Expanded Access Program FAQs
December 2023/Jan 2024

Expanded Access Investigational New Drug (EA IND) Applications

Q: Are patients already being treated under an ongoing intermediate-sized EA INDs eligible to be included in the studies of that same intervention proposed under RFA-NS-24-029?
A: Inclusion of patients currently treated under existing Intermediate-sized EA INDs may participate in studies proposed under RFA-NS-24-029 if their inclusion may aid proposed research goals. However, applicants are strongly recommended to expand existing EA INDs and prioritize resources to support the addition of new patients not currently treated through expanded access.

Q: How many patients can be included in an intermediate size expanded access protocol?
A: Intermediate size expanded access supports more than one patient and can include hundreds or thousands of patients. There is a link to the FDA website defining intermediate size population in the beginning of the RFA text and Expanded Access Categories for Drugs.

Q: How does FDA's review of expanded access requests intersect with NIH's grant approval process?
A: EA IND authorization is conducted through the FDA. Per the RFA, applicants to RFA-NS-24-029 must submit their EA IND by the time of application, and the EA IND must be allowed to proceed prior to award. NIH is not involved in the review or authorization of EA INDs.

Q: Can RFA-NS-24-029 support studies approved under Open Label Extensions?
A: No, studies under Open Label Extensions would not be eligible per the RFA. The proposed study must be conducted under an intermediate-sized EA IND that is in effect.

Q: Can a third party submit and secure IND approval? Is a third party eligible to be the sponsor for the trial?
A: Per the ACT for ALS legislation and RFA, the sponsor of the Phase 3 ALS clinical trial IND should be an eligible drug sponsor. Drug sponsor eligibility is defined in the ACT for ALS legislation and RFA. There are no eligibility requirements for the EA IND sponsor.

Q: Is it possible for two or more PIs to apply for EA IND?
A: EA IND authorization is a function of the FDA. Please contact the FDA with specific questions about their expanded access IND application process. Guidance and contact information can be found at .

Q: How will NIH ensure that the data from these studies will be shared broadly?
A: All NIH-funded awards are subject to a Data Management and Sharing (DMS) policy that promotes the sharing of scientific data generated from research funded or conducted by NIH. In addition, detailed expectations for data sharing are included in the request for application (RFA-NS-24-029: Amyotrophic Lateral Sclerosis (ALS) Intermediate Patient Population Expanded Access (U01 Clinical Trial Required) (nih.gov)) and the "Notice of Award" of all NIH-funded EA studies in ALS. This includes: 1) Submission of a complete de-identified dataset containing all variables collected in the intermediate EA protocol for ALS to NINDS for data sharing within an agreed upon timeframe; 2) registration of the intermediate EA protocol for ALS with Clinicaltrials.gov, a publicly accessible database of federally and privately supported research trials to test the effect of treatments and procedures for a wide range of diseases

and conditions; and 3) publication of study results in compliance with the NIH Public Access Policy (see NOT-OD-08-033 and the Public Access website) and in a timely manner (for example, the primary study results are expected to be submitted for publication in a peer-reviewed journal within one year of completion of the follow-up of study participants).

Small Business Eligibility

Q: How is small business concern eligibility determined?
A: A "small business concern" is defined by section 3(a) of the Small Business Act (15 U.S.C. 632(a)). The definition of a small business is complicated, so we encourage you to reach out to discuss eligibility criteria. NINDS cannot determine eligibility, but we can help you work through the criteria.

Q: Please comment on the small business definition requirement for companies who are 50% or more owned by private equity, venture capital firms. Once a biotech company has gotten to a Phase 3 trial, it is likely that given the amount of capital needed to get that far they will be over 50% owned by such firms.
A: Small businesses can be eligible and be more than 50% owned by venture capital firms or private equity. The key is that no one company or organization can own more than 50% of the business unless that organization is itself a qualifying small business. Please see the NIH Small business Education and Entrepreneurial Development (NIH SEED) website that has the more reader-friendly small business criteria. RFA-NS-24-029 contains a link to the Small Business Act where this is defined. We welcome discussing the criteria, although we note that NIH cannot make the determination of eligibility; instead, the drug sponsor must certify their eligibility as a small business within the application.

Q: Can the small business concern drug sponsor apply directly to RFA-NS-24-029?
A: No. Consistent with the ACT for ALS, RFA-NS-24-029 states that "Eligible applicants must be clinical trial sites that participate in a Phase 3/efficacy clinical trial supported by a small business concern that is the FDA-designated sponsor of a drug or biological product which is the subject of an IND under section 505(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)) to prevent, diagnose, mitigate, treat, or cure ALS."

