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Division of Research Infrastructure

Guidelines for the RCMI Clinical Research Infrastructure Initiative (RCRII) Program

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RCMI CLINICAL RESEARCH INFRASTRUCTURE INITIATIVE (RCRII)

PURPOSE

The **RCMI Clinical Research Infrastructure Initiative (RCRII)** is supported by the NCRR Division of Research Infrastructure (DRI). The initiative was established to expand the capacity for clinical research at RCMI institutions with affiliated medical schools by providing resources to develop the appropriate infrastructure. The long-range objectives of this initiative are to; 1) assist participating institutions to conduct clinical research to improve the health of the Nation's citizens, especially racial and ethnic minorities; 2) enhance the clinical research capacity of RCMI institutions with affiliated medical schools; 3) position these medical schools to compete successfully for clinical research support; and 4) enhance their probability of success in competing for funds to establish an independent Clinical Research Center. The primary distinction between the RCRII Program and the traditional RCMI Program is the paramount focus on the development of clinical research capacity by providing resources to develop the appropriate infrastructure. Since it is expected that the development of the institutional research capacity and infrastructure will allow for competition for non-RCMI support of a clinical research center and transition to an independent clinical research center, it is not anticipated that this initiative will be extended beyond a third cycle of support.

ELIGIBILITY REQUIREMENTS

Eligibility for this Program is limited to RCMI institutions that have affiliated medical schools that offer an M.D., D.D.S., Pharm.D., D.V.M. or other doctoral degree in the health professions and/or a Ph.D. in the sciences related to health. NCRR will not support more than one RCRII in any geographic region. Further, those RCMI medical schools that have successfully competed for an independent clinical research center are not eligible.

MECHANISM OF SUPPORT

The applicant will be solely responsible for the planning, direction, and execution of the grant. The total requested project period may not exceed five years. Awards of up to $1.5 million/year (direct costs) per institution may be made. This includes requests for alterations and renovations.

In accordance with NIH policy, all applicants whose total direct costs for any given year of the application, exceed $500,000 must submit a request to NCRR describing the nature of the application and its anticipated costs for each of the five years requested. This letter will be reviewed by the Division of Research Infrastructure staff and forwarded through NCRR channels to the Center for Scientific Review. This letter to waive the $500,000 rule must be received by NCRR six weeks prior to the proposed date of submission. Failure to submit the letter of waiver will result in the application being returned to the applicant organization. Please see the PHS 398 for all instructions.

In accordance with NCRR policy, the recurring direct costs (direct costs excluding equipment and other one-time costs) requested for the first year of a competing continuation center application cannot exceed the final noncompeting year's direct recurring costs budget by more than 20 percent. Where this policy may significantly limit the scope of the proposed program, the applicant may request a waiver of the 20-percent ceiling. A letter, clearly justifying the request for a waiver must be submitted to the Director, DRI, well in advance of the application receipt date. The waiver to the ceiling must be approved in writing by the Director before the Center's competing continuation application may be submitted and accepted.

ALLOWABLE COSTS

Requested allowable costs of activities should focus primarily on the establishment of clinical research infrastructure at the applicant institution. All requested items must be related to the needs of the institution's RCRII implementation plan and must be specifically and thoroughly justified.

RCRII funds are awarded and may be used only for specifically approved activities; not as discretionary funds for formula-type or general distribution within the institution, and not for broadly defined institutional needs. There must be a clear focus on the institutional clinical research development plan as proposed and approved for funding in managing RCRII funds.

CENTRAL FACILITIES

Support of central resources, such as outpatient-care facilities, shared-instrumentation facilities, core and clinical laboratories, computer and biostatistical resources, and grants and research-development offices, may be requested or charged only in direct proportion to their use for clinical research and only if these costs are consistently treated as direct costs by the institution.

RENOVATIONS

Costs for renovations associated with core laboratories may not exceed a total of $500,000, or one-third of the total direct costs, whichever is less. Requests that duplicate previously funded NCRR renovations will not be allowed.

EQUIPMENT

Expenditures for equipment are limited to the amount justified via the peer-review process.

DEVELOPMENT OF CLINICAL PROTOCOLS

Requests of up to $75,000 per year for the development of relevant clinical protocols may be included. Support for each protocol to be developed will be limited to three years, and no more than three clinical protocol developments will be supported during any single year. These funds are only for pilot projects for the development of clinical protocols and are not intended to support individual research projects. When protocol developments are to be led by junior clinical faculty, explicit mentoring plans need to be developed.

INDUSTRY-SPONSORED RESEARCH:

RCRIIs are sometimes used for projects funded in whole or in part by for-profit organizations. Investigator-initiated projects that are partially supported by such an organization through a grant of unrestricted funds or by a donation of drugs or devices may be pursued on the RCRII in the usual manner, subject to the usual IRB and RCRII Clinical Advisory Committee (RCAC) review and approval. Funds from the proprietary organization that are budgeted for research patient care must be credited to the patient care category of the RCRII grant if the RCRII is used. Copies of the agreement with the drug company or other source must be maintained in the RCRII's administrative files. In addition, copies of appropriate regulatory documents and other relevant correspondence are to be maintained in the RCRII's research project files. This includes, but is not limited to, all FDA-required documents and relative correspondence.

Those projects designed by for-profit organizations will be considered industry initiated. These organizations are expected to pay for the use of the RCRII facilities and ancillary costs at the rates established at the RCRII institution. This can be accomplished by classifying research subjects in such projects as Category D patients. (See Patient Care Costs). All Category D patient charges are to be paid to the hospital from funds provided by the commercial organization. In some cases, investigators may add additional research aims to the project. In that case, the RCAC ascertains the relative resource needs to be contributed by the company, RCRII, and investigator's resources.

All industry-initiated projects must be approved for use of the RCRII by the RCAC and include a DSM plan. **Industry-initiated projects should constitute only a small portion of total RCRII activity.** In some cases, a commercial organization may provide

clinical research funds for an investigator-initiated study. If investigator-initiated, the research project is appropriately classified as Category A or Category B rather than Category D. The funds provided by industry are to be credited to the patient-care category of the RCRII grant. The determination of whether a research project is industry-initiated or investigator-initiated is to be made by the RCAC, using the above general principles after reviewing the appropriate documents. Deliberations are to be documented in the minutes of the RCAC meetings. Investigators who are receiving industry support for projects conducted on the RCRII must be free to publish or distribute data from such studies without restriction.

PATIENT-CARE COSTS

Patient-care costs are allowable to provide routine and ancillary medical services, primarily on an outpatient basis, to patients as necessary in research protocols supported under the RCRII grant. In cases where a limited number of scatter beds have been included, patient-care costs are allowable for inpatients involved in approved research protocols.

I. General: Research patient-care costs incurred under RCRII grants by the grantee institution/facility must be computed using research patient-care rates or amounts established by the appropriate Regional Office of the Division of Cost Allocation of the Department of Health and Human Services (DCA, DHHS). Such rates must be used by the grantee institution/facility in all requests and claims for reimbursement for research patient care costs. The grantee institution/facility must submit patient-care rate proposals annually to the DCA, DHHS Regional Office and reply promptly to inquiries from that Office. If a facility incurring research patient-care costs under an RCRII grant is a consortium participant and not the grantee institution/facility, then the grantee institution/facility will be responsible for establishing with the consortium facility an appropriate rate or amount that will be reimbursed for such costs. However, if the consortium facility has an established research patient-care rate agreement with DHHS, then the DHHS rate must be used for calculation and reimbursement of research patient-care costs.

2. Patient Categories: Each patient admitted to the RCRII shall be assigned to one of three categories: Research (Category A), Research Service (Category B), or Industry-Initiated (Category D). These assignments are to be made prospectively for each research project by the PD and RCAC, in consultation with the involved investigator. The RCAC evaluation of research projects for RCRII use is to be made exclusively on the basis of the scientific merit of the projects and their need for the RCRII, without regard to the assignment of patients to Category A or B. In all cases, NIH-funded clinical research has the highest priority status.

