FDA Office of Orphan Products Development (OOPD)
Natural History Study Grants

Application instructions and helpful hints for 2022 receipt date

Application due date

The application submission deadline for the Request for Application (RFA) is **February 15, 2022** by 11:59 PM Eastern Time. The earliest submission date is December 17, 2021. There is only **one** receipt date for Fiscal Year 2022. Please see the RFA for details.

Helpful hints:

- Applicants should first review the following prior documents prior to submission:
  a. RFA
  b. FDA Draft Guidance for Industry: Rare Diseases: Natural History Studies for Drug Development (March 2019)
- Applicants are encouraged to apply early to allow adequate time to correct application errors found during the submission process prior to the due date.
- Please note: "on-time submission" means 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. **Late applications are not accepted for this funding opportunity announcement.**
- All applications must be submitted electronically through Grants.gov.

Pre-application registrations

Helpful hint: Applicants are encouraged to begin the pre application/registration process at least 4-6 weeks prior to the grant submission date.

Complete the following before electronically submitting a grant application:

Step 1: Obtain a Data Universal Number System (DUNS) number

Step 2: Register with the System for Award Management (SAM). A valid Taxpayer Identification Number (TIN) or Employer Identification Number (EIN) is necessary for SAM registration.

Step 3: Register with and obtain username and password on Grants.gov

Step 4: E-Business Point of Contact (EBiz POC) authorizes roles, which includes the Authorized Organization Representative (AOR) role on Grants.gov

Step 5: Track Role Request Status

Step 6: Register with eRA Commons

See registration page on Grants.gov for more information on registration. Please note there are multiple registrations required.

General application instructions

Application materials will open via Grants.gov approximately 60 days prior to the application receipt date. At that time (and after the pre-application process has been completed), applicants can download a copy of the application package on Grants.gov, complete it offline, and then upload and submit their application by following the Apply for Grants instructions.

Not all information in the Application Guide applies to the Orphan Products Natural History Grant application. Applicants are strongly encouraged to use the ‘‘Tips’’ posted on Grants.gov under the announcement number when preparing their submission.

Tips for Completing Form SF424 RESEARCH & RELATED (R&R)

This is not a full instruction guide and does not cover all sections of the SF424 (R&R) forms. See SF424 (R&R) Application Guide for detailed instructions on completing the SF424 (R&R) forms.

Page limitations for the application are the same as the page limits on the Application Guide. Specifically, the Research Strategy section page limit is 12 pages.

Applications may not be accepted for review for the following reasons:

- The applicant organization is ineligible.
- The application is received after the specified receipt date.
- The application is incomplete.
- The application is not responsive to the RFA.
- The material presented in the application is insufficient to permit an adequate review.

A. SF424 R&R APPLICATION FOR FEDERAL ASSISTANCE (Page 1)

Type of Submission:

“Pre-application” is not used in FDA’s grant application process.

Date Received by State/State Application Identifier:

Leave these fields blank.

Federal Identifier/Agency Routing Identifier:

If the “type of application” is “new” leave the federal identifier field blank. If you are submitting a “changed/corrected” application, please enter the Grants.gov tracking number previously assigned.

Agency Routing Identifier:

Leave this section blank as it is not used by FDA.

Type of Application:

The only application types allowed are “New,” “Resubmission,” or “Renewal.”

Name of Federal Agency:
Enter "Food and Drug Administration" in this block.

Descriptive Title of Applicant's Project:
In the title block, be sure to include **all** of the following information in the order provided: (1) the type of study (prospective or retrospective) and (2) the name of the disease(s)/condition(s) to be studied.

Helpful hint: The title field is limited to 200 characters, including spaces between words and punctuation to avoid errors. Use abbreviations as needed to ensure the descriptive title information does not become truncated. For example, an appropriate descriptive title is: "Prospective/Retrospective Study of Disease."

Proposed Project (Start and Ending Date):
Start date: The date the proposed project is expected to begin, not necessarily the date funding is expected.

Ending Date: The date the proposed project is expected to end.