Q: Can we apply as a company separately as well to NIH for the EAP program?
A: Applicants to RFA-NS-24-029 must be clinical trial sites that participate in a Phase 3 clinical trial for ALS sponsored by a qualifying small business concern. The small business drug sponsor cannot apply directly to RFA-NS-24-029. It is anticipated that the small business drug sponsor may be a partner in the project, such as a sub awardee or vendor.

Q: If a foreign company is conducting research in the US, is the center or network they are working with able to apply for the grant?
A: ACT for ALS language specifies that the qualifying Phase 3 clinical trial in ALS sponsor must be a U.S.-based small business. The drug sponsor itself must qualify under the Small Business Administration's definition of a small business, which includes being based in the U.S. in addition to other criteria. If it's the case that the applicant is a U.S. Phase 3 clinical trial site sponsored by a foreign-based company, it's unlikely to qualify for this RFA. However, the definition of a small business is complicated, so we encourage you to reach out to discuss eligibility criteria. NINDS cannot determine eligibility, but we can help you work through the criteria.

Q: As a small business foreign entity, what is the best funding opportunity for assistance with conducting a Phase 2 trial under an IND?
A: The NeuroNEXT clinical trial network run by NINDS is designed to run Phase 2 clinical trials for neurological diseases. A foreign drug sponsor may be allowed for this program. We encourage you to reach out to discuss the appropriate funding opportunity for your specific projects.

Q: Are STTR grants for technologies related to rehabilitations strategies to maximize quality of life included in funding opportunity?
A: Not through this RFA, but there are STTR funding opportunities applicable to this type of research. This RFA is not a SBIR/STTR funding opportunity, and, in fact, the small business is unlikely to be eligible as the applicant. The applicant needs to be the Phase 3 clinical trial site. Those kinds of projects, rehabilitation for ALS, are in scope for STTR funding opportunities that NINDS and other NIH ICs participate in. Please reach out to learn more about these opportunities.

Q: Are devices eligible for this EA program?
A: No, devices are not eligible for this program. However, NINDS does have other funding opportunities to support clinical testing of devices in ALS and other neurological indications outside of this RFA. If this is your focus, please reach out for further information.

Clinical Trial Phase and Sites

Q: Does the qualifying ALS Phase 3/efficacy clinical trial need to be ongoing at the time of application?
A: The IND for the ALS Phase 3/efficacy clinical trial must be active at the time of award for applications selected for funding under RFA-NS-24-029.

Q: Does the drug have to be in a Phase 3 trial (listed as 'recruiting"), before the application deadline, in order to be eligible for this RFA?
A: For the Phase 3 clinical trial IND, that IND needs to be in place or awarded by the FDA by the time of the award. The trial does not need to be active or recruiting at the time of the application. For the expanded access IND, you must submit the intermediate size EA to the FDA no later than the date of the submission of the application. FDA allocates 30 days to review and approve these protocols so we do anticipate that the EA IND will be active by the time of award. To that question specifically, the Phase 3 trial does not need to be recruiting at the time of application.

Q: If my Phase 3 trial has completed, am I still eligible?
A: If the regulatory determination has NOT been made regarding approval, it is eligible for this RFA. In other words, the drug or biologic must not be approved under a New Drug Application or licensed under a Biologics License Application. Once the drug or biologic is approved by the FDA, it becomes ineligible.

Q: How is NIH interpreting the "Phase 3 clinical trial" requirement? Are Phase 2/3 trials eligible? What about Phase 3 trials that have concluded but are awaiting regulatory consideration?
A: Phase 2/3 trials, ongoing Phase 3 trials, and concluded Phase 3 trials are eligible until a regulatory determination has been made regarding approval. As noted in the RFA, and consistent with the ACT for ALS, the investigational drug proposed under RFA-NS-24-029 must not be approved under a New Drug Application (NDA) or licensed under a Biologics License Application (BLA).

Q: When we went through TA of the 3 iterations of the bill, we initially had Phase 2 eligibility, but Congress changed it to just Phase 3 so as to ensure government money wasn't spent on a drug that had not proven some efficacy in a Phase 2 trial. E&C and HELP staff were particularly adamant about this. Does NINDS weigh this into their decision about Phase 2/3 trials?
A: The RFA language defines Phase 3. In our FAQ, we have stated that that definition includes Phase 2/3 trials, such that an IND for an ALS trial that is a combined Phase 2/3 trial would be eligible. The reasoning for this is that phasing is not always distinct. In these cases, the Phase 2/3 trial is the final study that FDA uses for approval.

Q: We have a large number of participating clinical sites in our study. Do we need site interest letters signed by all participating sites? Do signatures need to include the Business Official and Principal Investigator (PI)?
A: While interest letters are not required for all participating sites, they are recommended, particularly when recruitment may be a potential issue in the proposed study. While signatures from both the Business Official and PI are recommended, the PI signature alone is adequate.

