

# NIH GUIDE

# for GRANTS and CONTRACTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Vol. 11, No. 8, July 16, 1982

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### HAVE YOU MOVED?

*If your present address differs from that shown on the address label, please send your new address to: Grants and Contract Guide Distribution Center, National Institutes of Health, Room B3B10, Building 31, Bethesda, Maryland 20205, and attach your address label to your letter. Prompt notice of your change of address will prevent your name from being removed from our mailing list.*

*The GUIDE is published at irregular intervals to announce scientific initiatives and to provide policy and administrative information to individuals and organizations who need to be kept informed of opportunities, requirements, and changes in grants and contracts activities administered by the National Institutes of Health.*

*Two types of supplements are published by the respective awarding units. Those printed on yellow paper concern contracts: solicitations of sources and announcement of availability of requests for proposals. Those printed on blue paper concern invitations for grant applications in well-defined scientific areas to accomplish specific program purposes.*

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NOTICE

MISCONDUCT IN SCIENCE

The NIH currently is reviewing - and when necessary, refining - its procedures related to instances of real or apparent misconduct that occasionally arise in association with its programs. Included under the rubric "misconduct" are (1) mismanagement of funds, (2) fraudulent or markedly irregular practices in carrying out research procedures or handling research results, (3) serious failures to comply with requirements governing the protection of human subjects and the welfare of laboratory animals, and (4) serious failures to comply with any other conditions of an award such as the guidelines for research with recombinant DNA molecules. The purpose of these new procedures is to ensure, as far as possible, that NIH actions with respect to instances of real or apparent misconduct will serve to protect the public interest with due regard for the rights of individuals and institutions accused of wrongdoing. The following topics are being reviewed:

- o detection of real or apparent problems
- o determination of whether a real problem exists
- o imposition of temporary sanctions or other interim actions prior to completion of an investigation
- o investigation of problems
- o administrative action following completion of an investigation

Specific proposals to improve procedures are being developed by groups of NIH staff, including representatives of all awarding units and investigative offices, as well as representatives from PHS agencies with similar concerns. The process now underway includes opportunities for comments and suggestions from representatives of awardee institutions and advisory groups. This topic was discussed at the meetings of initial review group chairpersons in February and with the Director's Advisory Committee in March of this year. Discussions were also held during the May-June meetings of National Advisory Councils/Boards and will be continued as needed.

It is expected that several products will emerge from these efforts, including more explicit policy and procedural guidance to assist NIH staff in handling allegations of misconduct and dealing with instances of known improprieties in NIH research programs. Also underway are efforts to define more explicitly the responsibilities of awardee institutions to protect the integrity of federal funds, and the rights of participants in research (including human and animal subjects).

NIH welcomes comments and suggestions from the research community, particularly regarding the relationship of NIH procedures to institutional practices and individual investigators. Among the policy issues being considered are the following:

1. How can the NIH most appropriately work to ensure that its staff and awardees are highly sensitive to - and take necessary action in response to - instances of real or apparent misconduct in association with NIH programs?
2. How can the NIH best assess and promote compliance with the conditions of its awards?
3. What are the specific reporting responsibilities of awardee institutions when

misconduct involving an NIH award is known or suspected?

4. What sanctions are most appropriate for various types of misconduct, and how should they be imposed?

Please address any comments or suggestions to:

Dr. William F. Raub  
Associate Director for Extramural  
Research and Training  
National Institutes of Health  
Building 1 - Room 107  
Bethesda, Maryland 20205

NOTICE

HUMAN SUBJECTS IN RESEARCH PROPOSALS

**DIVISION OF RESEARCH GRANTS**

Applications submitted to the Division of Research Grants, National Institutes of Health (NIH), which involve human subjects are considered incomplete for initial review without an appropriately completed form HHS 596 (certification/assurance/declaration). It is requested that this form be submitted with the application, but if extenuating circumstances require a delayed submission, applicants should forward the form to the assigned review committee as designated on the post card advising applicants of the assignment of the application. Do not forward to other units of the NIH.

In addition, applications are considered incomplete without the detailed information requested under the section entitled "Research Plan" in the instructions having to do with human subjects.

NIH has no obligation either to accept or to review applications which are considered incomplete. On this basis, applicants are urged to give careful attention to the instructions for use of the "398 kit" to prevent either a return of the application or a deferral in the review.

