Guidelines
For
Multidisciplinary Clinical Research Centers

National Institute of Arthritis and Musculoskeletal and Skin Diseases

National Institutes of Health

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The NIAMS Grant Guidelines for a Multidisciplinary Clinical Research Center

I. THE NIAMS MULTIDISCIPLINARY CLINICAL RESEARCH CENTER PROGRAM

I.A. Introduction

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) leads the federal effort for the conduct and support of research into the causes, treatment and prevention of arthritis and musculoskeletal and skin diseases, the training of basic and clinical scientists to carry out this research, and the dissemination of information on research progress in these diseases.

In fulfilling its mission to support research and research training, NIAMS employs a number of support mechanisms. These include various types of research projects, program projects, and career development programs; institutional training grants and individual training fellowships; and a number of center grant mechanisms. The center grants are interrelated to and interdependent upon all of the other support mechanisms.

The Multidisciplinary Clinical Research Center program (MCRC) began in 2001 with the funding of three centers. Six additional centers were funded, three in 2002 and three in 2003. For a list of the currently funded MCRCs, see: http://www.niams.nih.gov/rtac/funding/grants/mcrclst.htm. The MCRC program was developed in response to a review of the NIAMS Centers Program and replaced the Multipurpose Arthritis and Musculoskeletal Diseases Center (MAMDC) program. The Centers Review report may be found at http://www.niams.nih.gov/ne/reports/sci_wrk/1997/cenrptfn.htm. The NIAMS P60 centers are known generically as Multidisciplinary Clinical Research Centers (MCRCs), although each center identifies itself by one or more of the NIAMS three broad disease areas: arthritis, musculoskeletal diseases/disorders, or skin diseases.

The following guidelines provide information about the Multidisciplinary Clinical Research Centers program, suggestions for preparation of an applications and criteria for review.

I.B. Overview of the Multidisciplinary Clinical Research Center Program

The aim of the MCRC program is to support a full range of outstanding multidisciplinary clinical research on arthritis and musculoskeletal and skin diseases (see Section III.A.). Each MCRC is organized around a methodology core and includes a minimum of three highly meritorious projects encompassing clinical research drawing from two or more clinical approaches (see discussion in Section III.I). The methodology core is the foundation of the Center, providing key

support for development and implementation of clinical projects. The director of the MCRC, aided by an executive committee and the methodology core, is expected to provide leadership to focus all research projects **on clinically relevant issues to prevent disease or to assess and/or to improve patient outcomes** and to assure a rigorous research approach. The proposed director should document this leadership with examples of the ability to network with colleagues from clinical and other areas of biomedical research.

A meritorious research base in patient-oriented research, biobehavioral and social sciences, epidemiology and/or health services are prerequisites for proposing an MCRC. Each MCRC defines its research base, goals for promoting clinical research utilizing that research base, and how multidisciplinary research will be promoted. The interaction with a General Clinical Research Center (GCRC), if present, must be documented.

Any given MCRC is not expected to include all disease areas within the NIAMS mission. An MCRC can focus on selected diseases (but not just one disease) within the mission of NIAMS. (These diseases are found through the NIAMS webpage, see http://www.niams.nih.gov/rtac/funding/faq.htm.) However, two or more clinical approaches (see discussion in Section III.I) must be encompassed by the projects supported in the MCRC. For instance, all projects should **not** be health services research projects or epidemiology projects or behavioral intervention studies. However, an MCRC might have one health services project, one epidemiologic project and one behavioral intervention study. Each project could address a different disease or condition. In addition, research on animals and animal models should not be proposed in the MCRC application.

Center grant awards are made for 5 years, with the possibility of competitive renewal. The total yearly direct cost requested may not exceed a maximum direct cost of $800,000 a year (exclusive of facilities and administrative costs of subcontracts with collaborating organizations) during any year over the 5-year grant period. Collaboration among institutions is permitted to bring in added expertise and/or patient populations.

In summary, the key elements of an MCRC must include:

X A Center Director, Associate Director and executive committee with outstanding credentials for promoting clinical research (see Section III.B.);

X A research base that encompasses diseases/disorders within the NIAMS mission and provides professional and patient resources for developing clinical projects using more than one clinical research approach (see Section III.C.);

X A methodology core that will play a key role in the design and implementation of ALL projects supported through the Center (see Section III.G.); and

X A minimum of three highly meritorious clinical research projects that encompass disease areas within the NIAMS mission, utilize the methodology core, and encompass two or

more clinical approaches (see Section III.I.).

Optional elements of an MCRC are:

X A developmental project (no more than one may be proposed) supported by the methodology core, with a yearly direct cost budget of $50,000 or less, and lasting no more than three years (see Section III.J.), and

X Other core(s) supportive of two or more of the proposed projects (see Section III.H.).

II. APPLICATION AND REVIEW PROCESS

II.A. Preapplication Process and Letter of Intent

Applications are solicited by Requests for Applications published in the NIH Guide to Grants and Contracts. See the NIAMS website for current RFAs:
http://www.niams.nih.gov/rtac/funding/grants/rfalist.htm

Individuals from institutions with potential interest in applying for an MCRC grant are encouraged to contact the NIAMS staff as early as possible after the RFA has been issued. Consultation between NIAMS staff and potential applicants prior to submission of the formal application may be useful. Applicants should not construe advice given by the NIAMS staff as assurance of favorable review. The staff will not evaluate or discuss the merit of the scientific aspects of the proposal.

