

GUIDELINES FOR REVIEWER'S WRITTEN COMMENTS
EXERPTED FROM PAR-12-265
Ancillary Studies to Major Ongoing Clinical Research Studies
to Advance Areas of Scientific Interest within the Mission of the NIDDK (R01)

The guidelines available here use language posted in the original funding opportunity announcement (FOA) and do not replace or modify the criteria established in the full announcement. If you have any questions, contact the Scientific Review Officer (SRO) in charge of the review panel. SRO contact information for your application can be found in [eRA Commons](#).

This Funding Opportunity Announcement issued by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH) invites investigator initiated research project applications (R01) for ancillary studies to major ongoing clinical trials, epidemiological studies and disease databases (described as parent studies) supported by the Institute, other Institutes and Centers of the National Institutes of Health, other government agencies and the private sector to capitalize on the already established infrastructure of the parent study to enhance the breadth and depth of its scientific output. Major studies include multi-center clinical research investigations, national databases and Phase 3 clinical trials. An ongoing study is one that is currently following and assessing study participants. In some cases grant applications may be submitted prior to implementation of a study (before the study is ongoing) with the anticipation by the applicant that funding will coincide with the beginning of recruitment.

Ancillary studies proposed under this FOA must be of scientific interest and within the mission of the NIDDK. Such studies may be proposed from both NIDDK supported parent studies and parent studies funded from other sources as described above. Typically, but not exclusively, ancillary studies are proposed for NIDDK supported parent studies. The NIDDK-supported parent studies are focused on a wide range of diseases and conditions including diabetes, obesity, acute and chronic liver disease, chronic kidney disease, acute kidney injury, benign prostatic hyperplasia and other lower urinary disorders, among others. Examples of NIDDK-supported parent studies for which ancillary studies may be conducted may be found at the following website: <http://www.niddk.nih.gov/research-funding/process/human-subjects-research/ancillary-studies-major-ongoing-clinical-studies/Pages/examples-parent-studies-ancillary-studies.aspx>. These studies are typically supported by cooperative agreements or contracts. This FOA also invites applications from investigators who plan to conduct ancillary studies utilizing major ongoing clinical research studies (multi-center clinical research investigations, national databases and Phase 3 clinical trials) supported by other Institutes and Centers of the NIH, other government agencies and the private sector. However, to be eligible for this FOA the ancillary study proposed must be clearly within the scientific mission of the NIDDK and focused on diseases and conditions of direct interest to the Institute. The scientific areas funded by the NIDDK may be found at <http://www.niddk.nih.gov/research-funding/research-programs/Pages/default.aspx>. Irrespective of the original goals of the parent study, the diseases or conditions of interest to NIDDK must have been rigorously defined and present in a sufficient number of study participants. It is strongly recommended that the applicant contact NIDDK program staff prior to submission of their grant application to verify that the proposed ancillary study addresses research goals within the mission and interest of the Institute. While it is recognized that ongoing studies funded by NIDDK may be useful for studying diseases outside the mission of the NIDDK, this FOA may not be used to support such studies. Applications addressing the research goals of other NIH Institutes may be submitted using the NIH parent R01 FOA (PA-11- 260), or relevant FOAs from other Institutes.

The NIDDK supports a large number of major multi-center clinical trials to determine the beneficial effect of therapies and interventions. In addition, the Institute supports a number of large-scale multi-institution epidemiological studies and disease databases to better characterize the natural history and response to treatment of a wide range of diseases and conditions. Each of these studies represents a substantial financial commitment from the NIDDK to establish an infrastructure for participant recruitment, examination, data collection and follow-up. These studies offer unique opportunities to conduct additional investigations to fully exploit the research potential of these established cohorts to study the diseases for which these studies were originally designed. These studies may also provide the opportunity to learn more about diseases and conditions outside the original scope of the study protocol but within the mission and interest of the NIDDK. It is also recognized that studies supported by other Institutes and Centers of the NIH, other government agencies and the private sector may also lend themselves to ancillary studies which will advance the research mission of the NIDDK.

The goal of this FOA is to obtain additional scientific information for the diseases and conditions of interest and within the mission of the NIDDK. It is recognized that there is considerable potential for obtaining new knowledge beyond the core activities of the parent study by means of ancillary studies. For this FOA, core activities are considered the measures described in the parent study protocol and are being carried out; having been previously

approved by the group responsible for conducting the study-e.g., the Steering Committee-and/or the study's oversight body-e.g., the Data and Safety Monitoring Board. This knowledge may include identification of additional risk factors for disease or genetic factors related to the development, diagnosis, or progression of disease or to the response to therapy. This FOA may also be used to extend the scope of participant data collection and assessment to identify co-morbidities and their impact on the primary disease/condition under study. It is also recognized that a parent study not originally designed to address diseases and scientific areas of responsibility of the NIDDK may yield important insights and additional information of interest to the Institute through ancillary studies. Generally, this FOA is not applicable to small and/or single center studies. For studies supported by Research Project Grants (R01) ancillary study grant applications may be submitted under the Funding Opportunity for Research Project Grants (Parent R01, PA-11-260). However, to determine eligibility of a parent study it is recommended that interested investigators contact NIDDK staff prior to submission of their grant application. Applications to this FOA must include a letter from the appropriate committee (e.g., Ancillary Study Committee) or person (e.g., Chairman of the Steering Committee) indicating that the parent study investigators have approved the ancillary study. In order to take advantage of new data and/or sample collection at the beginning of recruitment of study participants (at baseline) grant applications may be submitted prior to study implementation (before the study is considered ongoing). In those instances the applicant must include a letter from the parent study sponsoring organization/Project Scientist indicating the timetable for its implementation.

