Orphan Products Development (OPD)
Clinical Trials Grants Program:

Application Instructions and Helpful Hints for 2017-2018 Receipt Dates

Section I. General Information

Getting Started:

1. **Applicants should first review the detailed RFA announcement.**

2. **Letter of Intent**
Letters of Intent are not required for the Clinical Trials Grants Program.

3. All applications must be submitted **electronically** through Grants.gov. **Applicants should review the** Request for Application **(RFA) that has been published in the Federal Register as well as the publication in the** NIH Guide **prior to getting started.**

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

4. Prior to electronically submitting a grant application, the following steps are required:

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 & 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

Steps 1 through 5, in detail, can be found at:
http://www.grants.gov/web/grants/applicants/organization-registration.html

Step 6: Register with eRA Commons

5. The proposed clinical protocol should be submitted to the applicable FDA IND or IDE Review Division a minimum of 30 days before the grant application deadline. The

number of the assigned IND/IDE and the **date of submission/amendment** of the proposed clinical protocol to the IND/IDE should be included on the SF424 Form (R&R) of the grant application along with the title of the grant in the "Descriptive Title of Applicant's Project" field.

Note: Protocols that are eligible for an exemption from the IND regulations still must be conducted under an active IND to be eligible for funding under this FDA grant program. Studies of already approved products, evaluating new orphan indications, are also subject to these IND/IDE requirements. 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 application from the FDA Center for Devices and Radiologic Health indicating that the device is an NSR device.

Note: If the sponsor of the IND/IDE is not the Project Director/Principal Investigator (PD/PI) listed on the application, a letter from the sponsor permitting access to the IND/IDE must be submitted to both the IND/IDE and the grant application. The name(s) of the PI(s) involved with the grant application and the study protocol must be submitted to the IND/IDE.

OPD Hint: *The current version of the protocol that is included in the grant application and is intended to be used if the study is funded is the protocol that MUST be submitted to the IND/IDE before the application is reviewed. For resubmissions, if any changes have been made to the protocol since the last review, the revised protocol must be submitted as an amendment to the IND/IDE at least 30 days prior to the October resubmission date. The date the revised protocol was submitted to the IND/IDE as an amendment should be included along with the title of the grant and IND/IDE number on the Cover page of the SF424(R&R) Form.*

6. Application materials will open via Grants.gov approximately 60 days prior to the application receipt date. At this time (and after their 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 instructions in the Apply for Grants link on the website.

Note: Not all of the information in the Application Guide will apply to the Orphan Products Clinical Trials Grant application.

7. We strongly encourage using the ''Tips'' posted on Grants.gov under the announcement number when preparing your submission. **We also strongly encourage using the information contained in this document when preparing your submission.**

Application Due Date:

The application due dates are February 1, 2017 and February 7, 2018.
The resubmission due dates are October 16, 2017 and October 15, 2018.

Please note that there is only **ONE** receipt date per Fiscal Year for **new** applications, which

occurs in February. However, resubmissions will be allowed to resubmit in October. Resubmissions will also be accepted in the February receipt date. Please see the RFA for a complete list of dates.

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

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.

Late applications are generally not accepted for this FOA.

Award Amounts:

Application budgets should reflect the actual needs of the proposed project and should not exceed the following in maximum total costs (direct and indirect) and maximum years of support:

Phase 1 Studies:
YR 01: $250,000
YR 02: $250,000
YR 03: $250,000

Phase 2 and 3 Studies:
YR 01: $500,000
YR 02: $500,000
YR 03: $500,000
YR 04: $500,000

Please refer to the RFA for more detailed descriptions of the types of studies and the budget duration limitations.

Section II. Tips for Completing Form SF424 (R&R)

This is **not** a full instruction guide and does not cover all sections of the SF424 (R&R) forms. Please refer to the applicable SF424 (R&R) Application Guide posted by NIH for detailed instructions on completing the SF424 (R&R) forms. The following are **FDA/OPD specific** items that you may need to complete the application.

Please note that the following page limitations do differ from NIH page limits:

- Research Plan - maximum 25 pages

Applications may not be accepted for review and may be returned 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 Request for Applications (RFA).
- The material presented in the application is insufficient to permit an adequate review.
- The dollar amount requested in the application exceeds the recommended threshold stated in the RFA.