## NOTICE

### Enforcement of Page Limitations on Grant Applications

The PHS 398 grant application kit has specific instructions on page limitations for certain parts of an application. The biographical sketch is limited to two pages. In the Research Plan, the "Specific Aims" section is not to exceed one page, the "Significance" section is not to exceed three pages, and the "Progress Report/Preliminary Studies" section is not to exceed eight pages (excluding the lists of professional personnel and publications and the appendix).

Over the past two years, the NIH has given the scientific community an opportunity to become accustomed to these page limitations, but the increasing workload now necessitates a firm stance. Starting with the October 1, 1982 receipt date, applications that exceed the above page limitations without the required brief explanation will be returned.

### Please Conserve PHS 398 Forms

Each year the NIH distributes about 100,000 PHS 398 grant application kits, but only about 27,000 of these are returned as submitted applications. We don't know what happens to the other kits. We do know that each kit is expensive to print and mail, and that any funds saved by not wasting applications could be used elsewhere in the NIH system. In order to conserve forms and reduce costs, please follow these guidelines:

For applicant organizations:

- o Be sure the staff in your application control office maintain a tighter control over the distribution of the application kits.

For investigators:

- o If you have extra PHS 398 grant application kits, don't save them or throw them away. Give them to colleagues to use or return them to your institution's application control office.
- o When you need an application form, don't automatically phone the NIH. Check with your institution's application control office, for these offices have been sent copies of the PHS 398 kits in bulk for your use.

NOTICE

**NOTIFICATION OF CHANGE IN LEVEL OF EFFORT OF  
PRINCIPAL INVESTIGATOR OF NIH OR  
ADAMHA SUPPORTED GRANTS**

Principal Investigators and grantee institutions are reminded that it is the responsibility of both the Principal Investigator and the institution to keep the awarding unit fully informed of all changes that significantly affect the performance of grant-supported research, or create the presumption of such effect. A grant is awarded on the basis of certain commitments by the Principal Investigator and the applicant institution, as described in the application for support. When these commitments change, the awarding unit needs to be informed.

The current "biological revolution" with its attendant commercial interest in biological research has resulted in new relationships between universities and industry and between individual investigators and industry. As these relationships develop, there may be an impact on a particular investigator's research supported by NIH or ADAMHA.

The following are examples of the kinds of situations which can be occasioned by a shifting relationship with industry and which should be brought to the attention of the awarding unit:

1. Significant change in effort devoted to a grant by a Principal Investigator, including absence of a Principal Investigator for major portions of time, even if any one period of absence does not extend beyond three months.
2. Change in the employment status of a Principal Investigator such as leave without pay, or conversion from full-time to part-time employment.
3. Significant change in location of the facilities where the research will be conducted such that the conduct of the research might be affected.
4. Wide geographic separation of Principal Investigator's main locus of activity from the site where grant-supported research is to be conducted.
5. Major involvement of a Principal Investigator with a profit-making organization (other than the usual one-day-a-week consulting arrangements).

NOTICE

**MEETING ON CLINICAL TRIAL OF BLOOD GLUCOSE CONTROL AND  
EARLY VASCULAR COMPLICATIONS OF INSULIN DEPENDENT DIABETES**

The National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, NIH, is planning a meeting to explore private sector interests in the recently initiated, federally-supported multicenter clinical trial to assess the relationship between blood glucose control and development of the early vascular complications of insulin-dependent diabetes. The objective of this meeting will be to describe the study protocol and to discuss the purpose and scope of the trial. In addition to NIADDK staff members, the Chairman of the Steering Committee will be present to represent the participating investigators. Time will be available for questions and discussion.

The meeting will be held on July 28, 1982, at the NIH in Bethesda, Maryland. The NIADDK is seeking to identify parties interested in attending this meeting who have not already learned of the meeting through other sources. Questions should be directed to:

Carolyn Siebert, MPH  
Clinical Trials Coordinator  
Division of Diabetes, Endocrinology,  
and Metabolic Diseases  
National Institute of Arthritis, Diabetes,  
and Digestive and Kidney Diseases  
National Institutes of Health  
Westwood Building - Room 607  
Bethesda, Maryland 20205

Telephone: (301) 496-7645



DECREASE IN PRICE OF AGED FISCHER 344 RATS

NATIONAL INSTITUTE ON AGING

Investigators currently using Fischer 344 rats from the National Institute on Aging (NIA) contract-supported colony are hereby notified that a decrease in the price of F344 rats will become effective July 1, 1982. Investigators on new and renewal applications should use the new cost figures in estimating cost needs on grant applications.

