Department of Health and Human Services
Part 1. Overview Information

Participating Organization(s)	U.S. Food and Drug Administration (FDA) NOTE: The policies, guidelines, terms, and conditions stated in this Notice of Funding Opportunity (NOFO) may differ from those used by the NIH. Where this NOFO provides specific written guidance that may differ from the general guidance provided in the grant application form, please follow the instructions given in this NOFO. The FDA does not follow the NIH Page Limitation Guidelines or the NIH Review Criteria. Applicants are encouraged to consult with FDA Agency Contacts for additional information regarding page limits and the FDA Objective Review Process.
Components of Participating Organizations	Office of Orphan Products Development (OOPD)
Funding Opportunity Title	Reissue of RFA-FD-23-001- Clinical Studies of Orphan Products Addressing Unmet Needs of Rare Diseases (R01 Clinical Trials Required)
Activity Code	R01 Research Project Grant
Announcement Type	Reissue of RFA-FD-23-001
Related Notices	None
Funding Opportunity Number (FON)	RFA-FD-25-020
Companion Funding Opportunity	None

Number of Applications	See Part 2, Section III. 3. Additional Information on Eligibility.
Assistance Listing Number(s)	93.103
Funding Opportunity Purpose	The purpose of this Notice of Funding Opportunity (NOFO) is to fund clinical trials of products evaluating efficacy and/or safety in support of a new indication or change in labeling to address unmet needs in rare diseases or conditions. Additionally, through the funding of collaborative, efficient, and/or innovative clinical trials, FDA expects to increase the number of approved treatments for rare diseases and exert a broad and positive impact on rare disease drug development.
Funding Opportunity Goals	The goal of this Notice of Funding Opportunity (NOFO) is intended to support clinical trials of orphan products in all phases of product development (phase 1, 2 and/or 3) for rare diseases with unmet medical needs. These clinical trials should evaluate safety and/or efficacy of medical products in support of a new indication or a change in labeling.

Key Dates

Posted Date	July 11, 2025
Open Date (Earliest Submission Date)	August 22, 2025
Letter of Intent Due Date(s)	September 22, 2025 (Optional) September 21, 2026 (Optional) September 20, 2027 (Optional)

Application Due Date(s)

October 21, 2025, by 11:59 PM Eastern Time

October 20, 2026, by 11:59 PM Eastern Time

October 19, 2027, by 11:59 PM Eastern Time.

Applicants are encouraged to apply early to allow adequate time to make any corrections to errors found in the application during the submission process by the due date. Resubmissions ONLY Application Due Date(s): May 18, 2027; May 16, 2028 by 11:59 PM Eastern Time. See resubmission eligibility requirement below. Applicants should be aware that on-time submission means that an application is submitted error free (of both Grants.gov and eRA Commons errors) by 11:59 PM Eastern Time on the application due date.

All applications are due by 11:59 PM Eastern Time.

Applicants are encouraged to apply early to allow adequate time to make any corrections to errors found in the application during the submission process by the due date.

No late applications will be accepted for this Notice of Funding Opportunity (NOFO).

AIDS Application Due Date(s)

Not Applicable

Scientific Merit Review

New Applications: February/March 2026, 2027, 2028
Resubmissions: June 2027, 2028

Earliest Start Date

July 2026

Expiration Date	May 31, 2028

Advisory Council Review

Not Applicable

Due Dates for E.O. 12372	Not Applicable

Required Application Instructions

Conformance to all requirements, both in the the Research (R) Instructions How to Apply - Application Guide and in the NOFO, is required and strictly enforced. Applicants must read and follow all application instructions in the How to Apply - Application Guide as well as any program-specific instructions noted in Section IV of this NOFO or an applicable related Notice posted to the Guide for Grants and Contracts. When the program-specific instructions deviate from those in the How to Apply - Application Guide, follow the program-specific instructions.

Applications that do not comply with these instructions may be delayed or not accepted for review.

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Part 2. Full Text of Announcement

Section I. Notice of Funding Opportunity Description

1. Research Objectives

1.A. Background

The FDA Office of Orphan Products Development (OOPD) was created to identify and promote the development of orphan products. Orphan products are drugs, biologics, medical devices, and medical foods that are indicated for rare diseases or conditions. The term "rare disease or condition" is defined in 21 U.S.C. 360ee. For chronic diseases, FDA considers drugs, biologics, devices, and medical foods potentially eligible for grants under the Orphan Products Development (OPD) Clinical Trials Grants Program if they are indicated for a disease or condition that has a prevalence of fewer than 200,000 people in the United States. For acute diseases (i.e., less than 1 year duration), the annual incidence of the disease must be less than 200,000 per year. Diagnostics and vaccines are considered potentially eligible for such grants only if the U.S. population to whom they will be administered is fewer than 200,000 people in the U.S. per year.

There are over 10,000 rare diseases that affect ~30 million Americans but only a few hundred of these rare diseases currently have approved treatments. The Orphan Products Grants Program has been supporting clinical trial research since 1983 and more than 80 of the funded studies have facilitated the marketing approval of rare disease products. To address the remaining unmet need and the lack of treatments for the majority of rare diseases, FDA is focusing their efforts with this NOFO to facilitate drug development in safe yet efficient means by encouraging the use of established infrastructure and resources (e.g., clinical trial networks and data standardization, analytics, and sharing platforms), collaborative efforts between stakeholders (e.g., industry/academia/patient organizations), and early and ongoing patient engagement in trial design (e.g., study feasibility, assessment of important clinical outcomes).

Additionally, applications proposing innovative clinical trial designs (i.e., seamless, adaptive, basket, umbrella, platform trials) or innovative methods (i.e., data modeling and simulations) will be eligible for additional funding (see Section II below). These approaches are vital in expediting drug development and have the potential to make a broad and positive impact for rare diseases in general.

1.B. Research Objectives

This NOFO is intended to support clinical trials of orphan products in all phases of product development (phase 1, 2 and/or 3) for rare diseases with unmet medical needs. These clinical trials should evaluate safety and/or efficacy of medical products in support of a new indication or a change in labeling. Depending on the phase of development, these trials may need to include an appropriate comparator, such as a placebo, a concurrent external control, or a historical control. OOPD encourages applicants to refer to "Rare Diseases: Considerations for the Development of Drugs and Biological Products" for guidance on conducting more efficient and successful drug development programs. Applicants are also encouraged to refer to Guidance Documents for Rare Disease Drug Development for selected guidances relevant to rare disease drug development and information on the Orphan Products Grants Program website before applying for this opportunity.

To facilitate efficient product development, the use of shared, established infrastructure and resources and collaborative efforts between stakeholders in industry, academia, and patient organizations are highly encouraged under this NOFO. Additionally, patients living with a rare disease, or their caregivers have experiences and knowledge that contribute to important considerations in product development, such as with trial feasibility, thus early and ongoing patient engagement is also highly encouraged.

Innovative and Efficient Trial Approaches:
FDA is interested in supporting innovative and efficient trial designs and will allow for additional funding with justification for applications proposing the use of one or more of the following:

- Innovative trial designs such as seamless and adaptive trial designs, which compress the phases of a trial into one continuous trial, as well as basket, umbrella and platform trials, which allow for testing of multiple drugs and/or multiple diseases using a common infrastructure.
- Innovative methods using data simulations and modeling toward the study of safety and efficacy of a product.

These approaches may hold significant promise for the advancement of therapeutic treatments for rare diseases through all phases of product development. Early engagement with FDA review divisions to discuss the use of these innovative approaches is highly recommended prior to submitting a grant application (e.g., preIND, INTERACT, other meetings).

See Section VIII. Other Information for award authorities and regulations.

Section II. Award Information

Funding Instrument	Grant: A financial assistance mechanism providing money, property, or both to an eligible entity to carry out an approved project or activity.
Application Types Allowed	New Renewal Resubmission Revision The OER Glossary and the How to Apply - Application Guide provide details on these application types. Only those application types listed here are allowed for this NOFO.

Clinical Trial?	Required: Only accepting applications that propose clinical trial(s). Need help determining whether you are doing a clinical trial?
Funds Available and Anticipated Number of Awards	The number of awards is contingent upon Congressional appropriations to this FDA grants program and the submission of a sufficient number of meritorious applications. Award(s) will provide one (1) year of support and include future recommended support for an additional three (3) years contingent upon annual appropriations, availability of funding, and satisfactory recipient performance.
Award Budget	Application budgets need to reflect the actual needs of the proposed project and should not exceed the following in maximum total costs (direct and indirect costs) and maximum years of support. YR 01: $650,000 YR 02: $650,000 YR 03: $650,000 YR 04: $650,000 Applicants may request additional funding over the above listed maximums for innovative and efficient trial approaches. The additional funding request shall not exceed an additional $250,000 total costs per year (to a maximum total award cost of $900,000 per year) for up to 4 years. Justification for the additional funding request must be reflected in the budget request and will be reviewed annually by the program. See Appendix Section below for definitions of types of studies eligible for additional funding (Section IV.2).
Award Project Period	The scope of the proposed project should determine the project period. The maximum project period is four (4) years, however, the length of support will depend on the nature of the study. For those studies with an expected duration of more than 1 year, a second, third, or fourth year of noncompetitive continuation of support will depend on the following factors: (1) Performance during the preceding year; (2) compliance with regulatory requirements of IND/investigational device exemption (IDE), if applicable; and (3) availability of Federal funds.

HHS grants policies as described in the HHS Grants Policy Statement will apply to the applications submitted and awards made from this NOFO.

Section III. Eligibility Information

Eligible Organizations

Higher Education Institutions

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

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)

Local 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)

Federal Governments

U.S. Territory or Possession

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 Organizations)

Foreign Organizations

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

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

Foreign components, as defined in the *NIH Grants Policy Statement*, **are** allowed.