RCRII grant funds pay for research costs. They are not used to pay for established patient medical care or treatment during the course of research. When Category D patients are admitted to an RCRII, all costs for their care are charged to the patients or third parties rather than to the grant.

a. Research Patients (Category A): These are research outpatient visits utilized solely for research purposes. All hospitalization costs associated with Category A research days or visits are the financial responsibility of the institution through the RCRII grant or the investigator's research grant. Persons who are hospitalized for research purposes only, but whose care is partly supported by non-RCRII funds, (e.g., other grants, industry, the Center for Medicare and Medicaid Services under its Clinical Trials National Coverage Decision) also may be classified as Category A. This category includes normal volunteers or control subjects and patients who may participate in research projects that include unproven forms of therapy or diagnostic techniques that may subsequently become standards of medical therapy or diagnosis. Even though a patient may have a third party carrier and have an underlying disease, the RCRII assumes all research costs related to patients in this category. RCRII grant funds may be used to pay all costs, thereby encompassing the usual care costs, which are part of the research project, as well as research care costs. This financial responsibility is assumed for the entire period of hospitalization or outpatient visit, research testing or provided services for patients who would not otherwise have been hospitalized or received such tests or services except for their participation in the research study. Any exceptions should be documented in RCRII administrative records.

These patients may include persons to whom no health advantages may be expected to accrue as a result of the hospitalization or outpatient visit. Examples would be persons with genetic or other abnormalities of interest to the investigator, and those persons who, although sick, would not have been brought to the hospital except for the research studies.

b. Research Service Patients (Category B): This category pertains to patients who require hospitalization or outpatient studies for diagnosis or treatment according to established standards of care. Although these patients also participate in RCRII-based research studies, the cost of established medical care (i.e., non-research care for Category B patients) is not charged to the grant. The patient or third party carrier is responsible for those costs. The institution is responsible for all billings and collections on these patients. A patient care credit, or offset, for each Category B outpatient visit is credited to the patient care category of the grant based on the patientcare rate agreement or the rate developed by the RCAC for outpatient visits. The cost of those ancillary services performed solely for research on Category B patients and not related to their routine medical care should be charged to the grant and not appear on the patient's hospital bill that is submitted to either the patient or the insurance carrier. Patients who meet the Category B classification criteria may not be classified as Category A simply because they lack applicable insurance.

c. Industry-Initiated Projects (Category D): This category includes outpatient visits utilized for an industry-initiated study. All charges are paid by industry.

The RCRII receives a credit for each outpatient visit and use of any other RCRII resources. The charge for each project is to be developed by the RCAC and credited to the patient care category of the RCRII grant. It is essential that the presence of Categories D patients not compromise other research activities involving Categories A and B patients on the RCRII.

3. Scatter-bed Inpatient Days:

a. Category A:

i. The cost of occasional, unexpected, temporary use of special facilities, such as an intensive care unit or other off-site area uniquely required to accommodate a research patient, may be charged to the RCRII grant provided that the care is required by the nature of the clinical research or by an illness resulting from the research; the care is provided in a specialized area (intensive care unit, coronary care unit, etc.); the occasional patient remains on the RCRII census under the scatter-bed classification while in the special care unit; and there is no duplication of payment for patient care. The RCAC must review and approve this local activity.

ii. If the use of special facilities such as an intensive care unit or other off-site area is to be an established part of a RCRII research project and was not previously peer reviewed, prior written approval from the NCRR is required. The request is to be co-signed by the appropriate Business Official.

iii. If the cost of the proposed scatter-bed research activity combined with the support of the original peer-reviewed and recommended configuration of a RCRII exceeds the National Advisory Research Resources Council (NARRC) recommended funding level, then a competitive supplement may be submitted for peer review of the request.

b. Category B: As defined above for Category B inpatients, Category B scatter-bed patients require hospitalization for diagnosis or treatment according to established standards of care but are also research subjects. These inpatients may require ancillary services solely for research purposes that may be charged to the grant. Scatter-bed B research inpatients with ancillary costs charged to the RCRII grant will be tracked as scatter-bed B days. If a RCRII research nurse is required, the nurse's time is tracked separately as "Scatter-bed Research Nurse Hours." (See below.)

c. Category C and Category D: These categories are not classifications used for scatter-bed research days.

Scatter-bed Reimbursement: Some studies require that patients be cared for in beds not located on the RCRII. These are referred to as scatter-beds. If Category A scatter-bed days have been funded in the award statement, or prior approval has been obtained from the NCRR, patient-care costs will be provided using a negotiated inpatient routine per diem applicable to the area where the patient is housed, and the costs may not exceed 5% in direct costs of the total award. Scatter-bed patients often

are Category B, in which case the only cost to the grant is for the ancillary costs associated with the research.

4. Scatter-bed Research Nurse Hours:

a. Category A and Category B: An RCRII research nurse may be required to perform the research component of a study on a Category B inpatient hospitalized off-site on an approved scatter-bed research project. Scatter-bed research nurse hours will be tracked by project for nurses who are paid directly by the RCRII grant. The hours tracked will reflect all the requisite time associated for each research project (e.g., scheduling, preparation, direct patient research procedures, chart entry). Scatter-bed research nurse hours are entered in the Annual Report for each subproject by patient category (A, B, or D). The scatter-bed research nurse hours associated with all off-site research inpatients should be recorded. If ancillary costs are not charged to the RCRII grant, no Category B scatter-bed inpatient days are recorded. Off-site "B" research inpatient projects that have no ancillary charges will require only scatter-bed nurse hours to be tracked. Category A scatter-bed days are recorded since either inpatient costs or ancillary costs (or both) are paid by the RCRII grant. Scatter-bed research nurse hours for Category A projects will count only the hours of nurses paid directly by the RCRII grant, not those nurses whose salaries are included in a *per diem* charge.

b. Category D: With the approval of the RCAC, a Category D project with patients hospitalized off-site may have a scatter-bed research nurse assist in the study. Scatter-bed research nurse time for an off-site Category D research project should be tracked and appropriate financial credit should be made to the RCRII grant.

c. All scatter-bed research nurse activity must take place in a facility either accredited by JCAHO or certified to accept Medicare and/or Medicaid reimbursement.

4. Outpatient and Research Meal Visits: An RCRII research subject who is not hospitalized at midnight is considered to be an outpatient. Thus, an outpatient visit could be as short as a few minutes or as long as almost 24 hours. The visit may take place on the RCRII unit or at a remote site, as long as it is funded by the RCRII grant and/or involves an RCRII nurse. There is no category called "scatter outpatient visit."

When a research subject is on the unit to eat or pick up a research meal and has no contact with either RCRII nurses or investigators, the interaction is categorized as a research meal visit, not as an outpatient visit. The research meal visits should be tracked and reported in the Nutrition section of the Administrative Narratives in the Annual Progress Report (APR) and listed as "research meal visits." If a research subject comes to the RCRII for more than eating or picking up a research meal (such as contact with a bionutritionist for a diet history or diet instruction or a procedure such as anthropometric measurements), then it may be counted in the census as an outpatient visit.

5. Outpatient Visit Credits: Charges for Category D (industry-initiated) visits and the non-research portion of Category B visits are to be credited to the RCRII grant. This activity must be reflected in the computations on the census page of the APR, and it must be included as a credit in the patient care computation pages of the APR.

For each project, an appropriate credit, preferably based on an hourly rate, must be computed. When developing a rate, include all utilized components of the RCRII (i.e., program directorship, administration, RSA, research bionutrition, nursing, core laboratory, computer, biostatistical services, space charges, as well as any other appropriate RCRII resource). A rate should be established and approved by the RCAC.

6. Changes in Patient Category: A patient's category may change during the hospital stay on the RCRII. For example, a patient may be designated as Category B during the first part of an admission, when the patient would have been hospitalized regardless of research participation, and subsequently as Category A after the completion of standard care because components of the research project have yet to be completed. Similarly, part of a research subject's hospital stay may be Category D and another portion Category A or B.

The categorization is determined prospectively by the RCAC.

7. Ancillaries: All ancillary services provided to Category A patients and those provided to Category B patients that are not required for their routine medical care but are performed solely for research can be supported from RCRII grant funds. Ancillary services are defined as services routinely available through hospital departments for all patients in the hospital. This definition applies even when these services are purchased from sources outside the hospital for reasons of economy or efficiency. Tests needed by individual investigators for their research are not proper charges to the RCRII grant if the tests are not routinely available to all patients in the hospital. Also, services provided either by the laboratory of an RCRII researcher or by a hospital laboratory or service that is directed by an RCRII researcher (even if that researcher has a contractual arrangement with the hospital to provide these services) may not be charged to the RCRII grant for any project for which that researcher is the PI or a collaborator. Research ancillary charges must be reduced to cost (discounted according to the Medicare or RCRII rate) based upon the Negotiated Rate Agreement between the hospital and DHHS.