In order to regain part of the cost of the contract, users are currently being charged a price equal to \$3.44 for virgin male or female rats and \$4.84 for retired breeder rats, plus the product of a monthly maintenance charge (\$3.64) and the number of months the rats reside in the colony (age in months - 1 for virgins, age in months - 9 for retired breeders).

Effective July 1, 1982, the acquisition costs will increase to \$3.82 for virgin F344's and to \$5.39 for retired breeders. The monthly maintenance charge will decrease to \$2.40. Thus a 20 month old virgin F344 rat will cost \$49.42 and a 20 month old retired breeder F344 will cost \$31.79.

The acquisition costs are expected to remain at \$3.82 and \$5.39 through May 1985. Monthly maintenance charges will increase to \$2.80 on June 1, 1983 and to \$3.00 on June 1, 1984.

For additional information about prices, availability, or colony characteristics please contact:

Dr. Richard L. Sprott  
or  
Mrs. Jane Soban  
Animal Models Program  
National Institute on Aging  
National Institutes of Health  
Building 31 - Room 5C19  
Bethesda, Maryland 20205

NOTICENONHUMAN PRIMATES AVAILABLE

The National Institutes of Health (NIH) is reducing its colony inventory of Macaca mulatta (rhesus) monkeys. All requests should be in letter form and include the title or a brief description of the project, as well as specifications for the animals (number, age, sex and other special characteristics). Prices range from \$750 - \$1,200 each, and includes shipping within the continental United States. Prices are negotiable for groups of 50 or more. Availability is subject to prior sale. Commercial and foreign inquiries are invited. Contact:

Dr. Carl E. Miller  
National Institutes of Health  
Building 31 - Room 5B59  
Bethesda, Maryland 20205

Telephone: (301) 496-5175

The following animals are available.

<u>Year of Birth</u>		<u>Female</u>	<u>Number</u>	<u>Male</u>
1982	over	100		over 100
1981		134		80
1980		116		14
1979		78		9
1978		25		2
1977		14		9
1976		0		4
1975		15		2
1974		43		5
1973		141		10
1972		186		7

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1971	135	15
1970	48	9
1969	8	17
1968 and earlier	25	30

**REQUEST FOR RESEARCH GRANT APPLICATIONS:****RFA-NIH-NIDR-NCP-82-2****FLUORIDE AND THE PREVENTION OF ROOT SURFACE CARIES****NATIONAL INSTITUTE OF DENTAL RESEARCH**

Application Receipt Date: October 15, 1982

The National Caries Program (NCP) of the National Institute of Dental Research (NIDR) invites research applications for support of studies to investigate the effects of fluoride in the prevention of root surface caries.

Most of the research into the epidemiology, etiology, prevention and treatment of caries has focused on coronal lesions. Very little is known about the root caries process and factors which may prevent or inhibit the destruction of root surfaces. Epidemiologic surveys have shown that the incidence and prevalence of root surface caries is increasing in the U.S. population and that it is becoming a serious public health problem. The etiology of root caries is not fully understood; factors such as diet, salivary properties and rate of flow and the bacterial flora in the mouth are believed to play an important role in the disease process. Root caries is generally associated with gingival recession and advancing age.

Fluoride is an effective agent in the control and prevention of coronal decay. Clinical trials with school-aged children have shown that when fluoride is administered systemically or topically, the incidence of coronal decay is markedly reduced. In addition, life-long adult residents in communities with fluoridated water systems experience fewer carious lesions than those living in non-fluoridated areas. Evidence suggests that fluoride may also be effective against root surface decay. Studies, however, need to be undertaken to establish the effects of fluoride on cementum and its interactions with bacteria believed to be responsible for the destruction of cemental tissue.

**I. BACKGROUND INFORMATION**

The extent of the population affected with root surface lesions has not been established. However, epidemiologic surveys have shown that it presents a significant health problem in the United States. A study of elderly residents in a hospital for the chronically ill showed that almost 75 percent were affected. Studies on two younger populations, aged 30 to 59 years, consisting of military personnel and their dependents and patients in a Veterans Administration Hospital

This program is described in the Catalog of Federal Domestic Assistance, Caries Research, 13.840. Awards will be made under the authority of the Public Health Service Act, Title III, Section 301 (Public Law 78-410, as amended; 42 USC 241) and administered under PHS grant policies and Federal Regulation 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to requirements of OMB circular A-95 or Health Systems Agency review.

showed that about half of the subjects had root surface lesions. An examination of a civilian population between the ages of 18 and 82 years showed that a similar percentage were affected.

