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	**NeuroNEXT Clinical Trials: Stage 1 Preliminary Application (OT2)**
Activity Code	OT2: Other Transactions
Research Opportunity Number	OTA-24-013
Related Notices	OTA-24-014 (Stage 2)
Key Dates:	Posted Date: April 5, 2024
	Open Date (Earliest Submission Date): June 5, 2024
	Application Due Date(s): Rolling submission
Scientific Contacts	Hyun Joo 'Sophie' Cho, MD NeuroNEXT, NINDS hyunjoo.cho@nih.gov

Content by Sections

Section 2. Objectives of this Opportunity

The purpose of this research opportunity announcement (ROA) is to invite applicants to submit Stage 1 Preliminary Applications of assets proposed for exploratory clinical trials or biomarker studies focused on neurological diseases to be conducted within the Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT).

Background:

To facilitate the cooperation and partnering of public and private funding organizations, universities, academic medical centers, research institutes, contract research organizations, biotechnology companies, and pharmaceutical companies, the NINDS has formed the Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT: NINDS NeuroNEXT). The NeuroNEXT has a Clinical Coordinating Center (CCC), a Data Coordinating Center (DCC) and multiple clinical sites that are geographically distributed across the United States.

This clinical research network develops and conducts multiple, scientifically sound, possibly biomarker-informed exploratory clinical trials evaluating the most promising therapies, whether from academic, foundation, or industry discoveries. Examples include phase 2 clinical trials and clinical research studies aimed at validating biomarkers and clinical outcomes, phase 2-3 trials if warranted by the nature of the studied population (such as rare diseases), and platform trials where applicable. The network is not specific to one disease; it has the capacity to coordinate a cadre of specialist investigators to implement studies efficiently in response to disease-specific opportunities. The network supports clinical research in both pediatric and adult populations.

The network is designed to increase the efficiency of clinical trials, to facilitate patient recruitment and retention, to increase the quality of neuroscience clinical trials, and to enable public-private partnerships.

To foster the development of clinical trialists, the NeuroNEXT investigators who have been selected for their experience and training in neurological clinical research provide a source of strong mentorship and support to investigators who are early in their career as approved studies are implemented within the infrastructure.

Objectives:

NeuroNEXT clinical trial applications are reviewed in a two-stage process. Under this ROA, the NINDS will accept Stage 1 Preliminary Applications for clinical trials of investigational agents (drugs, biologics, surgical therapies or devices) that may contribute to the scientific justification for and provide the data required for designing a future clinical trial, for biomarker validation studies, or for proof of mechanism clinical studies. Applications for drugs or biologics should provide compelling scientific evidence that the investigational agent proposed for study will reach/act upon the designated target or that its mechanism of action is such that it is expected to be of benefit in ameliorating a specific aspect of the disease. Neurologic diseases chosen for study must fall within the primary responsibility of NINDS (www.ninds.nih.gov/funding/areas/index.htm).

The Stage 1 Preliminary Application may be submitted by academic investigators, industry applicants, private institutions, or nonprofits, and must include scientific background information supporting the asset and need of the 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. At Stage 2 the NeuroNEXT CCC is the applicant of record and may propose Multiple Principal Investigators (MPI). Please refer to Section 5: Application Information and Submission for detailed information.

Scope:

NeuroNEXT provides a robust, standardized, and accessible infrastructure to facilitate the rapid development and implementation of protocols in neurological disorders, in both adult and pediatric populations. Examples of studies appropriate for the NeuroNEXT include, but are not limited to, those designed to:

- Evaluate and optimize the dose, formulation, safety, tolerability or pharmacokinetics of an intervention in the target population.
- Select or rank the best of two or more potential interventions or dosing regimens to be evaluated in a subsequent trial, based on tolerability, safety data, biological activity, or preliminary clinical efficacy (e.g., futility trials).
- Validate biomarkers that are fit-for-purpose for a specific context of use and can be used in future clinical trials.
- Evaluate biological activity relative to clinical endpoints.
- For medical devices, in addition to providing initial clinical safety data, appropriate studies are those that inform the next phase of development, usually by finalizing the device design, establishing operator technique, and/or finalizing the choice of study endpoints for the design of a pivotal clinical trial.

This ROA is not intended to support the conduct of a clinical trial where the primary aim is to confirm efficacy of a drug or biologic unless warranted by the nature of the studied population (such as rare diseases).

Applications in rare diseases are encouraged, while recognizing that available patient pools may not be adequate to meet the sample size requirements normally required to establish the efficacy of an intervention. NINDS acknowledges that innovative, non-traditional trial designs including adaptive designs may be appropriate, especially in rare disease studies. While NeuroNEXT is primarily intended for exploratory trials, the network will consider phase 2/3 trials in rare diseases.

The proposed asset must have completed first-in-human studies and have preliminary information on safety in humans and sufficient data to inform dose selection for a phase 2 clinical trial.

If the intervention is a drug, biologic, or device, an open IND (Investigational New Drug)/IDE (Investigational Device Exemption) will be a funding milestone. Applicants must provide documentation from the FDA as per below:

- For assets with an open IND/IDE, applicants must provide documentation from FDA indicating “may proceed” or full approval.
- If the IND/IDE is on full or partial hold or conditionally approved, applicants should discuss how they will address the issues/conditions and when they anticipate having FDA approval to proceed.
- If the asset is IND/IDE exempt (or does not require approval because of determined nonsignificant risk), applicants must provide exemption letter or risk determination letter from FDA.