Required Registrations

Applicant Organizations

Applicant organizations must complete and maintain the following registrations as described in the How to Apply - Application Guide to be eligible to apply for or receive an award. All registrations must be completed prior to the application being submitted. Registration can take 6 weeks or more, so applicants should begin the registration process as soon as possible. Failure to complete registrations in advance of a due date is not a valid reason for a late submission, please reference the HHS Grants Policy Statement for additional information

- System for Award Management (SAM) Applicants must complete and maintain an active registration, **which requires renewal at least annually**. The renewal process may require as much time as the initial registration. SAM registration includes the assignment of a Commercial and Government Entity (CAGE) Code for domestic organizations which have not already been assigned a CAGE Code.

    - NATO Commercial and Government Entity (NCAGE) Code Foreign organizations must obtain an NCAGE code (in lieu of a CAGE code) in order to register in SAM.
    - Unique Entity Identifier (UEI) - A UEI is issued as part of the SAM.gov registration process. The same UEI must be used for all registrations, as well as on the grant application.
- eRA Commons - Once the unique organization identifier is established, organizations can register with eRA Commons in tandem with completing their Grants.gov registrations; all registrations must be in place by time of submission. eRA Commons requires organizations to identify at least one Signing Official (SO) and at least one Program Director/Principal Investigator (PD/PI) account in order to submit an application.
- Grants.gov Applicants must have an active SAM registration in order to complete the Grants.gov registration.

Program Directors/Principal Investigators (PD(s)/PI(s))

All PD(s)/PI(s) must have an eRA Commons account. PD(s)/PI(s) should work with their organizational officials to either create a new account or to affiliate their existing account with the applicant organization in eRA Commons. If the PD/PI is also the organizational Signing Official, they must have two distinct eRA Commons accounts, one for each role. Obtaining an eRA Commons account can take up to 2 weeks.

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) (PD(s)/PI(s)) is invited to work with their organization to develop an application for support.

For institutions/organizations proposing multiple PDs/PIs, visit the Multiple Program Director/Principal Investigator Policy and submission details in the Senior/Key Person Profile (Expanded) Component of the How to Apply - Application Guide.

The PD/PI should be an established investigator in the scientific area in which the application is targeted and capable of providing both administrative and scientific leadership to the development and implementation of the proposed program. The PD/PI will be expected to monitor and assess the program and submit all documents and reports as required.

Multiple PDs/PIs

The decision of whether to apply for a grant with a single PD/PI or multiple PDs/PIs is the responsibility of the investigators and applicant organizations and should be determined by the scientific goals of the project. Applications for grants with multiple PDs/PIs will require additional information, as outlined in the instructions below. More than one PD/PI (i.e., multiple PDs/PIs), may be designated on the application for projects that require a team science approach and therefore clearly do not fit the single-PD/PI model. Additional information on the implementation plans and policies and procedures to formally allow more than one PD/PI on individual research projects is available at http://grants.nih.gov/grants/multi_pi.

When multiple PDs/PIs are proposed, FDA requires one PD/PI to be designated as the "Contact PI, who will be responsible for all communication between the PDs/PIs and the FDA, for assembling the application materials outlined below, and for coordinating progress reports for the project. The contact PD/PI must meet all eligibility requirements for PD/PI status in the same way as other PDs/PIs, but has no other special roles or responsibilities within the project team beyond those mentioned above.

Information for the Contact PD/PI should be entered in item 14 of the SF424 Research & Related (R&R) form. All other PDs/PIs should be listed in the (R&R) Senior/Key Person Profile and assigned the project role of PD/PI. Please remember that all PDs/PIs must be registered in the eRA Commons prior to application submission. **The Commons ID of each PD/PI must be included in the Credential field of the Research & Related Senior/Key Person component. Failure to include this data field will cause the application to be rejected.** All projects proposing multiple PDs/PIs will be required to include a new section describing the leadership plan approach for the proposed project.

Multiple PD/PI Leadership Plan
For applications designating multiple PDs/PIs, a new section of the research plan, entitled Multiple PD/PI Leadership Plan [item 7 of the PHS 398 Research Plan], must be included. A rationale for choosing a multiple PD/PI approach should be described. The governance and organizational structure of the leadership team and the research project should be described, and should include communication plans, process for making decisions on scientific direction, and procedures for resolving conflicts. The roles and administrative, technical, and scientific responsibilities for the project or program should be delineated for the PDs/PIs and other collaborators.

If budget allocation is planned, the distribution of resources to specific components of the project or the individual PDs/PIs should be delineated in the Leadership Plan. In the event of an award, the requested allocations may be reflected in a footnote on the Notice of Award (NoA).

Applications Involving a Single Institution
When all PDs/PIs are within a single institution, follow the instructions contained in the SF424 (R&R) Application Guide.

Applications Involving Multiple Institutions
When multiple institutions are involved, one institution must be designated as the prime institution and funding for the other institution(s) must be requested via a subcontract to be administered by the prime institution. When submitting a detailed budget, the prime institution should submit its budget using the Research & Related Budget form. All other institutions should have their individual budgets attached separately to the Research & Related Subaward Budget Attachment(s) Form. See Section G.310 of the SF424 (R&R) Application Guide for further instruction regarding the use of the subaward budget form.

2. Cost Sharing
This NOFO does not require cost sharing as defined in the HHS Grants Policy Statement.

Applicant organizations may submit more than one application, provided that each application is scientifically distinct.

The FDA will not accept duplicate or highly overlapping applications under review at the same time, per 2.3.7.4 Submission of Resubmission Application. This means that the FDA will not accept:

- A new (A0) application that is submitted before issuance of the summary statement from the review of an overlapping new (A0) or resubmission (A1) application.
- A resubmission (A1) application that is submitted before issuance of the summary statement from the review of the previous new (A0) application.
- An application that has substantial overlap with another application pending appeal of initial peer review (see 2.3.9.4 Similar, Essentially Identical, or Identical Applications).

Section IV. Application and Submission Information

1. Requesting an Application Package
The application forms package specific to this opportunity must be accessed through ASSIST, Grants.gov Workspace or an institutional system-to-system solution. Links to apply using ASSIST or Grants.gov Workspace are available in Part 1 of this NOFO. See your administrative office for instructions if you plan to use an institutional system-to-system solution.

2. Content and Form of Application Submission
It is critical that applicants follow the instructions in the Research (R) Instructions in the How to Apply - Application Guide except where instructed in this notice of funding opportunity to do otherwise. Conformance to the requirements in the How to Apply - Application Guide is required and strictly enforced. Applications that are out of compliance with these instructions may be delayed or not accepted for review.

Letter of Intent

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows FDA staff to estimate the potential review workload and plan the review. No responsiveness decision will be made based on the letter of intent.

By the date(s) listed in Part 1. Overview Information, prospective applicants are asked to submit a letter of intent that includes the following information:

- Descriptive title of proposed activity
- Name(s), email address(es), and telephone number(s) of the PD(s)/PI(s)
- Names of other key personnel
- Participating institution(s)
- Number and title of this funding opportunity

The letter of intent should be sent via electronic mail as a PDF file with the NOFO Number and the Institution's Name in the message subject heading to:

Katherine Needleman
Director, Orphan Products Grants Program
Email: OOPD_CTGrants@fda.hhs.gov

Page Limitations

All page limitations described in the How to Apply - Application Guide and the Table of Page Limits must be followed.

, with the following exceptions or additional requirements:

For this specific NOFO, the Research Strategy section is limited to 12 pages.

A resubmission application must include an Introduction Section of the Research Strategy (1 page maximum) addressing the most recent objective review critique (Summary Statement).

Instructions for Application Submission

The following section supplements the instructions found in the How to Apply - Application Guide and should be used for preparing an application to this NOFO.

Applicable only to Resubmission, Renewal, and Revision Applications:

- For field **4. a. Federal Identifier** - The Federal Identifier is required. Include only the IC and serial number of the previously assigned award number (e.g., use FD007777 from 1U01FD007777-01).
- For field **8. TYPE OF APPLICATION** - select one of the following:
  - **Resubmission**- Check this option when submitting a revised (altered or corrected) or amended application. Please see additional Resubmission requirements under the Research Strategy.
  - **Renewal** - Check this option if you are requesting additional funding for a period subsequent to that provided by a current award. Please see additional Renewal requirements under the Research Strategy.
  - **Revision**- Check this option for competing revisions and non-competing administrative supplements.

SF424(R&R) Project/Performance Site Locations

All instructions in the How to Apply - Application Guide must be followed.

SF424(R&R) Other Project Information

All instructions in the How to Apply - Application Guide must be followed.

SF424(R&R) Senior/Key Person Profile

All instructions in the How to Apply - Application Guide must be followed.

R&R Budget

All instructions in the SF424 (R&R) Application Guide must be followed with the following additional instructions:

- Applications requesting multiple years of support must complete and submit a separate detailed budget breakdown and narrative justification for each year of financial support requested.
- **Applications requesting additional funding (up to $250,000 total costs per year) for innovative and efficient trial approaches must submit a clear description and justification as to how they have met the requirements as outlined in the Appendix Section below (limited to 3 pages). This description and justification must be included as an appendix to the application. Applications not meeting these requirements may be requested to reduce their budget.**
- Description of any additional funds expected to be contributed by other sources (including the applicant) to the study prior to FDA grant funding and those to be used during the proposed funding period should be included and described in the budget justification section separate from FDA request justification. Details should be provided on total amounts, location of sources, and confirmation if these funds have been secured.
- If an applicant is requesting indirect costs as part of their budget, a copy of the most recent Federal indirect cost rate or F&A agreement must be provided as part of the application submission. This agreement should be attached to the RESEARCH & RELATED Other Project Information Component as line #12 'Other Attachments.'
- If the applicant organization has never established an indirect cost rate and/or does not have a negotiated Federal indirect cost rate agreement, a de minimis indirect cost rate of 10 percent (10%) of modified total direct costs (MTDC) will be allowed. MTDC means all direct salaries and wages, applicable fringe benefits, materials and supplies, services, travel, and subaward and subcontracts up to the first $25,000 of each subaward or subcontract. MTDC excludes equipment, capital expenditures, charges for patient care, rental costs, tuition remission, scholarships and fellowships, participant support costs and the portion of each subaward and subcontract in excess of $25,000.
- Indirect/F&A costs under grants to foreign and international organizations will be funded at a fixed rate of 8 percent of modified total direct costs (MTDC), exclusive of tuition and related fees, direct expenditures for equipment, and subawards in excess of $25,000. (With the exception of the American University of Beirut and the World Health Organization, which are eligible for full F&A cost reimbursement). Awards to domestic organizations with a foreign or international consortium participant may include 8 percent of MTDC, exclusive of tuition and related fees, direct expenditures for equipment, and subawards in excess of $25,000.