Dissolution of both enamel and cementum is accomplished by bacterial acids produced from fermentable carbohydrates. Because of the different caries sites, it has been suggested that there is a unique bacterial flora responsible for each type of caries. However, while certain bacteria have consistently been identified in the progression of coronal caries, there is no clear indication that a unique bacterial flora exists in the case of root caries. Furthermore, bacteria present in enamel caries may also be found in cemental lesions.

Studies have shown that fluoride is an effective agent in the prevention of enamel caries. There is also some evidence that fluoridation of drinking water may reduce the incidence of cemental surface lesions. A comparison of lifelong residents in fluoridated and nonfluoridated communities showed that the percentage of subjects with root surface caries was lower in the fluoridated community.

The cariostatic mechanism of action of fluoride is generally thought to be twofold: (1) an inhibition of the bacterial production of acid; and (2) an increased resistance of enamel to attack and stimulate remineralization of early lesions.

The antibacterial effect of fluoride is related to a number of cellular reactions, not all of which are currently understood. It has been established that fluoride has the ability to bind with components of a number of bacteria found in coronal and root surface plaque and that it interferes with certain metabolic processes within the bacterial cell. For example, studies which have examined the effect of fluoride on streptococci have found that it acts as an inhibitor of enzymes, such as enolase and phosphoglucomutase, which are involved in glycolysis and acid production. Inhibition of the enzyme enolase may also reduce the ability of the cell to transport sucrose into the cell and to synthesize peptidoglycan, a structural component of the bacterial cell wall. Some evidence is available which shows that fluoride may reduce the ability of bacteria to survive in an acidic environment. It is suspected that fluoride may increase the permeability of the cell membrane to acid, decreasing the cytoplasmic pH and reducing the glycolytic activity of the bacteria.

Fluoride affects the crystalline structure of enamel and makes it more resistant to decay. It has also been observed that fluoride promotes the remineralization of partially demineralized enamel and may stimulate repair of incipient carious lesions. Hydroxyapatite, the major inorganic material of enamel, is converted into fluorapatite, which has a lower solubility rate in the presence of acid. Cementum also has been shown to contain hydroxyapatite. Furthermore, it appears that the caries process affects cementum and enamel in a similar manner in that the subsurface is decalcified before the surface layer.

On the basis of what is known about the effectiveness of fluoride in preventing enamel surface lesions, the variety of oral pathogens sensitive to fluoride, the histological and environmental similarities of enamel and cementum as well as the apparent similarities in the caries process in both tissues, it seems reasonable to presume that the preventive aspects of fluoride on enamel will also apply to cementum.

The increasing life span of the U.S. population coupled with the decreasing prevalence of coronal caries will result in a significant increase in the number of root surfaces at risk to decay, making the problem an urgent one at this time. Therefore, it is proposed that the effect of fluoride on cementum and on the bacteria associated with cemental lesions be investigated.

Individual research grant applications are invited for research on this topic. Initially, there will be a single competition with an application receipt date of October 15, 1982; this RFA may be re-issued at a later date.

## II. RESEARCH GOALS AND SCOPE

The purpose of this RFA is to solicit high quality research grant applications that would contribute to the understanding of the effect of fluoride on the mineralization, demineralization and remineralization of artificially or naturally induced incipient lesions on root surfaces and elucidate the anticariogenic effects of fluoride on the bacteria associated with this process.

The choice of research objectives, identification of specific aims, development of appropriate protocols and methodologies, and the procedures for analysis and interpretation of data are left to the investigator's initiative. However, once an award is made under this program, any substantial modification of the research originally proposed must be mutually agreed upon by the investigator and the NCP.

## III. MECHANISM OF SUPPORT

The support for this program will be the traditional grant-in-aid. It is anticipated that two or three awards will be made, if a sufficient number of high quality applications is received. Although funds have been allocated for this program in the NCP financial plans for fiscal years 1983 through 1985, award of grants resulting from this RFA is contingent upon receipt of appropriated funds for this purpose. Requests should be restricted to three years of support. Starting dates as early as July 1, 1983 may be requested. Funding beyond the first year of the grant will be contingent upon satisfactory progress during the preceding year. All policies and requirements which govern the research grant programs of the PHS, including cost sharing, will apply to grants made as a result of responses to this invitation.