8. Program Income: Program income is defined as the gross income earned by a grant recipient that is generated directly by an activity supported by the grant or earned as a result of the grant. (See 45 CFR 74.2 and 74.24 for additional information.) An example of program income is fees resulting from charges made for laboratory tests performed by the RCRII Core Laboratory. An estimate of the amount and source of program income expected to be generated as a result of the RCRII grant award must be included on the Checklist Page of all competing and noncompeting continuation applications. Net program income earned during a budget period must be reported on the long form FSR (except for program income earned as a result of inventions, to which special rules apply). Costs incident to the generation of program income may be deducted from gross income to determine program income, provided these costs have not been charged to the award. Program Income earned during the project period shall be retained by the

RCRII recipient and, in accordance with the terms and conditions of the award, used in the following way:
a. The first $25,000 earned during a budget period is added to funds committed to the project or program and used to further the objectives of eligible projects or program;
b. Any amount over $25,000 earned during a budget period is to be deducted from the total project or program allowable costs in determining the net allowable costs on which the Federal share of costs is based. NCRR may offset a future award by this amount or reauthorize it for expenditure on a future award.

9. Offsite Research Visits (non-JCAHO): Inpatient and outpatient areas of the RCRII must be located in facilities either accredited by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) or certified to accept Medicare and/or Medicaid reimbursement." Accordingly, any outpatient visit reported in the RCRII census must take place in such an accredited or certified facility.
The RCRII Guidelines allow low-risk research activity (e.g., administering a questionnaire, buccal swab) by RCRII grant-supported personnel (e.g., nurses) to take place in facilities that are neither JCAHO-accredited nor Medicare- or Medicaid-certified (e.g., school, church, home, museum). Such activity is to be reported in the RCRII census, not as outpatient visits, but rather as a new category called "offsite research visits" (ORVs). The following caveats apply to any RCRII research activity that takes place offsite:
1. Although all RCRII protocols continue to require approval of the IRB and RCAC before they may be initiated, and a DSM plan, the RCAC review of protocols involving ORVs must include (and document in the minutes) an assessment that the facility in which the ORV is to be conducted will not compromise research subject safety or data confidentiality, and that the medical coverage will be appropriate for the risk level of the proposed research activity.
2. As with all RCRII protocols, the protocol should not be coercive and investigators should exercise appropriate sensitivity regarding the populations to be studied.
3. Only category A and B ORVs are allowed. RCRII personnel are not allowed to participate in category D activity in non-accredited facilities.
4. Currently, ORVs are allowed only when they are part of a study receiving NIH or comparable peer-reviewed support other than the RCRII (P20) grant.

10. RCRII Modified Classification for Rare Disease Research: Advances in the treatment of rare diseases are not sufficiently likely to be commercially viable to attract industry-supported development. This is acknowledged by the Orphan Drug Act that specifically permits the Secretary of the DHHS to make grants and/or contracts to assist in defraying the costs of qualified clinical testing of drugs, devices, or foods for rare diseases and conditions.
The RCRII Program, following this lead, modified the RCRII research category classification to facilitate testing of new agents for patients with rare diseases. Consequently, clinical trials of drugs and other candidate therapies or interventions for rare diseases may be classified by the local RCAC as category A, instead of D, for

industry-initiated protocols. (All investigator-initiated trials, designed by a single investigator or a consortium of investigators, are already classified as category A.) The protocol must be for a rare disease. Rare disease refers to “any disease or condition that either (A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug or other therapeutic agent.” A broad group of appropriate experts, including some from outside the institution, must review and find the protocol meritorious prior to its presentation to the RCAC. The protocol must conform to the format and policies required by the RCAC.

CONTRACTUAL COSTS

Limited research-related costs at collaborating institutions are allowable as contractual costs. These costs must be related to the collaborative research and should augment existing resources.

STUDENT DEVELOPMENT

Costs related to student training are not allowable.

OBJECTIVES AND SCOPE

BACKGROUND

The RCMI Program has had relatively little impact on the clinical sciences. In recognition of these circumstances, Congress suggested in the FY 1993 appropriation language that efforts be made to improve the clinical research infrastructure of RCMI-eligible institutions. NCRR’s advisory council assigned high priority to this effort which it has enthusiastically endorsed. The RCRII guidelines were developed with input from the community of eligible applicants, which included two major findings: 1) there was a great need for enhancement of many different types of clinical research infrastructure, and 2) there was enormous diversity among the eligible institutions with respect to size, mission, resources, level of clinical research activity, and infrastructure needs. Because of the diversity of institutions and the variety of needs, applicants are given considerable flexibility as to the types of resources that can be requested, as long as they are deemed necessary to become more competitive. Institutions are asked to make a critical self-assessment of current clinical research capabilities, develop a plan to enhance this clinical research capacity significantly over the period of grant support, and justify the institutional plan and the need for the resources requested to achieve institutional RCRII goals.

The essential feature that is common to all RCRIIs is the broad range of patient-oriented

scientific inquiry. Investigators from research disciplines including medical subspecialties, bioengineering, and the basic sciences are encouraged to take full advantage of research advances including the rich databases containing important new data on the human genome and novel imaging technologies.

Because each RCRII is designed to support the investigator-initiated, peer-reviewed, clinical research projects within the institution, the configuration and available resources of the respective RCRII vary according to the research needs of the investigators. All studies must adhere to the NIH policies regarding inclusion of women, minorities, and children, Federal regulations that relate to human subject research (45 CFR 46), and FDA regulations and policies. The priorities of the research to be performed at each RCRII are determined by the local RCRII Advisory Committee (RCAC). This committee also anticipates future needs for clinical research within the institution and proposes new initiatives.

The RCRII Program allows flexibility in the design, accessibility, and scope of research. This facilitates rapid initiation of new and novel protocols and pilot studies. The RCRII Program provides financial support for the components essential to clinical research: operating expenditures; hospitalization and ancillary laboratory costs; and salaries of key personnel, including nurses, research subject advocates, research bionutritionists, administrators, core laboratory staff, biostatisticians, and computer personnel. Funds for renovation and equipment also may be provided.

CENTER CHARACTERISTICS

Governance

Principal Investigator

The Principal Investigator (PI) should be the President of the applicant institution or his/her designated representative for implementation of the RCRII. In addition, the governance structure must include a Program Director (PD), and a Clinical Research Advisory Committee (RCAC) selected by the PI. The PI is responsible for the overall development of the RCRII at the grantee institution and should be available for consultation with the PD to resolve issues related to RCRII management.

Program Director

The Program Director (PD) is nominated by and responsible to the PI; the PD must be willing to devote the time and effort necessary for effective management and implementation of the RCRII. S/he should be a full-time faculty member who is a licensed physician and an established clinical investigator. This individual should have expertise in one or more of the Center's major focus areas, publish regularly, and have had competitive extramural support within the last five years.

The PD is responsible for coordinating and conducting the Center in a manner consistent with the overall institutional plan for strengthening clinical research capability, as presented in the RCRII grant application. The PD also is responsible for the organization and operation of both the administrative and research/research-related efforts. The PD must be recommended for approval through the NCRR peer-review process or approved by the Director, DRI, if changes are made after peer-review.

Clinical Research Advisory Committee

A Clinical Research Advisory Committee (RCAC) that is advisory to the PI and PD must be established prior to submission of the application, as part of the application development process. Neither the PI nor the PD may serve as the chairperson or be a voting member of the Committee. The RCAC must be composed of an External Subcommittee (ES) and an Internal Subcommittee (IS). Depending on the scope and complexity of the RCMI program, the ES may consist of four to six members, and the IS six to eight members. Ideally, the members should be appointed on a rotating basis. The efforts and recommendations of these subcommittees should be coordinated. Meetings of the ES must be held at least semi-annually; the IS must meet at least quarterly. Video or teleconferencing or other means may be used in situations where some members may not be able to attend in person. Official minutes of these meetings must be kept on file. It is particularly important to document problems and issues, along with any necessary recommendations.

Conflicts of interest (or the appearance of a conflict of interest), must be avoided in selecting members, and at all times in carrying out the Committee's responsibilities. For this reason, consultants to, or collaborators with, RCRII-supported protocols may not be members of the External Subcommittee.