R&R Subaward Budget

All instructions in the How to Apply - Application Guide must be followed.

PHS 398 Cover Page Supplement

All instructions in the How to Apply - Application Guide must be followed.

PHS 398 Research Plan

All instructions in the How to Apply - Application Guide must be followed, with the following additional instructions:

Research Strategy:
The following sections should be included under the Research Strategy following the guidelines in Section V. Application Review Information:

1. Rationale
2. Study Design including Data Quality and Interpretability
3. Inclusion of Patient Input
4. Investigator(s), Infrastructure, and Financial Resources
5. Ability to Advance the Current Field

Rare Disease Prevalence:
The **Rationale Section of the Research Strategy** should also include a subsection with the specific heading "Rare Disease Population/Prevalence." This subsection should include **documentation to support that the estimated prevalence of the orphan disease or condition in the United States is rare. The term rare disease or condition is defined in** 21 U.S.C. 360ee**. Generally, FDA considers drugs, devices, and medical foods potentially eligible for grants under this grant program if they are indicated for a disease or condition that has a prevalence of fewer than 200,000 people in the United States or in the case of an acute disease (i.e., less than 1 year duration), an annual incidence of less than 200,000 per year.** (Please Note: Applications may be considered for the use of a product in an orphan subset of a non-rare disease or condition when the applicant can explain based on a characteristic or feature of the product (e.g., mechanism of action, toxicity profile, prior clinical experience) why the product will be limited to use in the subset of question**. An orphan subset is not based on an unmet need, or how a sponsor may wish to study or indicate a product. The explanation for the orphan subset must make it clear to OOPD that the product would not be appropriate in the disease or condition outside of the subset, including pediatric subpopulations).** For studies proposing assessing multiple rare diseases, supportive prevalence data for each rare disease is required.

Additional information may be required upon request, for example, regarding population estimate and rationale. This additional information may be required, in part, to assure that human clinical trials of drugs are eligible to receive funding under the OOPD Grants Program. 21 U.S.C. 360ee(b)(1)(A). See Section VIII, Other Information - Required Federal Citations, for policies related to this announcement.

Support of Product Development:
The **Rationale Section of the Research Strategy** should also include a subsection with the specific heading "Support of Product Development." This subsection should include an explanation of how the proposed study will either help support product approval or provide essential data needed for product development. If the proposal is for multiple products or multiple rare diseases, a plan as to how the applicant intends to proceed with product development (potentially in collaboration with multiple sponsors) should be provided in the grant application.

Resubmissions:
FDA will not accept any application in response to this FOA that is essentially the same as one currently pending initial merit review unless the applicant withdraws the pending application. However, FDA will accept a resubmission application addressing the criteria in this announcement. A resubmission application must include an **Introduction Section of the Research Strategy** (1 page maximum) addressing the most recent objective review critique (Summary Statement). The Summary Statement issued from the Office of Orphan Products Development must be included as an Appendix in the resubmission application. A resubmission application must otherwise also be complete and stand-alone from previous versions. Resubmissions are intended for those applications that were previously submitted to OOPD, reviewed and received a score on the application. **Note: Only previously submitted applications to the Orphan Products Clinical Trials Grants program that received a numeric score and that do not require an IND protocol amendment prior to application resubmission will be accepted.**

Study Monitoring Plan:
The **Study Design Section of the Research Strategy** should include a subsection with the specific heading "Study Monitoring Plan." This subsection should include a proposed plan for monitoring. The specific approach to monitoring will depend on features of the clinical trial to be conducted e.g., several levels of monitoring: Data and Safety Monitoring Board (DSMB), Study Monitoring Committee (SMC), and Independent Medical Monitor (IMM). Monitoring activities should be appropriate to the study, study phase, population, research environment, and degree of risk involved. Guidance is available at: https://www.fda.gov/media/116754/download. This section will detail the parties responsible for monitoring, what will be monitored, and the frequency (which will depend on such factors as the study design, interventions and anticipated recruitment rate). The plan will specify individual and study "stopping guidelines" and other criteria for the monitors to follow. Guidance on these topics is available at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127073.pdf

Renewals

For Renewal applications, the Research Strategy should include a brief Progress Report that summarizes Progress to Date and accomplishments achieved during the current funding period. The Progress Report should include a summary of the specific aims of the previous project period and the importance of the findings, progress made towards achievements, explanation on any significant changes to the specific aims and any new directions.

Letters of support:
Letters of support should not be included as part of the Research Strategy and instead should be uploaded to line 9 on the PHS 398 Research Plan Form.

Letters of support should be included for the following areas:
1) Study Sites: The leader(s) of the existing clinical research institutions that will conduct the study should describe their site support, including relevant resources and study infrastructure and an estimate of the number of patients with the target rare disease(s) who would be eligible for the study;

2) Product Availability: There must be evidence that the product(s) to be studied is available to the applicant in the form and quantity needed for the clinical trial proposed. A current letter(s) from the supplier as an appendix will be acceptable. If negotiations regarding the supply of the study product(s) are underway but have not been finalized at the time of application, please provide a letter indicating such in the application. Verification of adequate supply of study product(s) will be necessary before an award is made;

3) Patient Engagement: There must be evidence that patient input has been obtained in a meaningful way. A current letter(s) from patient(s)/caregiver(s)/patient organizations describing early and ongoing engagement in trial design should be provided.

Resource Sharing Plan: Individuals are required to comply with the instructions for the Resource Sharing Plans as provided in the How to Apply - Application Guide.

, with the following modification:

- All applications, regardless of the amount of direct costs requested for any one year, should address a Data Management and Sharing Plan.

Other Plan(s): Note: Effective for due dates on or after January 25, 2023, the Data Management and Sharing Plan will be attached in the Other Plan(s) attachment in FORMS-H application forms packages.

All instructions in the How to Apply - Application Guide must be followed, with the following additional instructions:

- All applicants planning research (funded or conducted in whole or in part by the FDA) that results in the generation of scientific data are required to comply with the instructions for the Data Management and Sharing Plan. All applications, regardless of the amount of direct costs requested for any one year, must address a Data Management and Sharing Plan.

Appendix:

Only limited Appendix materials are allowed. Follow all instructions for the Appendix as described in the SF424 (R&R) Application Guide, with the following additional requirements:

Do not use the Appendix section to circumvent page limits.

The Appendices must include the following, as appropriate for the proposed study:

1. Protocol: The full final protocol (IND/IDE submitted protocol) must be provided.

2. Informed Consent: Consent forms, assent forms, and any other information given to a subject must be provided and must comply with all elements of Human Subject Research per 21 CFR 50.25.

3. Innovative and Efficient Trial Approaches: Applications requesting additional funding (up to $250,000 total costs per year) for innovative and efficient trial approaches must submit a clear description and justification as to how the requirements as outlined below are met (limited to 3 pages):

- Innovative trial designs such as seamless and adaptive trial designs, which compress the phases of a trial into one continuous trial, as well as basket, umbrella and platform trials, which allow for testing of multiple drugs and/or multiple diseases using a common infrastructure.
- Innovative methods using data simulations and modeling toward the study of safety and efficacy of a product.

OOPD encourages applicants to refer to:

- "Interacting with the FDA on Complex Innovative Trial Designs" and "Adaptive Design Clinical Trials for Drugs and Biologics" for guidance on complex innovative designs and the use of data simulations and modeling for clinical trials intended to support the effectiveness and safety of drugs and biologics.

These approaches may hold significant promise for the advancement of therapeutic treatments for rare diseases through all phases of product development. Early engagement with FDA review divisions to discuss the use of these innovative approaches is highly recommended prior to submitting a grant application (e.g., preIND, INTERACT, other meetings).
Applications not meeting these requirements may be requested to reduce their budget.

4. Summary Statement: Resubmissions must provide the previous OOPD Summary Statement in an appendix section and may include a point-by-point rebuttal to those critiques.

PHS Human Subjects and Clinical Trials Information

When involving human subjects research, clinical research, and/or FDA-defined clinical trials (and when applicable, clinical trials research experience) follow all instructions for the PHS Human Subjects and Clinical Trials Information form in the How to Apply - Application Guide, with the following additional instructions:

If you answered "Yes" to the question “Are Human Subjects Involved?” on the R&R Other Project Information form, you must include at least one human subjects study record using the **Study Record: PHS Human Subjects and Clinical Trials Information** form or **Delayed Onset Study** record.

Study Record: PHS Human Subjects and Clinical Trials Information

All instructions in the How to Apply - Application Guide must be followed.

Foreign Organizations

Foreign (non-U.S.) organizations must follow policies described in the HHS Grants Policy Statement, and procedures for foreign organizations described throughout the How to Apply Application Guide.

4. Submission Dates and Times

Part I. contains information about Key Dates and times. Applicants are encouraged to submit applications before the due date to ensure they have time to make any application corrections that might be necessary for successful submission. When a submission date falls on a weekend or Federal holiday, the application deadline is automatically extended to the next business day.