To facilitate Institute planning, applicants are requested to submit a letter of intent on the date listed in the RFA. This letter should provide a descriptive title of the research projects and cores requested and the key participants. The letter of intent, and any inquiries about the program, should be directed to:

Madeline Turkeltaub, CRNP, Ph.D.
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Democracy 1
6701 Democracy Boulevard, Suite 800
Bethesda, MD 20892
Telephone: (301) 594-2463
FAX: (301) 480-4543
Email: mturkeltaub@mail.nih.gov

For fiscal and administrative matters, contact:

Melinda Nelson
Chief, Grants Management Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
6701 Democracy Boulevard, Suite 800
Bethesda, MD 20892
Telephone: (301) 594-3535
FAX: (301) 480-5450
Email: nelsonm@mail.nih.gov

II.B. Application Procedure

The research grant application form PHS 398 is to be used in applying for these grants. These forms are available at E-mail: grantsinfo@nih.gov or from the Internet Web site at: http://grants.nih.gov/grants/forms.htm

Each project and each core included in the MCRC application should be written as an individual project using form PHS 398. Page limitations will apply to the individual projects. It is desirable for MCRC applications to be arranged in a specified format. A detailed Table of Contents is strongly suggested (see Exhibit I). This not only makes it easier for reviewers to use, but it can also serve as a checklist for the applicant institution in preparing the application. The arrangement of materials should follow both the instructions in form PHS 398 application kit and the more specific instructions detailed in Section IV of these guidelines.

Receipt dates for MCRC applications are announced in the Request for Applications. *For applications submitted in response to RFAs, the application must ARRIVE AT NIH on or before the receipt date.*

The RFA label available in the application package must be affixed to the bottom of the face page. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review.

The original and three (3) signed, exact photocopies of the application should be sent 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)]

In addition to mailing the application to the Center for Scientific Review send two (2) copies of the application and ALL 5 copies of any appendix material, as well as a CD including all appendices to:

Chief, Review Branch
NIAMS/NIH
6701 Democracy Blvd., Suite 800 – MSC 4872
Bethesda, MD 20892-4872
[Bethesda, MD 20817 (for express/courier service)]
Telephone: (301) 594-4952

All appendix material must be clearly marked with the name of Center Director and the appropriate project or core. Separate copies of appendix material should be supplied for each core or project to which it is applicable (See Section IV.D.).

II.C. Review Process

Applications for MCRC grants will first be screened for completeness by the Center for Scientific Review and for responsiveness by NIAMS staff. Applications which are complete and responsive will be evaluated for scientific merit by a group of expert consultants convened by the Review Branch of the NIAMS. Each application should be complete upon submission. Site visits are not anticipated. A second level of review will be performed by the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council.

II.D. Center Evaluation Procedure

Since the NIAMS is interested in funding only the most highly meritorious research, individual components of lesser quality may not be funded, even if recommended, under the "umbrella" of the Center grant mechanism. Each project and core (including the administrative unit) will be individually reviewed for scientific merit and assigned a rating by committee consensus. Merit ratings will also be voted for the center elements: qualifications of the center leadership, the research base, the institutional environment and resources. If this is an application for competitive renewal, the progress during the last funding cycle will also be evaluated. To be funded, there must be a highly meritorious methodology core and at least three highly meritorious projects (not including the developmental/feasibility project, if any).

After the review of the individual components of the application, an application may be judged as non-competitive and not scored, or may be discussed and assigned an overall priority score. This score will reflect not only the individual quality of the projects, cores, and administration, but also how the proposed MCRC will bring together all these elements in a workable unit. The overall score may be higher or lower than the Aaverage@ of the descriptors based on the assessment of whether the whole is greater than the sum of its parts. (See Section III.K.)

III. PRESENTATION OF THE PROPOSED CENTER

This section describes the required and optional components of the proposed MCRC and the review criteria to be applied. The suggested content order for the overall application will be covered in Section IV. Note that these applications will be reviewed by a committee that will have three or more applications to review. Not every reviewer will necessarily read in detail every application. It is very helpful for reviewers to include cross-references in these center applications. A detailed Table of Contents is especially invaluable in providing a key for cross-references, e.g. *see Section I.A.2. for more details.* Exhibit I is an example of a detailed Table of Contents.

Note that NIH has policies for the inclusion of women, minorities and children which **must** be addressed in **each** project proposal and in **each** core, even if only to indicate why a full discussion is not applicable. The reviewers will be instructed to address the adequacy of inclusion plans for the work proposed as part of the scientific and technical merit evaluation. These policies may be accessed at the following sites:
Women & Minorities: http://grants.nih.gov/grants/funding/women_min/women_min.htm
Children: http://www.nih.gov/grants/funding/children/children.htm

The NIH expects investigators supported by NIH funding to make their research data available to the scientific community for subsequent analysis based on a data sharing plan approved as part of the award; see the NIH Data Sharing Policy website at http://grants.nih.gov/grants/policy/data_sharing/. This requirement on data sharing is an extension to NIH policy regarding sharing research resources, which expects that recipients of NIH support will provide prompt and effective access to research tools. The data sharing plan for the center should be described in the Administrative Unit.

III.A. Overview

Each application should have an OVERVIEW - a narrative section that serves as a synopsis of the key elements of the proposed Multidisciplinary Clinical Research Center, the qualifications of the Center Director, Associate Director and executive committee, the research base, and the resources and environment for the Center. *This section is intended to be read by all reviewers, even if they are not assigned to projects within this application, so that each reviewer can get a comprehensive view of the proposed Center.*

An additional purpose of the overview is to provide reviewers a sense of how the Center will leverage its resources. A Center operates on two levels. The first level is to assemble outstanding proposals and carry out the proposed research. The second level is to provide leadership at an institutional or broader level to promote quality research through the intellectual and material resources of the Center.

The Overview serves to introduce the proposed program, to state the Center objectives, and to identify the scope of patient problems to be addressed in the proposed Center. This includes a rationale of the diseases/conditions to be addressed. It is anticipated that some Centers may bring a multidisciplinary clinical approach to a narrow scope of diseases for which there is a paucity nationally of clinical research - e.g., juvenile rheumatic diseases. Other Centers may cover disparate diseases (but within the mission of NIAMS) because of unique multidisciplinary expertise. Describe the disciplines brought together for the proposed Center and explain the strategy for achieving the objectives of the overall program. It is important to indicate prior collaborative arrangements between investigators in the group, to emphasize the events that have led to the current application, and **especially to describe the anticipated unique advantages that would be gained by the research within the proposed MCRC**. Briefly describe each of the proposed projects, identifying how that project addresses a clinically relevant issue to prevent disease or to assess and/or to improve patient outcomes with a rigorous research approach. Briefly describe the Methodology Core and indicate how this core will assist each of the proposed projects. Describe the role of any additional supporting cores.