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

Type of Submission:
"Pre-application" is not used by this Agency.

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, unless you are submitting a "Changed/Corrected" application in which case you need to enter the grants.gov tracking number (########) previously assigned.

If "Type of Application" is "Renewal," "Revision," or "Resubmission," use the following format to denote your previously assigned grant application number from OOPD: FD00####.

OPD Hint: *If an application is a Resubmission, please indicate the previously assigned grant application number on the face page to avoid errors.*

Agency Routing Identifier:
Leave this section blank as it is not used by this Agency.

Type of Application:
For OPD, the only application types allowed are: "New," Renewal," "Resubmission," and "Revision."

Note: For OPD, you may only select "Resubmission" if you received a summary statement and score. If your application was non-responsive or had technical issues and did not get reviewed, you should select "New."

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 phase of the study; (2) the name of the drug/device; (3) the name of the disease/condition to be studied; (4) the IND/IDE number; and (5) the date the protocol you are requesting funding for was submitted to FDA review division.

OPD Hint: *Please note that the title field is limited to 200 characters, including the spaces between words and punctuation to avoid errors. An appropriate descriptive title example is "Ph **2a** Study of **Drug** for **Disease** IND **123,456** **(mm/dd/yyyy).**"*

OPD Hint: *Use abbreviations as needed to ensure the descriptive title information is not truncated.*

Proposed Project (Start and Ending Date):
Start Date: This should be the date that the clinical trial is proposed to begin, not necessarily the date funding is expected.

Ending Date: This should be the date that the clinical trial is proposed to end.

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

Estimated Project Funding:
Total Federal Funds Requested:
Enter total (direct and indirect) Federal funds requested from OPD for the entire project period. Please note that for Phase 1 studies, the application budget should not exceed the maximum of $250,000 total costs (direct and indirect) per year for a maximum of 3 years of support. For Phase 2 and 3 studies, the application budget should not exceed the maximum of $500,000 total costs (direct and indirect) per year for a maximum of 4 years of support.

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 "RESEARCH & RELATED Other Project Information":

Human Subjects:
All OPD grants involve human subject participation in a clinical trial, and are thus not exempt from Federal regulations regarding human subject protection. Always

check “no” to the question “is the project exempt from Federal regulations?”

Vertebrate Animals:
“No” should be checked to “are vertebrate animals used.”

Project Summary/Abstract (Project Description):
The Project Summary must contain a concise, self-contained summary of the proposed clinical study suitable for dissemination to the public. It should be informative to other persons working in the same or related fields and, insofar as possible, understandable to a scientifically or technically literate lay reader. The Project Summary is meant to serve as a succinct and accurate description of the proposed work when separated from the application. State the application’s broad, long-term objectives and specific aims, making reference to the health relatedness of the project (i.e., relevance to the mission of the Orphan Products Clinical Trials Grants Program). The objectives of the project should be clearly stated by 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. Make reference to the relevance of the project to the mission of the OPD grants program. Avoid describing past accomplishments and use of first person. Do not include proprietary or confidential information or trade secrets, as this description may be used for purposes other than review.

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

Project Narrative (Public Health Relevance Statement):
This section represents a second component of the Project Summary, which is Relevance. In two or three sentences, describe the relevance of the project to public health using succinct, plain language that can be understood by a general, 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).

Note: 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 that 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 clinical trials or other potential barriers that may limit enrollment.

OPD Hint: *Not providing justification that adequate enrollment can be attained within the proposed study timeframe is a frequent weakness of OPD 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 (US), or if the study requires the use of these to augment existing US resources. Indicate how the proposed project has specific relevance to the mission and objectives of FDA and has the potential for significantly advancing sciences in the United States.

"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 the design and conduct of the study.

OPD Hint: *Not including a detailed biosketch that supports the role of each senior/key person in the proposed study is a frequent weakness of OPD grant applications. A sample format of a biosketch can be found at* https://grants.nih.gov/node/826.

Budget:
The FDA OPD Grant Programs uses the Research & Related (R&R) Budget Component.

The RFA specifies that for Phase 1 studies, the application budget should not exceed the maximum of $250,000 total costs (direct and indirect) per year for a maximum of 3 years of support. For Phase 2 and 3 studies, the application budget should not exceed the maximum of $500,000 total costs (direct and indirect) per year for a maximum of 4 years of support.