Organizations must submit applications to Grants.gov (the online portal to find and apply for grants across all Federal agencies). Applicants must then complete the submission process by tracking the status of the application in the eRA Commons, FDA's electronic system for grants administration. FDA and Grants.gov systems check the application against many of the application instructions upon submission. Errors must be corrected and a changed/corrected application must be submitted to Grants.gov on or before the application due date and time. If a Changed/Corrected application is submitted after the deadline, the application will be considered late. Late applications will not be accepted for this FOA

Applicants are responsible for viewing their application before the due date in the eRA Commons to ensure accurate and successful submission.

Information on the submission process and a definition of on-time submission are provided in the How to Apply - Application Guide.

5. Intergovernmental Review (E.O. 12372)

This initiative is not subject to intergovernmental review.

6. Funding Restrictions

All FDA awards are subject to the terms and conditions, cost principles, and other considerations described in the HHS Grants Policy Statement.

Pre-award costs are allowable only as described in the HHS Grants Policy Statement.

Protection of Human Research Subjects

All institutions engaged in human subject research financially supported by HHS must file an assurance of protection for human subjects with the Office of Human Research Protections (OHRP) (45 CFR part 46). See Office of Human Research Protections for guidance on human subject protection issues. Federal regulations (45 CFR 46) require that applications and proposals involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.

The requirement to file an assurance applies to both awardee and collaborating performance site institutions. Awardee institutions are automatically considered to be engaged in human subject research whenever they receive a direct HHS award to support such research, even where all activities involving human subjects are carried out by a subcontractor or collaborator. In such cases, the awardee institution bears the responsibility for protecting human subjects under the award.

The awardee institution is also responsible for, among other things, ensuring that all collaborating performance site institutions engaged in the research hold an approved assurance prior to study initiation. No awardee or performance site institution may spend funds on human subject research or enroll subjects without the approved and applicable assurance(s) on file with OHRP. An awardee institution must, therefore, have a single IRB and assurance. The single IRB may be an IRB already being used by one of the performance sites, but it must specifically be registered as the single IRB with OHRP.

For further information, applicants should review the section on human subjects in the application instructions as posted on the Grants.gov application Web site. The clinical protocol should comply with ICHE6 Good Clinical Practice Consolidated Guidance which sets an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. All human subject research regulated by FDA is also subject to FDA's regulations regarding the protection of human subjects (21 CFR part 50 and 21 CFR part 56 and Guidance for Institutional Review Boards and Clinical Investigators). Applicants are encouraged to review the regulations, guidance, and information sheets on human subject protection and good clinical practice available at FDA's site on Clinical Trials and Human Subject Protection.

Key Personnel and Human Subject Protection Education

The awardee institution is responsible for ensuring that all key personnel receive appropriate training in their human subject protection responsibilities. Key personnel include all principal investigators, co-investigators, and performance site investigators responsible for the design and conduct of the study. HHS, FDA, and OOPD do not prescribe or endorse any specific education programs. Many institutions have already developed educational programs on the protection of research subjects and have made participation in such programs a requirement for their investigators. Other sources of appropriate instruction might include the online tutorials offered by the Office of Human Subjects Research, NIH at http://ohsr.od.nih.gov/ and by OHRP at https://www.hhs.gov/ohrp/education-and-outreach/index.html.

Within 30 days of the award, the principal investigator should provide a letter to FDA's grants management office that includes the names of the key personnel, the title of the human subjects protection education program completed for each key personnel, and a one-sentence description of the program. This letter should be signed by the principal investigator and cosigned by an institution official and sent to the Grants Management Specialist whose name appears on the official Notice of Grant Award (NGA).

7. Other Submission Requirements and Information

Applications must be submitted electronically following the instructions described in the How to Apply - Application Guide. Paper applications will not be accepted.

Applicants must complete all required registrations before the application due date. Section III. Eligibility Information contains information about registration.

For assistance with your electronic application or for more information on the electronic submission process, visit How to Apply - Application Guide. If you encounter a system issue beyond your control that threatens your ability to complete the submission process on-time, you must follow the Dealing with System Issues guidance. For assistance with application submission, contact the Application Submission Contacts in Section VII.

Important reminders:

All PD(s)/PI(s) must include their eRA Commons ID in the Credential field of the Senior/Key Person Profile form**.** Failure to register in the Commons and to include a valid PD/PI Commons ID in the credential field will prevent the successful submission of an electronic application to the FDA. See Section III of this NOFO for information on registration requirements.

The applicant organization must ensure that the unique entity identifier provided on the application is the same identifier used in the organization's profile in the eRA Commons and for the System for Award Management. Additional information may be found in the How to Apply - Application Guide.

See more tips for avoiding common errors.

Upon receipt, applications will be evaluated for completeness and compliance with application instructions by the assigned FDA Grants Management Specialist and responsiveness by components of participating organizations. Applications that are incomplete, non-compliant and/or nonresponsive will not be reviewed.

Mandatory Disclosure

Recipients or subrecipients must submit any information related to violations of federal criminal law involving fraud, bribery, or gratuity violations potentially affecting the federal award. See Mandatory Disclosures, 2 CFR 200.113 and HHS Grants Policy Statement.

Send written disclosures to the FDA Chief Grants Management Officer listed on the Notice of Award for the IC that funded the award and to the HHS Office of Inspector Grant Self Disclosure Program at grantdisclosures@oig.hhs.gov.

Post Submission Materials

Post-submission materials are those submitted after submission of the grant application but prior to objective review. They are not intended to correct oversights or errors discovered after submission of the application. FDA accepts limited information between the time of initial submission of the application and the time of objective review. Applicants must contact the assigned Grants Management Specialist to receive approval, prior to submitting any post submission materials. Acceptance and/or rejection of any post submission materials is at the sole discretion of the FDA. Any inquiries regarding post submission materials should be directed to the assigned Grants Management Specialist.

In unusual circumstances, additional information may be considered, on a case-by-case basis, for inclusion in the objective review, however, the FDA cannot assure inclusion of any information after the receipt date other than evidence of final IRB approval, FWA or assurance, and certification of adequate supply of study product.

Section V. Application Review Information

1. Criteria

Only the review criteria described below will be considered in the review process. Applications submitted to the FDA in support of the FDA mission are evaluated for scientific and technical merit through the FDA objective review system.

General Information

FDA grants management and program staff will review all applications sent in response to this funding opportunity announcement. To be responsive, an application must be submitted in accordance with the requirements of this notice. Applications found to be non-responsive will receive notice that the application will not be reviewed.

Program Responsiveness Review Criteria

The following criteria will be used to decide whether or not an application is responsive to this RFA.

1. Applications must propose clinical trials intended to provide safety and/or efficacy data for rare diseases or conditions. Applications must use the generic name of the proposed product(s).

2. The requested time must not exceed 4 years.

3. The Rationale Section of the Research Strategy must contain information documenting that the disease or condition to be treated meets the definition of a rare disease or condition, as defined in 21 U.S.C. 360ee. Prevalence calculations should be provided along with citations.

Applications may be considered for the use of a product in an orphan subset of a non-rare disease or condition when the applicant can explain based on a characteristic or feature of the product (e.g., mechanism of action, toxicity profile, prior clinical experience) why the product will be limited to use in the subset of question. An orphan subset is not based on an unmet need, or how a sponsor may wish to study or indicate a product. The explanation for the orphan subset must make it clear to OOPD that the product would not be appropriate in the disease or condition outside of the subset, including pediatric subpopulations.

Diagnostics and vaccines are considered potentially eligible for such grants only if the U.S. population to whom they will be administered is fewer than 200,000 people in the United States per year. Prevalence calculations should be provided along with citations.

For studies proposing to assess multiple rare diseases, supportive prevalence data for each rare disease is required. **If a designation by the Office of Orphan Products Development has been received by the institution submitting the grant for the drug for the disease subject to the grant, the designation number and date of designation should be provided in this section.**

4. There must be an explanation in the Rationale Section of the Research Strategy of how the proposed clinical trial will support of a new indication or change in labeling of a product(s).

5. To support a new indication or change in labeling, the study protocol proposed in the grant application (including studies of already approved products evaluating new orphan indications) must comply with the applicable regulations in 21 CFR 312 for drugs and biologics and 21 CFR 812 for devices, with the exceptions noted below for medical foods and non-significant risk devices. The protocol and all other required documents must be submitted to the applicable FDA IND/IDE review division a minimum of 30 days before the grant application deadline. The IND must be active (not on clinical hold or exempted) or the IDE must be approved to qualify the grant application for review.

Only medical foods that do not need pre-market approval and medical devices that are classified as non-significant risk (NSR) are free from these IND/IDE requirements. Applicants studying an NSR device should provide a letter in the grant application from the FDA Center for Devices and Radiologic Health indicating the device is an NSR device.

Note:

- **The final version of the protocol submitted to OOPD in the grant application is the protocol that MUST be submitted to an IND/IDE.**
- **The IND/IDE number and the date that the final version of the protocol was submitted to that IND/IDE should be included with the title of the projecton the face page of the grant application.**

6. If the sponsor of the IND/IDE is other than the principal investigator listed on the application, a letter from the sponsor permitting access to the IND/IDE must be submitted in both the IND/IDE and in the grant application. The name(s) of the Principal Investigator(s) named in the application and in the study, protocol must be submitted to the IND/IDE.

7. Appropriate documentation is needed including the protocol, informed consent form, and documentation and justification of innovative and efficient trial approach (if applicable). These should be submitted as appendices to the application. Letters of support regarding the availability of product, study sites, and patient engagement are also required.

8. Page limits, font size and margins should comply with the Application Guide, Electronic Submission of Grant Applications (https://grants.nih.gov/grants/how-to-apply-application-guide.html), with the exceptions noted in the Page Limitations section above for Resubmissions.