III.B. Qualifications of the Center Leadership

The emphasis in this section should be on the qualifications of the Center leaders. The administrative plans are presented in the Administrative Unit (see Section III.F.)

The Director of the MCRC, aided by an Associate Director and an executive committee, is expected to provide leadership to focus all research projects on clinically relevant issues to prevent disease and to assess and/or to improve patient outcomes and to assure a rigorous research approach. The collective expertise should reflect direct clinical interactions with the diseases included in the research base of the Center and experience with the recruitment of patients (and care givers, if applicable) for the type of projects undertaken. The leader of the methodology core should be a member of the executive committee.

Describe the qualifications of the Center Director and Associate Director to lead the MCRC. Describe the qualifications of each member of the executive committee and the rationale for including these individuals in the leadership of the Center. Applicants are advised to include sufficient information to address the following review criteria:

Review Criteria for MCRC leadership: (Included in, "Review Criterion for Administrative Unit," in the RFA).

X Do the Director and Associate Director have the leadership and research qualifications to lead a Center? Does the leadership team (Director, Associate Director, and executive committee) have the collective expertise to assure focused development and implementation of high quality and meaningful clinical research projects?

III.C. The Research Base for the MCRC

Describe the research base upon which the MCRC builds, including descriptions of independently funded research projects so that reviewers can determine the extent and quality of research activities related to the proposed MCRC. The descriptions should include: the principal investigator and other key research personnel, the project=s objectives and progress toward them; the project=s relevance to a NIAMS disease area, and important publications that have resulted from this research in the past five years. In addition, it is helpful to include a table of the relevant research grants (see Exhibit II). Describe how members of this research base will interact with the proposed MCRC. Will there be services or activities available through the proposed MCRC for investigators who are not directly involved in the MCRC funded projects (i.e., Center investigators)? The research base should also serve as a source for new projects that the MCRC may mentor and assist in obtaining resources through NIH or foundation research support programs. Describe the vision for this process. Applicants are advised to include sufficient information to address the following review criteria:

Review Criteria for Research Base: (Included in, "Overall Priority Score," in the RFA).

X Is there a substantial productive and funded research base? Is the research base sufficiently broad to foster new multidisciplinary research? Is there a definition of who will be a Center investigator and what this designation might mean?

III.D. Institutional Environment and Resources

Briefly describe the features of the institutional environment that are relevant to the effective implementation of the proposed program. As appropriate, describe available resources, such as clinical and laboratory facilities, participating and affiliated units, patient populations, geographic distribution of space and personnel, and consultative resources. Indicate if any of the proposed cores will utilize or expand cores already existing at the institution. What institutional commitments for space or other resources are there for the proposed MCRC? Include any letters of support for the proposed Center by appropriate institutional officials.

Applicants from institutions that have a General Clinical Research Center (GCRC) funded by the NIH National Center for Research Resources may wish to identify the GCRC as a resource for conducting the proposed research. Details of the interactions of the MCRC staff with the GCRC staff and research personnel may be provided in a statement describing the collaborative linkages being developed. A letter of agreement from the GCRC Program Director must be included with the application. Applicants are advised to include sufficient information to address the following review criteria:

Review Criteria for Institutional Environment and Resources: (Included in, "Overall Priority Score," in the RFA).

X Is the institutional commitment to the program, including lines of accountability regarding management of the Center, the institution's partnership with the Center, and the institutional commitment to individuals responsible for conducting essential Center functions, clearly stated? Is the academic environment and resources in which the activities will be conducted, e.g., the availability of space, equipment, facilities, and the potential for interaction with scientists from other departments and schools, appropriate to carry out the goals of this grant? Is there evidence of a supportive institutional environment for the proposed MCRC? Will the MCRC add an important multidisciplinary element to the institutional environment? Does the proposed MCRC utilize available resources well?

III.E. Competing Continuation Applications: Additional Material Required

All applications for competitive renewal must provide the following information in the progress report:

X A description of the changes that have resulted from the presence of the Center (e.g., increased numbers of research grants and research papers);

X A description of the activities before the existence of the Center (or at the beginning of the last award period) compared with any changes brought about by the Center's activities;

X The results of each project supported and conducted by the Center during the previous grant period;

X A synopsis of the activities of the Methodology Core including the implementation of data safety and monitoring for clinical projects; (A more complete report should be found in the Methodology Core.)

X A synopsis of other core units (if any) in operation during the previous award period and an evaluation of their usefulness to the Center; (A more complete report should be found in the core.) and

X A list of publications that have resulted specifically from Center funding.

Applicants are advised to include sufficient information to address the following review criterion:

Review Criterion for past progress of a MCRC:

X Does the progress report reflect significant accomplishments? Is the work of the MCRC reflected in new concepts and publications? Are the justifications for adding new projects or cores or deleting previous components appropriate and acceptable?

III.F. Administrative Unit

The purpose of an MCRC is to promote research on clinically relevant issues to prevent disease and to assess and/or to improve patient outcomes in the many diseases within the mission of NIAMS. The Administrative Unit is responsible for the planning, development, coordination, and overall administration of the Center. A key role of this unit is to foster productive interactions at the host institution through Center personnel and appropriate committees.

The Center Director is responsible for the organization and operation of the Center. An Associate Director should be named who will be involved in the administrative and scientific aspects of the Center, and will serve as Acting Center Director in the absence of the Director. An executive committee representing the research base for the Center and including the methodology core leader should also be identified. The Director, Associate Director and executive committee provide the leadership to identify and focus research projects on clinically relevant issues. Their collective expertise should reflect direct clinical interactions with the diseases included in the research base of the Center and experience with the recruitment of patients (and care givers, if applicable) for the type of projects undertaken. (Their qualifications are to be presented elsewhere in the application in a section on Qualifications of the Center Leadership - see Section III.B.)