Applicants must provide a detailed budget for each requested year and attach a budget justification.

The budget justification should:
- Clearly explain the rationale for all costs requested in the proposed project.
- If a resubmission, include a rationale for any significant increases or decreases from the initial budget.
- 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 of the requested costs are higher than usual and customary.
- Be appropriate for the length of the study and not be 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 (i.e. other grants, corporate funding, etc).
- State if other grants have been or will be applied for, and describe contingency plans should those funds not be obtained.

Note: The PHS 398 Modular Budget program does not apply to the OPD Clinical Trials grant program and should not be used.

OPD Hint: *Not including a well justified budget (R&R Budget Component item K) is a frequent weakness of OPD 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 and funding for the 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 Research & Related Subaward Budget Attachment(s) Form. A separate budget justification should also be submitted for each subaward.

D. <u>SF424 "PHS 398 Research Plan":</u>

The goal of FDA's OPD Clinical Trials Grants Program is to support the clinical development of products for use in rare diseases or conditions where no current therapy exists or where the proposed product will be superior to the existing therapy. Each application should propose one discrete clinical study designed to facilitate FDA approval of the product for use in a rare disease or condition. The study may address an unapproved new product or an unapproved new use for a product already on the market. A description of how the proposed study will either help support product approval or provide essential data needed for product development should be provided.

Application Type:
Specify whether the application is New, Resubmission, Renewal, or Revision as noted on SF424 (R&R) Page 1 item 8.

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.

Note: 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.

OPD 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. Applications found not to comply with the requirements at any point may delay the review process.*

Introduction to Application (Resubmitted or Revised Applications only):
Applicants resubmitting proposals may include **one additional page** at the beginning of the resubmission in which to respond briefly and clearly to the comments from the previous review.

Note: The previous summary statement along with a more detailed point by point response to the summary statement critiques should be included as an appendix.

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 that will solve a specific problem, challenge an existing paradigm or clinical practice, address a critical barrier to progress in the field and how that will either result in, or substantially contribute to, market approval of the proposed product and be followed by a list of the Specific Aims.

Research Strategy:
The entirety of the Research Strategy Section is limited to 25 pages for the OPD Clinical Trials Grants Program. Please note, FDA does not follow the order/headings that are included in the NIH's 424 R&R Application Guide. The following are suggestions for the organization of this Section:

Note: For Resubmissions, if prior reviewer's comments have been incorporated into the revised application, clearly mark with *italics*, **bold**, or other formatting in the text as well as on the margin of the page so that it is clear where you have made revisions to your project. Be clear to identify to reviewers what markings are being used to indicate revisions, so they do not think that a draft proposal has been submitted.

Background and Significance:

- Applicants must include documentation, supplemented by authoritative references, to support that the estimated prevalence of the rare disease or condition in the US is less than 200,000 (or in the case of a vaccine or diagnostic, information to support that the product will be administered to fewer than 200,000 people in the US per year). If applicable, if you have received or applied for Orphan Drug designation, please include your designation number and date of submission in this section. Additional information regarding the

population estimate and rationale may be required upon request.

- Explain the importance of the problem or critical barrier to progress in the field that the proposed project addresses. Describe the state of existing knowledge, including literature citations and highlights of relevant data and explain the gaps that the project is intended to fill. Show that the objectives are attainable within a stated time frame.
- Explain how the proposed study will either help support product approval or provide essential data needed for product development.
- Evidence that the product to be studied is available to the applicant in the form and quantity needed for the clinical trial must be included in this section. A current letter from the supplier placed in an Appendix is acceptable.
- Explain how the application may challenge and seek to shift current research or clinical practice paradigms.
- Describe any improvements to or novel theoretical concepts, approaches or methodologies, instrumentation or interventions to be developed or used, such as with study design and outcomes, and their advantages over existing approaches.