The RCAC reviews the operations of the clinical research program, including the core laboratories, sets general policies, and evaluates projects for Center use. No studies may be undertaken at a Center without the approval of this committee, except that temporary approval may be given by the RCRII Program Director and the Institutional Review Board (IRB) for urgent studies to take advantage of unexpected opportunities to study unusual research patients. Other RCAC functions include the review of research protocols, including design and data analysis, and the assignment of protocol priority scores for scientific merit as well as the need for Center resources to conduct the research. The protocol development projects to be conducted in the first year of the grant will be evaluated in the NIH peer-review process; the Internal Subcommittee must review all subsequent protocol development projects, with further review by the External Committee at its next scheduled meeting. The Internal Subcommittee should include a biostatistician and other members with the expertise required to evaluate adequately scientific merit and need. Meetings of the RCAC should be held at least quarterly and official minutes must be kept.

The RCAC should prospectively prioritize projects for RCRII use to assist the PD in allocating resources. In all cases, NIH-funded clinical research must be given preference. The RCAC is responsible for ensuring implementation of existing NIH policy on the inclusion of women, minorities, and children as study subjects and for approval of DSM plans for all RCRII protocols. In addition, the RCAC shall determine if a protocol involves significant risk, and if so, will evaluate and approve the required Data and Safety Monitoring Board (DSMB). The RCAC must also designate for each protocol, the category of outpatient visits as Category A, B, or D. For appropriate classification of industry-related projects, the RCAC may request additional materials. The RCAC must review copies of the research agreement between the investigator and industry, an itemized budget, and other relevant correspondence, detailing the drug or other therapeutics or devices supplied.

The RCAC should review all RCRII operations to ensure that RCRII resources are used for the most scientifically justified and relevant projects. It also should encourage junior faculty members to perform clinical research and assist them in applying appropriate concepts and methods. Mentoring plans for these junior investigators should be clearly delineated. Meetings of the full RCAC should be held at least annually, and detailed records must be kept (note: the minutes of the RCAC meetings are examined at the site visit when the RCRII grant application is reviewed). The RCAC may form subcommittees to carry out some of its functions, which may include the review of biostatistical design of projects, ethical concerns, or the assessment of scientific merit as well as their need for RCRII resources.

The RCAC should include a biostatistician both to assist with the review of project design and to optimize subsequent data analysis.

The RCAC is to work closely with the PD to proactively address investigator resource needs, encourage RCRII use by investigators at the institution who are not currently using the resource, and provide outreach to investigators from institutions without an RCRII or comparable resources. All requests to NCRR for funds (competitive renewal, noncompetitive renewal, supplements) shall be endorsed by the RCAC prior to submission of the request to NCRR. Once funds are awarded, all significant rebudgeting shall be endorsed by the RCAC. During the grant year, the RCRII PD and Administrative Manager are to work closely with the RCAC and provide systematic updates on financial matters including: comparison of projected expenditures with actual expenditures to date; and actual use to date of RCRII resources (outpatient visits, ancillaries) by specific protocols. In addition, the RCRII PD and Administrative Manager are to report to the RCAC on apparent unmet needs of investigators, career development and other related activities, and other topics relevant to the host institution.

The minutes of the RCAC meetings shall document all reports to the RCAC and all recommendations made by the RCAC.

Research Subjects Advocate (RSA)

Federal regulations and policies have been promulgated to ensure that appropriate efforts are made during the conduct of clinical research protocols to protect the participating individuals and ensure that their safety is accorded the highest priority. These regulations complement policies already in place within academic centers.

To assist RCRII investigators in meeting these requirements, NCRR will provide support for an RSA for participants in clinical research within each RCRII to assure compliance and conduct as detailed in the institution's IRB-approved protocol to maximize patient safety. Because the monitoring of research subjects is a high NCRR priority, funding for the RSA will initially be provided as an administrative supplement to ongoing RCRII grants, then funded as part of the normal renewal process. Funds awarded for RSA positions may not be rebudgeted for any other purpose. Once an individual is appointed to the primary RSA position, each RCRII grantee must notify the RCRII Program of his/her name, including a paragraph about his/her qualifications.

The Research Subjects Advocate – each RCRII may select its own title – must be qualified, understand the protocols involved, and have sufficient stature within the institutional community to achieve the goals as outlined. This person may be an M.D., Ph.D., research nurse, pharmacist, or other appropriately trained individual. The responsibilities of the RSA may be divided among more than one qualified individual, but one individual must be identified as principal RSA. The RSA position(s) shall not be filled by the RCRII Principal Investigator, Program Director, Associate Program Director, or Assistant Program Director.

The PI of the RCRII grant will determine the RSA(s)'s responsibilities and position within the institution's organizational structure. The RSA(s) at each RCRII must report directly to the PI of the RCRII grant, work closely with the PD and RCAC, and assist in the interpretation of the clinical and scientific aspects of protocols to facilitate both regulatory compliance and patient safety. The effort of the RSA(s) funded through the RCRII grant must be dedicated exclusively to RCRII activities.

Since the intensity of clinical research and associated risks vary widely among RCRII sites, the level of effort and responsibilities of the RSA(s) will also vary. Accordingly, an RCRII must provide detailed justification as part of any request submitted to NCRR to fund these positions. Additional support for secretarial assistance may be requested, also with detailed justification.

Examples of RSA responsibilities may include but are not limited to:
1. Serving as an unbiased observer during the consent process
2. Providing clear and appropriate information to patients/volunteers participating in Phase I or II clinical trials and other research that is above minimal risk
3. Ensuring that information is understood by the patient
4. Assisting RCRII investigators in formulating, and the RCAC in reviewing, data and safety monitoring plans

a. Investigators whose Phase I and II clinical trial protocols are NIH-funded must submit a data and safety monitoring plan to the sponsoring categorical Institute for approval
b. Protocols that are performed on the RCRII but are not funded by an NIH component are not required to have NCRR approval of the monitoring plan, however, such a monitoring plan must be included within the protocols proposed to the IRB and, subsequently, to the RCRII RCAC for approval

5. Overseeing, at the request of the RCRII PI, implementation of monitoring plans for any of the IRB-approved RCRII protocols irrespective of sponsorship
6. Assuring that RCRII studies are performed in accordance with the IRB-approved protocol and monitoring plan
7. Facilitating the reporting of Serious Adverse Events and Conflicts of Interest to the appropriate local committees and Federal agencies
8. Providing access to minutes of RCAC meetings that relate to the review of monitoring plans upon request of NCRR staff or site visit team members during the RCRII competing continuation process
9. Assuring that the RCRII investigators are appropriately trained to remain current on their regulatory and patient-safety responsibilities
10. Participating in other relevant activities, such as RCAC and IRB meetings, as determined by the RCRII PI

For all RCRII grantees, a request should be made for five years of support of the RSA position in the competing continuation application. If the research requires a data-safety monitoring board, the competitive request must include a section entitled Data and Safety Monitoring that describes the overall effort in data and safety monitoring of RCRII protocols and the activities of the RSAs.

The request for the RSA must be approved by the RCAC (with documentation of discussion and approval of the plan in the RCAC minutes) and specify:

Title of the position(s), e.g., Research Subjects Advocate, Clinical Advocate for Research, Data and Safety Monitor, et cetera
Degrees proposed for person(s) to be recruited for this position (e.g., M.D., Ph.D., R.N., Pharm.D.), and justification as to why persons with the proposed degree(s) are qualified to carry out the intended duties
FTEs proposed to be supported by the RCRII grant for this position (e.g., 0.25 FTE), and dollars requested for this support
Which of the divided tasks of the RSA position is to be the individual(s)'s responsibility
Justification for the requested level of support

The effort of the RSA(s) funded through the RCRII grant must be dedicated exclusively to RCRII activities. Thus, for example, if 25 percent of an institution's clinical research activity is conducted on the RCRII (and 75 percent outside of the RCRII), and the institution decides that a single full-time individual will fulfill RSA duties for both RCRII

and non-RCRII clinical research, then the RCRII grant will support only 25 percent of that individual's salary.

Nature and Scope

It is recognized that the nature and scope of the RCRII application may vary widely in different institutional settings. Each applicant institution must assess and address its own needs. The applicant must describe and justify how existing and requested resources will be utilized to implement the institutional plan to create and maintain an environment and framework suitable to achieve the objectives of the RCRII.