The administrative framework the Center proposes should be described. The emphasis should be on coordination of administrative needs in the Center. The Center Director is expected to devote substantial effort to the Center, generally no less than 10% nor more than 25%. An Associate Director is expected to have no less than 10% nor more than 20% effort. Members of the executive committee may be budgeted in the Administrative unit. However, if a member has a substantial role in another component, such as the director of the methodology core, then one role of that position should be to serve as a member of the executive committee and that should not be budgeted in the Administrative unit. Administrative support personnel may be budgeted in at no more than one full time equivalent (FTE) which may be divided among one or more positions. This FTE must be fully justified.

Applications should include yearly travel expenses in the Administrative Unit to pay for two individuals to attend one 2-day meeting related to the MCRC program.

Describe the plan for the administrative oversight of the Center. Describe the mechanisms by

which the Director, Associate Director and executive committee will provide the leadership for the Center. Experience has demonstrated that Centers benefit from having outside advisors as well. Describe plans for using outside advisors individually or as an Advisory Committee.

The NIH expects investigators supported by NIH funding to make their research data available to the scientific community for subsequent analysis based on a data sharing plan approved as part of the award; see the NIH Data Sharing Policy website at http://grants.nih.gov/grants/policy/data_sharing/ . The data sharing plan for the center should be described in the Administrative Unit.

Applicants are advised to include sufficient information to address the following review criteria:

Review Criteria for the Administrative Unit:

1. Do the Director and Associate Director have the leadership and research qualifications to lead a Center? Do the proposed MCRC Director, Associate Director and executive committee have the collective expertise and leadership to identify and focus research projects on clinically relevant issues?

2. Is the management proposed appropriate for scientific administration as well as fiscal administration, procurement, property and personnel management, planning, budgeting, etc.?

3. Is there a plan for establishment and maintenance of internal communication and cooperation among the MCRC investigators, core leaders and executive committee? Are there plans for outside review and input?

4. Is there scientific and administrative leadership, commitment and ability, and adequate time commitment of the MCRC Director and Associate Director for the effective management of the MCRC program?

5. Is there documentation of institutional support for the MCRC by the parent institution?

6. Is a plan for data sharing included?

III.G. Methodology Core

A Methodology Core is a required component of the MCRC and must serve **all** projects proposed in the Center.

X The core should have sufficient professional personnel to provide an interactive leadership role not only in supporting the projects within the MCRC, but also promoting rigorous methodological and biostatistical support for the research base. As a minimum, the Methodology Core should provide professional expertise in biostatistics and clinical research design. However, additional professional expertise will be appropriate as justified by the research supported and the research base.

X An important role of the Core should include teaching functions that might include regular meetings for presentation and critique of proposals and draft manuscripts by Center investigators, fellows and students.

X The Methodology Core designs and implements an independent process for data and safety monitoring for the projects funded by the MCRC. See the requirement for data and safety monitoring below.

X The Methodology Core may include support services for the projects such as subject recruitment, data entry or database management. These services should not be extended to non-MCRC funded projects without cost sharing. Such arrangements should be described.

Describe the qualifications of the professional and support personnel in the budget justification. In the research plan indicate the scope of services to be provided and the mechanisms by which the core will provide both support and oversight for the proposed projects.

Data and safety monitoring It is the policy of the NIH that all NIH-sponsored clinical trials should have in place a system for appropriate oversight and monitoring of the conduct of clinical trials to ensure the safety of participants and the validity of data. These monitoring activities should be commensurate with the nature, size and complexity of the trial and will require a safety officer or in some cases a data safety and monitoring board (DSMB).

The Methodology Core should describe support for data safety and monitoring of the proposed MCRC projects that are clinical trials. Each clinical trial should include a data safety and monitoring plan within the project proposal. The following activities should be included in a monitoring plan:

X Review of the research protocol with emphasis on data integrity and patient safety issues.
X Monitoring of adverse effects and determining stopping rules for the trial.
X Protecting the confidentiality of the trial data and the results of monitoring.
X Twice yearly review of recruitment and adverse events by a Safety Officer or a DSMB.

Note that the NIAMS will determine at the time of award whether a Safety Officer or a DSMB will be appointed for each clinical trial. NIAMS will appoint the Safety Officer or DSMB members in consultation with the principal investigator. The Safety Officer or DSMB members must not be affiliated with the host institution. NIAMS will provide logistical support when a

DSMB is required and will provide any travel funds or consultant fees for DSMB members. The Methodology Core must outline support for producing the twice yearly reports for review by the Safety Officer or DSMB and for communicating serious adverse events. The individual projects should budget any travel for MCRC staff to travel to a DSMB meeting once yearly.

To assist in planning, NIAMS has posted the document *DATA AND SAFETY MONITORING GUIDELINES for Investigator-Initiated Clinical Trials* at the following website: http://www.niams.nih.gov/rtac/clinical/safe_monitoring_plan.htm

Applicants are advised to include sufficient information about the Methodology Core to address the following review criteria:

Review Criteria for the Methodology Core:

X Does the methodology core serve all projects proposed in the Center (mandatory)? Have issues relating to data and safety monitoring been addressed? Is there a plan for offering teaching services to the research base?

X Are the services offered appropriate and of high quality, especially for the projects directly supported? How is cost reimbursement proposed?

X Will the core likely promote multidisciplinary research? Are unique services offered? Is there a plan for prioritizing services to the research base?

X Are the qualifications of the professional and support personnel appropriate? Is there a plan for interactive leadership of the methodology core and the proposed projects?

X Are the facilities and equipment adequate? Is there institutional commitment to the core?