OPD Hint: *Orphan designation is encouraged (although not required), especially if it is questionable whether the population served by the proposed use would qualify for orphan drug status.*

Study Plan:

- Describe the overall strategy, methodology, and analyses to be used to accomplish the specific aims of the proposed clinical trial. Include a brief description of the experimental design, how data will be collected, analyzed, and interpreted, as well as any resource sharing plans as appropriate. Please provide the complete clinical protocol in an appendix along with informed consent forms and investigational brochures (see **Appendix** below).
- Preliminary Studies for New Applications: For New applications include information on Preliminary Studies. Discuss the PD/PI's preliminary studies, data, and/or experience pertinent to the application, or any other study results to support the proposed study.
- Progress Report for Renewal and Revision Applications: For Renewal/Revision applications, provide a Progress Report. Provide the beginning and ending dates for the period covered since the last competitive review. Summarize the specific aims of the previous project period and the importance of the findings, and emphasize the progress made toward their achievement. Explain any significant changes to the specific aims and any new directions including changes to the specific aims.
- Discuss challenges, potential problems, alternative strategies, and benchmarks for success anticipated to achieve the aims.
- If the project is in the early stages of development, describe any strategy to establish feasibility, and address the management of any high risk aspects of the proposed work.
- The statistical analysis should be described in adequate detail to show that the power of the study is sufficient to detect a meaningful benefit.

OPD Hint: *An inadequately justified or not well detailed statistical analysis is a frequent weakness noted by panel reviewers of OPD grant applications.*

Note: If an applicant has multiple Specific Aims, the applicant may address Significance and Approach for each Specific Aim individually, or may address Significance and Approach for all of the Specific Aims collectively.

Protection of Human Subjects:

The purpose of this section is to describe the involvement of human subjects to ensure the protection of the rights and welfare of the participants in a research project:

- Describe the proposed involvement of human subjects in the work outlined in the Research Strategy section. Describe and justify the characteristics of the subject population, including their anticipated number, age range, and health status if relevant. Describe and justify the sampling plan, as well as the recruitment and retention strategies and the criteria for inclusion or exclusion of any subpopulation.
- Explain the rationale for the involvement of special vulnerable populations, such as fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals, or others who may be considered vulnerable populations.
- If relevant to the proposed research, describe procedures for assignment to a study group. As related to human subjects protection, describe and justify the selection of an intervention's dose, frequency, and administration.
- List any collaborating sites where human subjects research will be performed, and describe the role of those sites and collaborating investigators in performing the proposed research. Explain how data from the site(s) will be obtained, managed, and protected.
- Describe the research material obtained from living individuals in the form of specimens, records, or data. Indicate who will have access to individually identifiable private information about human subjects. Provide information about how the specimens, records, and/or data will be collected, managed, and protected as well as whether material or data that include individually identifiable private information will be collected specifically for the proposed research project.
- Describe the potential risks to subjects (physical, psychological, financial, legal, or other), and assess their likelihood and seriousness to the human subjects. Where appropriate, describe alternative treatments and procedures, including the risks and potential benefits of the alternative treatments and procedures, to participants in the proposed research.
- Describe plans for the recruitment of subjects (where appropriate) and the process for obtaining informed consent. If the proposed studies will include children, describe the process for meeting requirements for parental permission and child assent. Consent forms, assent forms, and any other information given to a subject, even if in draft form, are a requirement of the RFA and should be sent with the grant application and included in an Appendix.
- Discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Studies that involve clinical procedures must include a general description of the plan for data and safety monitoring and

adverse event reporting to the IRB, the FDA, and others, as appropriate, to ensure the safety of subjects.

OPD Hint: *Not submitting at least a draft consent/assent form is a frequent weakness noted by panel reviewers of OPD grant applications.*

The OPD 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:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf

In small, single-site studies, safety monitoring is often performed by the independent medical monitor or a safety monitoring committee in conjunction with the study statistician. Phase 3 studies and high risk Phase 1 or 2 clinical trials frequently use a DSMB. It may be desirable to utilize a DSMB for:

- Trials involving highly experimental therapies or specialized review procedures external to the OPD (e.g., gene therapy or xenotransplantation);
- Trials involving substantial risk to study participants (e.g., studies with irreversible outcomes); or
- Trials involving particularly vulnerable study participants (e.g., children or persons with impaired ability to consent).