For example, support may be requested for a PD and staff, clinical research support staff, a biostatistician, a core laboratory with multipurpose research equipment, support for the development of up to three clinical protocols, and a faculty development component. Renovation of space devoted to clinical research and recruitment of faculty, i.e., a clinical investigator, is an additional option. Patient-care costs will be limited primarily to outpatients. Should inpatient care be necessary for short-term studies, collaborative arrangements may be pursued with more established clinical research centers. Alternatively, a limited number of scatter beds may be allowed for inpatient studies. The RCRII will not provide support for discrete patient care clinical research units.

Once the general approach for an RCRII has been determined, efforts can be focused on developing the specific research and research-related infrastructure necessary to implement the plan. While the RCRII is designed to allow maximum flexibility in requesting the types of clinical research resources required for accomplishing the RCRII goals at the applicant institution, it must be viewed as an essential and integrated component of other RCMI related activities such as the Comprehensive Centers on Health Disparities (CCHD), Clinical Research Education and Career Development (CRECD) award, and the Centers of Clinical research Excellence (CCRE). The most important criterion for inclusion of any component in the RCRII application is the extent to which the activity will enable the program to achieve its stated goals.

Elements which are considered key to a successful RCRII include:

Core Laboratories:
The primary functions of Core Laboratories are to provide sophisticated support to ongoing RCRII protocols and to develop or validate new methods. In addition, the laboratories may provide clinical research training for investigators. In all cases, it is imperative that requests for Core Laboratory support take into account the full range of existing NIH-supported facilities at the institution. Duplication of existing Core facilities will not be supported.

Core Laboratory requirements vary widely. Some RCRIIs may not need a full Core Laboratory; rather, only a small sample-processing area may be required. Laboratory

equipment, supplies, and personnel supported through the RCRII grant serve several investigative groups. Under special circumstances, a test for a single group of investigators may be supported if it is within the Core Laboratory's capabilities and is critical to conduct an investigation of high scientific merit and program relevance.
In general, routine tests, such as blood chemistries, hematologic determinations, and urinalyses, that are available in the hospital's clinical chemistry laboratories or in another Medicare-approved clinical chemistry laboratory are not performed in the RCRII Core Laboratory; rather, they are supported through ancillary funds unless the project involved is directly supported through the RCRII. However, such tests may be performed in the RCRII Core Laboratory when this is critically important for timeliness, when an extreme degree of accuracy is needed, or if patient safety is at stake. Cost sharing of Core Laboratory functions should be sought from funded investigators.

Core Laboratories may specialize in, but are not limited to, areas such as exercise physiology and body composition, mass spectrometry, magnetic resonance imaging, ultrasound, positron emission tomography, tissue culture, cell biology, molecular genetic analyses of DNA obtained from patient material, and cell and gene therapy.
Core Laboratories are encouraged to make their areas of specialized expertise available to other RCRIIs. Records of such services and collaborations should be kept, as they may be helpful in justifying continued support of the laboratory. See above regarding Program Income.

Core Laboratory research facilities should be within the boundaries of the RCRII or in a nearby location. A specimen processing area is often an essential part of the RCRII, even when no analytical Core Laboratory is required.

A Core Laboratory Director may supervise the Core Laboratory operations if the scope and sophistication of the laboratory procedures justify such a position; otherwise, the laboratory is supervised by the PD or Associate PD, often through a senior laboratory technician. A Core Laboratory Director is an individual with an advanced degree who may also provide training in sophisticated laboratory techniques to RCRII-based investigators, their laboratory personnel, junior faculty, or fellows. This position usually requires only a small fraction of an FTE. A larger portion of a Core Laboratory Director's time may be required in the initial establishment of complex laboratory procedures, with a smaller fraction of the Laboratory Director's time being required for routine laboratory activities. When there are multiple Core Laboratories with different functions (e.g., body composition core, mass spectrometry core), the RCRII grant may support a fraction of an FTE for the Director of each core.
b. Core Laboratory Personnel: The Core Laboratory staff must possess the expertise needed to provide reliable and accurate analyses required by RCRII research activities.
c. Quality Control and Confidentiality: The RCAC must assure that quality control and confidentiality are maintained in compliance with existing Federal and local requirements, such as the Clinical Laboratory Improvement Act. The RCAC is responsible for reviewing the Core and other resource Laboratories to ensure that

the activities are serving the research needs of a wide array of investigators, that laboratory tests are not routine, and that priorities are set for the use of the Laboratory when concurrent demands exceed the Laboratory's capacity. In all cases, NIH-supported investigations are to be given the highest priority.

Informatics Core:
A clinical investigator must be able to publish his/her scientific findings. This requires that data be 1.) collected accurately, 2.) monitored appropriately, 3.) secured, 4.) managed effectively, and 5.) accessible for analysis and reporting. The mission of the Informatics Core is to provide the information infrastructure necessary to accomplish this.

For an RCRII to be successful and efficient, information flow between the RCRII Cores must be both timely and accurate. The Informatics Core interacts with the other RCRII Cores, integrating the information needs of the Center. The Informatics Core should facilitate the secure and confidential sharing of scientific data between RCRIIs. The Informatics Core should provide leadership in exploring and implementing new technologies to stimulate and promote clinical research. The Informatics Core should provide education and training in the use of information technologies and research data management to the RCRII staff and research teams.

At institutions where there is an NIH-supported Informatics Core, the CRC must utilize that facility to the greatest extent possible. A separate Informatics Core will not be supported, although justified additions to the Core (personnel, software, and hardware) will be permitted. **However, the availability of a fully functional Informatics Core is a required component of an RCRII facility**.

The requirements of the Informatics Core will depend on both the specific needs of the RCRII and the existing institutional resources. In all cases, each Informatics Core should have a file server to comply with current and anticipated NCRR bioinformatics goals to communicate within and between RCRIIs. The file server should meet standards for the secure storage, archiving, management, and analysis of protocol data. A network should be in place to facilitate RCRII operations and investigations associated with all RCAC-approved studies. The Informatics Core should ensure that RCRII network facilities are accessible to all RCRII Core components and promote the adherence to data management standards. The Informatics Core also should provide or facilitate ongoing training and education in the use of its resources.

The RCAC is responsible for reviewing the Informatics Core activities to ensure that the research needs of a wide array of investigators are being served. The RCAC will prioritize the use of the Informatics Core resources when concurrent demands exceed capacity, with NIH-supported investigations being given the highest priority. Initiatives that may have a substantive impact on the Informatics Core should be presented to the RCAC for review and approval.

The Informatics Core Manager is responsible for its overall operation. Due to the evolving nature of information technology, the Informatics Core Manager should work closely with the PD to ensure that current technologies are employed to meet the RCRII's goals. The Informatics Core Manager should be competent to assist in the organization and analysis of research data and be familiar with the broad array of basic methods of data analyses. He/she must ensure that the tasks necessary to achieve the goals of the Informatics Core are implemented, including:

a. Work with RCRII investigators to further patient-oriented research.
b. Instruct RCRII staff and investigators in the use of Informatics Core resources.
c. Facilitate the dissemination of information within and outside of the RCRII.
d. Work with the biostatistical staff on RCRII-approved protocols.
e. Supervise network and data security to ensure the proper operation and maintenance of RCRII computer hardware and software.
f. Develop and maintain a strategic plan for the Informatics Core.
The minimum qualifications for the Informatics Core Manager include a Master's degree or formal training in research methods and 2 years of experience in application development or computer/network management.
Additional Informatics Core staff may be employed when needed to fulfill the goals of the Informatics Core.

The Informatics Core should be located in dedicated space on or adjacent to the RCRII. The physical facilities should include an Informatics Core Manager's office, a user/training room, and a secured room for the file server(s). The computer facilities should be configured for both local and remote access. Both hardware and software should be the focus of a rational renewal strategy to maintain and upgrade information technologies that meet the evolving needs of the investigators.

Biostatistician: The RCRII Biostatistician should hold a doctoral degree in biostatistics or statistics, or have comparable training and experience. The RCRII Biostatistician should have experience in the planning, design, and evaluation of clinical research. The RCRII Biostatistician reviews all protocols and is a voting member of the RCAC. The RCRII Biostatistician consults, and may collaborate, with investigators on study design, implementation, analysis, interpretation, and dissemination of results. He/she should develop new statistical methods as needed for specific projects and train clinical researchers in the principles of study design and analysis. Total support of up to 1.0 FTE will be provided to an RCRII for this individual or other biostatisticians working under his/her direction.

