

CLINICAL TRIAL PLANNING GRANT

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National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIAMS,
(<http://www.niams.nih.gov/>)

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THIS PA CONTAINS THE FOLLOWING INFORMATION

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PURPOSE OF THIS PA

The purpose of the NIAMS Clinical Trial Planning Grant is to provide support for the organization of activities critical for the successful implementation of clinical trials in areas within the NIAMS mission. The planning grant is intended to (a) allow for early peer review of the rationale and design for high risk, complex, or large-scale clinical trials; (b) provide support for the development of a detailed clinical trial research plan, including a manual of operations and procedures, as a means of decreasing the long start-up time often needed for initiating large trials after award; and

(c) provide support to refine critical components of a clinical trial, such as experimental design, analytical techniques, recruitment strategies, data management, and collaborative arrangements. The purpose of the NIAMS planning grant is not to obtain preliminary data, nor to conduct studies to support the rationale for the clinical trial.

Applicants should be aware that the award of a planning grant does not guarantee NIAMS acceptance of the full-scale clinical trial for peer review, or subsequent funding of the trial following peer review. However, it is expected that the applicant will develop a full-scale clinical trial for submission to a public or private agency if the Clinical Trial Planning Grant is recommended for funding.

RESEARCH OBJECTIVES

Complex, high risk, or large-scale clinical trials require extensive planning. The NIAMS Clinical Trial Planning Grant supports the development of specific elements essential to the conduct of a successful clinical trial. Examples of these elements include adequate plans for recruitment and retention of patients, experimental design and protocols, data management, analytical techniques, identification of facilities, administrative procedures, and collaborative arrangements. Detailed information regarding the rationale of the clinical trial, based on adequate, preclinical science and preliminary clinical research, must be developed prior to submission and included in the application for a Clinical Trial Planning Grant. The purpose of the planning grant is not to obtain preliminary data or to conduct studies to support the rationale for the clinical trial. The expected product of the Clinical Trial Planning Grant is a detailed clinical trial research plan including a complete manual of operations and procedures (MOP). The NIAMS Clinical Trial Planning Grant is intended to help support this and other related activities necessary for a successful clinical trial.

For some diseases of interest to the NIAMS the design and implementation of successful clinical trials has been hampered by the lack of refined outcome measures, difficulties with recruitment of patients with rare diseases, and lack of information about standardization of procedures among participating clinics. The NIAMS Clinical Trial Planning Grant also provides an opportunity to support these activities.

The actual activities performed during the planning period will depend upon the nature of the trial, and the degree to which the investigators have already developed their trial. The planning activities should be such that they would enable imminent commencement of the actual clinical trial. A few examples are:

- o Evaluating recruitment strategies

- o Developing subject retention strategies

- o Conducting meetings to address issues such as trial design, methodologies, etc.

- o Preparing a Manual of Operations and Procedures (MOP), a specific safety plan, etc.

Detailed information regarding the rationale of the clinical trial, based on adequate preclinical science and preliminary clinical research, must be developed prior to submission and included in the Clinical Trial Planning Grant application. The purpose of the planning grant is not to support activities of a pilot trial or to conduct studies to support the rationale for the clinical trial.

Examples of expected products of the planning grant are a complete Manual of Operations and Procedures, validated outcome measures, or proven feasibility of a new recruitment plan.

Any disease area that is within the NIAMS mission is appropriate for consideration under this PA.

MECHANISM(S) OF SUPPORT

This PA will use the NIH R21 award mechanism. As an applicant, you will be solely responsible for planning, directing, and executing the proposed project.

This PA uses just-in-time concepts. It also uses the modular budgeting format. (see <http://grants.nih.gov/grants/funding/modular/modular.htm>). This is a one-year award, for up to a total direct cost request of \$100,000.

ELIGIBLE INSTITUTIONS

You may submit (an) application(s) if your institution has any of the following characteristics:

- o For-profit or non-profit organizations
- o Public or private institutions, such as universities, colleges, hospitals, and laboratories
- o Units of State and local governments
- o Eligible agencies of the Federal government
- o Domestic
- o Faith-based organizations

INDIVIDUALS ELIGIBLE TO BECOME PRINCIPAL INVESTIGATORS

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

Also, new investigators are encouraged to apply. They may wish to develop small, focused research projects that provide initial findings for larger research proposals in the future. It would be expected that such applications also would have smaller budgets reflecting the scope of the research proposed.