III.H. Other Cores (optional)

Other cores supporting two or more of the proposed MCRC projects may be requested.

Applicants are advised to include sufficient information to address the following review criteria:

Review Criteria for the Other Cores:

X Will the core have utility to at least two of the MCRC projects?

X Is the quality of services high? Are there procedures for quality control? Is the core cost effective?

X Do the services offered best fit within a core structure? If this is an add on to a

preexisting core, what is the benefit to the Center over direct purchase of services from the existing core? If the core offers new services that may be used by non-MCRC funded projects, how will the non-MCRC funded projects purchase these services from the core?

X Are the personnel appropriate?

X Are the facilities and equipment adequate? Is there institutional commitment to the core?

III.I. Clinical Research Projects

A minimum of three highly meritorious clinical research projects, **each with a focus to prevent disease or to assess and/or improve outcomes of patients**, must be present in an MCRC. Each MCRC project will define the patient problem under study and the anticipated improvement in preventing disease or in assessment and/or outcome for the patient that might be realized through this project. The MCRC projects together must encompass two or more of the following clinical research approaches: mechanisms of human disease, therapeutic interventions, clinical trials, development of new technologies, epidemiologic studies, behavioral studies, social science research, outcome research and health services research. These approaches are extracted from the current NIH definition of clinical research:

Clinical Research: NIH defines human clinical research as: (1) Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, or (d) development of new technologies. (2) Epidemiologic and behavioral studies. (3) Outcomes research and health services research. Note: Studies falling under Exemption 4 for human subjects research are not considered clinical research by this definition.
For the MCRC program only, clinical research projects may not include animals.

A unique feature of an MCRC clinical project is that the principal investigator must clearly identify the clinical assessment and/or outcome or approach to disease prevention under study in the background section of each project proposal. What are the data that support this as a clinically important issue? What difference will the answer provided by this research make to prevention, or to the assessment or outcomes of patients? What is original about the approach taken in this study? If the research is a refinement of an existing approach, what important insights will be gained?

A clinical project may use an existing large database or registry that serves as a resource for research. Examples of such national databases include, but are not limited to: Medicare, National Health and Nutrition Examination Survey, Women=s Health Initiative, Study of Osteoporotic Fractures, Framingham cohort and Nurses Health Study. However, it is not the primary purpose of an MCRC to develop registries or databases.

Data and safety monitoring It is the policy of the NIH that all NIH-sponsored clinical trials should have in place a system for appropriate oversight and monitoring of the conduct of clinical trials to ensure the safety of participants and the validity of data. These monitoring activities should be commensurate with the nature, size and complexity of the trial and will require a safety officer or in some cases a data safety and monitoring board (DSMB).

The Methodology Core will describe logistical support for data and safety monitoring activities.

However, each project that is a clinical trial should include a data safety and monitoring plan within the proposal. The individual projects should budget any travel for MCRC staff to travel to a DSMB meeting once yearly.

Each project should be written in compliance with the guidelines for a research project using form PHS 398. Note that the human subjects section is not part of the 25 page limitation and should be complete.

Applicants are advised to include sufficient information to address the following review criteria:

Review Criteria for Clinical Research Projects:

Significance: Does this study address an important clinical issue, especially one not well studied? Is it likely that the research may have a clinically important impact? Will these studies influence concepts or methods that drive this field?

Approach: Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the investigator acknowledge potential problem areas and consider alternative tactics? Does the project utilize the multidisciplinary resources of the Center, especially the Methodology Core? If this is a clinical trial, is a plan for data safety and monitoring included?

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? Is there synergy with this project and the other proposed projects in the Center?

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 collaborators? Does the investigative team bring complementary and integrated expertise to the project?

Environment: Does the scientific environment of the Center contribute to the probability of success? Do the proposed experiments take advantage of unique features of the Center and employ useful collaborative arrangements? Is there evidence of institutional support?

III.J. Developmental/Feasibility Project (optional)

An optional component in an MCRC is a development/feasibility project lasting no more than three years and with a yearly direct cost budget of $50,000 or less. The goal of the development

and feasibility project is to gather preliminary data or to develop a resource or tool for a future study. The developmental/feasibility research proposal should document that the goal is to address a clinically important issue and to describe the potential impact seen in future work, if successful. The principal investigator should have a faculty position. This section is limited to 10 pages.

Review Criteria for the Developmental/Feasibility Project:

Significance: Will the proposed work likely yield meaningful preliminary data leading to a research proposal?

Approach; Are the experimental approaches adequate?

Innovation; Is the research topic one that promotes innovative research related to the core center?

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?

Environment; Is the project appropriate to the research base of the core center? Does one or more of the cores offer needed materials/assistance?

PROTECTION OF HUMAN SUBJECTS FROM RESEARCH RISK: The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed. (See criteria included in the section on Federal Citations).

INCLUSION OF WOMEN, MINORITIES AND CHILDREN IN RESEARCH: 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 in the sections on Federal Citations).

III.K. Review Criteria for the Overall Application

After the review of the individual components of the application, an overall priority score will be assigned to the application. This score will reflect not only the individual quality of the projects, cores, and administration, but also how the proposed MCRC will bring together all these elements in a workable unit. The overall score may be higher or lower than the average of the descriptors based on the assessment of whether the whole is greater than the sum of its parts:

1. Is there a substantial productive and funded research base? Is the research base sufficiently broad to foster new multidisciplinary research? Is there a definition of who will be a Center investigator

and what this designation might mean?

2. Is the relevance and interrelationship of each research project to the goals of the Center clearly explained? Is there a likelihood of meaningful collaboration among Center investigators? Does the application convey how the proposed Center will enhance significantly the established research base of the host institution? (In a competing continuation application, the application should document the impact of the Center. This includes the qualifications, experience, and commitment of the Center investigators and their willingness to interact with each other.)

