GUIDE FOR ASSIGNED REVIEWERS' PRELIMINARY COMMENTS ON EXPLORATORY/DEVELOPMENTAL GRANT MECHANISM (R21)

The R21 mechanism is designed to encourage exploratory or developmental research allowing investigators to conduct research on innovative ideas or develop new concepts or technologies. The NIH Institutes and Centers utilize the R21 grant mechanism for a variety of purposes within that broad concept. R21 applications must identify a Funding Opportunity Announcement (formerly called a Program Announcement) for electronic submission. Many Institutes/Centers participate in the overall Parent Announcement (PA-06-181) but there are also many topic-specific Funding Opportunity Announcements sponsored by one or more Institutes/Centers. Reviewers must keep in mind that FOAs cover a variety of goals. For example, some support high impact-high risk investigations, some support exploratory non-hypothesis driven studies, and some support the development of techniques. The eligibility criteria or focus many differ and there may be specific review criteria.

The characteristic of the R21 application varies among the different FOAs. Generally fifteen pages is the limit for the Research Plan and the Introduction is limited to one page, but there may be variations. Maximum duration of award varies by announcement from one to five years, but generally R21s are for two years duration. Budgets also vary, but are typically between $75,000 and $150,000 per year and for U.S. institutions follow the modular budget requirements (applications from outside the United States must always have full budgets).

Therefore, before initiating your review of an R21 grant application, familiarize yourself with the FOA. Final scores must reflect the scientific and technical merit of the application not whether the proposed studies meet the goals of the FOA. Issues of compatibility with the goals of the FOA are addressed in an administrative comment that is separate from the scientific evaluation.

The objective of the R21 grant is to lead to a larger research grant (e.g., R01, P01, U01, etc.); therefore R21s cannot be renewed. Please use the following guidelines when preparing written comments on R21 grant applications. You should comment on the following aspects of the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of the goals described in the announcement. NOTE: Your written reviews should not bear personal identifiers because essentially unaltered comments will be sent to the applicant. Reviewers must keep in mind that Preliminary Data are not required for the R21 mechanism. Although any preliminary data provided should be evaluated, no new data should be requested. Applications should not be penalized for lacking preliminary data.

DESCRIPTION: As a reviewer you will need to be prepared to provide members of the Study Section sufficient information on the application so that they can follow the critiques and discussion.

CRITIQUE: Include as little descriptive information in this section as possible. Please address, each of the following:

Significance: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge or clinical practice be advanced? What will be the effect of these studies on the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Approach: Are the conceptual or clinical framework, design, methods, and analyses adequately developed, well integrated, well reasoned, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics? For applications designating multiple Program Directors/Principal Investigators (PD/PI)s, is the leadership approach, including the designated roles and responsibilities, governance and organizational structure consistent with and justified by the aims of the project and the expertise of each of the PD/PIs?

Innovation: Is the project original and innovative? For example: Does the project challenge existing paradigms or clinical practice; address an innovative hypothesis or critical barrier to progress in the field? Does the project develop or employ novel concepts, approaches, methodologies, tools, or technologies for this area?

Investigators: Are the PD/PI(s) and other key personnel appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the PD/PI(s) and other researchers? Do the PD/PI(s) and the investigative team bring complementary and integrated expertise to the project (if applicable)?

Environment: Do(es) the scientific environment(s) in which the work will be done contribute to the probability of success? Do the proposed studies benefit from unique features of the scientific environment(s), or subject populations, or employ useful collaborative arrangements? Is there evidence of institutional support?

Multiple PD/PI Leadership Plan: For applications designating multiple PD/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 or Section I of the Research Plan in the PHS 398), 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, including 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 PD/PIs and other collaborators. If budget allocation is planned, the distribution of resources to specific components of the project or the individual PD/PIs must be delineated in the Leadership Plan. In the event of an award, the requested allocation may be reflected in a footnote on the Notice of Grant Award (NOGA).

Overall Evaluation: In one paragraph, briefly summarize the most important points of the Critique, addressing the strengths and weaknesses of the application in terms of the five review criteria. Recommend a score reflecting the overall impact of the project on the field, weighing the review criteria, as you feel appropriate for each application. An application does not need to be strong in all categories to be judged likely to have a major scientific impact and, thus, deserve a high merit rating.