SPECIAL REQUIREMENTS

The Research Plan should be presented in two parts as described below, and must be limited to 15 pages. Appendix material, with the exception of color glossy photographs, will not be accepted. Applicants are encouraged to address issues listed in "Review Criteria" and "Other Review Criteria" in this PA.

PART 1 - FUTURE CLINICAL TRIAL (Approximately 2-5 pages)

This part may or may not be written using the standard headings of PHS form 398 (Specific Aims, Background and Significance, Preliminary Studies, Research Design and Methods, and Human Subjects) but should clearly describe the following items:

- o Specific Aims, including a clear statement of any hypotheses that the clinical trial would address.

- o Background/Rationale - Provide rationale for the trial. The rationale must be supported by existing data/information. The planning grant is not to be used to conduct studies in order to rationalize the clinical trial.

- o Significance - Give information documenting significance and the need to perform the clinical trial. Describe the potential impact of the clinical trial on health care: What is the need for new therapy? What are the potential advantages and disadvantages of competitive therapies?

o Research Design and Methods - No details are required, but enough information should be provided to evaluate how the trial would be conducted. Pertinent information must be included on: (a) Intervention(s) to be used, reasons for the selection of intervention(s), and mode(s) of delivery; (b) study design, treatment group(s), trial size, and inclusion/exclusion criteria (if not developed yet, please state so, and you may include it as a part of your planning grant part 2); (c) control group(s) if applicable; (d) outcome measures; and (e) data analysis plan if applicable.

o Proposed Clinical Sites and Investigators-provide a list. Letters of commitment are not required at this stage.

Discussion of the below two topics are not subject to page limits.

o Gender, Minorities and Children Issues - Proposed population description in terms of gender, minorities and children; justification for excluding any gender, minority groups or children; plans for recruitment outreach, as appropriate.

o Human Subjects Issues - Ethical considerations for placebo/control groups, risk/benefit for the participants; availability of the requisite eligible patient pool.

PART 2 - PLANNING GRANT (Approximately 10-13 pages)

This part must be written using the PHS form 398 headings, and should include:

- a. Specific Aims for the planning period (examples include: "We will prepare a Manual of Operations and Procedures"; "We will conduct meetings to address the following issues:"; "We will test recruitment strategies"; "We will organize essential safety committees"; etc.).
- b. Background and Significance, including rationale for planning period; why is the planning period needed? Why not start the trial now?
- c. Preliminary Studies - Not required, but if any preliminary work already completed is included, it should be relevant to the work proposed in the planning period, and to the trial proposed in Part 1.
- d. Research Design and Methods - Detailed approach for each Specific Aim of the planning period. Highlight any innovations applicable to the planning period.

Discussion of the below topic is not subject to page limits.

e. Human Subjects - Address all the required items on human subjects for anticipated issues arising in the planning phase. If no human subjects issues are involved during the planning period, state so.

WHERE TO SEND INQUIRIES

We encourage your inquiries concerning this PA and welcome the opportunity to answer questions from potential applicants.

o Direct your questions about scientific/research issues to:

Dr. Deborah Ader
Behavioral & Prevention Research
NIH, NIAMS, EP
One Democracy Plaza
6701 Democracy Blvd., Suite 800
Bethesda, MD 20892-4872
Telephone: (301) 594-5032
FAX: (301) 480-4543
Email: aderd@mail.nih.gov

Dr. Gayle Lester
Osteoarthritis Initiative & Diagnostic Imaging
NIH, NIAMS, EP
One Democracy Plaza
6701 Democracy Blvd., Suite 800
Bethesda, MD 20892-4872
Telephone: (301) 594-5055
FAX: (301) 480-4543
Email: lester1@mail.nih.gov

Dr. Joan McGowan
Bone Diseases
NIH, NIAMS, EP
One Democracy Plaza

6701 Democracy Blvd., Suite 800
Bethesda, MD 20892-4872
Telephone: (301) 594-5055
FAX: (301) 480-4543
Email: mcgowanj@mail.nih.gov

