GUIDELINES FOR REVIEW OF CLINICAL RESEARCH TRIAL APPLICATIONS

National Institutes of Diabetes and Digestive and Kidney Diseases

INTRODUCTION

A clinical research trial grant or contract is intended to support clinical evaluation of various methods of therapy or treatment in specific disease areas. These are usually collaborative programs between sponsoring institutions and key investigators in participating clinical research hospitals. Thus, a sufficiently large patient population becomes available for study to enable the investigation to come to fruition within a reasonable period of time. This document provides guidelines for preparation and review of such applications with specific reference to the necessary components of such a collaborative relationship and the standards by which these components should be assessed.

REVIEW OF APPLICATIONS

PRIMARY REVIEWERS

Items 1 and 2 listed below apply to the Primary Reviewer(s) of each application. However, the Secondary Reviewer(s) are free to include these sections if they wish.

1. Overall Evaluation — Briefly summarize the most important points of your critique, weighting the review criteria as you feel appropriate. Evaluate the overall impact 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.)

2. Description — This section is optional: you may summarize succinctly the proposed research from the information provided by the investigator or utilize the abstract from the application. Do not evaluate the application in this section.

PRIMARY AND SECONDARY REVIEWERS

Secondary reviewers do not need to provide an Overall Evaluation or a Description unless they wish. Both the Primary and Secondary reviewers should address each item, **A-G** listed below. Using the guidelines for review, evaluate the five review criteria: significance, approach, innovation, investigator, and environment of the proposed clinical trial. Address each criterion as a separate heading. If this is a competing renewal application, evaluate the progress made during the previous funding period either as a separate paragraph or under the individual criteria as appropriate.

A: REVIEW CRITERIA

1. **Significance:** Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced and what will be the potential impact on the course of the disease? What will be the effect of these studies on the concepts or methods that drive this field?

2. **Approach**: Are the conceptual framework, design (including the composition of the study population), medical approach(es) or protocol(s) and medical aspects, 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?

In addition, consider these aspects of the study design in your comments:

- Feasibility and likelihood of achieving the objectives of the clinical trial, including ability to recruit, retain, and follow subjects;
- Evidence of pilot phase experience and patient accession; and

For competing renewals, the progress, publications, and findings to date.

For coordinating center activities, consider the following issues:

- Specific competence and experience of the professional and technical staff pertinent to clinical trial coordination, data management and quality control, and statistical analysis functions (assess the time and effort to be devoted for appropriateness to the trial);
- Adequacy of the proposed facility, including technical hardware and space;
- Adequacy of organizational and administrative structure for the proposed project and of systematic planning for the design of operations; and
- Merit of the statistical features of the study, including such characteristics as sample size projections, statistical power, methods of analyses, and sequential analyses of data where indicated.

For participating institutions such as clinical centers, which will take part in the trial but will not have coordinating functions, consider the following aspects:

- Qualifications and experience of the investigators;
- Availability of technical resources;
- Appropriateness of internal organization and administration;
- Commitment of the institution and relevant staff;
- Availability of patients, including the ability to recruit and retain appropriate subjects;
- Commitment to following joint protocols and furnishing data in a timely and accurate manner;
- Actual or proposed commitment to cooperate with other participating hospitals and the coordinating center; and

For competing renewals, progress, recruitment, and cooperative activities to date.

3. **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?

4. **Investigator:** Is the principal investigator 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 participating researchers and staff? Do not include descriptive biographical information.

5. **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? Do not describe available facilities and equipment.

B. 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. With regard to personnel, do not be concerned with the salary requested but with the percent effort proposed.

C. RECOMMENDATION

If not deferred or recommended for no further consideration, assign a merit descriptor term and a numerical priority score to the application.

D. WOMEN, CHILDREN AND MINORITIES IN STUDY POPULATIONS

Examine whether the minority and gender characteristics of the study population are scientifically acceptable and consistent with the aims of the trial, using the categories of 1 to 4 (below). 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 study population 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.

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.

An example of the use of these codes to classify an application is as follows:

Females and males, Acceptable, G1A
Minority and non-minority, Acceptable, M1A.
Both children and adults, C1A.

E. DATA SAFETY MONITORING PLAN

Evaluate the Data Safety Monitoring plan provided by the applicant. As of the October 2000 receipt date, the NIH requires that all applicants must supply a general description of the Data and Safety Monitoring Plan for all Phase I, II, and III clinical trials as part of the research application. In addition, Phase III clinical trials require a Data Safety Monitoring Board. The principles of data and safety monitoring require that all biomedical and behavioral clinical trials be monitored to ensure the safe and effective conduct of human subjects research, and to recommend conclusion of the trial when significant benefits or risks are identified or if it is unlikely that the trial can be concluded successfully. Risks associated with participation in research must be minimized to the extent practical and the methods and degree of monitoring should be commensurate with risk. Please refer to page 2 and page 4 of the "NIH INSTRUCTIONS TO REVIEWERS FOR EVALUATING RESEARCH INVOLVING HUMAN SUBJECTS IN GRANT AND COOPERATIVE AGREEMENT APPLICATIONS- APRIL 5, 2002". This document is available on the enclosed CD and at the following website: http://grants1.nih.gov/grants/peer/hs_review_inst.pdf.

Also please refer to the NIDDK web site for additional information at:
http://www.niddk.nih.gov/patient/patient.htm#policy

F. HUMAN SUBJECTS 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://ohrp.osophs.dhhs.gov/humansubjects/guidance/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. 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, as described above you will be asked to recommend a code for the application.

G. OTHER CONSIDERATIONS

FOREIGN INSTITUTION: 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.

BIOHAZARDS: Note any materials or procedures that are potentially hazardous to research personnel and indicate whether the protection proposed is adequate. If biohazardous materials are to be used in the proposed research, the principal investigator should address the proper handling of such items.

SCIENTIFIC/BUDGETARY OVERLAP: If identified in an application, overlap should be noted in a statement separate from the critique and should not be considered in the merit 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.

**'A "clinical trial" is a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or control intervention of comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition include pharmacological, non-pharmacological, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.' (NIH Guide, v.23, n.11; 3/18/94)