B. SF424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE (Page 2)

"Estimated Project Funding" section describes two types of funds**:**

Total Federal Funds Requested:
Enter total (direct and indirect) federal funds requested from OOPD for the entire project period for a maximum of 4 years for a prospective study or 2 years for a retrospective study.

Total Non-Federal Funds Requested:
Enter total amounts that will be used for this study that are not from federal sources. Please include sources and more detailed information on allocations in the budget justification sections.

C. SF424 (R&R) Other Project Information

Human Subjects:
All OOPD grants involve human subject participation and thus, are not exempt from federal regulations regarding human subject protection. Always check "no" to the question: "is the project exempt from federal regulations?"

Project Summary/Abstract (Project Description):
The project summary must contain a concise, self-contained summary of the proposed natural history study suitable for dissemination to the public. It should be informative to a technical audience and understandable to lay readers. The project summary serves as a succinct, accurate description of the proposed work when separated from the application.

In writing your summary or abstract, please state the broad, long-term objectives and specific aims, making reference to the project's health relatedness (e.g., how this helps address significant unmet medical needs for patients with rare diseases). Clearly state project objectives, including such items as a brief background and rationale, hypotheses and expected results, specific aims, unique features, and study design and methods for achieving the stated goals. Avoid describing past accomplishments and use of first person. Do not include proprietary or confidential information or trade secrets, as summary or abstract may be used for purposes other than grant review.

Helpful hint: Be concise and complete. There is a one-page limit for this section (no longer than 30 lines of text). This page limit is based on single-spaced text with 0.5-inch page margins in 11 point font or larger. An abstract exceeding the allowable length may be flagged as an error upon submission. This would require a corrective action before the application can be accepted.

Project Narrative (public health relevance statement):
In two or three sentences, describe the relevance of the project to public health using succinct, plain language that can be understood by a lay audience. There is a one-page limit for this section.

Facilities and Other Resources:
Describe the resources available at each performance site. Describe how the scientific environment and existing resources in which the research will be done contributes to the probability of success (e.g., institutional support, physical resources, intellectual rapport and database platforms). Describe any special facilities used for working with biohazards or other potentially dangerous substances. Information about select agents must be described in the research plan (select agent research). "Select agents" means those biological agents or toxins that have the potential to pose a severe threat to public health and safety, animal or plant health, or animal or plant product.

Clinical resources associated with the study performance site(s) need to be described in detail. A discussion of the resources available to the applicant to show adequate enrollment can be achieved within the proposed timeframe of the study should be included, such as the number of patients presenting to the clinic yearly with the disease or condition that meet the proposed entry criteria of the study along with a discussion of any competing natural history studies or other potential barriers that may limit enrollment.

Helpful hint: Failure to provide justification that adequate enrollment can be attained within the proposed study timeframe is a frequent weakness of grant applications.

Other Attachments - Foreign Component:
Please provide justification if the proposed study requires the use of unusual talent, resources, populations or environmental conditions in other countries that are not readily available in the United States (U.S.), or if the study requires the use of foreign components to augment existing U.S. resources. Indicate how the proposed project is relevant to the mission and objectives of FDA and has the potential for significantly advancing sciences in the U.S.

"Senior/Key Person Profile (expanded) Form":
Provide a biographical sketch (biosketch) for each senior/key person involved with the study. Key personnel include all principal investigators, co-investigators, and performance site investigators responsible for study design and conduct.

Helpful hint: Failure to include a detailed biosketch that supports the role of each senior/key persons is a frequent weakness of grant applications. See Biosketch Format Pages, Instructions and Samples for more information.

Budget:
FDA's Orphan Products Natural History Grant Program uses the R&R Budget Component. Application budgets are limited to $400,000 for prospective studies and $150,000 for retrospective studies.

Applicants must provide a detailed budget for each requested year and attach a budget justification. Reviewers will consider whether the budget and the requested period of support are fully justified and reasonable in relation to the proposed research.

