Ultra-rare Gene-based Therapy (URGenT) Clinical Trials Conducted within NeuroNEXT: Stage 1 Preliminary Application (OT2)

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	**Ultra-rare Gene-based Therapy (URGenT) Clinical Trials Conducted within NeuroNEXT: Stage 1 Preliminary Application (OT2)**
Activity Code	OT2: Application for an Other Transaction Agreement
Research Opportunity Number	OTA-24-011
Related Notices	Revision of: OTA-24-002 Companion of: OTA-24-12
Key Dates:	Posted Date: March 1, 2024 Open Date (Earliest Submission Date): March 1, 2024 Application Due Date: Rolling submission
Scientific Contacts	Hyun Joo 'Sophie' Cho, MD NeuroNEXT, NINDS hyunjoo.cho@nih.gov Chris Boshoff, PhD URGenT, NINDS chris.boshoff@nih.gov

Content by Sections

Section 2. Objectives of this Opportunity

The purpose of this research opportunity announcement (ROA) is to invite Stage 1 Preliminary Applications for clinical trials of gene-based and gene-targeted therapies for ultra-

rare neurological diseases, to be conducted within the Network for 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 Food and Drug Administration (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, 6000 or fewer individuals; in the US, this equates to one in 50,000 people or less.

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, many in children. 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.

The 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.

This ROA expands the URGenT program to support the 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, supporting from first-in-human to confirmatory clinical trials, 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, which is funded via a separate grant mechanism; applicants who were not part of the URGenT pre-clinical program may apply to this ROA.

URGenT clinical trials may be conducted within the NeuroNEXT clinical trial network. The NeuroNEXT provides funded infrastructure to efficiently conduct multiple, scientifically sound, possibly biomarker-informed 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.

The 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. Additionally, the NeuroNEXT has established a Gene Therapy Consortium (GTC) consisting of members with expertise in gene-based and gene-targeted therapies, ultra-rare and rare diseases, industry aspects, 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 provide support and advice as requested for URGenT clinical trials proposed for and/or conducted within the NeuroNEXT. Clinical trials conducted in the NeuroNEXT undergo rigorous scientific vetting.

Objectives:

Under this ROA the NINDS will accept Stage 1 Preliminary Applications for gene-therapy products that have an active Investigational New Drug (IND) designation and are proposed for URGenT clinical trials to be conducted within the NeuroNEXT. URGenT clinical trial applications are reviewed in a two-stage process. The Stage 1 application must include scientific background information supporting the gene-therapy products/therapeutics and proposed clinical trial. Stage 2 Protocol Applications (see Related Notices for the Companion ROA) will be accepted by invitation only and will include the submission of more detailed information on the proposed clinical trial and related activities. Please refer to Section 5: Application Information and Submission for detailed information.

Scope:

The URGenT program is focused on the development of gene-based therapeutics for patients with serious, life-threatening ultra-rare neurological diseases. The following therapeutic modalities are amenable to the development of individualized genomic-based medicine approaches:

<u>Oligonucleotide-based approaches</u>
Oligonucleotides offer the potential to treat many monogenic diseases by either ameliorating splicing mutations, promoting exon skipping, or targeting dominantly acting transcripts. Oligonucleotides-based interventions for neurological diseases include but are not limited to antisense oligonucleotides and small interfering RNAs.

<u>Viral vector-based approaches</u>
Viral-based therapeutics (e.g., Adeno-Associated Viruses) and other potential vector and/or delivery vehicles, containing the correct gene construct, may be used as an *in vivo* therapeutic approach to replace or knockdown expression of a disease-causing gene. Alternatively, cell therapies involving *ex vivo* gene targeting may offer another therapeutic approach.

<u>Genome editing-based approaches</u>
Several platform technologies such as Zinc Finger Nucleases, Transcription Activator-like Effector-based Nucleases, and Clustered Regularly Interspaced Short Palindromic Repeats - associated protein systems, have emerged as promising alternative approaches for editing DNA owing to both their versatility and ease of use.

<u>Other gene-based therapeutic approaches</u>
Small-molecule drugs that can selectively bind RNA and modulate pre-mRNA splicing have potential as a treatment strategy for human disease. These nucleic acid–targeted small molecules have therapeutic potential in the treatment of some ultra-rare neurological diseases.