## IV. METHODS AND CRITERIA FOR REVIEW

Applications in response to this invitation will be reviewed in competition with each other. The initial review of the applications for scientific and technical merit will be by a special study section of the Division of Research Grants (DRG); secondary review will be by the National Advisory Dental Research Council in May 1983. Applicants will be informed of the outcome of the review shortly thereafter. The earliest possible beginning date will be July 1, 1983.

Questions concerning this RFA and other grant-related activities of the NCP should be addressed to:

John D. Townsley, Ph.D.  
Chief

or

Anna M. Barish  
Health Scientist Administrator  
Caries Research Grants and Contracts Branch  
National Caries Program  
National Institute of Dental Research  
Westwood Building - Room 522  
5333 Westbard Avenue  
Bethesda, Maryland 20205

Telephone: (301) 496-7884

Applications must be responsive to the objectives of this RFA. Applications judged nonresponsive by the DRG and the NIDR will be processed as regular grant applications, as will applications received after October 15, 1982. The DRG will not accept an application in response to this announcement that is the same as one concurrently being considered by any other NIH awarding unit.

The factors to be considered in evaluating each application will be: (a) the importance of the research problem and the information sought; (b) the adequacy of the experimental design; (c) the feasibility and promise of the methods proposed; (d) the novelty or originality of the application; (e) the training, experience and research competence of potential of the investigator(s); (f) the suitability of the facilities, including the availability of any special resources required; and (g) the appropriateness of the requested budget relative to the work proposed.

Applications should be prepared on form PHS 398, the application form for the traditional research grant, which can be obtained from the DRG, NIH, or from the Institution's application control office. The first (face) page of the application and the outside of the mailing package should be labeled "RESPONSE TO RFA NIH-NIDR-NCP-82-2 Fluoride and Root Surface Caries." The conventional presentation in format and detail for regular research grant applications should be followed and the points identified under the "Review Criteria" must be fulfilled.

The receipt date, for an original and six copies of the completed application is on or before October 15, 1982. Applications should be sent to:

Division of Research Grants  
National Institutes of Health  
Westwood Building - Room 240  
5333 Westbard Avenue  
Bethesda, Maryland 20205

## ANNOUNCEMENT

### PULMONARY ACADEMIC AWARD

#### NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Application Receipt Date: November 1, 1982  
Letter of Intent: September 1, 1982

The Division of Lung Diseases, National Heart, Lung, and Blood Institute invites national competition for Pulmonary Academic Awards, which have the dual purpose of improving the quality of pulmonary curricula and of fostering research and careers in the respiratory field. Each school of medicine or osteopathy in the United States or its possessions and territories is eligible for such an award. (Awards are limited to one for each eligible school, for a project period up to five years.)

The Division initiated the Pulmonary Academic Award Program to provide a stimulus for development of a pulmonary curriculum in those schools that do not have one and to strengthen and improve the pulmonary curriculum in those schools that do. Awards provide support to individual faculty members for their educational development and for implementation of the pulmonary curriculum. This announcement is expected to be the final invitation to eligible schools to compete for a Pulmonary Academic Award.

This award is intended to:

- encourage development of a quality pulmonary curriculum that will attract outstanding students to pulmonary research and medical practice;
- ensure superior learning opportunities in pulmonary medicine;
- develop promising young faculty whose interest and training are in pulmonary medicine;
- develop superior faculty who have a major commitment to, and possess educational skills for, teaching pulmonary medicine;
- facilitate interchange of educational ideas and methods among awardees and institutions; and
- develop at the grantee institution the ability to strengthen continuously the improved pulmonary curriculum, with local funds, subsequent to the award.

#### I. CRITERIA FOR THE AWARD

Competitive review for a Pulmonary Academic Award will include assessment of both the sponsoring institution and the proposed awardee. The institution must propose a candidate with competence in pulmonary medicine and a major career interest in improving educational programs. Plans must be presented which will indicate the development or improvement of the pulmonary educational program.



The awardee must be provided with time to acquire the educational skills necessary for personal development as a teacher and for the development of the pulmonary curriculum. Facilities for rigorous pulmonary research and quality patient care must be available.

The candidate must hold an academic appointment at the sponsoring institution at the time of application and have sufficient research training or clinical experience in pulmonary disease to be able to develop and implement a high quality curriculum within the institution. Plans for evaluating the outcome of this effort must be presented. If the candidate's background requires further educational development, the plans to acquire this additional training should be described. Relevant training in epidemiology, clinical trials, behavioral science or other areas could be advantageous in the broader role of the candidate in stimulating an understanding of pulmonary diseases among other peer health professionals in the institution.