9. Additional information may be required upon request after submission of an application to determine responsiveness, for example, regarding population estimate and rationale. This additional information may be required, in part, to assure that human clinical trials of drugs are eligible to receive funding under the OPD grant program per 21 U.S.C. 360ee(b)(1)(A).

Applicants are strongly encouraged to contact FDA to resolve any questions about criteria before submitting their application. Please direct all questions of a technical or scientific nature to the OPD program staff and all questions of an administrative or financial nature to the grants management staff (see Agency Contacts in Section VII of this document).

Responsive applications will be reviewed and evaluated for scientific and technical merit by a panel of experts in the subject field of the specific application. Consultation with the proper FDA experts may also occur during this phase of the review to determine whether the proposed study will provide acceptable data that could contribute to product approval. Funding decisions will be made by the Commissioner of Food and Drugs or his designee. **By submitting an application in response to this RFA, applicants understand and agree that members of the objective review panel of experts may be provided access to non-public information contained in the grant application, as necessary for evaluation of the application and are subject to the necessary restrictions on the further disclosure of the information.**

A score will be assigned to each application based on the scientific/technical review criteria. The review panel may advise the program staff about the appropriateness of the proposal to the goals of the OPD grant program.

A proposed Clinical Trial application 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 lead to new avenues of scientific investigation.

Overall Impact

Reviewers will provide an overall impact score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following review criteria and additional review criteria (as applicable for the project proposed).

Scored Review Criteria

Reviewers will consider each of the review criteria below in the determination 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. In addition, an application with moderate correctable weaknesses in a criterion may still receive a high overall impact score because one or more of the other review criteria are critically important to the research and have significant strengths. The relative importance of strengths and weaknesses, not simply the number of strengths and weaknesses, are considered in developing the impact score.

1. Rationale

Does the project address an important problem or a critical barrier to progress in the field? Is the prior research that serves as the key support for the proposed project rigorous? If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Are the scientific rationale and need for a clinical trial to test the proposed hypothesis or intervention well supported by preliminary data, clinical and/or preclinical studies, or information in the literature or knowledge of biological mechanisms? For trials focusing on clinical or public health endpoints, is this clinical trial necessary for testing the safety, efficacy or effectiveness of an intervention that could lead to a change in clinical practice, community behaviors or health care policy? For trials focusing on mechanistic, behavioral, physiological, biochemical, or other biomedical endpoints, is this trial needed to advance scientific understanding?

The soundness of rationale in relation to the current understanding of the rare disease(s) and the likelihood the proposal will facilitate a clinical trial in support of a new indication(s) for use or change in labeling of a product(s) to address unmet needs in a rare disease(s).

- Description of the state of existing knowledge, including literature citations and highlights of relevant preliminary studies and previous preclinical and/or clinical data, including the natural history of the disease(s) in relation to the proposed safety/efficacy evaluation.
- Explanation of the importance of knowledge gap(s) and critical barrier(s) to progress in the field such as lack of treatments that the proposed project will address.
- Explanation of how the proposed study will provide essential data needed to support a new indication or a change in labeling.

2. Study Design including Data Quality and Interpretability:

Are the PD(s)/PI(s), collaborators, and other researchers well suited to the project? If Early Stage Investigators or those in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? If the project is collaborative or multi-PD/PI, do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the project?

With regard to the proposed leadership for the project, do the PD/PI(s) and key personnel have the expertise, experience, and ability to organize, manage and implement the proposed clinical trial and meet milestones and timelines? Do they have appropriate expertise in study coordination, data management and statistics? For a multicenter trial, is the organizational structure appropriate and does the application identify a core of potential center investigators and staffing for a coordinating center?

The quality and appropriateness of the study design, research methodology, and data analyses to accomplish the specific aims of the proposed study and its potential to make an impact for rare diseases.

- Description of the study including a clear hypothesis, study aims, and experimental design, including the appropriateness of the eligibility criteria and endpoints for the proposed study population and how data will be collected, analyzed, and interpreted.
- Explanation of the trial design and how it will meet the objectives efficiently (e.g., the use of basket, umbrella, platform trials, etcetera should be explicitly stated). Depending on the phase of development, these trials may need to include an appropriate comparator, such as a placebo, a concurrent external control, or a historical control.
- Description of how the study may have potential to provide a broad and positive impact for rare diseases.
- Description of the statistical analysis plan in adequate detail to show that the power of the study and data analyses will be sufficient to detect a meaningful benefit.
- Description of plans for ensuring data quality including but not limited to standardized data collection, data entry, data access, data monitoring, and data sharing.
- Description of plans for protecting the rights, safety, and welfare of study participants in compliance with federal law.
- Description of how data will be collected according to Good Clinical Practice Guidelines.
- Discussion of challenges, potential problems, alternative strategies, and benchmarks for success anticipated to achieve the aims within a stated timeframe.

3. Inclusion of Patient Input:

Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

Does the design/research plan include innovative elements, as appropriate, that enhance its sensitivity, potential for information or potential to advance scientific knowledge or clinical practice?

The inclusion of patient and caregiver perspectives as is critical in the planning and design of the clinical study to improve protocol design and medical product development.

- Description of plans to include early and ongoing patient/interested parties input in the study (e.g., protocol design, data elements, feasibility, data sharing).
- Description of plans to reduce patient and caregiver burden to participate in the study, impact on daily living, and potential issues with trial design feasibility.

4. Investigator(s), Infrastructure, and Financial Resources:

Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? Have the investigators included plans to address weaknesses in the rigor of prior research that serves as the key support for the proposed project? Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed? Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?

If the project involves human subjects and/or FDA-defined clinical research, are the plans to address 1) the protection of human subjects from research risks, and 2) inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion or exclusion of individuals of all ages (including children and older adults), justified in terms of the scientific goals and research strategy proposed?

Does the application adequately address the following, if applicable

Study Design

Is the study design justified and appropriate to address primary and secondary outcome variable(s)/endpoints that will be clear, informative and relevant to the hypothesis being tested? Is the scientific rationale/premise of the study based on previously well-designed preclinical and/or clinical research? Given the methods used to assign participants and deliver interventions, is the study design adequately powered to answer the research question(s), test the proposed hypothesis/hypotheses, and provide interpretable results? Is the trial appropriately designed to conduct the research efficiently? Are the study populations (size, gender, age, demographic group), proposed intervention arms/dose, and duration of the trial, appropriate and well justified?

Are potential ethical issues adequately addressed? Is the process for obtaining informed consent or assent appropriate? Is the eligible population available? Are the plans for recruitment outreach, enrollment, retention, handling dropouts, missed visits, and losses to follow-up appropriate to ensure robust data collection? Are the planned recruitment timelines feasible and is the plan to monitor accrual adequate? Has the need for randomization (or not), masking (if appropriate), controls, and inclusion/exclusion criteria been addressed? Are differences addressed, if applicable, in the intervention effect due to sex/gender and race/ethnicity?

Are the plans to standardize, assure quality of, and monitor adherence to, the trial protocol and data collection or distribution guidelines appropriate? Is there a plan to obtain required study agent(s)? Does the application propose to use existing available resources, as applicable?

Data Management and Statistical Analysis

Are planned analyses and statistical approach appropriate for the proposed study design and methods used to assign participants and deliver interventions? Are the procedures for data management and quality control of data adequate at clinical site(s) or at center laboratories, as applicable? Have the methods for standardization of procedures for data management to assess the effect of the intervention and quality control been addressed? Is there a plan to complete data analysis within the proposed period of the award?

The probability of success of the proposed project given the environment in which the work will be done.

- Description of the competence of the PI(s), collaborators, and other support staff in conducting the proposed research, including their academic qualifications, research experiences, productivity, and any special attributes.
- If applicable, description of the rationale, leadership approach, governance, and organizational structure for a multi-PD/PI project.

- Description of the applicant's ability to recruit and complete the proposed study within budget and stated time limits, including a detailed recruitment plan and timeline for implementation of the project upon funding.
- Description of institutional support, equipment, and other resources, such as with existing research networks, industry, academia and/or patient organizations and resource sharing plans as appropriate.
- Evidence that the product(s) to be studied is available to the applicant in the form and quantity needed for the clinical trial.
- Description of any additional funds expected to be contributed by other sources (including the applicant) prior to FDA grant funding and those to be used during the proposed funding period.
- Explanation of sustainability plans for acquiring additional funding for further phases of development beyond the proposed funding period, including a description of plans for leveraging FDA funding for additional resources needed for the proposed trial/overall development of the product(s). For some products (such as gene therapy products) that may require long-term safety follow-up, an outline of a sustainability plan is needed.

5. Ability to Advance the Current Field:

Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?

If proposed, are the administrative, data coordinating, enrollment and laboratory/testing centers, appropriate for the trial proposed?

Does the application adequately address the capability and ability to conduct the trial at the proposed site(s) or centers? Are the plans to add or drop enrollment centers, as needed, appropriate?

If international site(s) is/are proposed, does the application adequately address the complexity of executing the clinical trial?

If multi-sites/centers, is there evidence of the ability of the individual site or center to: (1) enroll the proposed numbers; (2) adhere to the protocol; (3) collect and transmit data in an accurate and timely fashion; and, (4) operate within the proposed organizational structure?

The ability of the project to shift current research or clinical practice paradigms towards future product development and to exert a significant influence on product development.

- Explanation of how the proposed study will exert a sustained, powerful influence on the research field.
- Explanation of novel or improved concepts, approaches, or methodologies, instrumentation or interventions to be developed or used, such as with pharmacokinetic, pharmacodynamic modeling or clinical study design (e.g., adaptive design trials, modeling, or simulations), and/or outcome measures, and their advantages over existing approaches.
- Explanation of sustainability plans beyond the proposed funding period, including a description of plans for leveraging data for use in further phases of development beyond the proposed funding period.