Q: Are all Phase 2 clinical trials eligible, such as Phase 2A or 2B?
A: Investigational drugs in Phase 2a stage or Phase 2b stage clinical trials are not eligible under the RFA. Investigational drugs in a clinical trial staged as Phase 2/3 or Phase 3 are eligible.

Q: Please clarify whether "in Phase 2/3 trial" is defined as having received "To Proceed Letter " from FDA or the trial has already enrolled the first patient.
A: The IND of the eligible Phase 2/3 or Phase 3 ALS trial must be approved prior to award.

Q: Will this grant program fund a Phase 1/2 clinical trial of a new chemical entity?
A: No. Only Phase 2/3 trials, ongoing Phase 3 trials, and completed Phase 3 trials awaiting regulatory determination has been made regarding approval are eligible for this RFA. Phase 1/2 are not eligible for this RFA.

Q: Would an investigational product that is in late phase development for another indication be eligible through this RFA?
A: The investigational product must be in an ALS Phase 2/3 trial, ongoing ALS Phase 3 trial, or awaiting regulatory determination after a completed ALS Phase 3 trial. An investigational product in late Phase development for another indication is eligible as long as the product is also being investigated in an ALS Phase 3/efficacy clinical trial.

Q: Are other rare neurodegenerative diseases eligible for the EAP funds?
A: Only ALS studies are eligible for this RFA.

Q: Do all clinical trial sites need to be identified for the application?
A: The RFA does not require that all clinical sites be identified in the application. However, as stated in the Section 5 of RFA-NS-24-029, reviewers will evaluate “Approach” as part of the review process. This would include aspects of recruitment, retention, trial design, and proposed study populations which may be supported by providing detailed information on the clinical study within the application such as the proposed clinical sites.

Q: Does the PI of the Expanded Access Program need to be the lead PI of the ALS Phase 3 clinical trial?
A: The PI of the application for the Expanded Access study does not need to be the Phase 3 clinical trial lead PI; however, the application must be from a clinical trial site for the ALS Phase 3 clinical trial for that product.

Q: If a study is halted due to futility, but the IMP appears to be beneficial to a subgroup of participants, would this be considered?
A: Funding for the EA protocol will continue until the withdrawal or termination of the IND for the investigational agent by the sponsor or a decision by the FDA to put the EA protocol on hold, e.g., should information emerge that alters the acceptability of the EA use

Budget and Funding

Q: Will there be future funding and future RFAs to support this effort?
A: Future funding and future RFAs will be determined by congressional appropriations for this program. As with all NIH-funded awards, funding of future years depends on availability of funds.

Q: Regarding the NINDS total $40 million funds available for FY 2024 awards (3-5 awards), are these awards representing the TOTAL budgets for the full projects, or just Year 1 of the projects?
A: NINDS intends to commit up to $40M to applications to RFA-NS-24-029 in FY 2024, contingent upon appropriations. NINDS expects these funds will be allocated to the first-year budget periods of funded projects.

Q: What are the allowed and non-allowed budget items? Are there NINDS guidelines for what can be included in an EAP grant application budget (e.g., CRO, lab collection, etc.)?

A: Per RFA-NS-24-029 Section IV. Application and Submission Information, funds may be requested for:

- Payment to the manufacturer or sponsor for the direct costs of the investigational drug or biological product of the intermediate EA protocol for ALS, as authorized under section 312.8(d) of title 21, Code of Federal Regulations (or successor regulations)
- Direct costs incurred in providing such drug/biological product consistent with the research objectives of the grant
- Direct and indirect costs of participating clinical trial sites in conducting research with respect to such drug/biological product
- Personnel effort, support for study participant travel/meals, and other budget items within the overall budget cap to ensure that this goal of appropriate inclusion is met
- Costs associated with the Data Management and Sharing Costs may be included in the budget:
    - Curating data
    - Developing supporting documentation
    - Formatting data according to accepted community standards, or for transmission to and storage at a selected repository for long-term preservation and access
    - De-identifying data
    - Preparing metadata to foster discoverability, interpretation, and reuse

- Local data management considerations, such as unique and specialized information infrastructure necessary to provide local management and preservation (for example, before deposit into an established repository).
- Preserving and sharing data through established repositories, such as data deposit fees.
- If the Data Management & Sharing (DMS) plan proposes deposition to multiple repositories, costs associated with each proposed repository may be included.