Budget justification should:
- Clearly explain the rationale for all costs requested in the proposed project.
- Include a rationale if the budget has more than a standard escalation from the initial to the future year(s) of support.
- Explain any exclusions applied to the facilities and administrative (F&A) base calculation.
- Provide a rationale if any requested costs are higher than usual and customary.
- Be appropriate for the length of the study and not padded to meet the maximal limitations of the RFA.
- Correlate with all costs specified in the detailed budget.
- State if the overall costs for the proposed study exceeds the limitations of this funding mechanism, and if so, explain how the additional costs to complete the proposed study will be covered (e.g., other grants, corporate funding).
- State if other grants have been or will be applied for and describe contingency plans should those funds not be obtained.

The PHS 398 Modular Budget program does not apply to the Orphan Products Natural History Grants Program and should not be used.

Helpful hint: Failure to include a well justified budget (R&R Budget Component Item K) is a frequent weakness of grant applications.

Budgets for Multiple Institutions - R&R Subaward Budget Attachment(s) Form:
When multiple institutions are involved, one institution must be designated as the primary institution; funding for other institution(s) must be requested via a subcontract to be administered by the primary institution. Individual budgets for all institutions that will be subcontracts should be attached separately to the R&R subaward budget attachment(s) form. A separate budget justification should also be submitted for each subaward.

D. SF424 "PHS 398 Research Plan"

The goal of FDA's Orphan Products Natural History Grants Program is to support studies that advance medical product development through characterization of the natural history of rare diseases/conditions with unmet needs. Through support of efficient and innovative natural history studies, FDA expects to address critical knowledge gaps, to remove major barrier(s) to progress in the field, to exert a significant and broad impact on a specific rare disease or multiple rare diseases with similar pathophysiology, to inform current or future product development including the design of clinical trial(s) and to ultimately advance development of medical products that meet patient needs.

Application Type:
For the February 15, 2022 receipt date all applications will be "New", "Resubmission", or "Renewal."

Research Plan attachments:
The Research Plan should include sufficient information for evaluation of the project independent of other documents such as previous applications. Be specific and informative and avoid redundancies.

Each of the items below should be saved and attached as a single file. Begin each text section of the Research Plan with a section header: Introduction, Specific Aims, Research Strategy, etc.

Helpful hint: Please follow the page limitations for each section. Agency validations will include checks for page limits, which may result in errors. However, while these computer validations help minimize incomplete and/or noncompliant applications, they do not replace the validations conducted by FDA staff. Failure to comply with the requirements at any point may delay the review process.

Specific Aims:
This section is limited to 1 page. Generally, this section begins with a brief narrative describing the overall goals and objectives of the project and the hypothesis to be tested. The section should concisely state how the proposed natural history study will advance medical product development in rare diseases/conditions with unmet needs. Through the support of natural history studies with high quality and interpretable data elements, FDA expects to address critical knowledge gaps, remove major barriers to progress in the field, exert a significant and broad impact on a specific rare disease or multiple rare diseases with similar pathophysiology, and facilitate rare disease product development and be followed by a list of the Specific Aims.

Research Strategy:
The Research Strategy Section is limited to 12 pages. FDA does not follow the order/headings that are included in the NIH's 424 R&R Application Guide.

The following sections should be included under the Research Strategy section of the application:

1. Rationale:
The soundness of rationale in relation to the current understanding of the rare disease(s) and the likelihood this natural history proposal will facilitate medical product development to address an unmet medical need in a rare disease(s) or provide highly significant improvements in treatment or diagnosis and assist or substantially contribute to market approval of product(s).

- Description of the state of existing knowledge, including literature citations and highlights of relevant preliminary studies, subgroups, existing natural history studies/data, standard of care, treatment options and relevant completed or ongoing studies.
- 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 for product development and/or approval.

2. Study Design/Data Quality and Interpretability:
The quality and appropriateness of the study design, research methodology, data collection, and data analyses to accomplish the specific aims of the proposed natural history study and its potential to inform rare disease product development and make a broad impact in rare diseases in general.