For Biomarker Validation Studies, biomarkers are defined as a characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Categories of biomarkers include susceptibility/risk, diagnostic, monitoring, prognostic, predictive, pharmacodynamic/response, and safety. Biomarker studies should define their intended Context of Use (a statement that fully and clearly describes the way the biomarker will be used in future clinical trials).

A separate clinical trials network has been established and funded by NINDS to conduct clinical trials and biomarker studies for stroke treatment, prevention, and recovery; thus, NeuroNEXT has been established for the conduct of studies in neurological disorders other than stroke. Multi-site studies in stroke prevention, treatment and/or recovery are not appropriate for this

ROA; those studies would be considered by NIH StrokeNet: http://www.nihstrokenet.org/. Separate clinical trial networks also exist for the conduct of studies in neurological emergencies (SIREN: https://siren.network/) and pain (EPPIC-NET: https://www.ninds.nih.gov/Current-Research/Trans-Agency-Activities/NINDS-Role-HEAL-Initiative/NINDS-Role-HEAL-Initiative-EPPIC). Studies on these topics should be directed to the dedicated networks.

Studies primarily focused on biomarker discovery and validation may also apply to one of the NINDS Biomarker funding opportunities https://www.ninds.nih.gov/Current-Research/Focus-Tools-Topics/Biomarkers.

Phase 1 clinical trials should be directed to the exploratory clinical trial NOFO (PAR-22-142 and PAR-21-266). Phase 1b/2a trials requiring multi-center implementation can be considered under this ROA.

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
(e) NINDS Common Data Elements

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

Section 3. Potential Award Information

Please note: No funding is provided at Stage 1 Preliminary Application. 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 neurotherapeutics or biomarkers for NeuroNEXT clinical trials. An Other Transaction (OT) Agreement will be used to fund clinical studies conducted within NeuroNEXT, pursuant to the 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). 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

Foreign components are defined as performance of any significant element or segment of the project outside the United States either by the applicant or by a researcher employed by a foreign organization, whether grant funds are expended. Activities that would meet this definition include the following:

- The involvement of human subjects 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:

The NeuroNEXT program uses a two-stage application and review process.

Stage 1 Preliminary Application: The asset holder will submit a Stage 1 Preliminary Application under this ROA, including all required documents. This application should include detailed information on the asset, including prior basic, pre-clinical, and clinical research completed that support the proposed study. Include rationale, as well as brief information on the proposed study population and clinical trial design. Stage 1 Preliminary Applications are received and reviewed on a rolling basis. The review 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 NeuroNEXT to develop a full clinical protocol (including budget and timeline) for submission under the Stage 2 Protocol Application ROA (see Related Notices for the Companion ROA). The NeuroNEXT CCC will be responsible for submission of the Stage 2 application package but may propose MPIs. The following will be considered in making funding decisions: 1) Scientific and technical merit of the proposed project as determined by scientific independent/objective 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, OT trial funds will be awarded to the NeuroNEXT CCC and study implementation within the NeuroNEXT may begin.

NeuroNEXT 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 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 and must include the following information.

1. **Cover Page, Abstracts 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 applicant's
    - Legal entity name
    - Address and contact information
    - Unique Entity ID#
    - 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.

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. 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 or relevant documentation from the owner.
    - Asset type
        a. Therapeutic modality
        b. Mechanism of action
        c. Target
        d. If biomarker, type of biomarker (consistent with BEST glossary) and context of use
    - Asset development status
    - Asset regulatory status (include all relevant FDA documentation which may be submitted as Other Attachment)

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 Supporting Data

- Laboratory/in vitro data supporting the therapeutic concept
- Animal studies
- Clinical studies
- Evidence of target engagement
- PK/PD data
- Toxicology data

IV. Brief Trial Design (Expanded details included in Stage 2 application)

- Objectives
- Outcome measures
- Inclusion/Exclusion criteria
- Controls
- Randomization/blinding/masking
- Study procedures/investigational agent administration
- Go/No-go criteria for a future (phase 3) trial

V. Statistical Considerations

- Proposed sample size
- Preliminary power calculation and statistical basis
- Proposed statistical methods for data analysis for primary and secondary aims

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 **NeuroNEXT Clinical Trials: Stage 1 Preliminary Application (OT2)** may be submitted after the first receipt 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 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 examples.

- Nonclinical studies of disease mechanism or therapeutic mechanism of action studies
- Animal studies
- Single site studies
- Research focused entirely on natural history studies

Section 6. Independent/Objective Review Information

Stage 1 Preliminary Applications will undergo objective, independent review. Independent review is an assessment of 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 minimizing prejudices and biases. The Independent reviewers consider only the review criteria below in their individual assessment 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, and 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. 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 likely is the asset 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. How convincing is the evidence that equipoise exists in the medical and patient communities and the intervention is ready for clinical development?
    b. Is the asset clearly scalable for both the proposed clinical trial and eventual clinical use?
    c. Are safety considerations for use of the asset in humans clearly addressed?
    d. If the clinical trial is successful, is there a path forward for eventual clinical adoption?
    e. How is the competitive landscape addressed?

3. Data
    a. Is the prior research that serves as the key support for the proposed project rigorous?
    b. Are the preclinical and clinical data robust?
    c. How robust are the clinical data in support of the proposal provided?

d. How robust is the pharmacokinetic/pharmacodynamic information provided (as applicable)?

4. Approach
    a. Is the proposed trial design appropriate for the proposed goals?
    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 study execution?

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.