Administrative Support: The Administrative Director/Manager is a skilled specialist, responsible to the PD for the day-to-day management of RCRII administration, fiscal matters, and records of RCRII activities. He or she maintains the statistical and financial data needed by the grantee institution, the NCRR Office of Grants Management (OGM), and for inclusion in Annual Reports to NCRR. In the interest of RCRII efficiency, the PD

may delegate some administrative authority in non-scientific and non-healthcare delivery matters to the Administrative Director/Manager. AN RCRII may use the title "Administrative Director" or "Administrative Manager." If warranted by the size of the RCRII, a full- or part-time Administrative Assistant may be supported to perform duties related to RCRII operations, such as maintaining RCAC meeting records and consent forms. Administrative Assistants are not supported from RCRII funds to prepare renewal applications or to provide support for developing scientific publications for the PD or other investigators. In general, Facilities and Administrative (F&A) costs provided to an institution by the grant support clerical assistants who prepare grant applications and manuscripts for publication.

Nursing:

a. **Nurse Manager:** The Nurse Manager is responsible for the administrative organization of the RCRII nursing staff (cost-effective staff distribution), training, patient care delivery, and interaction with investigators to ensure that research projects are carried out as approved by the IRB and the RCAC.

b. The Nurse Manager should have a Bachelor of Science degree in Nursing, must be licensed within the state, and have staff privileges within the hospital where the RCRII is located. RCRIIs that have many complex projects or a large number of outpatient research visits may require an Associate Nurse Manager to assist in providing the research patient care needs. That individual should have an educational background and nursing experience comparable to that of the Nurse Manager of the RCRII.

b. Nursing Staff: The RCRII nursing staff should be trained to make complex research observations and perform precise collections of specimens, while providing exemplary patient care. The professional level and number of nursing personnel required for a RCRII are determined by the size of the unit, the number of research outpatient visits, and the complexity of the research and medical care performed on the RCRII. All nurses must be licensed and have staff privileges either at the hospital where the RCRII is located or at an off site location.

Data and Safety Monitoring Plans:

In 1998 and 2000, NIH issued policies on Data and Safety Monitoring for Clinical Trials. These policies, NIH Policy for Data and Safety Monitoring, and Further Guidance on a Data Safety and Monitoring For Phase I and Phase II Trials, provide NIH requirements for data and safety monitoring of clinical trials supported by NIH funds.

In addition, NCRR requires that all RCRII protocols, not just clinical trials, must have a DSM plan that has been approved by the RCAC. Based on an exemption from the Office of the Director of NIH, RCAC-approved protocols do not require additional approval by NCRR staff. However, RCAC approval does not supplant the required approval by staff at other NIH Institutes that support the research. Further, the NCRR requires that all protocols that place participants at significant risk must have an independent DSMB. The determination of significant risk is to be made by the local

RCAC. The charter (or list of the responsibilities, meeting frequency, etc.) and membership of any DSMB, as detailed in the NIH Guidances on Data and Safety Monitoring referenced above, must be included in the DSM plan of any protocol that includes a DSMB. The RCAC is to maintain a log of the minutes that relate to its review of the DSM plans. Those minutes may be reviewed by NCRR or other NIH program staff who are responsible for oversight of specific clinical trials conducted on the RCRII. In addition, RCRII program staff or members of the site-visit team may request access to the log during the competitive renewal process of the RCRII.

Patient Care Issues

Provisions for Medical Care:
1. General: All RCRII research subjects must receive optimal medical care. It is the responsibility of each PI to ensure that appropriate care is provided to patients participating in his or her research protocols. This responsibility may be discharged either personally, if the PI is a physician or dentist with the requisite expertise, or by a physician co-investigator, fellow, or resident who possesses the requisite clinical expertise and admitting privileges.

The qualifications and expertise of physicians or dentists who provide clinical care for research participants must meet institutional as well as applicable local guidelines and bylaws. RCAC review of protocols must include a determination that medical coverage for research subjects will be optimal. Plans for emergency coverage by licensed M.D.s and, where appropriate, for night care, must be formalized for each protocol, or for the entire RCRII.
2. Intercurrent Illnesses: The appropriate disposition of a patient who develops an illness during the course of study depends on the severity of the illness and its relationship to the research. The patient may be treated on the RCRII when the illness is unrelated to the research but is anticipated to be of short duration. If the intercurrent illness requires termination of the studies or their interruption for a substantial period, other arrangements for the patient's care should be made.

Reporting Serious Adverse Events (SAEs):
Federal regulations (45 CFR Part 46, Subpart A, i.e., the "Common Rule"), which are applicable to all RCRII studies, require reporting of "unanticipated problems" involving risks to participants to the IRB, the appropriate institutional officials, and the Federal Department or Agency head. In addition, for those studies regulated by the FDA (21 CFR 312.32), sponsors must notify the FDA and participating investigators of any adverse event associated with the use of test article that is "both serious and unexpected." In addition, the NIH has issued several policies and guidances related to adverse event reporting and serious adverse event reporting.
These include:
NIH Policy for Data and Safety Monitoring (http://grants.nih.gov/grants/guide/notice-files/not98-084.html);

Further Guidance on a Data Safety and Monitoring For Phase I and Phase II Trials (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html);
Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials (http://grants2.nih.gov/grants/guide/notice-files/not99-107.html); and
Notice to NIH Grantees/Contractors Regarding Letters or Notices from the Food and Drug Administration (FDA) (http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-00-053.html).
In addition, whenever a gene transfer protocol conducted on the RCRII results in a report to the FDA of a serious unexpected adverse event or a report to the IRB of an unanticipated problem involving risks to subjects or others, a copy of that report should be sent at the same time to: the Office of Biotechnology Activities, NIH; NCRR's DRI; and the categorical NIH Institute (e.g., NCI, NIAID) supporting the study. In all such SAE reports to NIH, no names or other patient-identifiable material should be included.

Clinical Research Infrastructure

The aforementioned flexibility notwithstanding, the major focus of RCRII funding is for institutional resource development, i.e., clinical research infrastructure. In most instances, at least two-thirds of the requested funds is expected to be directed to multi-user resources, rather than for support of clinical protocols and collaborative research projects. The RCRII is not intended to duplicate or supplant funding from the wide array of programs currently available for support of specific investigator-initiated research projects.

Institutional Requirements

The institution must ensure that each clinical faculty member involved in this initiative will be provided the necessary time for conducting specific clinical research protocols. It is anticipated that these protocols will enable faculty to address specific clinical research questions that will lead to publishable data in refereed journals and enable faculty to seek independent research support.

The institution must also provide written certification in the application that appropriate space has been identified for the clinical research center, as well as space to house major research equipment or other shared resources. This space must be in a facility accredited as a hospital by the Joint Commission on Accreditation of Health Care Organizations (JCAHCO). Accreditation is an absolute requirement; however, rental of space in a JCAHCO-approved hospital might be an option until approval is obtained for the designated clinical research center.

Coordination and Collaboration

There must be coordination of resources provided through the RCRII with the RCMI-supported activities at the grantee institution. Institutions that hold CRECD Awards must present plans for developing the graduates of this programs into successful clinical investigators. Collaboration with investigators involved in NCRR-supported programs such as CCHDs and CCREs is required. Collaborations between basic and clinical scientists are strongly encouraged, and utilization of NCRR supported Core facilities is considered essential.

The establishment of collaborative agreements for the conduct of clinical investigations with more clinical research-intensive institutions, such as those with NCRR's General Clinical Research Centers or other clinical research centers, is strongly encouraged and may be essential in some cases to maximize the impact of the RCRII.
Program plans for enhancement of clinical research capacity must be consistent with the long-range goals of the applicant institution and must include an evaluation component to determine the extent to which the program goals are being achieved.

UP-TO-DATE INFORMATION

All applicants and grantees must ensure they have the latest information about the RCRII Program and its policies and procedures by visiting the RCRII Web page at http://www.ncrr.nih.gov/resinfra/ri_rcrii.asp .

