It remains unclear how an executive order would have any effect, given that the administration cannot create new legal authority for the FDA – only Congress can do that. The ALS Association strongly supports all effective ALS therapies making it to market – and to people living with ALS – as soon as possible. The ALS Association also believes the best path for the review and approval of potential therapies is through the appropriate channels at the FDA including through the expedited approval pathways available to drug developers such as Accelerated Approval, Priority Review, Fast Track, and Breakthrough Therapy designations. The ALS Association's advocacy and leadership are working hard behind the scenes through meetings and calls with numerous stakeholders to try to ensure that treatments get to people with ALS as quickly as possible.