To be eligible under this ROA, URGenT clinical trial proposals are expected to: 1) utilize modalities described above (or related approaches), 2) propose conducting the study within the

NeuroNEXT, 3) have an open IND, and 4) be ready for clinical trials.

This program is structured so that the existing Intellectual Property (IP) owner retains their rights and controls the patent prosecution and licensing negotiations for candidate therapeutics developed in this network. It is expected that the owning institution will take responsibility for patent filings and maintenance and licensing efforts toward eventual commercialization. The asset owner is expected to work closely with technology transfer/business development officials at his or her institution to ensure that royalty agreements, patent filings, and all other necessary IP arrangements are completed in a timely manner and that commercialization plans are developed and updated over the course of the project.

NIH Resources
As appropriate, applicants are encouraged to make use of the following resources for clinical research including:
a) Clinical and Translational Science Award (CTSA) program;
b) NeuroQOL;
c) NIH Toolbox;
d) PROMIS; and
e) NINDS Common Data Elements.

Potential applicants are STRONGLY encouraged to contact the NeuroNEXT/URGenT Program Staff to discuss their application and the application process prior to submission.

Section 3. Potential Award Information

Please note: No funding is provided as a result of a Stage 1 Preliminary Application outcome determination. Funding may only be awarded after Stage 2 Protocol Application, based on favorable review and programmatic priority.

After a successful review of the Stage 1 Preliminary Application and upon receiving an invitation to proceed to Stage 2 (see Related Notices for the Companion ROA) the asset holder will work with the NeuroNEXT to further develop the clinical trial protocol. At Stage 2 the NeuroNEXT CCC becomes the applicant of record for the Stage 2 Protocol Application. NIH funds to conduct the study are awarded to the NeuroNEXT CCC only after successful completion of both stages of application and review, and approval by the NINDS Director following National Advisory Neurological Disorders and Stroke (NANDS) Council review. The NeuroNEXT CCC then administers the funds to other NeuroNEXT research components as appropriate.

Authority:

This Research Opportunity Announcement (ROA) is issued with the goal of soliciting assets with an active IND for URGenT clinical trials. An OT Agreement will be used to fund URGenT clinical trials conducted within the NeuroNEXT after the Stage 2 review and funding approval, pursuant to OT authority described in section 402(n) of the Public Health Service Act, 42 U. S. C. 282(n).

Section 4. Eligibility

Eligible Individuals (Program Director/Principal Investigator): Any individual(s) with the skills, knowledge, and resources necessary to carry out the proposed research as the Program

Director(s)/Principal Investigator(s) is invited to work with their organization to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH support.

Organizations:

The following entities are eligible to apply under this ROA:

Higher Education Institutions
- Public/State Controlled Institutions of Higher Education
- Private Institutions of Higher Education

The following types of Higher Education Institutions are always encouraged to apply for NIH support as Public or Private Institutions of Higher Education:
- Hispanic-serving Institutions
- Historically Black Colleges and Universities (HBCUs), Tribally Controlled Colleges and Universities (TCCUs), Alaska Native and Native Hawaiian Serving Institutions
- Asian American Native American Pacific Islander Serving Institutions (AANAPISIs)

Nonprofits Other Than Institutions of Higher Education
- Nonprofits with 501(c)(3) IRS Status (Other than Institutions of Higher Education)
- Nonprofits without 501(c)(3) IRS Status (Other than Institutions of Higher Education)

For-Profit Organizations
- Small Businesses
- For-Profit Organizations (Other than Small Businesses)

Governments
- State Governments, County Governments
- City or Township Governments, Special District Governments
- Indian/Native American Tribal Governments (Federally Recognized), Indian/Native American Tribal Governments (Other than Federally Recognized)
- Eligible Agencies of the Federal Government
- U.S. Territory or Possession Independent School Districts

Other
- Independent School Districts
- Public Housing Authorities/Indian Housing Authorities
- Native American Tribal Organizations (Other than Federally Recognized Tribal Governments)

Faith-based or Community-based Organizations
- Regional Organizations
- Non-domestic (non-U.S.) Entities (Foreign Institutions)

Foreign Institutions
- Non-domestic (non-U.S.) Entities (Foreign Institutions) are eligible to apply.
- Non-domestic (non-U.S.) components of U.S. Organizations are eligible to apply.