Protection of Human Subjects from Research Risks: Evaluate the application with reference to the following criteria: risk to subjects, adequacy of protection against risks, potential benefit to the subjects and to others, importance of the knowledge to be gained. If all of the criteria are adequately addressed, and there are no concerns, write "Acceptable Risks and/or Adequate Protections." A brief explanation is advisable. If one or more criteria are inadequately addressed, write, "Unacceptable Risks and/or Inadequate Protections" and document the actual or

potential issues that create the human subjects concern. If the application indicates that the proposed human subjects research is exempt from coverage by the regulations, determine if adequate justification is provided. If the claimed exemption is not justified, indicate "Unacceptable" and explain why you reached this conclusion. Also, if a clinical trial is proposed, evaluate the Data and Safety Monitoring Plan. (If the plan is absent, notify the SRA immediately to determine if the application should be withdrawn.) Indicate if the plan is "Acceptable" or "Unacceptable", and, if unacceptable, explain why it is unacceptable.

Inclusion of Women Plan:
Inclusion of Minorities Plan:
Inclusion of Children Plan:
Public Law 103-43 requires that women and minorities must be included in all NIH-supported clinical research projects involving human subjects unless a clear and compelling rationale establishes that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. NIH requires that children (individuals under the age of 21) of all ages be involved in all human subjects research supported by the NIH unless there are scientific or ethical reasons for excluding them. Each project involving human subjects must be assigned a code using the categories "1" to "5" below. Category 5 for minority representation in the project means that only foreign subjects are in the study population (no U.S. subjects). If the study uses both then use codes 1 thru 4. Examine whether the minority and gender characteristics of the sample are scientifically acceptable, consistent with the aims of the project, and comply with NIH policy. For each category, determine if the proposed subject recruitment targets are "A" (acceptable) or "U" (unacceptable). If you rate the sample as "U", consider this feature a weakness in the research design and reflect it in the overall score. Explain the reasons for the recommended codes; this is particularly critical for any item coded "U".

Category	Gender (G)	Minority (M)	Children (C)
1	Both Genders	Minority & non-minority	Children & adults
2	Only Women	Only minority	Only children
3	Only Men	Only non-minority	No children included
4	Gender unknown	Minority representation unknown	Representation of children unknown
5		Only Foreign Subjects	

NOTE: To the degree that acceptability or unacceptability affects the investigator's approach to the proposed research, such comments should appear under "Approach" in the five major review criteria above, and should be factored into the score as appropriate.

Vertebrate Animals: Express any comments or concerns about the appropriateness of the responses to the five required points, especially whether the procedures will be limited to those that are unavoidable in the conduct of scientifically sound research. The Five Points on Vertebrate Animals in the Research Plan are:

- Detailed description of proposed use, species/strains, sex, numbers, etc
- Justification of use and numbers
- Veterinary care
- Limitation of discomfort, distress, pain, and injury
- Method of euthanasia.

Biohazards: Note any materials or procedures that are potentially hazardous to research personnel, the public, or the environment and indicate whether the protection proposed will be adequate.

Other comments that may be required, but which do not influence the score are:

Budget: All budgets are modular, except for applications from foreign institutions which must always have full budgets. Evaluate the direct costs only. Do not focus on detail. Determine whether the total budget is appropriate for the project proposed. Provide a rationale for suggested modification in duration or amount of support.

Model Organism Sharing Plan: All NIH applications that will produce new, genetically modified variants of organisms and related resources are expected to include a sharing plan or to state why sharing is restricted or not possible. Assess the sharing plan in an administrative note. You must take into consideration the organism, the timeline, the applicant's decision to distribute the resource or deposit it in a repository, and other relevant considerations.

Data Sharing Plan: Some PAs required inclusion of a data sharing plan. The reasonableness of the data sharing plan or the rationale for not sharing research data will be assessed by the reviewers. However, reviewers will not factor the proposed data sharing plan into the determination of scientific merit or priority score.

Program Announcement (PA) Goals: Reviewers may comment briefly on whether the proposed studies meet the goals of the PA. However, this matter is considered an administrative comment and should not be used to influence the final score, which should be based solely on the scientific and technical merits of the application.

Foreign Institution: Applications from foreign institutions or international organizations will be evaluated and scored by reviewers using the standard review criteria. In addition, after scoring, they should assess whether the project presents special opportunities for furthering research programs through the use of unusual talent, resources, populations, or environmental conditions in other countries that are not readily available in the United States or that augment existing U.S. resources This requirement does not apply to applications from U.S. organizations containing a foreign component.

Revised 04/11/2007