Additional Review Criteria

As applicable for the project proposed, reviewers will evaluate the following additional items while determining scientific and technical merit, and in providing an overall impact score, but will not give separate scores for these items.

Study Timeline

Is the study timeline described in detail, taking into account start-up activities, the anticipated rate of enrollment, and planned follow-up assessment? Is the projected timeline feasible and well justified? Does the project incorporate efficiencies and utilize existing resources (e.g., CTSAs, practice-based research networks, electronic medical records, administrative database, or patient registries) to increase the efficiency of participant enrollment and data collection, as appropriate?

Are potential challenges and corresponding solutions discussed (e.g., strategies that can be implemented in the event of enrollment shortfalls)?

Protections for Human Subjects

For research that involves human subjects but does not involve one of the categories of research that are exempt under 45 CFR Part 46, the committee will evaluate the justification for involvement of human subjects and the proposed protections from research risk relating to their participation according to the following five review criteria: 1) risk to subjects, 2) adequacy of protection against risks, 3) potential benefits to the subjects and others, 4) importance of the knowledge to be gained, and 5) data and safety monitoring for clinical trials.

For research that involves human subjects and meets the criteria for one or more of the categories of research that are exempt under 45 CFR Part 46, the committee will evaluate: 1) the justification for the exemption, 2) human subjects involvement and characteristics, and 3) sources of materials. For additional information on review of the Human Subjects section, please refer to the Guidelines for the Review of Human Subjects.

Biohazards

Reviewers will assess whether materials or procedures proposed are potentially hazardous to research personnel and/or the environment, and if needed, determine whether adequate protection is proposed.

Resubmissions

For Resubmissions, the committee will evaluate the application as now presented, taking into consideration the responses to comments from the previous scientific review group and changes made to the project.

The adequacy of the responses to comments from the most recent scientific review group will be assessed including the appropriateness of the improvements in the resubmission application. Resubmission applications must include an Introduction addressing the previous objective review critique (Summary Statement). The Summary Statement issued from OOPD must also be included as an Appendix in the resubmission application.

Renewals

For Renewal applications, the Research Strategy should include a brief Progress Report that summarizes Progress to Date and accomplishments achieved during the current funding period. The Progress Report should include a summary of the specific aims of the previous project period and the importance of the findings, progress made towards achievements, explanation on any significant changes to the specific aims and any new directions.
Letters of support: Letters of support should not be included as part of the Research Strategy and instead should be uploaded to line 9 on the PHS 398 Research Plan Form.
Letters of support should be included for the following areas: 1) Study Sites: The leader(s) of the existing clinical research institutions that will conduct the study should describe their site support, including relevant resources and study infrastructure and an estimate of the number of patients with the target rare disease(s) who would be eligible for the study;
2) Product Availability: There must be evidence that the product(s) to be studied is available to the applicant in the form and quantity needed for the clinical trial proposed. A current letter(s) from the supplier as an appendix will be acceptable. If negotiations regarding the supply of the study product(s) are underway but have not been finalized at the time of application, please provide a letter indicating such in the application. Verification of adequate supply of study product(s) will be necessary before an award is made;
3) Patient Engagement: There must be evidence that patient input has been obtained in a meaningful way. A current letter(s) from patient(s)/caregiver(s)/patient organizations describing early and ongoing engagement in trial design should be provided.

Revisions

For Revisions, the committee will consider the appropriateness of the proposed expansion of the scope of the project. If the Revision application relates to a specific line of investigation presented in the original application that was not recommended for approval by the committee, then the committee will consider whether the responses to comments from the previous scientific review group are adequate and whether substantial changes are clearly evident.

Additional Review Considerations

As applicable for the project proposed, reviewers will consider each of the following items, but will not give scores for these items, and should not consider them in providing an overall impact score.

Applications from Foreign Organizations

Reviewers will assess whether the project presents special opportunities for furthering research programs through the use of unusual talent, resources, populations, or environmental conditions that exist in other countries and either are not readily available in the United States or augment existing U.S. resources.

Select Agent Research

Reviewers will assess the information provided in this section of the application, including 1) the Select Agent(s) to be used in the proposed research, 2) the registration status of all entities where Select Agent(s) will be used, 3) the procedures that will be used to monitor possession use and transfer of Select Agent(s), and 4) plans for appropriate biosafety, biocontainment, and security of the Select Agent(s).

Resource Sharing Plans

Reviewers will comment on whether the Resource Sharing Plan(s) (i.e., Sharing Model Organisms) or the rationale for not sharing the resources, is reasonable.

Authentication of Key Biological and/or Chemical Resources:

For projects involving key biological and/or chemical resources, reviewers will comment on the brief plans proposed for identifying and ensuring the validity of those resources.

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 research.

Applications will be evaluated for scientific and technical merit by (an) appropriate Objective Review Committee convened by the FDA, using the stated review criteria.

As part of the objective review, all applications will receive a written critique.

Appeals of objective review will not be accepted for applications submitted in response to this NOFO.

Applications will compete for available funds with all other recommended applications submitted in response to this NOFO. The following will be considered in making funding decisions:

- Scientific and technical merit of the proposed project as determined by objective review.
- Availability of funds.
- Relevance of the proposed project to program priorities.

3. Anticipated Announcement and Award Dates

Successful applicants will be notified of additional information that may be required or other actions leading to an award. The decision not to award a grant, or to award a grant at a particular funding level, is discretionary and is not subject to appeal to any FDA or HHS official or board.

Information regarding the disposition of applications is available in the HHS Grants Policy Statement.

Section VI. Award Administration Information

1. Award Notices

A Notice of Award (NoA) is the official authorizing document notifying the applicant that an award has been made and that funds may be requested from the designated HHS payment system or office. The NoA is signed by the Grants Management Officer and emailed to the recipient's business official.

In accepting the award, the recipient agrees that any activities under the award are subject to all provisions currently in effect or implemented during the period of the award, other Department regulations and policies in effect at the time of the award, and applicable statutory provisions.

Recipients must comply with any funding restrictions described in Section IV.6. Funding Restrictions. Any pre-award costs incurred before receipt of the NoA are at the applicant's own risk. For more information on the Notice of Award, please refer to the HHS Grants Policy Statement.

Institutional Review Board or Independent Ethics Committee Approval: Recipient institutions must ensure that protocols are reviewed by their IRB or IEC. To help ensure the safety of participants enrolled in FDA-funded studies, the recipient must provide FDA copies of documents related to all major changes in the status of ongoing protocols.

Individual awards are based on the application submitted to, and as approved by, the FDA and are subject to the IC-specific terms and conditions identified in the NoA.

ClinicalTrials.gov: If an award provides for one or more clinical trials. By law (Title VIII, Section 801 of Public Law 110-85), the "responsible party" must register and submit results information for certain applicable clinical trials on the ClinicalTrials.gov Protocol Registration and Results System Information Website (https://register.clinicaltrials.gov). The FDA expects registration and results reporting of all trials whether required under the law or not. For more information, see the HHS Grants Policy Statement.

Data and Safety Monitoring Requirements: The FDA policy for data and safety monitoring requires oversight and monitoring of all FDA-conducted or supported human biomedical and behavioral intervention studies (clinical trials) to ensure the safety of participants and the validity and integrity of the data. Further information concerning these requirements is found at the HHS Grants Policy Statement and in the application instructions (SF424 (R&R) and PHS 398).

Investigational New Drug or Investigational Device Exemption Requirements: Consistent with federal regulations, clinical research projects involving the use of investigational therapeutics, vaccines, or other medical interventions (including licensed products and devices for a purpose other than that for which they were licensed) in humans under a research protocol must be performed under a Food and Drug Administration (FDA) investigational new drug (IND) or investigational device exemption (IDE).

2. Administrative and National Policy Requirements

All FDA grant and cooperative agreement awards include the HHS Grants Policy Statement as part of the NoA.

If a recipient is successful and receives a Notice of Award, in accepting the award, the recipient agrees that any activities under the award are subject to all provisions currently in effect or implemented during the period of the award, other Department regulations and policies in effect at the time of the award, and applicable statutory provisions.

HHS recognizes that research projects are often limited in scope for many reasons , such as the principal investigator's scientific interest, funding limitations, recruitment requirements, and other considerations. Thus, criteria in research protocols that target or exclude certain populations are warranted where justifications establish that such criteria are appropriate with respect to the health or safety of the subjects, the scientific study design, or the purpose of the research. For additional guidance regarding how the provisions apply to FDA grant programs, please contact the Scientific/Research Contact that is identified in Section VII under Agency Contacts of this NOFO.

In accordance with the statutory provisions contained in Section 872 of the Duncan Hunter National Defense Authorization Act of Fiscal Year 2009 (Public Law 110-417), FDA awards will be subject to the Federal Awardee Performance and Integrity Information System (FAPIIS) requirements. FAPIIS requires Federal award making officials to review and consider information about an applicant in the designated integrity and performance system (currently FAPIIS) prior to making an award. An applicant, at its option, may review information in the designated integrity and performance systems accessible through FAPIIS and comment on any information about itself that a federal agency previously entered and is currently in FAPIIS. The Federal awarding agency will consider any comments by the applicant, in addition to other information in FAPIIS, in making a judgment about the applicant's integrity, business ethics, and record of performance under Federal awards when completing the review of risk posed by applicants as described in 45 CFR Part 75.205 and 2 CFR Part 200.206 "Federal awarding agency review of risk posed by applicants." This provision will apply to all FDA grants and cooperative agreements.

FDA considers the sharing of research resources developed through FDA-sponsored research an important means to enhance the value and further the advancement of research. When research resources have been developed with FDA funds and the associated research findings published, those findings must be made readily available to the scientific community.