Dr. Alan N. Moshell
Skin Diseases
NIH, NIAMS, EP
One Democracy Plaza
6701 Democracy Blvd., Suite 800
Bethesda, MD 20892-4872
Telephone: (301) 594-5017
FAX: (301) 480-4543
Email: moshella@mail.nih.gov

Dr. James S. Panagis
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NIH, NIAMS, EP
One Democracy Plaza
6701 Democracy Blvd., Suite 800
Bethesda, MD 20892-4872
Telephone: (301) 594-5055
FAX: (301) 594-4543
Email: panagisj@mail.nih.gov

Dr. Susana A. Serrate-Sztejn
Rheumatic Diseases
NIH, NIAMS, EP
One Democracy Plaza
6701 Democracy Blvd., Suite 800
Bethesda, MD 20892-4872
Telephone: (301) 594-5032
FAX: (301) 480-4543
Email: szteins@mail.nih.gov

o Direct your questions about peer review issues to:

John Lymangrover, Ph.D.
Scientific Review Branch
NIH, NIAMS, EP
One Democracy Plaza
6701 Democracy Blvd., Suite 800
Bethesda, MD 20892-4872
Telephone: (301) 594-4952
FAX: (301) 480-4543
Email: broadwat@mail.nih.gov

o Direct your questions about financial or grants management matters to:

Melinda Nelson
Grants Management Office
NIH, NIAMS, EP
One Democracy Plaza
6701 Democracy Blvd., Suite 800
Bethesda, MD 20892-4872
Telephone: (301) 594-3535
FAX: (301) 480-5450
Email: nelsonm@mail.nih.gov

SUBMITTING AN APPLICATION

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). The PHS 398 is available at <http://grants.nih.gov/grants/funding/phs398/phs398.html> in an interactive format. For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov.

SPECIFIC INSTRUCTIONS FOR MODULAR GRANT APPLICATIONS: Because the CTPG applications are limited to \$100,000 per year in direct costs, they must be submitted in a modular grant format. The modular grant format simplifies the preparation of the budget in these applications by limiting the level of budgetary detail. Applicants request direct costs in \$25,000 modules. Section C of the research grant application instructions for the PHS 398 (rev. 5/2001) at <http://grants.nih.gov/grants/funding/phs398/phs398.html> includes step-by-step guidance for preparing modular grants. Additional information on modular grants is available at

<http://grants.nih.gov/grants/funding/modular/modular.htm>.

SENDING AN APPLICATION TO THE NIH: Submit a signed, typewritten original of the application, including the checklist, and five signed photocopies in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710
Bethesda, MD 20817 (for express/courier service)

APPLICATION PROCESSING: Applications must be received by or mailed on or before the receipt dates described at <http://grants.nih.gov/grants/funding/submissionschedule.htm>. The CSR will not accept any application in response to this PA that is essentially the same as one currently pending initial review unless the applicant withdraws the pending application. The CSR will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of a substantial revision of an application already reviewed, but such application must include an Introduction addressing the previous critique.

PEER REVIEW PROCESS

Applications submitted for this PA will be assigned on the basis of established PHS referral guidelines. An appropriate scientific review group convened by NIAMS in accordance with the standard NIH peer review procedures (<http://www.csr.nih.gov/refrev.htm>) will evaluate applications for scientific and technical merit.

As part of the initial merit review, all applications will:

- o Receive a written critique
- o Undergo a selection process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed and assigned a priority score
- o Receive a second level review by the appropriate national advisory council or board

REVIEW CRITERIA

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, reviewers will be asked to discuss the following aspects of your application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals:

- o Significance
- o Approach
- o Innovation
- o Investigator
- o Environment

The scientific review group will address and consider each of these criteria in assigning your application's overall score, weighting them as appropriate for each application. Your 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, you may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

(1) SIGNIFICANCE: Does your study address an important problem? If the aims of your application are achieved, how do they advance scientific knowledge? What will be the effect of these studies on the concepts or methods that drive this field?

