**INSTRUCTIONS FOR PREPARATION OF CRITIQUES (R21/R33)**
National Institutes of Diabetes and Digestive and Kidney Diseases

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments, please discuss 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 these goals. Each of these criteria will be addressed and considered in assigning the overall score, weighting them as appropriate for each application. Note that the application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

## EVALUATION OF APPLICATIONS

PRIMARY REVIEWERS should provide an overall evaluation, briefly summarize the most important points of your critique, weighting the review criteria as you feel appropriate, and evaluating the overall impact of the research on the field. (Note: 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.) A description, which should be taken from the abstract of the application, is optional. In the critique, the five review criteria should be addressed as separate sections.

SECONDARY REVIEWERS need only prepare written critiques addressing the five criteria and recommendations, although comments on any other sections are welcome.

DISCUSSANT should have read the assignment carefully and be conversant with it but are not required to supply a written critique, although it is appreciated.

## REVIEW CRITERIA

The R21/R33 application must include the specific aims for each phase and clear measurable goals (milestones) that would demonstrate feasibility and justify transition to the R33 phase. Applications must include a specific section labeled Milestones following the Research Plan of the R21 phase. Milestones should be well described, quantifiable and scientifically justified and not simply a restatement of the specific aims. A discussion of the milestones relative to the progress of the R21 phase, as well as, the implications of successful completion of the milestones for the R33 phase should be included. The review criteria for the R21/R33 applications are as follows:

**(1) Significance**: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field? What may be the anticipated societal benefit of the proposed activity? Is the research partnership likely to contribute to new and important discoveries about type 1 diabetes?

**(2) Approach**: Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

**(3) Milestones**: How appropriate, realistic and quantifiable are the proposed research milestones against which to evaluate the demonstration and feasibility for transition to the R33 development phase? What is the timeframe for achieving the milestones and is it appropriate?

**(4) Innovation**: Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

**(5) Investigators**: Are the investigators appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers?

**(6) Environment:** Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

**Additional Criteria**:

For the R21/R33 applications the initial review group will evaluate the specific goals for each phase and the feasibility of the milestones that would justify expansion to the R33 phase. A single priority score will be assigned to each scored application. As with any grant application, the initial review group has the option of recommending support for a shorter duration that that requested by the applicant, and basing the final merit rating on the recommended portion of the application. For the R21/R33 application, this may result in a recommendation that only the R21 phase be supported, based upon concerns related to the application's specific goals and the feasibility milestones justifying expansion to the R33 phase. Deletion of the R33 phase by the review panel or presentation of inadequate milestones in the application may affect the merit rating of the application. In addition to the above criteria, in accordance with NIH policy, all applications will also be reviewed with respect to the following specific goals for each phase and the feasibility of the milestones that would justify expansion to the R33 phase. A single priority score will be assigned to each scored application.

In addition to the above criteria, in accordance with NIH policy, all applications will also be reviewed with respect to the following:

Budget: Evaluate direct costs only. For all years, determine whether all items of the budget are appropriate and justified. Provide a rationale for each suggested modification in amount or duration of support.

Recommendation: If not recommended for no further consideration, assign a merit descriptor term/priority score. With regard to personnel, do not be concerned with the salary requested but with the percent effort proposed.

## OTHER CONSIDERATIONS

WOMEN, CHILDREN AND MINORITIES IN STUDY POPULATIONS: Examine whether the minority and gender characteristics of the sample are scientifically acceptable and consistent with the aims of the project, using the categories of 1 to 4 as follows. Determine whether children have been included or appropriately excluded from the study population. (Also determine whether the research is a Phase III clinical trial.)

| CODE | Minority (M) | Gender (G) | Children (C) |
|---|---|---|---|
| 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 project. NOTE: To the degree that acceptability or unacceptability impacts on 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.

FOREIGN INSTITUTIONS: If the applicant organization is foreign, comment on any special talents, resources, populations, or environmental conditions that are not readily available in the United States or that provide augmentation of existing U.S. resources. In addition, indicate whether similar research is being performed in the U.S. and whether there is a need for such additional research. These aspects do not apply to applications from U.S. organizations for projects containing a significant foreign component.

HUMAN SUBJECTS: If Exemptions are Claimed, express any comments or concerns about the appropriateness of the exemption(s) claimed (e.g., for Exemption 4, is it clear that the information will be recorded by the investigator so that subjects cannot be identified directly or indirectly?). If No Exemptions are Claimed, express any comments or concerns about the appropriateness of the responses to the six required points, especially whether the risks to subjects are reasonable in relation to the anticipated benefits to the subjects and in relation to the importance of the knowledge that may reasonably be expected to result from the research.

ANIMAL WELFARE: 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.

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

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 of 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.

## HUMAN SUBJECTS, ANIMAL WELFARE, AND BIOHAZARDS CONCERNS

Human subjects concerns are important to the NIH. As you evaluate the treatment of human subjects as proposed in the application, please weigh the risks and benefits to the subjects of entering a protocol and indicate whether: (a) they will be at risk as the result of a procedure; (b) an informed consent form has been reviewed by an Institutional Review Board; (c) procedures have been included to deal with potential untoward effects of a treatment; and (d) measures have been taken to protect the anonymity of the subjects. For those applications that deal with human subjects, an indication of concern or no concern should be given as regards treatment of patients. (For more information, see http://grants.nih.gov/grants/oprr/humansubjects/45cfr46.htm.)

In conformance with NIH policy, the use of women, children, and minority individuals in patient populations is an issue that should be addressed in any application which involves clinical research (for more information, see (http://grants.nih.gov/grants/guide/notice-files/not98-024.html and http://grants.nih.gov/grants/oprr/humansubjects/guidance/59fr14508.htm). Clinical research includes "...human biomedical and behavioral studies of etiology, epidemiology, prevention (and preventive strategies), diagnosis, or treatment of diseases, disorders or conditions, including but not limited to clinical trials" (OER 90-5). If there is no compelling rationale provided for the exclusion or under-representation of women, children, and minorities from the patient study population, this constitutes a flaw in experimental design and should be reflected in the priority score. Reviewers are asked to inform the Scientific Review Administrator before the review if such concerns exist and to comment specifically on these issues in their critiques. In addition, you will be asked to recommend a code for the application.

Careful scrutiny also should be given to treatment of animals in experimental protocols (for more information, see http://www.nap.edu/readingroom/books/labrats/.) The following issues shall be addressed in the application: (a) the identification of the species and approximate number of animals required; (b) the rationale for using animals and the appropriateness of the species and numbers indicated for the work proposed; (c) a complete description of the anticipated use of the animals; (d) an assurance that discomfort and injury to animals will be limited to unavoidable situations and that analgesic, anesthetic, and tranquilizing drugs will be employed where possible to minimize discomfort and pain; and (e) a description of any euthanasia method to be applied. Please indicate in your written critique if you have reason to be concerned over any of these issues.

If biohazardous materials are to be used in the proposed research, the principal investigator should address the proper handling of such items.