Foreign components defined as performance of any significant element or segment of the project outside the United States either by the recipient or by a researcher employed by a foreign organization, whether or not grant funds are expended. Activities that would meet this definition include the following:

- The involvement of human subjects or vertebrate animals at a foreign site.
- Extensive foreign travel by recipient project staff for the purpose of data collection, surveying, sampling, and similar activities.
- Any activity of the recipient that may have an impact on U.S. foreign policy through involvement in the affairs or environment of a foreign country.

Section 5. Application Information and Submission

Application Process Overview:

For URGenT clinical trials conducted within the NeuroNEXT there are two stages of application and review.

Stage 1 Preliminary Application: The asset holder will submit a Stage 1 Preliminary Application under this ROA, including all required documents. This application must include detailed information on the proposed asset, including prior basic, pre-clinical and clinical research completed and rationale as well as brief information on the proposed study population and design. Stage 1 Preliminary Applications are received and reviewed on a rolling basis. The review for this stage includes an independent /objective review by a panel of external experts convened by the NINDS. No funding is provided at Stage 1.

Stage 2 Protocol Application: Upon completion of the Stage 1 review process, the applicant may be invited to work with the GTC and the NeuroNEXT to develop a full clinical protocol (including a budget and timeline) for submission under the Stage 2 Protocol Application (see Related Notices for the Companion ROA). The NeuroNEXT CCC will be responsible for submission of the Stage 2 application package. The following will be considered in making funding decisions: 1) Scientific and technical merit of the proposed project as determined by scientific peer review, 2) Availability of funds, and 3) Relevance of the proposed project to program priorities. Protocols selected following the review will be presented to the NANDS Council. Following review by the NANDS Council, a funding decision will be made by the NINDS Director. If funded, the OT trial funds will be released to the NeuroNEXT CCC and study implementation within the NeuroNEXT may begin.

URGeNT Clinical Trial Stage 1 Preliminary Application Information:

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. Full applications must be submitted in text-recognizable PDF (Adobe) format.

1. **Cover Page, Abstract, and Specific Aims:** Applicants for NIH Other Transactions shall include a cover page, an abstract and specific aims in each application. Abstracts are limited to one page, and specific aims are limited to three pages.

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

- Number and title of this ROA
- Project title
- The Recipient'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 Recipient's Business Official, the person authorized to negotiate and bind the Recipient.

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.

2. **Clinical Trial Preliminary Application** (no more than 12 pages): The Clinical Trial Preliminary Application should include the following information, as applicable. The application must include all the components listed in this section. If certain components are not applicable, please indicate it clearly.

    I. Scientific Rationale/Background
    - Target disease/population specifics
    - Therapeutic need
    - Proposed advance to the therapeutic space

    II. Asset Information
    - Asset name
    - Asset owner (include all relevant IP information); if applicant does not own the asset, include freedom-to-operate statement and relevant documentation from the owner.
    - Asset type
        a. Therapeutic modality
        b. Mechanism of action
        c. Target
    - Asset development status
    - Asset regulatory status (include all relevant FDA documentation)
        a. IND/IDE number

b. Pre-IND/IDE FDA interaction
c. Known adverse effects/safety concerns (both on- and off-target)
d. Manufacture and scale-up
e. Stability storage, shipping, handling and usage information
f. Availability of comparator drug/matching placebo
g. Continued development and marketing plans

III. Preliminary Data
- Laboratory/in vitro data supporting the therapeutic concept
- Animal studies
- Clinical studies
- Evidence of target engagement
- PK/PD data
- Toxicology/carcinogenicity/teratogenicity data

IV. Trial Plan
- Clinical trial phase
- Trial objectives
- Outcome measures (efficacy and safety, as appropriate for CT phase and objectives)
- Inclusion/Exclusion criteria
- Controls
- Therapeutic procedures / investigational agent administration

V. Statistical Considerations
- Proposed sample size
- Preliminary power analysis
- Proposed statistical methods for data analysis for trial objectives

VI. References

3. **NIH Biosketches:** Biosketches of the PD/PI(s) must be included (no more than five (5) pages in length). NIH biosketches must conform to a standardized format.

Submission Information:

Applications to the Ultra-rare Gene-based Therapy (URGenT) Clinical Trials Conducted within NeuroNEXT: Stage 1 Preliminary Application (OT2) may be submitted after the first open date shown under the "Key Dates" section of this announcement. Applications are submitted via eRA ASSIST. 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).