(2) APPROACH: Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate to the aims of the project? Do you acknowledge potential problem areas and consider alternative tactics?

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

(4) INVESTIGATOR: Are you appropriately trained and well suited to carry out this work? Is the work proposed appropriate to your experience level as the principal investigator and to that of other researchers (if any)?

(5) ENVIRONMENT: Does the scientific environment in which your 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 REVIEW CRITERIA: In addition to the above criteria, your application will also be reviewed with respect to the following:

PROTECTIONS: The adequacy of the proposed protection for humans or the environment, to the extent they may be adversely affected by the project proposed in the application.

INCLUSION: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated. (See Inclusion Criteria included in the section on Federal Citations, below)

BUDGET: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research.

OTHER REVIEW CRITERIA:

The criteria used to evaluate Clinical Trial Planning Grant applications are based on the "Specific Requirements," as spelled out in an earlier section of this PA. The reviewers will provide a two-part critique on the application.

Please note that there may be high enthusiasm for the future trial (part 1) but little enthusiasm for the planning (part 2), or vice versa, or high enthusiasm for both, etc. Review committees should indicate their enthusiasm for the two sections separately (with only one priority score for the overall application).

o PART 1 - This will be a brief critique of the future clinical trial, and will be based upon the items requested under part 1 of "Special Requirements" of this PA. General enthusiasm (low, medium, high) about the proposed trial should be based on the following:

(1) Significance: Would the future clinical trial address an important problem? Would conduct of the trial influence standard of care, develop a new therapy, or provide a better understanding of the disease? Is there convincing rationale to conduct the trial?

(2) Investigator: Is the investigative team qualified to conduct the clinical trial?

(3) Feasibility: Do the research design and methods appear appropriate and reasonable for the successful conduct of the proposed trial? (Please note that detailed research design and methods are NOT required.)

(4) Human Subjects: Any concerns involving the participation of human subjects will be noted.

o PART 2 - This will be a detailed critique of the planning period activities, and will be based upon the items requested under part 2 of "Special Requirements" of this PA.

(1) Significance: Will the proposed planning process address major barriers in conducting the future clinical trial? Is the planning period necessary?

(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) 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 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 researchers (if any)?

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

(6) Gender, Minorities, and Children: (Applicable only if human subject issues are involved in the planning period.) The adequacy of plans to include both genders, minorities, and children as appropriate for the scientific goals of the research will be evaluated.

(7) Human Subjects: (Applicable only if human subject issues are involved in the planning period) Ethical issues surrounding human subjects will also be evaluated.

AWARD CRITERIA

Applications submitted in response to a PA will compete for available funds with all other recommended applications. The following will be considered in making funding decisions:

- o Scientific merit of the proposed project as determined by peer review
- o Availability of funds
- o Relevance to program priorities

REQUIRED FEDERAL CITATIONS

INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH: It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing clinical research should read the AMENDMENT "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research - Amended, October, 2001," published in the NIH Guide for Grants and Contracts on October 9, 2001

(<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html>); a complete copy of the updated Guidelines is available at

http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm.

The amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS:

The NIH maintains a policy that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and

ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the inclusion of children as participants in research involving human subjects that is available at <http://grants.nih.gov/grants/funding/children/children.htm>.

REQUIRED EDUCATION ON THE PROTECTION OF HUMAN SUBJECT PARTICIPANTS: NIH policy requires education on the protection of human subject participants for all investigators submitting NIH proposals for research involving human subjects. You will find this policy announcement in the NIH Guide for Grants and Contracts Announcement, dated June 5, 2000, at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html>.

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF INFORMATION ACT: The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm.

Applicants may wish to place data collected under this PA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

URLS IN NIH GRANT APPLICATIONS OR APPENDICES: All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

HEALTHY PEOPLE 2010: The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This PA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at <http://www.health.gov/healthypeople>.

AUTHORITY AND REGULATIONS: This program is described in the Catalog of Federal Domestic Assistance No. 93.846, and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and administered under NIH grants policies described at <http://grants.nih.gov/grants/policy/policy.htm> and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

<http://grants.nih.gov/grants/guide/pa-files/PA-02-015.html>.

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