## II. PROVISIONS OF THE AWARD

Subject to the availability of funds, the non-renewable Pulmonary Academic Award will include funds for the awardee's salary up to \$30,000, fringe benefits, curriculum development and actual indirect costs not to exceed 8% of total allowable direct costs.

The proportion of the applicants total salary which is requested from this grant must be commensurate with the time or effort (at least 50%) to be devoted to the Pulmonary Academic Award. The total salary on which it is based must be consistent both with the established salary structure at the institution and with salaries actually provided by the institution from its own funds to other staff members of equivalent qualifications, rank and responsibilities in the department concerned. If full-time salaries are not currently paid to comparable staff members, the proposed salary must be appropriately related to the existing part-time salary structure.

The Awardee may serve as a principal or participating investigator on an NIH-supported grant or contract and may draw salary from it (not to exceed 50%).

## III. REVIEW OF APPLICATION

Applications for Pulmonary Academic Awards will be appraised in terms of criteria outlined for the institution and the Awardee in CRITERIA FOR THE AWARD.

The review will include an assessment of the written proposal and will require an interview with the prospective Awardee in Bethesda, Maryland. (Travel expenses for this interview must be paid by the applicant institution). The initial review group will recommend applicants for consideration to the National Heart, Lung, and Blood Advisory Council.

## IV. METHODS OF APPLYING

Each prospective applicant should forward a brief letter of intent not later than September 1, 1982, to:

Carol H. Letendre, Ph.D.  
 Contracts, Clinical Trials, and Training Section  
 Review Branch, Division of Extramural Affairs  
 National Heart, Lung, and Blood Institute  
 Westwood Building - Room 548  
 Bethesda, Maryland 20205

The Institute requests such letters only to have some idea of the number of applications that may be expected and to start planning for their review.

Application forms (PHS 398) may be obtained from the administrative office of the applicant institution or from the Division of Research Grants, NIH.

V. DEADLINE FOR RECEIPT OF APPLICATIONS

<u>Application Receipt</u>	<u>Council Review</u>	<u>Start Date</u>
November 1, 1982	May, 1983	July 1, 1983

VI. FOR ADDITIONAL INFORMATION

Prospective applicants are encouraged to review the Pulmonary Academic Award Announcement dated June, 1982, which will detail the eligibility requirements and applications procedures. Requests for copies of this announcement and questions related to the Pulmonary Academic Award should be directed to:

Robert M. Conant, Ph.D.  
 Chief, Prevention, Education, and  
 Manpower Branch  
 Division of Lung Diseases  
 National Heart, Lung, and Blood Institute  
 Westwood Building - Room 6A12  
 Bethesda, Maryland 20205

Telephone: (301) 496-7668

**REQUEST FOR RESEARCH GRANT APPLICATION:**

**RFA NIH-NCI-DRCCA-82-10**

**COMMUNITY CLINICAL ONCOLOGY PROGRAM**

**NATIONAL CANCER INSTITUTE**

Application Receipt Date: November 9, 1982

**I. PURPOSE**

The Director of the National Cancer Institute (NCI) is interested in establishing a large scale cancer control effort which involves practicing community oncologists in the NCI clinical trials programs. The purpose of the program is to utilize as a resource the increasing number of highly trained oncologic specialists who have entered community practice in recent years. Combining the expertise of community physicians with ongoing clinical research projects will result in a dynamic development and exchange of the newest clinical treatment research findings at the community level. The Community Clinical Oncology Program (CCOP) should: (1) provide adequate support for expanding the clinical research effort in the community setting; (2) involve primary care physicians early in the course of clinical treatment research to provide the benefits of clinical investigation to communities; (3) establish a base for an extension of other cancer control efforts in the areas of prevention, early detection, rehabilitation, and supportive care; and (4) examine selected issues in CCOP performance (e.g., patient accrual and evaluability) and the diffusion of innovative information.

**II. BACKGROUND AND PROGRAM PLANNING**

The Director of the NCI first expressed the intention to develop the Community Clinical Oncology Program in March 1981. In response to the NCI interest, the Association of Community Cancer Centers established a Committee on Clinical Research. Recommendations with extensive documentation from a series of deliberations by the membership, consisting of 55 health professionals representing communities in 20 states, were presented to NCI.