- Description of the study including a clear rationale, study aims, study design, and data elements to be collected including how potential sources of bias will be minimized to maintain reliability/reproducibility, and how quality data will be collected, analyzed, and interpreted.

- Description of methods to be used such as disease definition and eligibility criteria and justification, background standard of care (e.g., concomitant medications, dietary therapy, assistive devices, supportive therapies), methods to be used for defining the natural history, assessments, sample collection, and schedule of assessment intervals. The rationale for assessments and assessment intervals should be well supported.

  Methods should address: (1) handling of missing data; (2) contingency plans for visits in case of emergencies; (3) recruitment of patients; and (4) study monitoring including rationale for assessments and assessment intervals. Specifically address whether clinical outcomes tools are validated tools.

- Discussion of challenges, potential problems, alternative strategies, and benchmarks for success anticipated to achieve the aims within a stated timeframe.

- Description and explanation of the use of innovative and efficient approaches, and/or flexible methods/techniques of data collection, modeling and simulation of data, common data elements and data extrapolation among rare diseases with similar pathophysiology, and collaborative means for data and resource sharing.

- Description of the statistical analysis plan for each specific aim and methods in

adequate detail.

- 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.

3. Inclusion of Patient Input:
The inclusion of patient and caregiver perspectives in the planning of the proposed natural history study to improve protocol design through understanding of disease and treatment burden, impact on daily living, and potential issues with study feasibility.

- Description of plans to include early and ongoing patient/stakeholder input in the study (e.g., protocol design, data elements, feasibility, data sharing and dissemination).

- Description of plans to reduce patients' burden to participate in the study.

4. Investigator(s):
The qualifications of the Principal Investigator(s) (PIs), collaborators, and other support staff.

- 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. A study team member with expertise (e.g., statistical and epidemiologic training) in the design, conduct and analysis of long-term cohort studies should be included as appropriate.

- If applicable, description of the rationale, leadership approach, governance, and organizational structure for a multi-Program Director (PD)/PI project.

5. Infrastructure and Financial Resources:
The probability of success of the proposed project given the environment in which the work will be done.

5A. Infrastructure Resources:

- Description of evidence that supports the applicant's ability to implement the study when funded, recruit patients, and complete the proposed study within its budget and within stated time limits with the infrastructure in place. A detailed timeline for implementation of the project should be provided.

- Description of evidence 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.

5B. Financial Resources:

- 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.

- Description of sustainability plans for acquiring additional funding, including plans for leveraging FDA funding for additional resources needed for continuing the proposed study and/or for further phases of development beyond the proposed funding period.

6. Ability to Advance the Current Field:

The ability of the project to advance 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 address unmet needs and exert a sustained, powerful influence in the field. Considerations include studies that have the potential to exert a broad impact in advancing multiple rare diseases sharing a similar pathophysiology.

- Explanation of how the innovative approaches to be developed or used would contribute to medical product development for the rare disease(s).

- Description of plans for sharing/disseminating data to benefit rare disease community and inform medical product development, including a publication strategy and adherence to any relevant criteria for reporting.

- Explanation of sustainability plans beyond the proposed funding period, including a description of plans for leveraging data in the future beyond the proposed funding period.

Rare Disease Prevalence:

The Rationale Section of the Research Strategy should also include a subsection with the heading "Rare Disease Prevalence." This subsection should include documentation to support the estimated prevalence of the rare disease or condition in the United States is fewer than 200,000.[1] 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 natural history studies are eligible to receive funding under the OOPD Grants Program.

[1] Federal Food Drug and Cosmetic Act (FD&C Act) § 526; 21 U.S.C. 360bb (defining a rare disease or condition as "any disease or condition that affects fewer than 200,000 persons in the United States.").

Support of Product Development:
The Rationale Section of the Research Strategy should also include a further subsection with the heading "Support of Product Development." This subsection should include an explanation of how the proposed study will address critical knowledge gaps, remove major barrier(s) to progress in the field, exert a significant and broad impact on a specific rare disease or multiple rare diseases with similar pathophysiology, or meet data standards to inform rare disease product development. If the proposed study may ultimately support product development, please provide such information on how this will be accomplished. If you intend to proceed with product development in collaboration with multiple sponsors, please describe this in the grant application.