3. Is the institutional commitment to the program, including lines of accountability regarding management of the Center, the institution's partnership with the Center, and the institutional commitment to individuals responsible for conducting essential Center functions, clearly stated? Is the academic environment and resources in which the activities will be conducted, e.g., the availability of space, equipment, facilities, and the potential for interaction with scientists from other departments and schools, appropriate to carry out the goals of this grant? Is there evidence of a supportive institutional environment for the proposed MCRC? Will the MCRC add an important multidisciplinary element to the institutional environment? Does the proposed MCRC utilize available resources well?

4. The overall priority score assigned to the application will also reflect how well the policies regarding (a) the inclusion of women, minorities and children in study populations, (b) the protection of human subjects from research risks, (c) sharing research data, and (d) the budget have been addressed.

IV. SUGGESTED CONTENT ORDER FOR APPLICATION

IV.A. Face Page, Abstract Page, Table of Contents

Form PHS 398 is required for all applications. (See II.B. for how to obtain this form). Each budget unit (project or core) should be written in the style and within the page limitation described in the PHS 398 instruction kit. To aid in the review of these applications, the applicant should assemble the component units following the format described below. Applicants may also consult with NIAMS staff concerning the technical aspects of preparing the application.

Face Page of form PHS 398. Complete all items on the face page as directed. In the title block, item 1, put "NIAMS Multidisciplinary Clinical Research Center". Mark item 2 "yes" and write in the RFA code as listed in the NIH Guide to Grants and Contracts and "NIAMS: MCRC" for the title.

Page 2 - Abstract: Describe the proposed program indicating the goals and objectives of the projects. Do not exceed the space allowed. **Key personnel** are those doctoral level investigators with a percent effort listed in the application.

Table of Contents: Discard this page from form PHS 398 and write a Table of Contents

appropriate for the MCRC grant application. This is paginated to follow the list of Key Personnel. **Do not use letters (e.g., 4a, 4b, 4c, etc.)** The Table of Contents should list

- Each summary narrative
- Each core or project for which funding is sought *with the core or project listed by the title and Principal Investigator;* subsections should also be identified (see Exhibit I for suggested format)
- The location of the checklist pages
- The location of the various required sections, e.g., human subject assurance, biographical sketches.

IV.B. Budgets and Other Supporting Forms

Budget: See Exhibits III, IV and V. To aid in the review of your application, it is suggested that the forms found as pages 4 and 5 in form PHS 398 be used for all budgets. Justify and document all costs for current and future years throughout.

The overall Center budget, "Summary Center Budget," is to be presented first using form PHS 398 page 4 entitled "Detailed Budget for First 12-Month Period" (see Exhibit IV). Note that no details need be given for the individual categories. To provide budget information in a format that is clear to reviewers and therefore provides the most positive review possible, presentation of a consolidated budget for the first 12 months in a tabular form such as the sample shown as Exhibit III is suggested. Page 5 of form PHS 398, "Budget Estimates for All Years of Support Requested Direct Costs Only", should then follow, a composite like that in Exhibit IV, summarizing all individual budgets (see suggested format in Exhibit V). For the purpose of establishing future year budget requests, the applicant should use cost escalations as specified in the RFA or less. However, **the direct cost budget cannot exceed $800,000 in any year**. For purposes of establishing the $800,000 direct cost limit, the F&A (indirect) costs of subcontracts will not be counted.

Both first 12 month and 5 year individual budgets should be included *in the sections for each project and core*. Details and justifications for all budget items must be part of the individual budgets. Read carefully pages 11 - 13 of the Instructions for PHS 398 on how to prepare budget pages and justifications.

< A separate, detailed budget for each project subcontracted to a consortium institution is required as well as a form PHS 398 face page signed by the principal investigator and appropriate officials in the consortium institution.

< This grant mechanism is not intended for the acquisition of costly equipment which should be funded through other sources. Under unusual circumstances, where costly items of equipment are requested, the application must document available equipment within the institution and provide clear justification.

< It is not the purpose of a Center grant to provide funding for alterations or renovations.

< Support for research training positions is not to be included.

< The production of audiovisual material with Center grant funding is not appropriate.

< The travel of personnel to attend Center-sponsored symposia is not appropriate.

Biographical Sketches: Biographical sketches are required for all professional level personnel who are (1) listed with a percent effort (including consultants) in the MCRC application; (2) serving as advisors; and (3) members of the research base. The forms found in Form PHS 398 should be used. Place individual sketches in alphabetical order after the budget pages. These pages should not be duplicated in the individual component projects and cores.

Assurance Documentation: See sample suggested table, Exhibit VI. In addition to the assurance pages, a master table listing the status of human subject approval dates and the human subjects education requirement certification will aid in the timely processing of your application.

IV.C. Presentation of the Proposed MCRC

IV.C.1. Narrative Sections

In a narrative fashion, present the components described in Sections III.A. - III.E.: Overview, Qualifications of the Center Leadership, Research Base for the MCRC, Institutional Environment and Resources, and Progress Report (if applicable). It is helpful for the reviewers to locate each of these components in the Table of Contents (See Exhibit I).

IV.C.2. Budgeted Components

The components with budgets are described in Sections III.F. through III.J.: Administrative Unit, Methodology Core, Other Cores (optional), Clinical Research Projects (minimum of three), and Developmental/Feasibility Project (optional).

Each component should be written up as a separate unit following these supplemental instructions and the instructions accompanying form PHS 398. It is important that each component include a section on human subjects, gender and minority inclusion, and inclusion of children as participants in research involving human subjects, even if to indicate that a full discussion is not applicable. An individual target enrollment table must be included with each project. Cores may cross reference detailed presentations to projects and vice versa as appropriate to avoid lengthy repetitions of complex arrangements.

X A cover page for an individual component is needed only when that component will be administered through a subcontract to another institution. Facilities and administrative (indirect) costs from these subcontracts do not count against the $800,000 cap for direct costs for an MCRC.

X An abstract and key personnel page must be included for each component.