APPLICATION PROCEDURES

GENERAL INFORMATION

It is important to communicate with RCRII Program staff early in the planning process to ensure that both national Program goals and institutional goals are being addressed appropriately in the proposed approach for expanding clinical research capacity. In addition, successful applicants have found it useful to maintain communication with RCMI/RCRII Program staff throughout the application development process. A request for Program staff review and comment on a near-final draft of the entire proposal, at least two months prior to formal submission of the application, is encouraged.

It is important for applicants to seek constructive evaluations from peers of each clinical research-related RCRII activity for which funds are sought, i.e., from established clinical scientists in the respective disciplines involved. These critiques of draft proposals, which may be obtained simultaneously with Program staff feedback, have proven invaluable to many successful applicants.

The RCAC must be an integral part of the planning and development process, which should begin with a self-assessment of the institution's current status in terms of its clinical research capabilities.

Once existing resources and competencies have been identified, a general approach can be formulated to move the institution to a higher level of competitive clinical research capability, in concert with the national RCRII goals. It is critically important to keep in mind that to be a meaningful and successful effort, the approach chosen must contribute to and be synergistic with the overall mission and long-range plans of the institution.

The general plan must be realistic; i.e., it must be achievable within a prescribed time frame and convincing as a logical approach to expand clinical research capability at the applicant institution, taking into account the institution's previous track record in these areas and its current developmental status. Communication with RCMI/RCRII Program staff, directors of successful programs at similar institutions, and scientific leaders in the clinical research areas of interest may be very useful to the RCAC and to institutional officials in formulating a workable plan.

SPECIFIC REQUIREMENTS

Applicants must use the *Application for a Public Health Service Grant*, form PHS 398 (Rev. 09/2004), following standard instructions except where modified according to the RCRII section of the Appendix to these Program Guidelines: Supplemental Instructions for the PHS 398 Grant Application - RCRII. Updated instructions for form PHS 398 may be viewed at http://grants1.nih.gov/grants/forms.htm .

Applicants must also review the **General Information for DRI Applicants and Grantees** section of these Guidelines for other important information.

In addition, it is important to emphasize that a critical component of all competing continuation and supplemental applications is an assessment of the impact of RCRII grant funds in the following areas:

Institutional clinical research development
Organizational and administrative improvements
Clinical research environment
Clinical research infrastructure
Clinical faculty development and achievement
Clinical research productivity

Baseline information on all elements of the criteria identified to measure progress and program impact is necessary and must be included in the initial application for RCRII support. Institutional officials and the RCAC need to ensure that all of these elements are addressed in the monitoring and evaluation process, so that appropriate information is available for annual progress reports, periodic review of program accomplishments, and guidance for improving program performance. These categories are described in further detail in the supplemental instructions.

SUGGESTED STEPS IN PLANNING AN RCRII APPLICATION

Start by thoroughly reviewing this document 12 to 18 months before target submission date. Communicate with RCMI/RCRII Program staff as soon as there is interest in applying
Establish a Clinical Research Advisory Committee to utilize throughout the planning process
Conduct a self-assessment to determine the current status of clinical research resources (physical, human, and financial) at the institution; communicate with directors of other clinical research centers and scientific leaders in the areas to be developed for further insight and suggestions
Develop a brief concept paper outlining the corporate plan to move to a more competitive level in clinical research within the proposed period of RCRII support
Communicate with RCMI/RCRII Program staff at this stage to review the nature and scope of the overall plan, preferably 8 to 12 months before submission
Develop specific components as needed to implement the plan, focusing on infrastructure development; seek critiques from peer-reviewers for each activity to facilitate elimination of weak components and to strengthen others
Consider appropriate inclusion of Gender and Minorities and Children as noted in the Instructions for the *Application for a Public Health Service Grant*, form PHS 398 (Rev. 09/2004)
Provide a near final draft of the entire application to RCMI/RCRII Program staff for review and comment two months before submission; simultaneously, obtain additional feedback from established scientists on specific components
Submit the application by the deadline (see **Receipt, Review, and Award Cycles**, below)

REVIEW CONSIDERATIONS

REVIEW CRITERIA

The primary criterion for the evaluation of an RCRII grant application will be the direct impact that the proposed program will have on enhancement of the clinical research program of the applicant institution. The impact will be measured in terms of the merit of the specific plan for achieving the overall program goals identified by the institution. The value of each component will be determined by the extent to which that activity will contribute to the stated RCRII goals.

Major Factors

Major factors to be considered in the overall evaluation of the application include:

Adequacy of the planning process, including self-assessment of current clinical research capabilities, concept development, and involvement of advisory resources

Appropriateness of institutional RCRII goals, including plans for reasonable expansion of clinical research capacity within the time frame proposed and for sustaining this enhanced capacity beyond the period of grant support; an appreciation of the uniqueness of the institution and its current capacity to pursue clinical research is critical to this assessment
Appropriateness of the organizational and administrative structure established to accomplish RCRII goals
Qualifications, experience, and commitment of the PD, and his/her ability to provide effective leadership in implementing the institutional RCRII plan
Appropriateness of the RCAC and other consultative resources for guiding the RCRII
Adequacy of institutional commitment to clinical research
Appropriateness and adequacy of the institution's evaluation plan
Appropriateness of requested budget and proposed project period
Scientific merit of clinical protocol developmental projects, qualifications of the investigators to conduct the research, and their potential for career development
Diversity in staff – gender, race/ethnicity, academic rank
Explicit attention to human subjects protection and appropriate inclusion of women, minorities and children as noted on pages 19-27 and 45-47 of the Instructions for the *Application for a Public Health Service Grant*, form PHS 398 (Rev. 09/2004).

The institution's track record and success in carrying out previous institutional goals for its RCRII is a critical and essential element of the review of competing continuation and supplemental applications. Specific measures to be used to evaluate progress are listed under **Evaluation Plan**, below.

Institutional and Administrative Plan

The adequacy of the planning process, including self-assessment of current biomedical research capabilities, budgeting, concept development, and involvement of advisory committees are major factors that will be considered in the overall evaluation of the application.

Description of the Institution

The progress of the institution in achieving the goals of its RCRII program during the funding period (usually five years) will be evaluated. For new applications, history that is relevant to the proposed RCRII, as well as a detailed and thorough description of the current status of the institution's clinical research infrastructure, capabilities and activities, and a self-evaluation, will be expected. The following factors will be evaluated:

Specific examples of how these goals were achieved and how they enhanced clinical research-related activities and institutional developments
If previous goals were not fully achieved, specific examples of the shortcomings and how they affected progress of institutional development

The quality and number of new clinical research faculty recruited
The strengthening and enhancement of institutional research support services
Institutional incentives and support for clinical research development
Research productivity as measured by the number and quality of peer-reviewed publications, scientific presentations, and successful grant applications
For amended applications, response of the submitted application to the previous critiques

General Plan for Expanding Clinical Research Capabilities

All aspects of planning and goal-setting for the RCRII will be evaluated, including:

Identification and prioritization of major clinical research development areas
Adequacy of the planning process and self-assessment of current clinical research capabilities
Appropriateness of future institutional RCRII goals, including plans for reasonable expansion of clinical research capacity within the time frame proposed and for sustaining this enhanced capacity beyond the period of the grant support
Plans and timeline for transitioning to a GCRC or other clinical research center
Adequacy of institutional commitment to clinical research and appropriateness of an institutional evaluation plan
Consistency of long-term goals with enhancement of clinical research and how the evaluation component of the program is functioning
Organizational structure and administration of the program

Organizational and Administrative Structure

Appropriateness of the organizational and administrative structure; institutional commitment to clinical research and to the RCRII; and the qualifications, experience and commitment of the PD will be evaluated, using the following criteria:

Organizational changes, if any, designed to enhance clinical research activities
Rationale and need for these resources to achieve institutional RCRII goals, including the potential for developing high-quality research programs
Adequacy and appropriateness of administrative leadership for implementing and managing the resources, including collaborative and consultative arrangements
Appropriateness of the plan for the resources, including objectives, implementation strategy and timetable, and involvement of the RCAC
Appropriateness and effectiveness of the organizational and administrative structure and lines of authority within the Center
The qualifications and experience of the PD and his/her ability to provide effective leadership in implementing the institutional RCRII plan

Clinical Research Advisory Committee

Appropriateness of the Clinical Research Advisory Committee (RCAC) and other consultative resources for guiding the RCRII. As noted earlier, the RCAC must be composed of two subcommittees, external and internal. The RCAC will be evaluated using the following criteria:

The appropriateness of the composition of the RCAC for providing the needed guidance for the RCRII
The degree of involvement and appropriateness of the external subcommittee members' scientific and administrative expertise
The role of the internal subcommittee in the review of developmental/collaborative research projects, including the involvement of women, minorities, and children in clinical studies
The Committee's role in developing the RCRII center grant application and other RCRII-related grant applications

Budgets

Appropriateness of requested budget and proposed project period will be scrutinized. A complete and detailed budget and budget justification is necessary for each subsection of the application and must be in agreement with the Overall Summary Budget.