Study Monitoring Plan:
The Study Design/Data Quality and Interpretability Section of the Research Strategy should include a further subsection with the heading "Study Monitoring Plan." This subsection should include a proposed plan for protocol adherence, data integrity, and interim data monitoring, as applicable.

This section should detail who is to be responsible for monitoring, their credentials, what data will be monitored (e.g., performance and safety data. If you plan to include an interim look, please provide a rationale for having such an assessment(s) with timing(s). Your protocol will specify "stopping rules" and other criteria for monitors to follow during the study. See Guidance for Clinical Trial Sponsors for more information. In your protocol, please include withdrawal rules, i.e., that a patient can withdraw at any time and for any reason. We strongly encourage you that if a patient withdraws and later wants to return to the study, that you allow them to do so.

Other Research Plan Section

Vertebrate Animals:
Not applicable for OOPD's natural history grants.

Select Agent Research:
Typically not applicable for OOPD's natural history grants.

Multiple PD/PI Leadership Plan:
For applications designating multiple PDs/PIs, a new section of the research plan, entitled Multiple PD/PI Leadership Plan [Section 10 of the Research Plan Component in the SF424 (R&R)], must be included. For example, please describe: (1) the rationale for choosing a multiple PD/PI approach; (2) leadership team governance and organizational structure; (3) communication plans; (4) process for making decisions on scientific direction; (5) procedures for resolving conflicts; and (6) roles and responsibilities for PDs/PIs and other collaborators.

In the Leadership Plan, regarding budget allocation, please delineate the distribution of resources to specific components of the project or the individual PDs/PIs. In the event of

an award, the requested allocations may be reflected in a footnote on the Notice of Award (NoA).

Consortium/Contractual Arrangements:
Explain the programmatic, fiscal, and administrative arrangements to be made between the applicant organization and the consortium organization(s) as outlined in the How to Apply – Application Guide.

Letters of support:
Letters of support should be included for the following areas:

1) Study Sites: Leader(s) of the 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; and

2) 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 study design should be provided.

Resource Sharing Plan:
Individuals are required to comply with the instructions for the Resource Sharing Plans as provided in the SF424 (R&R) Application Guide, with the following modification:

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

Protection of Human Subjects
This section describes compliance with protection of the rights and welfare of the participants in a research project.

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 its own IRB of record and assurance. The IRB of record may be an IRB already being used by one of the performance sites, but it must specifically be registered as the IRB of record with OHRP.

Helpful hint: Failure to submit at least a draft consent/assent form is a frequent weakness noted by panel reviewers of OOPD grant applications.

While IRB approval is not needed at time of submission of a grant application, IRB approval from the IRB of record must be on file with the FDA grants management office before an award to fund the study will be made. If IRB approval has been attained, please specify such in this section and include a copy of the approval letter.

Inclusion of Women, Minorities, and Children

This section is required for applicants answering "yes" to the question "are human subjects involved?" on the R&R Other Project Information Cover Page and the research does not fall under Exemption 4.

When the proposed project involves human subjects and/or FDA-defined clinical research, the committee will evaluate the proposed plans for the inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion (or exclusion) of children to determine if it is justified in terms of the scientific goals and research strategy proposed. For additional information on review of the inclusion, please refer to the Guidelines for the Review of Inclusion on the Basis of Sex/Gender, Race, Ethnicity, and Age in Clinical Research.

Multiple PD/PI Leadership Plan:

For applications designating multiple PDs/PIs, a new section of the research plan, entitled Multiple PD/PI Leadership Plan [Section 10 of the Research Plan Component in the SF424 (R&R)], 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 NoA.