Upon acceptance for publication, scientific researchers must submit the author's final manuscript of the peer-reviewed scientific publication resulting from research supported in whole or in part with FDA funds to the NIH National Library of Medicine's (NLM) PubMed Central (PMC). FDA defines the author's final manuscript as the final version accepted for journal publication, which includes all modifications from the publishing peer review process. The PMC archive is the designated repository for these manuscripts for use by the public, health care providers, educators, scientists, and FDA. Please see the FDA Public Access Policy.

Termination provisions in 2 CFR 200.340 (a) (1-4) are applicable to awards issued under this Notice of Funding Opportunity.

Additional terms and conditions regarding FDA regulatory and FDA Orphan Products programmatic requirements may be part of the Notice of Award.

Standard Terms and Conditions of Award

Reporting Requirements:

All FDA grants require both Financial and Performance reporting.

Financial Reporting:

A. Financial Expenditure Reports

A required Federal Financial Report (FFR) must be submitted annually. All annual FFRs must be submitted electronically using the Payment Management System (PMS). This includes all initial FFRs being prepared for submission and any revised FFRs being submitted or re-submitted to FDA. Paper expenditure/FFR reports will not be accepted.

Annual FFRs must be submitted for each budget period no later than 90 days after the end of the calendar quarter in which the budget period ended. The reporting period for an annual FFR will be that of the budget period for the particular grant; however, the actual submission date is based on the calendar quarter. If a grant is under expanded authorities, the grantee must indicate the carryover amount in Section 12. Remarks of the annual FFR.

Performance Progress Reporting:

When multiple years (more than one budget period) are involved, awardees will be required to submit the Research Performance Progress Report (RPPR) annually as required in the Notice of Award. Annual RPPRs must be submitted using the RPPR module in eRA Commons. The annual RPPR must include a detailed budget. Annual RPPRs are due no later than 60 days prior to the start of the next budget period.

Failure to submit timely reports may affect future funding. Additional Financial and Performance Progress reports may be required for this award. Any additional reporting requirements will be listed under Section IV – Special Terms and Condition of the Notice of Award.

Salary Caps:

None of the funds in this award shall be used to pay the salary of an individual at a rate in excess of the current Executive Level II of the Federal Executive Pay Scale.

Certificates of Confidentiality – 42 U.S.C. 241(d)

Awardees are responsible for complying with all requirements to protect the confidentiality of identifiable, sensitive information that is collected or used in biomedical, behavioral, clinical, or other research (including research on mental health and research on the use and effect of alcohol and other psychoactive drugs) funded wholly or in part by the Federal Government. See 42 U.S.C. 241(d). All research funded by FDA, in whole or in part, that is within the scope of these requirements is deemed to be issued a "Certificate of Confidentiality" through these Terms and Conditions. Certificates issued in this manner will not be issued as a separate document.

Awardees are expected to ensure that any investigator or institution not funded by FDA who receives a copy of identifiable, sensitive information protected by these requirements, understand they are also subject to the requirements of 42 U.S.C. 241(d). Awardees are also responsible for ensuring that any subrecipient that receives funds to carry out part of the FDA award involving a copy of identifiable, sensitive information protected by these requirements understand they are also subject to subsection 42 U.S.C. 241(d).

Acknowledgment of Federal Support:

When issuing statements, press releases, publications, requests for proposal, bid solicitations and other documents --such as tool-kits, resource guides, websites, and presentations (hereafter "statements")-- describing the projects or programs funded in whole or in part with FDA federal funds, the recipient must clearly state:

1. the percentage and dollar amount of the total costs of the program or project funded with federal money; and,

2. the percentage and dollar amount of the total costs of the project or program funded by non-governmental sources.

When issuing statements resulting from activities supported by FDA financial assistance, the recipient entity must include an acknowledgment of federal assistance using one of the following statements.

If the FDA Grant or Cooperative Agreement is NOT funded with other non-governmental sources:

This [project/publication/program/website, etc.] [is/was] supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award [FAIN] totaling $XX with 100 percent funded by FDA]/HHS. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA/HHS, or the U.S. Government.

If the FDA Grant or Cooperative Agreement IS partially funded with other nongovernmental sources:

This [project/publication/program/website, etc.] [is/was] supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award [FAIN] totaling $XX with XX percentage funded by FDA/HHS and $XX amount and XX percentage funded by non-government source(s). The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA/HHS, or the U.S. Government.

The federal award total must reflect total costs (direct and indirect) for all authorized funds (including supplements and carryover) for the total competitive segment up to the time of the public statement. Any amendments by the recipient to the acknowledgment statement must be coordinated with FDA. If the recipient plans to issue a press release concerning the outcome of activities supported by FDA financial assistance, it should notify FDA in advance to allow for coordination.

Additional prior approval requirements pertaining to Acknowledgement of Federal Support, publications, press statements, etc. may be required, and if applicable, will be listed under Section IV – Special Terms and Condition of the Notice of Award.

Prior Approval:

All prior approval requests must be submitted using the Prior Approval module in eRA Commons. Any requests involving budgetary issues must include a new proposed budget and a narrative justification of the requested changes. If there are any questions regarding the need or requirement for prior approval for any activity or cost, the grantee is to contact the assigned Grants Management Specialist prior to expenditure of funds.

For grant awards not covered under Expanded Authorities, Carryover and No Cost Extension (NCE) requests will require prior approval. All Carryover and NCE requests should be submitted using the Prior Approval module in eRA Commons. ****Please review the section on Expanded Authorities to determine if this award is covered/not covered under Expanded Authorities and whether prior approval is needed for carryover and no cost extension requests.****

The following activities require prior approval from FDA on all awards:

1. Change in Grantee Organization

2. Significant Re-budgeting

3. Change in Scope or Objectives

4. Deviation from Terms and Conditions of Award

5. Change in Key Personnel which includes replacement of the PD/PI or other key personnel as specified on the NoA.

6. Disengagement from the project for more than three months, or a 25 percent reduction in time devoted to the project, by the approved PD/PI. No individual may be committed to more than 100% professional time and effort. In the event that an individual's commitment exceeds 100%, the grantee must make adjustments to reduce effort. For FDA-sponsored projects, significant reductions in effort (i.e., in excess of 25% of the originally proposed level of effort) for the PD/PI and key personnel named on this Notice of Award must receive written prior approval from FDA.

Additional prior approval requirements may be required for this award, and if applicable, will be listed under Section IV – Special Terms and Condition of the Notice of Award.

Audits and Monitoring:

Audit Requirements:

1. Recipients of Federal funds are subject to annual audit requirements as specified in 45 CFR 75.501 (https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=1&SID=8040c4036b962cc9d75c3638dedce240&ty=HTML&h=L&r=PART&n=pt45.1.75#se45.1.75_1501). Grantees should refer to this regulation for the current annual Federal fund expenditure threshold level which requires audit.

2. Foreign recipients are subject to the same audit requirements as for-profit organizations (specified in 45 CFR 75.501(h) through 75.501(k).

3. For-profit and foreign entities can email their audit reports to AuditResolution@hhs.gov or mail them to the following address:

U.S. Department of Health and Human Services

Audit Resolution Division, Room 549D

Attention: Robin Aldridge, Director

200 Independence Avenue, SW

Washington, DC 20201

Monitoring:

Recipients are responsible for managing the day-to-day operations of grant-supported activities using their established controls and policies, as long as they are consistent with Federal, DHHS and FDA requirements. However, to fulfill their role in regard to the stewardship of Federal funds, FDA monitors our grants to identify potential problems and areas where technical assistance might be necessary. This active monitoring is accomplished through review of reports and correspondence from the recipient, audit reports, site visits, and other information available to FDA.

1. Desk review: FDA grants monitoring specialists will periodically reach out to recipients to request information for the completion of desk reviews. Requested information may include:

- Policies and procedures
- List of grant expenditures
- Accounting records
- Supporting documents (e.g., invoices, receipts, paystubs, timesheets, contracts, etc.)
- Financial statements
- Audit reports
- Other related documentation

2. Site visits: FDA will conduct site visits when necessary and will notify the recipient with reasonable advance notice of any such visit(s).

3. Foreign entities: All Foreign entities are subject to the same monitoring requirements as domestic entities. Foreign entities covered under immunity Executive Orders will provide supporting documents for monitoring requirements unless such an action is a violation of the Executive Orders. Recipients may discuss with the FDA to come up with an alternate approach to satisfy the award monitoring requirements.

All recipients will make reasonable efforts to resolve issues found, including audit findings. Successful resolutions to issues are important as they are part of the grant performance review. All recipients are responsible for submitting all requested information in an expeditious manner. Failure to submit timely reports and/or respond to inquiries from FDA may affect future funding or enforcement actions, including withholding, or conversion to a reimbursement payment method.

Financial Conflict of Interest (FCOI):

This award is subject to the Financial Conflict of Interest (FCOI) regulation at 42 CFR Part 50 Subpart F.

Closeout Requirements (when applicable):

A Final Research Performance Progress Report (FRPPR), Final Invention Statement HHS-568 (if applicable), Tangible Personal Property Report SF-428 (if applicable), and Statement of Disposition of Equipment (if applicable) must be submitted within 120 days after the expiration date of the project period. All closeout documents must be submitted electronically in eRA Commons.

The Final Federal Financial Report (FFR SF-425) must be submitted in PMS and indicate the exact balance of unobligated funds and may not reflect unliquidated obligations. There must be no discrepancies between the Final FFR expenditure data and FFR cash transaction data in the Payment Management System (PMS). The expended funds reported on the Final FFR must exactly match the disbursements and the charge advances in PMS. It is the recipient's responsibility to reconcile reports submitted to PMS and to the FDA.

Program Income:

The grantee is required to report any Program Income generated during the Project Period of this grant. Except for royalty income generated from patents and inventions, the amount and disposition of Program Income must be identified on lines 10 (l), (m), (n), and (o) of the grantee's Federal Financial Report (FFR) SF-425.

