Section 1. Overview Information

Participating Organization(s)	National Institutes of Health (NIH)
Components of Participating Organizations	National Institute of Neurological Disorders and Stroke (NINDS)
Research Opportunity Title	**Gene Therapy Consortium (GTC) for Gene-based Clinical Trials Conducted within NeuroNEXT (OT2)**
Activity Code	OT2: Application for an Other Transaction Agreement
Research Opportunity Number	OTA-23-012
Related Notices	RFA-NS-22-029
Key Dates:	Posted Date: 09/18/2023
	Open Date (Earliest Submission Date): 10/20/2023
	Application Due Date(s): 10/20/2023
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Section 2. Objectives of this Opportunity

The purpose of this research opportunity announcement (ROA) is to fund the establishment and operation of a Gene Therapy Consortium that provides advice on gene-based and gene-targeted therapies proposed for clinical trials conducted within the Network of Excellence in Neuroscience Clinical Trials (NeuroNEXT).

Background:

The National Institutes of Health (NIH) reports that nearly 7,000 rare diseases affect more than 25 million Americans. In the United States (US), based on the definition created by Congress in the Orphan Drug Act of 1983 and adopted by the FDA, a rare disease is defined as a condition that affects fewer than 200,000 people in the US. Ultra-rare diseases affect substantially fewer people, less than or equal to 6,000; in the US, this equates to as few or fewer than one in 50,000 people. Approximately 95% of rare diseases, including ultra-rare diseases, have no FDA-approved

therapeutic available and an estimated 80% of rare diseases have an identified genetic origin. These rare diseases are often due to pathogenic variants in a single gene that alter gene product function. Many rare and ultra-rare diseases are caused by different pathogenic variants, some of which may be unique to a single individual or to a very small number of individuals. Many of these rare diseases are serious or life-threatening conditions. The overall economic burden of rare diseases is $966 billion, of which 43% ($418 billion) are direct medical costs and 57% ($548 billion) are indirect costs associated with productivity losses ($437 billion) and non-medical costs, ($111 billion). Cumulatively, these diseases represent a large unmet medical need as there are few available effective treatments and limited commercial incentive for therapeutic development. Successful gene-based therapies for some genetic diseases, such as spinal muscular atrophy, have fueled promise for the rarest of diseases and reports of custom-designed treatments for individual patients have gained public attention. Such efforts present challenges for safety and efficacy research, regulatory approval, and business processes built around larger patient populations.

NINDS supports gene-based therapy research through the Ultra-Rare Gene-based Therapy (URGenT) program. The URGenT program is a major initiative funded by the NINDS to provide bench to bedside resources that remove impediments to gene-based therapy development. Specifically, it is a late-stage pre-clinical therapy development program that aims to address challenges of gene-targeting technologies, de-risk these approaches for industry adoption, and coordinate their entry into clinical trials. URGenT facilitates data standardization and sharing, allocation of resources, and engenders best practices across diseases to make therapy development for rare and ultra-rare diseases more efficient and accessible. It supports Investigational New Drug (IND)-enabling studies and planning activities for First-in-Human clinical testing.

NINDS now intends to expand the URGenT program to support conduct of gene-based therapy clinical trials for ultra rare neurological diseases (URGenT clinical trials) following IND acquisition. The addition of clinical trials to the URGenT program will expedite progression of an asset from the pre-clinical to clinical phase, thereby accelerating the time course of gene therapy development. The URGenT clinical trials program will not be limited to assets developed through the URGenT pre-clinical program: applicants may apply to this program directly at the clinical trial stage.

URGenT clinical trials may be conducted within the NeuroNEXT clinical trial network. NeuroNEXT provides funded infrastructure to efficiently conduct multiple, scientifically sound, possibly biomarker-informed exploratory clinical trials evaluating the most promising therapies, and to facilitate collaborations between academia, industry, non-profit foundations, government organizations, and other possible stakeholders. The network consists of a Clinical Coordinating Center (CCC), a Data Coordinating Center (DCC), and geographically distributed clinical sites. Additionally, NeuroNEXT can include ad hoc clinical sites for particular clinical trials, if needed. The network utilizes a central IRB of record and other central resources, including central pharmacy and laboratory facilities. Clinical trials conducted in NeuroNEXT undergo strong scientific vetting. Awarded projects must meet milestones for progress to advance through successive phases of support.