In July 1981, the Board of Scientific Counselors of the Division of Resources, Centers, and Community Activities (DRCCA) formed a Subcommittee on Community Oncology and Technology Transfer which included academic and community oncologists, cancer center directors and cooperative group chairmen. A position paper developed by this subcommittee was presented to the DRCCA Board of Scientific Counselors, which gave concept approval for the CCOP in October

This program is described in the Catalog of Federal Domestic Assistance No. 13.399, Cancer Control. Awards will be made under the authority of the Public Health Service Act, Title IV, Section 403 (Public Law 78-410, as amended; 42 USC 284) and administered under PHS grant policies and Federal regulations 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to A-95 Clearinghouse or Health Systems Agency review.

1981. There has been a broad and extensive involvement of the potential CCOP participants in the development of this new cancer control effort after concept approval. Following the initial developmental activities from January through June 1982, the NCI staff conducted CCOP regional workshops in a number of areas (e.g., California, Texas, New Jersey, Louisiana, Florida, Georgia, Illinois, Massachusetts, Missouri, Virginia, and Washington, D.C.). NCI staff also made presentations in conjunction with the professional meetings of organizations such as the Association of American Cancer Institutes, National Surgical Adjuvant Breast Project, North Central Oncology Group, Eastern Cooperative Oncology Group, and American Society of Clinical Oncology. During this time information was exchanged informally by NCI staff and community participants through individual telephone inquiries and written commentaries. As a result of this vast external informational input, many problem areas have been resolved.

The CCOP initiative is intended to meet the needs of cancer patients by utilizing the trained specialists now practicing in community hospitals and clinics and establish a system of community clinical oncology programs which will participate in clinical research trials. Over 80 percent of patients with cancer are treated in the community with only a small number entering clinical trials. The Division of Cancer Treatment (DCT) of NCI supports a national clinical trials program largely through academic centers. These have included (1) multimodal national and regional cooperative groups, (2) groups in which the investigators have a particular expertise (such as pediatricians), (3) groups that are designed to deal primarily with high technology single modality studies and (4) groups that are specifically disease-oriented. Additional large cancer centers are involved in implementation of local clinical research protocols.

Over the past decade, increasing numbers of highly trained clinical cancer specialists, experienced in clinical research and protocol care, have been entering private practice in the community. Experience within several Cooperative Groups has indicated that physicians caring for cancer patients in the community can maintain high quality clinical research activities similar to that of the academic centers. Evidence exists that new technology can be transferred effectively by having community physicians participate in clinical research activities.

The CCOP will be developed and supported by the Division of Resources, Centers and Community Activities (DRCCA), National Cancer Institute. Participating community programs will be required to enter or refer into NCI-approved clinical trials, designated as high priority by a research base with which the CCOP is affiliated. These research bases may be national or regional multi-disease cooperative groups, specialized cooperative groups or cancer centers currently participating in NCI approved clinical research protocols. Participants are encouraged to enter patients with early stage disease with common cancers and to enter or refer, if appropriate, patients with uncommon cancers.

Patient entry onto clinical trials will be done through collaboration with a maximum of (1) two primary multi-disease research bases (with two, only one may be a cooperative group) having a spectrum of clinical trial protocols available and (2) a maximum of three specialty research bases. Participation with specialty or multi-disease research bases will be considered equal and a CCOP may choose only one of either or a maximum of five when combined affiliations occur. Eligible patients in a single disease category should be allocated to one protocol in the case where multiple affiliations have resulted in overlapping protocols.

The diffusion hypothesis will be tested during the course of the program. A separate CCOP evaluation is planned to test this hypothesis. According to this hypothesis, it is anticipated that participation of some patients in research will beneficially influence those patients not participating in research protocols. Information diffusion in future cancer control programs of the NCI will similarly be tested.

### III. OBJECTIVES OF THE COMMUNITY CLINICAL ONCOLOGY PROGRAM

The CCOP initiative is designed:

- A. To bring the advantages of clinical research to cancer patients in their own communities, by having practicing doctors and their patients participate in clinical treatment research protocols, and thus foster an exchange between clinical research and cancer control.
- B. To reduce national mortality by speeding the transfer of newly developed cancer treatment technology to widespread community application.
- C. To provide a basis for involving a wider segment of the community in cancer control activities and investigate the diffusion of cancer therapy advances in community medical practices. The diffusion hypothesis presumes that introduction of quality-controlled clinical research trials in the community will also benefit those patients not treated as part of this protocol.
- D. To develop programs to serve as part of a broadly based nationwide resource for quality-controlled distribution of increasing numbers of experimental anti-cancer agents.
- E. To facilitate wider community participation in future cancer control and prevention research activities planned by NCI.