Upon receipt, applications are evaluated by the NINDS for completeness, compliance with application requirements and responsiveness. Applications that are incomplete, non-compliant, and/or nonresponsive will not be reviewed and the applicant will be so notified.

Applications not responsive to this ROA:

Nonresponsive applications include those that involve any of the following activities:

- Nonclinical studies of disease mechanism or therapeutic mechanism of action studies

- Animal studies
- Development of diagnostics or diagnostic devices
- Research focused entirely on biomarkers and/or clinical endpoint development
- Clinical trials that seek to develop therapeutics (including gene-based therapy) for common neurological disorders
- Clinical trials that seek to develop therapeutics without involving a gene modification technique

Section 6. Independent/Objective Review Information

Study proposals will undergo objective/independent review. Independent review is an assessment of the scientific or technical merit of applications by individuals with appropriate scientific knowledge and expertise. Conflicts-of-interest of review panel members are appropriately managed during the review process in accordance with standard NIH policies. Independent review provides information essential to ensuring selection of meritorious applications that best meet the needs of the program using the criteria delineated below and ensures that application selection is conducted in a fair, objective manner free of prejudices and avoidable biases. The Independent reviewers are instructed to consider only the review criteria below in their individual assessments of scientific merit. An application does not need to be strong in all categories to be judged likely to have major scientific impact. For example, a project that by its nature is not innovative may be essential to advance a field, or a proposed clinical trial may include study design, methods, or an intervention that are not by themselves innovative but address important questions or unmet needs. Additionally, the results of the clinical trial may indicate that further clinical development of the intervention is unwarranted or that it might lead to new avenues of scientific investigation.

Independent/Objective Review Criteria:

1. Significance/Innovation
    a. Do the asset and approach target an area of clear therapeutic need?
    b. Are the preliminary/supporting data rigorous with respect to the choice of therapeutic modality and target for the identified disease? Is the rationale for the selection of the target, the level of agreement in the field regarding the target's role in disease pathogenesis and clinical relevance of the target well explained?
    c. How is the asset likely to yield significant advancements in therapy?
    d. How innovative is the proposed therapeutic approach?
    e. How significant of an advantage does the proposed therapeutic candidate offer over existing treatments or those under development?

2. Feasibility/Readiness
    a. Is the candidate therapeutic ready for the current phase of clinical trial?
    b. Is the asset clearly scalable for both the proposed clinical trial and eventual clinical use?
    c. Are safety and biohazard considerations for use of the asset in humans clearly addressed?
    d. Is manufacturing consistent with relevant standards and safety testing? Are scale-up, good manufacturing practices, and needed resources adequately addressed?
    e. What is the likelihood that completion of the research objectives will lead to a therapy (i.e., is there a clear path into the clinic)?
    f. How is the competitive landscape addressed?

3. Data
    a. How robust are the pre-clinical data provided in support of the proposed asset?
    b. How robust are the clinical data provided in support of the proposed asset?
    c. How robust is the pharmacokinetic/pharmacodynamic information provided (as applicable)?
4. Approach
    a. With the understanding that the trial design will be fully developed for the final, Stage 2 Protocol Application review, is the preliminary design appropriate for the stated goals of trial and the indication?
    b. Are the study populations (size, gender, age, demographic group), proposed intervention arms/dose, and duration of the trial, appropriate and well justified?
    c. Has the need for randomization (or not), masking (if appropriate), controls, and inclusion/exclusion criteria been addressed?
    d. How appropriate are the primary and secondary outcome measures?

5. Expertise and Resources
    a. Does the application demonstrate that the investigators have the relevant experience and expertise in the subject matter and clinical trial execution?
    b. Are the institutional support, equipment, and other physical resources available to the investigators adequate for the project proposed?

Composition of Objective Review Panel:

Application review is carried out by a panel of experts with complementary knowledge in multiple areas related to the proposed study subject matter and the conduct of clinical trials such as pharmacokinetics, biological mechanisms, pharmaceutical industry development, and other relevant scientific and clinical expertise. NIH program officials attend the review meetings to provide programmatic input. Summary statements of the review panel meetings will not be made available. However, feedback on the independent/objective review and the NINDS decision on the application are provided to applicants. Appeals are not allowed.

Selection Process:

Applicants will be selected for Stage 2 invitation based on the scientific merit of their Stage 1 proposal, including consideration of issues identified during independent/object review, and relevance of the proposed project to program priorities as approved by the NINDS Director.