Examples of Program Income include (but are not limited to): fees for services performed during the grant or sub-grant period, proceeds from sale of tangible personal or real property, usage or rental fees, patent or copyright royalties, and proceeds from the sale of products and technology developed under the grant.

Any Program Income generated during the Project Period of this grant by the grantee or sub-grantee will be treated as identified below.

Treatment of Program Income:

Prohibition on certain telecommunications and video surveillance services or equipment:

(a) As described in 2 CFR 200.216, recipients and subrecipients are prohibited to obligate or spend grant funds (to include direct and indirect expenditures as well as cost share and program) to:

(1) Procure or obtain;

(2) Extend or renew a contract to procure or obtain; or

(3) Enter into contract (or extend or renew contract) to procure or obtain equipment, services, or systems that use covered telecommunications equipment or services as a substantial or essential component of any system, or as critical technology as part of any system. As described in Pub. L. 115-232, section 889, covered telecommunications equipment is telecommunications equipment produced by Huawei Technologies Company or ZTE Corporation (or any subsidiary or affiliate of such entities).

i. For the purpose of public safety, security of government facilities, physical security surveillance of critical infrastructure, and other national security purposes, video surveillance and telecommunications equipment produced by Hytera Communications Corporation, Hangzhou Hikvision Digital Technology Company, or Dahua Technology Company (or any subsidiary or affiliate of such entities).

ii. Telecommunications or video surveillance services provided by such entities or using such equipment.

iii. Telecommunications or video surveillance equipment or services produced or provided by an entity that the Secretary of Defense, in consultation with the Director of the National Intelligence or the Director of the Federal Bureau of Investigation, reasonably believes to be an entity owned or controlled by, or otherwise, connected to the government of a covered foreign country.

Other:

This award is subject to the requirements of 2 CFR Part 25 for institutions to maintain an active registration in the System of Award Management (SAM). Should a consortium/subaward be issued under this award, a requirement for active registration in SAM must be included.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75.

Cooperative Agreement Terms and Conditions of Award

Not Applicable

3. Data Management and Sharing

Consistent with the FDA Policy for Data Management and Sharing, when data management and sharing is applicable to the award, recipients will be required to adhere to the Data Management and Sharing requirements as outlined in the HHS Grants Policy Statement. Upon the approval of a Data Management and Sharing Plan, it is required for recipients to implement the plan as described.

4. Reporting

When multiple years are involved, recipients will be required to submit the Research Performance Progress Report (RPPR) annually and financial statements as required in the HHS Grants Policy Statement.

A final RPPR, invention statement, and the expenditure data portion of the Federal Financial Report are required for closeout of an award, as described in the HHS Grants Policy Statement. FDA NOFOs outline intended research goals and objectives. Post award, the FDA will review and measure performance based on the details and outcomes that are shared within the RPPR, as described at 2 CFR Part 200.301.

All new and continuing grants which have referenced INDs/IDEs must comply with all regulatory requirements necessary to keep the status of their IND/IDE active and in effect, that is, not on clinical hold.

The Federal Funding Accountability and Transparency Act of 2006 as amended (FFATA), includes a requirement for recipients of Federal grants to report information about first-tier subawards and executive compensation under Federal assistance awards issued in FY2011 or later. All recipients of applicable FDA grants and cooperative agreements are required to report to the Federal Subaward Reporting System (FSRS) available at www.fsrs.gov on all subawards over the threshold. See the HHS Grants Policy Statement for additional information on this reporting requirement.

In accordance with the regulatory requirements provided at 2 CFR Part 200.113 and Appendix XII to 2 CFR Part 200, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts from all Federal awarding agencies with a cumulative total value greater than $10,000,000 for any period of time during the period of performance of a Federal award, must report and maintain the currency of information reported in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (Responsibility/Qualification in SAM.gov, formerly FAPIIS). This is a statutory requirement under section 872 of Public Law 110-417, as amended (41 U.S.C. 2313). As required by section 3010 of Public Law 111-212, all information posted in the designated integrity and performance system on or after April 15, 2011, except past performance reviews required for Federal procurement contracts, will be publicly available. Full reporting requirements and procedures are found in Appendix XII to 2 CFR Part 200 Award Term and Condition for Recipient Integrity and Performance Matters.

Monitoring Activities

The guidelines below are intended to provide information for principal investigators who are conducting clinical trials. The procedures outlined herein are in addition to (and not in lieu of) Institutional Review Board (IRB), Office for Human Research Protections (OHRP), other Food and Drug Administration (FDA), and Good Clinical Practices requirements.

It is an OOPD policy that data and safety monitoring of a clinical trial is to be commensurate with the risks posed to study participants and with the size and complexity of the study. OOPD requires that a Grantee and any third party engaged in supporting the clinical research be responsible for oversight of data and safety monitoring, ensuring that monitoring systems are in place, that the quality of the monitoring activity is appropriate, and that the OOPD Program Official is informed of recommendations emanating from monitoring activities.

FDA Requirements for Monitoring

OOPD requires that each clinical trial it supports, regardless of phase, has data and safety monitoring procedures in place to safeguard the well-being of study participants and to ensure scientific integrity. Monitoring must be performed on a regular basis throughout the subject accrual, treatment, and follow-up periods.

The specific approach to monitoring will depend on features of the clinical trial to be conducted e.g., several levels of monitoring: Data and Safety Monitoring Board (DSMB), Study Monitoring Committee (SMC) and Independent Medical Monitor (IMM). Monitoring activities should be appropriate to the study, study phase, population, research environment, and degree of risk involved. Guidance is available at: https://www.fda.gov/media/116754/download

Oversight Activities

The program official will monitor grantees periodically. The oversight may be in the form of telephone conversations, e-mails, or written correspondence between the program official/grants management officer or specialist and the principal investigator. Information including, but not limited to, information regarding study progress, enrollment, problems, adverse events, changes in protocol, study monitoring activities, new collaborations, publications, financial and data leveraging, and changes in clinical guidelines based on the project will be requested. Periodic grant evaluations (teleconference or on-site) with officials of the grantee organization may also occur. To ensure that funded studies support the long-term goal of product approval, regulatory milestone meetings will be initiated as needed. OOPD may request information related to the impact of this study on future approvals and other outcomes such as publications or data leveraging. The results of these monitoring activities will be recorded in the official grant file and will be available to the grantee upon request consistent with applicable disclosure statutes and with FDA disclosure regulations. Also, the grantee organization must comply with all special terms and conditions of the grant, including those which state that future funding of the study will depend on recommendations from the OOPD program official. The scope of the recommendations will consider the following: (1) progress toward enrollment, based on specific circumstances of the study; (2) adequate supply of the product/device; and (3) compliance with applicable FDA and HHS regulatory requirements for the trial.

Documentation of assurances with the Office of Human Research Protection (OHRP) (see Section IV.5.A of this document) must be on file with the FDA grants management office before an award is made. Any institution receiving Federal funds must have a single institutional review board (IRB) even if that institution is overseeing research conducted at other performance sites. To avoid funding studies that may not receive or may experience a delay in receiving IRB approval, documentation of IRB approval and Federal Wide Assurance (FWA) for the single IRB for all performance sites must be on file with the FDA grants management office before an award to fund the study will be made.

Section VII. Agency Contacts

We encourage inquiries concerning this funding opportunity and welcome the opportunity to answer questions from potential applicants.

Application Submission Contacts

eRA Service Desk (Questions regarding ASSIST, eRA Commons, application errors and warnings, documenting system problems that threaten submission by the due date, and post-submission issues)

Finding Help Online: https://www.era.nih.gov/need-help (preferred method of contact)
Telephone: 301-402-7469 or 866-504-9552 (Toll Free)

Grants.gov Customer Support (Questions regarding Grants.gov registration and Workspace)
Contact Center Telephone: 800-518-4726
Email: support@grants.gov

Scientific/Research Contact(s)

Katherine Needleman
Director, Orphan Products Grants Program
Office of Orphan Products Development
Food and Drug Administration
10903 New Hampshire Avenue
WO32-5295
Silver Spring, MD 20993-0002
Phone: 301-796-8660
E-mail: katherine.needleman@fda.hhs.gov

Peer Review Contact(s)

Patrick Johnson
Office of Acquisitions & Grants Services (OAGS)
Food and Drug Administration
Email: Patrick.Johnson@fda.hhs.gov

Financial/Grants Management Contact(s)

Patrick Johnson
Office of Acquisitions & Grants Services (OAGS)
Food and Drug Administration
Email: Patrick.Johnson@fda.hhs.gov

Section VIII. Other Information

Recently issued policy notices may affect your application submission. A full list of policy notices is provided in the Guide for Grants and Contracts. All awards are subject to the terms and conditions, cost principles, and other considerations described in the HHS Grants Policy Statement.

Authority and Regulations

Awards are made under the authorization of Sections 301 of the Public Health Service Act as amended (42 USC 241), section 573(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 360ccc-2(b)) and under Federal Regulations 42 CFR Part 52, 45 CFR Part 75, and 2 CFR Part 200.

Awards are made under the authorization of Section 301 of the Public Health Service Act as amended (42 USC 241) and under Federal Regulations 42 CFR Part 52 and 45 CFR Part 75 and 2 CFR Part 200. All grant awards are subject to applicable requirements for clinical investigations imposed by sections 505, 512, and 515 of the act (21 U.S.C. 355, or 360e) or safety, purity, and potency for licensing under section 351 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262), section 351 of the PHS Act, including regulations issued under any of these sections.

All human subject research regulated by FDA is also subject to FDA's regulations regarding the protection of human subjects (21 CFR Parts 50 and 56).

Applicants are encouraged to review the regulations, guidance, and information sheets on human subject protection and Good Clinical Practice available on the Internet at http://www.fda.gov/oc/gcp/.

The applicant is referred to HHS regulations at 45 CFR 46.116 and 21 CFR 50.25 for details regarding the required elements of informed consent.