X A detailed budget for the initial budget period and budget for the entire proposed period of support [pages 4 and 5 of form PHS 398] must be included with each component. The budget justification should be thorough. Do not assume that any item or percent effort is obvious. If this is a project for which specific services are to be performed in one of the cores, the percent effort of specific personnel and the associated costs should be detailed at the end of the budget justification. Similarly, the budget justification for each core (but not the administrative unit) should include the specific percent efforts and costs to service each individual project. It is recognized that 100% of core costs need NOT be justified by service to specific projects to allow for teaching, quality control and other research-base functions.

X The biographical sketches are put centrally in one location (see IV. B.) and should not be duplicated in the individual component.

X A resources page should be included for each component.

X The checklist page needs to be included with each institutional cover page.

IV.D. Appendices

See the instructions in the PHS 398 booklet for appropriate appendix materials.

Following these suggestions will insure that correct appendix material can be sent to the appropriate reviewers:

X The five sets of all appendix material as well as a CD including all appendices should be sent directly to the Review Branch, NIAMS (see Section II.B. page 5 for the address) and **NOT** to the Center for Scientific Review.

X Each piece should be marked with (1) the name of the MCRC Director - not the name of the component PI and (2) a **single** component of the application to which it pertains - MCRC Leadership, Research Base, Resources and Environment, Past Progress, Administrative Unit, or individual cores and projects.

X The marked materials should be grouped by the identified components. Thus, all five copies of appendices pertaining to a given project or component should be grouped together.

V. NONCOMPETING APPLICATIONS: ANNUAL REPORTING REQUIREMENTS

Annual progress reports, submitted as part of the noncompeting continuation application, are due two months before the anniversary date of the award. These reports are used by the National Institute of Arthritis and Musculoskeletal and Skin Diseases to review the Center and its progress. They serve to verify in detail the achievement of the objectives outlined in the initial application and award and are an important source of material for program staff in preparing reports, planning programs, and communicating scientific accomplishments.

The application for continuation of a PHS Grant, PHS Form 2590, is sent each year. In addition, an overall progress report containing the following information should be included:

X A summary (equivalent to no more than 2-4 single-space typewritten pages) of the goals and significant activities of the Center. This summary should be prepared for a general audience. *Honors and/or promotions of professional personnel should be mentioned.*

X A discussion of the effectiveness of the Center grant in furthering the goals of the Centers program. This should include a summary of the specific accomplishments that can be attributed to the Center grant, e.g., new research funding, changes in curricula, or organizational improvements within the institution and in the community.

X An itemization of collaborative efforts the Center established.

X A discussion of problems that impede accomplishment of the stated goals in the administration of the Center grant.

X The administrative component report should include a list of administrative meetings held, evaluations from advisory committees, speakers or symposia sponsored. These may be included as appendix material.

X A table listing the IRB (institutional review board for use of human subjects in research) and certifications education for the protection of human research participants for key personnel for all Center-funded projects is optional, but will assist the timely processing of your award. (See Exhibit VI). The notice describing the requirement for education for the protection of human subject participants may be found at http://www.niams.nih.gov/rtac/funding/grants/notice/notod00-039.htm

X A detailed summary of each Center-funded component (including the Administrative Unit) and project, including the title, principal investigator and key personnel, their percent effort, proposed budgets, description, progress, and evaluation. This progress report should include all Center-supported projects. It is especially important that the significance and ultimate utility of each project be discussed in the summary description and that this discussion be in terms understandable to an informed nonscientist.

X A budget page for the coming year for each component and project funded by the Center. The timely review of your application will be facilitated by the inclusion of a composite budget for the entire Center as illustrated in Exhibit IV.

X Other information that, from year to year, may be requested by the NIAMS staff.

The expanded progress report is in addition to, and does not replace, other management reports required by PHS policy.

VI. GUIDELINES FOR SUPPLEMENTAL APPLICATIONS

Applications submitted for supplemental projects to an NIAMS MCRC program must have prior approval of the NIAMS Centers Program Director. Applications submitted without prior approval will be withdrawn and returned to the applicant. Approval will be based upon the following:

X A component research project was recommended for less time than was the rest of the P60 grant in order to permit an early assessment of progress;

X A persuasive case can be made that an alternative, additional or expanded project is important for the MCRC program AND the new total direct cost budget for the MCRC will not exceed the budget cap;

X The proposed project is in response to well defined NIAMS program initiatives and/or rapidly developing health areas related to the NIAMS' mission.

Additional developmental and feasibility studies and additional core units may NOT be requested.

Supplemental applications will undergo a competitive review by and the Initial Review Group (IRG) convened by the NIAMS Review Branch. In general, applications should be submitted so that at least two years remain on the parent grant at the time of award of the supplement. Major factors to be considered in the evaluation of a supplemental application will include:

1. The relevance of the proposed research to the MCRC concept outlined in these guidelines;

2. If a request for continuation, what findings have been developed that justify additional years;

3. Scientific merit of the proposed project, including significance, approach and innovation;

4. Competence of the investigators to accomplish the proposed research goals, their commitment, and the time they will devote to the research program;

5. How the MCRC environment enhances the project;

6. Appropriateness of the budget for the proposed program; and

7. Appropriateness of plans to include children, women, and minorities in the study populations.

A supplemental project will be assigned a priority score based on its merit as an individual research project. The review will also comment on how the proposed project fits with the MCRC program. Funding will be based on merit, program relevance and availability of funds.

VI. GUIDELINES FOR REVISED APPLICATIONS

See the guidance from the NIH Office of Extramural Research on revised applications: http://grants2.nih.gov/grants/guide/notice-files/NOT-OD-03-041.html

Before a revised application can be submitted, the Principal Investigator must have received the summary statement from the previous review. There must be substantial changes in the content of the application.

The Overview section of the application must include an Introduction of not more than three pages that summarizes overall the substantial additions, deletions, and changes. The Introduction must also include responses to the criticisms and issues raised in the summary statement.