This ROA will allow funding of a Gene Therapy Consortium (GTC) consisting of members with expertise in gene-based and gene-targeted therapies, ultra-rare and rare diseases, and clinical trial planning and execution, with particular emphasis on first-in-human or first-in-disease trials, small clinical trials, and adaptive trial designs. The GTC will be organized by the NeuroNEXT CCC and will provide support and advice as requested for trials proposed for and/or conducted within NeuroNEXT.

Objectives:

With this ROA the NeuroNEXT CCC will establish the GTC. The GTC will provide support and advice on gene-based clinical trials to facilitate the design and conduct of scientifically rigorous trials and to establish harmonized best practices for early-stage clinical trials involving gene-based

therapies for ultra-rare neurological disorders. The GTC will work in collaboration with the NeuroNEXT CCC, DCC, clinical trial PI, and relevant sites. Sites involved in an URGenT clinical trial conducted within NeuroNext may be NeuroNEXT sites or external sites depending on individual project needs.

Scope:

The scope of this ROA includes, but is not limited to:

- Development of an organizational plan that outlines the following:
    - GTC structure
    - GTC Standard Operating Procedures (SOP)
    - Methods for collaboration and dissemination of information between GTC and other stakeholders, including managing conflicts of interest and confidentiality agreements
    - Plans for start-up activities
- Recruitment/appointment of GTC members with appropriate expertise
- Development of a detailed timeline and milestones for establishment and operation of the GTC to include creation of the consortium's Articles of Collaboration, defined below.

Articles of Collaboration:
Articles of collaboration are a set of rules, created by the consortium, which will govern the consortium under the proposed project. This document sets down policies and procedures that are unique to each team of individual awardees. There are no limits to what may be covered, but at a minimum, the following questions must be addressed:

- Who are the members of the governance team? Who is in charge? How will new members be added? How will members leave the consortium?
- How will leadership be changed? Are all members committed to the project by sharing resources and by communicating among themselves?
- Who is responsible for what programmatic, financial, or technical tasks?
- If one member is authorized by the others to sign an agreement, and any modifications, on behalf of the others, who is that member and what, if any, are that member's limits?

Once the award is granted, the GTC scope of work may include but is not limited to:

Conceptual phase

- Providing feedback on pre-application materials for proposed URGenT clinical trials
- Offering guidance in the development of URGenT clinical trial protocols

Planning phase

- Providing guidance and assistance in the finalization of the clinical trial protocol and consent form
- Actively participating in regular investigator meetings

Implementation phase

- Ensuring proper protocol implementation and adherence throughout the trial process
- Providing guidance on adverse events and protocol deviations
- Actively participating in regular investigator meetings

Analysis phase

- Collaborating with protocol investigators on manuscript preparation
- Providing guidance on regulatory reports as necessary

Please note that the objective of this ROA is to request applications to establish and operate the GTC, not clinical trials. Clinical trial proposals will be requested and through separate ROAs.

Section 3. Potential Award Information

Authority:

This Research Opportunity Announcement (ROA) is issued with the goal of establishing an "other transactions" agreement for funding the establishment and operation of a Gene Therapy Consortium. OT Agreements are used to fund gene therapy clinical trials through the URGenT program, pursuant to OT authority described in section 402(n) of the Public Health Service Act, 42 U. S. C. 282(n).

Section 4. Eligibility

Organizations:

The following entities are eligible to apply under this ROA: The NeuroNEXT CCC.

Eligible Individuals (Program Director/Principal Investigator):

Any individual(s) identified by the NeuroNEXT CCC as having the skills, knowledge, and resources necessary to carry out the proposed research as the Program Director(s)/Principal Investigator(s). Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH support.