Areas of Research Interest: It is anticipated that grant applications may include but are not limited to identification of additional and/or unique/emerging risk factors, pathogenic mechanisms, genetic factors, predictors of drug response (pharmacogenetics, pharmacogenomics), proteomics, metabolomics, biomarker discovery and/or validation as well as better characterization of the co-morbid illnesses suffered by the subjects enrolled in the parent studies. The natural history, risk factors and effect of clinical trial interventions of diseases and conditions for which the parent study was not originally designed may also be studied by means of additional data collection and/or assay of already collected or newly obtained biological samples as long as new questions being addressed are within the scientific mission of NIDDK.

EVALUATION OF APPLICATIONS

The Primary (1) and Secondary (1,2,3 etc.) reviewers should each address all of the review criteria outlined below. The Discussant reviewer will prepare a brief written critique. A short paragraph highlighting the strengths and weaknesses of the application or bulleted lists of strengths and weaknesses are both examples of acceptable critiques written by the Discussant reviewer. If you prefer to prepare a full critique equivalent to a Primary (1) or Secondary reviewer, you also have that option. The scientific review group will address and consider each of the following criteria in assigning the application's overall score, weighting them as appropriate for each application. The application does not need to be strong in all categories to receive a high priority score. These criteria are listed in logical order and not in order of priority.

Overall Evaluation: Provide an overall impact/priority 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. In a paragraph, briefly summarize the most important points of your critique indicating the major strengths and weaknesses that contributed to your assessment of the scientific merit of the proposed research.

Significance: Does the project address an important problem or a critical barrier to progress in the field? 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?

Investigators: Are the PD(s)/PI(s), collaborators, and other researchers well suited to the project? If Early Stage Investigators or New Investigators, or 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(s)/PI(s), do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the project?

Innovation: 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?

Approach: Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? 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?

If the project involves clinical research, are the plans for 1) protection of human subjects from research risks, and 2) inclusion of minorities and members of both sexes/genders, as well as the inclusion of children, justified in terms of the scientific goals and research strategy proposed?

Environment: 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?

Additional Review Criteria

In addition to the above criteria, the following items will continue to be considered in the determination of scientific merit and the priority score:

Has the burden of the proposed ancillary study on the parent study participants been adequately described?

Protections for Human Subjects: For research that involves human subjects but does not involve one of the six 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 six 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 [Human Subjects Protection and Inclusion Guidelines](#).

Inclusion of Women, Minorities and Children: When the proposed project involves clinical research, the committee will evaluate the proposed plans for inclusion of minorities and members of both genders, as well as the inclusion of children. For additional information on review of the Inclusion section, please refer to the [Human Subjects Protection and Inclusion Guidelines](#).

<u>CODE</u>	<u>Minority (M)</u>	<u>Gender (G)</u>	<u>Children (C)</u>
1	minority and non-minority	both females and males	both children and adults
2	only minority	females only	children only
3	only non-minority	males only	no children included
4	representation unknown	unknown	unknown

Evaluate acceptability as "A" (acceptable) or "U" (unacceptable). If you rate the sample as "U", consider this feature a weakness or a deficiency in the design of the project reflected in the overall scoring of the application. NOTE: To the degree that acceptability or unacceptability impacts on the investigator's approach to the proposed research, such comments should also appear under Approach in the five major review criteria above and should be factored into the score as appropriate.

Vertebrate Animals: The committee will evaluate the involvement of live vertebrate animals as part of the scientific assessment according to the following five points: 1) proposed use of the animals, and species, strains,

ages, sex, and numbers to be used; 2) justifications for the use of animals and for the appropriateness of the species and numbers proposed; 3) adequacy of veterinary care; 4) procedures for limiting discomfort, distress, pain and injury to that which is unavoidable in the conduct of scientifically sound research including the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices; and 5) methods of euthanasia and reason for selection if not consistent with the AVMA Guidelines on Euthanasia. For additional information on review of the Vertebrate Animals section, please refer to the [Worksheet for Review of the Vertebrate Animal Section](#).

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.

Renewals: For Renewals, the committee will consider the progress made in the last funding period.

Additional Review Considerations

Budget and Period of Support: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research. The priority score should not be affected by the evaluation of the budget.

Scientific/Budgetary Overlap: If it is identified in an application, it should be noted in a statement separate from the critique and should not be considered in the evaluation of the application. Identify if there is an overlap of aims or excessive effort between this application and other active or pending support. Reviewers are asked to focus on the scientific and technical merit of the application. The Scientific Review Administrator will ensure that such issues are documented in the summary statement as an administrative note. Purported overlap must be resolved by NIH staff before an award is made.

Resource Sharing Plans: Reviewers will comment on whether the following Resource Sharing Plans, or the rationale for not sharing the following types of resources, are reasonable: 1) Data Sharing Plan; 2) Sharing Model Organisms; and 3) Genome Wide Association Studies (GWAS).

Foreign Institutions: 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. These aspects do not apply to applications from U.S. organizations for projects containing a significant foreign component.