Q: Will the grant funding available help fund clinicians and clinic staff who often incur the direct and ancillary costs of administering expanded access programs?
A: Costs associated with the treatment and research proposed under RFA-NS-24-029 are eligible per the RFA, the following costs are allowed:

- Payment to the manufacturer or sponsor for the direct costs of the investigational drug or biological product of the intermediate EA protocol for ALS, as authorized under section 312.8(d) of title 21, Code of Federal Regulations (or successor regulations)
- Direct costs incurred in providing such drug/biological product consistent with the research objectives of the grant
- Direct and indirect costs of participating clinical trial sites in conducting research with respect to such drug/biological product
- Personnel effort, support for study participant travel/meals, and other budget items within the overall budget cap to ensure that this goal of appropriate inclusion is met

Q: Does the applicant need an EA IND "may proceed" response before submitting a grant application to NIH? Are there requirements for an EAP start date following grant award?

A: The EA IND request should be submitted to the FDA on or before the date the RFA application is submitted. Based on the FDA expanded access review timeline, it is anticipated that the EA IND will be authorized prior to award, and that the expanded access research study funded through the RFA will begin at or shortly after the time of award. Start-up activities preceding initiation of the expanded access study are allowable under RFA funding with sufficient justification.

Study Design and Review

Q: Could you highlight some elements that will be important from the review perspective?
A: In addition to providing expanded access to these therapies, one of the main goals of these applications should be to address a research question relevant to ALS. The reviewers will focus on the research question and will use review criteria published in Section V of the RFA. Typically, the major drivers are the approach, rigor of the proposed experiments, and significance of the research question. There will also be evaluation of the impact and how the program will not detract from or interfere with any ongoing clinical trials.

Q: Given NINDS' focus on the need for biomarkers in the Strategic Plan, will NINDS ensure that every drug sponsor measures biomarkers?
A: Applicants are not required to include biomarkers in their proposals. Reviewers will review any research questions that are proposed. The RFA suggests that applicants could include biomarker collection and analysis, but collection of safety outcome information, survival, other significant medical events, patient experience data that is not specifically tied to efficacy, etc., are also acceptable. Outside of this RFA, NINDS recently released a Notice of Special Interest (NOT-NS-23-062) on a number of

funding opportunities related to ALS, including opportunities for clinical data harmonization and biomarker studies.

Q: Given that the goal of the bill was to provide EAP to as many people as possible, how does NINDS decide how many sites to approve so as to minimize administrative and IRB costs and to maximize treatment funding?

A: These studies are designed by investigators. Investigators propose the study sites, number of participants, and budget in their grant application to NIH. NIH reviews and funds grant applications using established grant review processes. If the grant application is deemed meritorious (i.e., scientifically rigorous and important) by peer review and if there are sufficient funds, NIH funds the entire project as proposed by the applicants and does not make decisions at the level of individual study sites unless a concern is explicitly raised during peer review.

Q: Can you confirm that only the large percentage of people who have NOT ever qualified for a clinical trial will be given treatment through expanded access with ACT for ALS funds?

A: The RFA states that applicants must address this issue. The ACT for ALS legislation requires that the EAP should not impede on ongoing clinical trials. The intent is to focus expanded access for individuals that are not otherwise eligible for investigational drugs. The applicants do have to address how their expanded access plans will not interfere with ongoing clinical trials.

Q: How will the ALS community be involved?

A: Per the RFA, applicants are strongly encouraged to establish relationships with patient advocacy groups and solicit their input on recruitment (including equitable access to investigational drugs by minority and underserved populations), the clinical meaningfulness of the question under study, the relevance of the proposed clinical outcomes, and approaches to minimizing the burden on study participants. Additionally, NIH will include people affected by ALS (people living with ALS, caregivers, or people at risk for developing ALS) in the Scientific Review Group (also known as a study section) that is the first level of review for applications.

Q: What are the necessary components of a complete grant application for both the drug sponsor and research institution?

A: Please see these annotated application forms for a list of application components.

Q: What is a typical length of period of performance?

A: The period allowed is up to four (4) years, though no "typical" period length has been established given the newness of the program. The period of performance should be informed by the project plans, and applicants should consider time for recruitment, time necessary for the sites you are working with, the availability of the drug you are proposing, etc. All of these are factors that would determine a reasonable period of performance for your particular period within the limit of four years. Four years are not required.

Q: Section 2 of ACT for ALS, which authorizes the expanded access grant program, sunsets on September 30, 2026. What happens to grants that have been awarded before that date but have not yet completed the expanded access study?
A: NIH will not award new grants after that date. However, grants that have been awarded before September 30, 2026 will be allowed to continue until the project end date. Funding for grant awards will continue to be contingent upon appropriations.

Other

Q: How can I participate in an expanded access trial?
A: NIH is not involved in recruitment. The clinical sites or networks that receive grants through this research program are responsible for all aspect of recruiting study participants.

Q: Is an EA clinical trial required to post in clinicaltrials.gov?
A: Yes. Like any other clinical trials, registration in clinicaltrials.gov is required for these expanded access research programs.