Appendix:

The Appendix is used to allow the applicant to include certain required and supportive documents. A maximum of 10 appendices are allowed. Please do not use the appendix to circumvent page limits. Follow all instructions for the appendix as described in the SF424 (R&R) Application Guide with the following additional instructions:

The appendices should include the following, as appropriate for the proposed study:

- Protocol: The full final protocol must be provided in an appendix section.
- Informed Consent: Consent forms, assent forms, and any other information given to a subject are part of the grant application and must be provided, even if in a draft form. The applicant is referred to HHS and FDA regulations at 45 CFR 46.116 and 21 CFR 50.25 for details regarding the required elements of informed consent.
- Summary Statement: Resubmissions must provide the previous FDA OOPD Summary Statement in an appendix section and should include a point-by-point rebuttal to those critiques.
- Letters of collaboration/support for conduct of the study.

An application that does not observe the required page limitations may be delayed or rejected in the review process. Applicants must follow the specific instructions on appendix materials as described in the SF424 (R&R) Application Guide.

Helpful hint: Missing study protocols and informed consent/assent documents are a frequent weakness noted by panel reviewers of OOPD's natural history grant applications. A draft form of these documents should be submitted if a final form is not yet available.

Items that should not be included in the appendix:

- Photographs or color images of gels, micrographs, etc., are no longer accepted as appendix material. These images must be included in the Research Strategy PDF. However, images embedded in publications are allowed.

- Publications that are publicly accessible. For such publications, the URL or PMC submission identification numbers along with the full reference should be included as appropriate in the Bibliography and References cited section, the Progress Report Publication List section, and/or the Biographical Sketch section.

All attachments must be in PDF format and not be password protected. There is a limit of 10 appendices. If the pages in any attachment are greater than 11 x 11 inches or less than 8.5 x 8.5 inches, please adjust with software that can change the page size from actual to an 8.5 x 11 inch size. See the applicable SF424 (R&R) Application Guide for page limitations and appendix guidance in detail.

Applicants are encouraged to be as concise as possible while including the information

needed for expert scientific review of their proposal.

Helpful hint: Appendices should be given a name that is meaningful to reviewers rather than relying on sequential order. Appendix material may not appear in the assembled application in the order attached. Thus, it is important to use filenames for attachments that are descriptive of the content. A summary sheet listing all items included as appendices is encouraged but not required. When including a summary sheet, it should be included in the first appendix attachment. Applications that do not follow the appendix requirements may be delayed in the review process. Extensive appendices are noted by panel reviewers of OOPD grant applications as being extremely difficult to review in their entirety.

E. Other Information

Please be aware that the following documentation must be received by the FDA before an award is made:

1. **Federal Wide Assurance:**
   Federal Wide Assurance (FWA or assurance) obtained from Office for Human Research Protections (OHRP) for the IRB of record for all performance sites must be on file with the FDA grants management office before an award to fund the study will be made. 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.

2. **IRB of Record:**
   Any institution receiving federal funds must have an institutional review board (IRB) of record even if that institution is overseeing research conducted at other performance sites. An awardee institution must have its own IRB of record. The IRB of record may be an IRB already being used by one of the "performance sites," but it must specifically be registered as the IRB of record with OHRP.

Useful Links:

- FDA Orphan Products Grants Program
- Natural History RFA
- Grants 101
- Electronic Research Administration Commons registration process
- Electronic Research Administration help
- Office for Human Resource Protections
- Office of Research Integrity – Handling misconduct
- PHS administrative action bulletin board
- Data Universal Number System (DUNS) number
- System for Award Management (SAM)
- Credential provider registration
- HHS financial management
- Grants.Gov Submitting your Application

- NIH forms and applications
- Salary cap summary (FY 1990 to present)
- Grants.gov applicant FAQs
- How to apply – application guide

Additional Resources for Applicants:

- Rare Diseases: Common issues in drug development
- Rare Diseases: Natural history studies for drug development
- Use of electronic health record data in clinical investigations guidance for industry
- Submitting documents using real-world data and real-world evidence to FDA for drugs and biologics guidance for industry
- Real-world data: Assessing electronic health records and medical claims data to support regulatory decision-making for drug and biological products