Section 5. Application Information and Submission

Application Process Overview

Submission Information:

Applications to the Gene Therapy Consortium (GTC) for Gene-based Clinical Trials Conducted within NeuroNEXT must be submitted no later than the application due date shown under the "Key Dates" section of this announcement. Applications are submitted via eRA ASSIST at https://public.era.nih.gov/assist/public/login.era?TARGET=https%3A%2F%2Fpublic.era.nih.gov%3A443%2Fassist%2F. Use this ROA number when submitting the application. Detailed instructions for submitting OT Applications can be found at ASSIST-Instruction-Guide-for-NIH-Other-Transactions.docx (live.com)

Application Requirements:

Complete applications must be submitted by the Recipient Business Official/Signing Official. The organization must be registered in eRA Commons with one person designated as the Principal Investigator (PI) and one person designated as the Signing Official (SO). The SO's signature certifies that the applicant has the ability to provide appropriate administrative and scientific oversight of the project and agrees to be fully accountable for the appropriate use of any funds awarded and for the performance of the OT award-supported project or activities resulting from the application.

The application must clearly and fully demonstrate the applicant's capabilities, knowledge, and experience and the budget proposed. Full applications must be submitted by the due date, in text-recognizable PDF (Adobe) format.

The Cover Page should include (no more than 1 page):

- Number and title of this ROA
- Project title

- The Awardee's
    - Legal entity name
    - Address and contact information
    - SAM # and expiration date
    - Unique Entity ID# and expiration date
    - EIN number
- Principal Investigator(s) first and last name, title, organization, mailing address, email address and phone number (with NIH Commons Account information). If multiple PIs are named, the Contact PI must be clearly identified.
- The name and contact information for the Awardee's Business Official, the person authorized to negotiate and bind the Awardee as a signatory to the Other Transaction agreement.
- The total cost proposed.

The applications shall include a detailed project plan addressing how the scope of work outlined in Section 2 of this ROA will be accomplished, as well as a detailed budget for establishment and operation of the GTC, with justification as further explained below. The proposed budget should only be directly related to consortium start-up activities (i.e., consortium meetings to set up organizational structure and SOPs) and operational meetings, not to clinical trials. Personnel efforts of GTC members related to clinical trials will be supported through trial-specific funds. The NeuroNEXT CCC activity is currently supported by the grant, and any additional CCC requests should not overlap with the scope of the existing grant. The application should include biosketches of the PI(s) and proposed GTC members.

Abstract ("Abstract.pdf"; no more than 1 page):

The project abstract is a succinct and accurate description of the proposed work and should be able to stand on its own (separate from the application). It should be informative to other persons working in the same or related fields and understandable to a scientifically literate reader. Do not include proprietary, confidential information or trade secrets in the abstract. If the application is funded, the project abstract will be entered into an NIH database and made available on the NIH Research Portfolio Online Reporting Tool (RePORT) and will become public information. The attachment is limited to one page.

Specific Aims ("SpecificAims.pdf"; no more than 3 pages):

State concisely the goals of the proposed research and summarize the expected outcome(s), including the impact that the results of the research will have on the research field(s) involved. List succinctly the specific objectives of the research. This attachment is limited to three pages.

Budget information (no page count):

The budget shall contain sufficient information to allow the Government to perform a basic analysis of the proposed cost of the work. This information shall include the amounts of the line items of the proposed cost. These elements will include the following elements by milestone event and/or proposed period as applicable:

- Direct Labor – Individual labor category or person, with associated labor hours and unburdened direct labor rates;
- Indirect Costs – Fringe Benefits, F&A, etc. (Must show base amount and rate). Offerors must submit a copy of their most recent indirect cost rate agreement negotiated with any federal audit agency, if applicable;
- Travel – Separate by destinations and include rationale for travel, number of trips, durations - number of days, number of travelers, per diem (hotel and meals in accordance with the Federal Travel Regulations), airfare, car rental, if additional miscellaneous expense is included, list description and estimated amount, etc.;

- Subawardee – A separate detailed budget shall be submitted by each proposed subawardee. The subawardee's proposal should include on company letterhead the following:

  - Complete company name and mailing address, technical and administrative/business point of contacts, email address, and telephone number.
  - Include the Unique Entity ID and CAGE code.
  - A commitment letter from the proposed subawardee's business official that includes:
    - Willingness to perform as a subawardee for specific duties (list duties);
    - Proposed period of performance;
    - Supporting documentation for proposed costs (personnel documents to verify salaries, vendor quotes for equipment, negotiated indirect cost rate agreement.
- Consultants – For proposed consultants, provide draft consulting agreement or other document which verifies the proposed loaded daily/hourly rate and labor category;
  - Written verification from the consultant of their proposed rate, along with a statement that it is their usual and customary rate charged to other customers;
  - Description of the work to be performed by the consultant and direct relevance to the work. Include information on why this expertise is not available in-house.
- Materials & Supplies – Should be specifically itemized with costs or estimated costs. Include supporting documentation, i.e., vendor quotes, catalog price lists, and past invoices of similar purchases.
- Other Direct Costs – Especially any proposed items of equipment. Equipment generally must be furnished by the Offeror. Justifications and vendor quotes must be provided when Government funding for such items is sought.

<u>Salary Rate Limitation:</u>

- Pursuant to current and applicable prior NIH appropriations acts, it is anticipated that Offerors submitting applications under this ROA will be subject to a salary rate limitation on funds used to pay the direct salary of individuals.
- Congress has stipulated in the NIH appropriations act that, under applicable extramural awards appropriated funds cannot be used to pay the direct salary of an individual at a rate in excess of the Federal Executive Schedule Level II.
- For purposes of the salary rate limitation, the terms "direct salary," "salary," and "institutional base salary," have the same meaning and are collectively referred to as "direct salary", in this clause. An individual's direct salary is the annual compensation that the Offeror pays for an individual's direct effort (costs) under the award. Direct salary also excludes fringe benefits, overhead, and G&A expenses (also referred to as indirect costs or facilities and administrative [F&A] costs). Note: The salary rate limitation does not restrict the salary that an organization may pay an individual working under an NIH award; it merely limits the portion of that salary that may be paid with Federal funds.
- The salary rate limitation also applies to individuals under subawards.
- See the salaries and wages pay tables on the U.S. Office of Personnel Management Web site for Federal Executive Schedule salary levels that apply to the current and prior periods.

Section 6. Objective Review Information

Applications will undergo an objective review by internal Program staff at NINDS.

Objective review is an assessment of scientific or technical merit of applications by individuals with appropriate scientific and/or human subjects research program management knowledge and expertise. Conflicts-of-interests of review members are appropriately managed during the review process in accordance with standard NIH policies. The review provides information essential to ensuring the submitted application meets the needs of the program using the criteria delineated below following a review that is conducted in a fair, objective manner free of prejudices and biases.

Reviewers provide individual assessments of the likelihood of the applicant to successfully establish and manage a GTC. The reviewers will only consider the review criteria below in their individual assessments of merit. An application does not need to be strong in all categories to be judged likely to have major impact.

Objective Review Criteria:

1. Does the applicant present an achievable plan to establish and operate the GTC?
2. Does the applicant have an acceptable plan for implementing standardized operating procedures for GTC?
3. Does the applicant have the necessary expertise to complete the project?
4. Does the applicant have the resources/infrastructure to complete the project?
5. Is the proposed budget justified?

Additional Review Criteria and considerations:

As applicable for the project proposed, reviewers will evaluate the following additional criteria and considerations:

Timeline:

a. Is the timeline described in detail, taking into account start-up activities? Is the projected timeline feasible and well-justified?
b. Are potential challenges and corresponding solutions discussed (e.g., strategies that can be implemented in the event of barriers or complications during implementation)?

Budget and Period of Support:

Reviewers will consider whether the budget and the requested period of support are fully justified and reasonable in relation to the proposed activities.

Composition of Objective Review Panel:

Review of the application will be conducted by internal NIH program staff. Summary statements of the review meeting will not be made available. However, feedback on the objective review and the NINDS decision on the application are provided to the applicant by NINDS program staff.

Decision Process:

NINDS will select applications based on their technical merit, the consideration of the issues identified during the objective review and the relevance of the proposed project to program priorities for the award of Other Transaction funding and project implementation within the NeuroNEXT.