Evaluation Plan

Appropriateness and adequacy of the institution's plan for evaluation of both short-term and long-term goals of the RCRII and the relevance of these goals to the mission of the institution will be evaluated. The inclusion of adequate evaluation parameters, mechanisms, and timetables will be assessed.

Baseline data must be included in new applications. Data demonstrating program impact must be included in all subsequent applications. The application should address:

Plans for Institutional Development measured by
- number and quality of clinical research faculty
- plans for further development of clinical research faculty, including appropriate mentoring plans and time commitments for junior faculty
- number of graduate degrees awarded in the health sciences
- enhancement of institutional incentives and support for clinical research development
- strengthening/enhancement of institutional clinical research support services
- number of postdoctoral fellows and research associates at the institution involved in clinical research

Organizational and Administrative Improvements measured by
- major organizational changes that enhanced clinical research

increased proficiency for grants and contracts management

Improvement of the Clinical Research Environment measured by
hiring of skilled technical personnel
development of new or enhanced clinical research capabilities (give examples)
number and quality of scientific seminars and colloquia sponsored by the institution
number of visiting scientists, nature of interactions, and benefits gained

Improvement of the Clinical Research Infrastructure measured by
improvements and expansion of the facilities dedicated to clinical research
acquisition and utilization of major instrumentation

Clinical Research Faculty Development and Achievement measured by
scientific honors and awards to faculty
number of grant applications submitted for peer-review and number funded
participation in peer-review activities
election to national and international professional societies
participation of faculty members in peer-review activities outside of the institution
involvement in planning national and international scientific meetings

Clinical Research Productivity measured by
number of peer-reviewed faculty publications
number of presentations at major scientific meetings

number and amount of research grants and contracts received
number and nature of active collaborative research activities

Clinical Research/Research-Related Activities

Assessments of infrastructure components are not based solely on specific evaluations of individual scientific protocols, but rather on a broader analysis of the feasibility of achieving what is proposed with the resources requested.

In addition, it must be recognized that for a developmental program, a major activity may be implemented at any time during a five-year project period, not only in the first year or two as might be expected for a specific research project. Therefore, the inclusion of requests for facilities, major equipment and/or additional faculty in year three or year four (for example) may be justifiable, provided that the application adequately describes unmet needs, and plans for the future use of the resource that are consistent with the institutional plan.

Infrastructure Components and Core Laboratories

Major factors to be considered in the evaluation of infrastructure components and core laboratories include:

Rationale and need for these resources to achieve institutional RCRII goals, including the potential for developing high-quality clinical research programs
The facility's importance to the clinical research of the faculty, both RCRII-supported pilot clinical protocol developmental projects and other Center faculty
Description of existing NIH-supported facilities relevant to clinical research
The number and qualifications of investigators utilizing the core facility, and the number of projects or protocols that utilize the core facility, including the demonstrated need for current or requested equipment; the existence of a user community (current and/or projected) is critical
Adequacy and appropriateness of administrative and scientific leadership for implementing and managing the resources, including collaborative and consultative arrangements
The qualifications of the director of the core facility
Appropriateness of the plan for the resource, including objectives, implementation strategy and timetable, and involvement of the RCAC
Reasonableness of plans to institutionalize support for the resources over time
For competing continuation and supplemental requests, the assessment of progress toward original goals for the infrastructure component is an essential element in the review

Clinical Protocol Development Projects

Major factors to be considered in the evaluation of clinical protocol developmental projects include:

Significance and relevance of proposed protocol
Potential of the protocol to advance the concepts or methods that drive the field, and scientific knowledge in general
Approach, including appropriateness of research plan, specific aims, experimental design, methodology, consideration of alternatives, data analysis, scope, and timetable
Innovation is a significant consideration in some, although not all, types of protocols; innovation is characterized by novel concepts, approaches, or methods, original and innovative aims, development of new methodologies, or paradigms challenged
Investigator training and qualifications, and in the case of junior investigators, mentoring plans
Environment in which the clinical protocol will be performed, adequacy of resources, availability of any specialized facilities needed, institutional support for the protocol, and degree to which the clinical research takes advantage of any

unique features of the scientific environment or employs useful collaborative arrangements
Relevance of proposed project to the institutional plan for expansion of clinical research capacity and enhanced opportunities for collaboration
Explicit attention to human subjects protection and appropriate inclusion of women, minorities and children as noted on pages 19-27and 45-47 of the Instructions for the *Application for a Public Health Service Grant*, form PHS 398 (Rev. 05/2001).

AWARD CRITERIA

The Principal Investigator will be notified of the Council's recommendation shortly after it meets. Award decisions will be based on the technical merit of the application as determined by peer-review, amounts recommended through the peer-review process, other programmatic priorities to ensure a balance among the various types of programs, populations served, and/or geographic distribution. Grant awards are subject to availability of funds.

Support of an application for competing continuation of an RCRII for an additional project period will be contingent upon the outcome of peer and Council review, and the availability of funds.

REPORTING/MONITORING

The following material supplements the **General Information for DRI Applicants and Grantees** section of these Guidelines.

ANNUAL REPORTS

A Non-Competing Grant Progress Report (NIH form 2590) is required annually as part of the non-competing continuation award process, as described in the NIH Grants Policy Statement, http://grants1.nih.gov/grants/policy/nihgps_2003/index.htm. Instructions for the NIH form 2590 can be found at: http://grants.nih.gov/grants/funding/2590/2590.htm. For NCRR-supported Center and Resource grants, the PHS form 2590 incorporates an Annual Progress Report (APR), which provides information in greater detail than the standard NIH form 2590. The NCRR uses the information contained in the APR to facilitate programmatic stewardship of the grant and to respond to inquiries from other governmental agencies and the public. Specific instructions for completing an APR and including it with the NIH form 2590 can be found at http://aprsis.ncrr.nih.gov.

Technical questions about the APR should be directed to the APR System staff at ncrraprsis@mail.nih.gov <mailto:ncrraprsis@mail.nih.gov> or 301-435-0866.

Additional information or non-technical questions either about the PHS 2590 or the APR should be directed to Dr. Maureen Beanan<mailto:benanm @mail.nih.gov> or 301-435-0788.

Investigators in their final year of funding that submitted or intend to submit a competitive continuation application need only submit the APR.

Credit on Publications:

All publications resulting from the use of RCRII facilities must cite/acknowledge NCRR support. A suggested acknowledgment and disclaimer follow:

"This publication was made possible by NIH Grant Number RR-[insert grant number] from the [insert name of DRI program] Program of the National Center for Research Resources." or "The project described was supported by NIH Grant Number RR-[insert grant number] from the [insert name of DRI program] Program of the National Center for Research Resources." and, as appropriate, "Its contents are solely the responsibility of the authors and do not necessarily represent the official views of NIH."

OTHER EVALUATIVE MECHANISMS

Midway through the project period (at the end of the third year of a five-year RCRII project period, for example), or as deemed necessary by NIH staff, site visits may be conducted to assess the progress of the grantee institution's RCRII and to estimate the future impact that can be expected from continuing RCRII support.

Alternatively, grantees may benefit significantly by conducting their own mid-course assessment, utilizing RCAC external members and other reviewers appropriate for this type of evaluation. These analyses may lead to mid-course adjustments and a better informed basis for future plans. DRI must approve any changes recommended.

In addition, administrative visits by NIH staff will be arranged when indicated to facilitate achievement of both institutional and national RCRII goals.

INQUIRIES

Written and telephone inquiries concerning the RCRII Program are strongly encouraged, especially during the planning phase of the application. Please contact the NCRR staff listed below.

Maureen Beanan, Ph.D.
Division of Research Infrastructure

National Center for Research Resources
One Democracy Plaza
Room
926
Bethesda, MD 20892-4874 (Use 20817 for courier deliveries)
301-435-0961
FAX 301-480-3770
beananm@mail.nih.gov