Each core and project that is revised should also include an Introduction of not more than three pages that summarizes overall the substantial additions, deletions, and changes. The Introduction must also include responses to the criticisms and issues raised in the summary statement.

The changes in the Research Plan must be clearly marked by appropriate bracketing, indenting, or changing of typography, unless the changes are so extensive as to include most of the text. This exception should be explained in the Introduction. Do not underline or shade changes. The Preliminary Studies/Progress Report section should incorporate any work done since the prior version was submitted.

EXHIBIT I - TABLE OF CONTENTS

ABC University

Application for a Multidisplinary Clinical Research Center

SAMPLE OF SUGGESTED FORMAT

Page #

EXHIBIT II – GRANTS SUPPORTING THE RESEARCH BASE
SAMPLE OF SUGGESTED FORMAT

Supporting Organization & Grant Number	Key Personnel	Title	Project Period	Current Annual Amount
NIH 5 R01 ARnnnnn	Chen, Chin-Mei (PI) Doe, John	New Therapeutic Agents for Autoimmune Disease	3/1/2004 – 2/28/2009	$467,000

EXHIBIT III -- CONSOLIDATED BUDGET FOR THE FIRST YEAR OF REQUESTED SUPPORT

SAMPLE OF SUGGESTED FORMAT

BUDGET CATEGORY	Administrative Unit	Methodology Core	CORE B	Project 1	Project 2	Project 3	Project 4	D/F1	TOTAL ALL UNITS
PERSONNEL									
CONSULTANT COSTS									
EQUIPMENT									
SUPPLIES									
TRAVEL									
INPATIENT COSTS									
OUTPATIENT COSTS									
ALTERATIONS/ RENOVATIONS									
OTHER EXPENSES									
SUBTOTAL DIRCECT COSTS									
CONSORTIUM/ CONTRACT COSTS									
TOTAL DIRECT COSTS									

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
DIRECT COSTS ONLY

FROM 4/01/2006 THROUGH 3/31/2011

PERSONNEL *(Applicant organization only)* NAME	ROLE ON PROJECT	TYPE APPT. *(months)*	% EFFORT ON PROJ.	INST. BASE SALARY	DOLLAR AMOUNT REQUESTED *(omit cents)* SALARY REQUESTED	FRINGE BENEFITS	TOTAL
	Principal Investigator						
SUBTOTALS →					441,498	132,449	573,947

CONSULTANT COSTS		20,225
EQUIPMENT *(Itemize)*		
SUPPLIES *(Itemize by category)*		25,972
TRAVEL		15,000
PATIENT CARE COSTS	INPATIENT	
	OUTPATIENT	6,000
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
OTHER EXPENSES *(Itemize by category)*		86,356
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		**$** 801,006
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	72,500
	FACILITIES AND ADMINISTRATIVE COSTS	17,500
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)* →		**$** 817,500

BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS		INITIAL BUDGET PERIOD *(from Form Page 4)*	ADDITIONAL YEARS OF SUPPORT REQUESTED			
			2nd	3rd	4th	5th
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*		573,947	587,970	626,547	629,664	666,617
CONSULTANT COSTS		20,225	12,203	12,554	12,370	675
EQUIPMENT						
SUPPLIES		25,972	10,188	10,531	10,258	9,928
TRAVEL		15,000	13,905	14,321	14,751	15,193
PATIENT CARE COSTS	INPATIENT					
	OUTPATIENT	6,000	6,180	6,365		
ALTERATIONS AND RENOVATIONS						
OTHER EXPENSES		86,356	94,831	53,641	33,174	21,899
SUBTOTAL DIRECT COSTS		801,006	799,287	799,504	799,853	799,166
CONSORTIUM/ CONTRACTUAL COSTS	DIRECT	72,500	74,000	75,545	99,636	78,775
	F&A	17,500	18,025	18,566	19,123	19,696
TOTAL DIRECT COSTS		817,500	817,312	818,070	181,976	818,862

TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD *(Item 8a, Face Page)* —————— **$** 4,090,720

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

EXHIBIT VI -- HUMAN SUBJECTS APPROVAL DATES
HUMAN SUBJECTS EDUCATION REQUIREMENT
SAMPLE OF SUGGESTED FORMAT

GENERAL:

1. Initial application: IRB approval and certification is not required with the submission or prior to review and may be listed as pending prior to the review.

2. Initial funding: This table may need updating. The NIH no longer requires IRB approval and certification prior to NIH review. This information will be required when a decision is made to fund the application. Certifications for the Human Subjects Education Requirement may be submitted at the time of application but are not required until a funding decision is made. If the Human Subjects Education Requirement certification is not included in the application, please mark Apending@.

3. Yearly progress reports: This table should be updated and included with each yearly progress report. Human Subjects Education Requirement Certifications are needed only for investigators new to the grant. Mark Apreviously submitted@ for continuing investigators.

SPECIFIC:

Please make a table for each Performance Site. If there is only one performance site, then only one table is needed. A certification letter must be attached for each project using Human Subjects. Each letter should include the registered IRB number from the Office of Human Research Protections.

Performance Site: University A

Principal Investigator	**Project**	**Human Subjects IRB Approval Date (Attach certification letter)**	**Human Subjects Education Requirement (Attach certifications)**
Dr. A	1	9/5/2006	3/1/2004
Dr. B	2	9/5/2006	3/1/2004
Dr. C	3	8/5/2006	3/1/2004
Dr. E	5	9/5/2006	3/1/2004
Dr. B	Core A	Not Applicable	Not Applicable
Dr. D	Core B	Not Applicable	Not Applicable

Performance Site: University B
Human Subjects assurance number:
Animal welfare assurance number.

Principal Investigator	**Project**	**Human Subjects IRB Approval Date (Attach certification letter)**	**Human Subjects Education Requirement (Attach certifications)**
Dr. X	1 (subproject)	9/6/2006	6/1/2004
Dr. D	4	8/5/2006	6/1/2004
Dr. Y	Core B (subproject)	Not Applicable	Not Applicable