The OPD requires that the protocol document include a section describing the proposed plan for interim data monitoring. This section will detail who is to be responsible for interim monitoring (i.e., a DSMB, an SMC, or the study investigator), what data will be monitored (i.e., performance and safety data only vs. efficacy data as well), the timing of the first data review (e.g., "the first interim look will occur when the initial 20 participants have completed the 6 month follow-up visit"), and the frequency of interim reviews (which will depend on such factors as the study design, interventions and anticipated recruitment rate). The plan will specify "stopping guidelines" and other criteria for the monitors to follow in their review of the interim data. Guidance on these topics is available at:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127073.pdf

Note: A preliminary monitoring plan must be submitted as part of the Research

Plan portion of the grant application for a clinical trial. The plan will be examined as part of the peer review process, including evaluating the informed consent documents as well as the plan to monitor the integrity of the data collected and protocol compliance. Any comments and concerns will be included in an administrative note in the summary statement. OPD staff will ensure that all concerns are resolved before a grant award is made. 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 and Minorities:

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.

Applicants for PHS clinical research grants are encouraged to include minorities and women in study populations so that research findings can be of benefit to all people at risk of the disease or condition under study. It is recommended that applicants place special emphasis on including minorities and women in studies of diseases, disorders, and conditions that disproportionately affect them. This policy applies to research subjects of all ages. If women or minorities are excluded or poorly represented in clinical research, the applicant should provide a clear and compelling rationale that shows their inclusion is inappropriate.

Cumulative Inclusion Enrollment Report (Renewal Applications Only):

Renewal applications must report on the enrollment of research subjects and their distribution by ethnicity/race and sex/gender by attaching the following form, available at: http://grants.nih.gov/grants/funding/424/SF424R-R_enrollmentreport.doc

Progress Report Publication List (Renewal Applications Only):

List the titles and complete references to all appropriate publications, manuscripts accepted for publication, patents, and other printed materials that have resulted from the project since it was last reviewed competitively.

Targeted/Planned Enrollment:

Provide a description of the planned enrollment of research subjects and their distribution by ethnicity/race and sex/gender by attaching the following form available at:
http://grants.nih.gov/grants/funding/424/SF424R-R_enrollment.doc

Inclusion of Children:

FDA regulations at 21 CFR parts 50, subpart D contain additional requirements that must be met by IRBs reviewing clinical investigations regulated by FDA and involving children as subjects. FDA is part of HHS; accordingly, the research project grants under this program are supported by HHS, and HHS regulations at 45 CFR parts 46, subpart D also apply to research involving children as subjects.

Vertebrate Animals:
Not applicable for OPD grants.

Select Agent Research:
Typically not applicable for OPD 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 14 of the Research Plan Component in the SF424 (R&R)], must be included. For applications designating multiple PD/PIs, all such individuals must be assigned the PD/PI role on the Senior/Key Profile form, even those at organizations other than the applicant organization. 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, the 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.

Consortium/Contractual Arrangements:
Explain the programmatic, fiscal, and administrative arrangements to be made between the applicant organization and the consortium organization(s). If consortium/contractual activities represent a significant portion of the overall project, explain why the applicant organization, rather than the ultimate performer of the activities, should be the grantee. The signature of the Authorized Organization Representative on the SF424 (R&R) cover form (Item 17) signifies that the applicant and all proposed consortium participants understand and agree to the following statement:

> *The appropriate programmatic and administrative personnel of each organization involved in this grant application are aware of the agency's consortium agreement policy and are prepared to establish the necessary inter-organizational agreement(s) consistent with that policy.*

Describe any contractual arrangements briefly. This would include such things as collaborating clinical study sites or subcontracts to groups providing drug supply and data monitoring/auditing, laboratory, or statistical services. Include any letter of support in the "Letters of Support" Section.

Letters of Support (e.g., Consultants):
Attach all appropriate letters of support, including any letters necessary to demonstrate the support of consortium participants and collaborators such as Senior/Key Personnel and Other Significant Contributors included in the grant application. Letters are not required for personnel (such as research assistants) not contributing in a substantive, measurable way to the scientific development or execution of the project. Examples of letters that should be included in this section include:

- A letter of collaboration from each PD/PI at all clinical sites outside of the primary clinical site acknowledging their commitment to the study.
- Letters acknowledging a subcontracted service such as data management, statistical support, consulting services, or testing services.
- Letters of support from individuals serving on a steering committee or DSMB.
- Letters acknowledging drug supply from a manufacturer.

Provide letters from each explaining how they will support the study. Letters should include what rates/charges for services are, if applicable. If letters note rates/charges, please make sure the costs corroborate with those specified in the budget section.

OPD Hint: *Not providing these letters (including from each study site PI in multicenter studies) of support is a frequent weakness noted by panel reviewers of OPD grant applications.*

Resource Sharing Plan(s):
Not applicable for OPD grants.

Appendix:
The appendix should include the following items:

- Complete, detailed clinical protocol that matches the most recent protocol submitted to the IND/IDE.
- Informed consent/assent form(s) and other documents provided to patients.
- Investigator's brochure (if applicable).
- Copies of publications of supporting preliminary preclinical or clinical studies.
- IRB approval letter (if available).
- Correspondences between the applicant and the FDA Review Division regarding the clinical trial.
- A copy of the applicant's orphan drug designation letter (if applicable).
- Surveys, questionnaires, and other data collection instruments.
- Financial support records such as other grants obtained, private funding secured, etc. to complete the study.
- Letters of collaboration/support for conduct of the study.
- For resubmissions, a copy of the prior summary statement issued by FDA and detailed responses to the reviewers' concerns.

OPD Hint: *Missing study protocols and informed consent/assent documents are a frequent weakness noted by panel reviewers of OPD grant applications. A draft form of these documents should be submitted if a final form is not yet available.*

OPD Hint: *Not adequately addressing or ignoring prior summary statement concerns is a frequent weakness noted by panel reviewers of OPD grant resubmissions. If you disagree with a reviewer's comments, be clear and polite in your reply, but it is important to address each issue.*

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.

Note: All attachments must in PDF format only and not be password protected. **There is a limit of 10 appendices total.** 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 at http://grants.nih.gov/grants/how-to-apply-application-guide.htm 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; however, the appendices should not be used to circumvent page limitations, such as the specified page limit for the Research Strategy.

OPD Hint: *It is recommended that all appendices 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, so it is important to use filenames for attachments that are descriptive of the content. A summary sheet listing all of the items included as appendices is also 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 OPD 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:

- **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.
- **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 the OHRP.

- **IND/IDE**
  All new and continuing grants 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. Only medical foods that do not need pre-market approval and devices that are classified as non-significant risk (NSR) are free from these IND/IDE requirements.

Useful links:
OOPD Web Page:
(http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ucm2005525.htm)

RFA Link:
http://grants.nih.gov/grants/guide/rfa-files/RFA-FD-15-001.html

Grants 101:
http://www.grants.gov/web/grants/learn-grants/grants-101.html

eRA:
Creating User Accounts
(http://grants.nih.gov/grants/ElectronicReceipt/files/Grantee_Registration_Process_for_Commons.pdf)
(https://commons.era.nih.gov/commons-help/174.htm)

Federal Wide Assurance:
Office for Human Resource Protections
(http://www.hhs.gov/ohrp/)
(http://ori.hhs.gov/reg-sub-part-a)
(http://ori.hhs.gov/phs-admin-action-bulletin-board)

Data Universal Number System (DUNS) number:
(http://fedgov.dnb.com/webform)

System for Award Management (SAM):
(https://governmentcontractregistration.com/default.asp?key=sam&source=bing)

Credential Provider registration:
(https://apply07.grants.gov/apply/OrcRegister)

HHS/Financial Management:
(https://rates.psc.gov/)

Orphan Research Grants Program Resource List:
Grants.Gov Submitting your Application
(http://grants.nih.gov/grants/submitapplication.htm)
NIH Forms and Applications (http://grants.nih.gov/grants/forms.htm)

Salary Cap Summary (FY 1990 to Present)
(http://grants.nih.gov/grants/policy/salcap_summary.htm)

Grants.gov Registration Instructions for Domestic and Foreign Organizations:
Grantee Registration Process in NIH eRA Commons: Detailed Steps
(http://grants.nih.gov/grants/ElectronicReceipt/files/grantee_registration_process_for_commons.pdf)

Additional Grants.gov Electronic Submission Process Resources:
(http://www.grants.gov/web/grants/applicants/applicant-faqs.html)
(http://grants.nih.gov/grants/ElectronicReceipt/preparing.htm)