### IV. CRITICAL ELEMENTS FOR A CCOP

- A. The CCOP may be a single clinic, a group of practicing physicians, a single hospital, or a consortium of physicians and/or clinics and/or hospitals.

NCI recognized comprehensive and clinical cancer centers (holding CORE grants) are not eligible. A University hospital which is the major teaching institution for that university will not be eligible. University hospitals and Veterans Administration hospitals may participate as a non-dominant member of a consortium led by a community institution. University hospitals participating as Division of Cancer Treatment funded Cooperative Group members will not be eligible. Unfunded, non-university group members will be eligible. Those institutions that currently participate as part of the Division of Resources, Centers, and Community Activities funded Cooperative Group Outreach Program or Cancer Centers Outreach Program will be eligible. Cooperative Group Outreach Program support will be terminated for successful CCOP applicants. This funding will revert to the National Cancer Institute Cancer Control Program.

- B. Each CCOP must have a demonstrated potential and stated commitment to contribute a minimum of 50 evaluable patients per year to approved clinical research protocols active in the center or group with which the community

center is affiliated. Although the CCOP is most appropriate for adult patients, for pediatric CCOPs, the 50 patient minimal requirement will be reduced for those applicants able to place a majority of their eligible patients on protocol. The written affiliation agreements between the CCOP and its research bases will specify the priority protocols which can meet this obligation. As one measure of performance, it is expected that 10 percent or more of eligible patients in suitable disease categories available for study to physicians listed as participating in a CCOP application will be placed on protocols. The mix of cancer patients to meet the reporting requirement will be negotiated in advance with the research base. Patients transferred from the community to any NCI supported clinical research program in order to receive protocol treatment, will be credited to the CCOP. Referrals to centers for NCI supported protocol treatment will result in a credit to the referring CCOP of 1.25 per patient toward the minimum patient requirement.

- C. Each CCOP is expected to have a committed multidisciplinary professional team appropriate for their expected protocol participation. This may include surgeons, radiation oncologists, medical oncologists, pathologists, oncology nurses, and psychiatrists. Administrative and data management personnel will be necessary. Other appropriate disciplines may be added (e.g., gynecologic oncologists, pediatric oncologists). One of this group will serve as principal investigator. An associate investigator should be named to assure continuity in the event of departure of the principal investigator.
- D. Each CCOP must delineate its patient referral area. Consideration will be given to demographic and geographic distribution of CCOPs in the final selection process. Multiple CCOPs competing for the same patient population will be considered but may not be awarded unless warranted by the population density. Individual institutions or consortia may apply but a single administrative focus should be designated.
- E. Each CCOP must provide evidence that an affiliation has been established with a nationally recognized clinical cancer research base (e.g., clinical or comprehensive cancer center, national or regional cooperative group). A list of research base options is available upon request (see Section XII). Multiple affiliations are permitted provided they are not conflicting. These affiliations must exist in the form of a written agreement between the CCOP applicant and corresponding research base(s) at the time of application submission. This agreement must specifically state how the problem of competing protocols is to be resolved. Initial affiliations must be maintained during the first three-year funding cycle. Unusual circumstances may require changes in research base affiliations, subject to NCI staff approval. CCOP affiliations with centers and regional cooperative groups must be geographically appropriate. A CCOP applicant may not bypass regional research base programs to establish ties with distant centers unless there is clear justification and NCI staff approval.
- F. The conditions of affiliation with a maximum of two multi-disease research bases (with two, only one may be a cooperative group) and three special category research bases must be provided in the CCOP Research Base Affiliation Agreement(s).
- G. Quality-controlled clinical research data is a performance requirement. Assurance of quality is the joint responsibility of the CCOP and its research

base affiliate(s). Quality control procedures, operational in the center or group, will be applied to the CCOPs and must be specified in the CCOP-Research Base Affiliation Agreement.

- H. Each CCOP must have a defined space for administrative activities and administrative personnel which will serve as a focus for data management, quality control, and communication.
- I. Allocation of CCOP funds to support community and research base costs for receipt, handling, and analysis of patient data should be specified in the written agreement between the CCOP applicant and its research base. Allowable items in the budget would be for administrative personnel, data handlers, and study assistants, supplies and services directly related to study activities (e.g., processing and sending material for pathology review, processing and sending port films for radiation therapy quality control) and limited travel to meetings directly related to study activities. Physician compensation would be allowable only for time spent on the project other than clinical care. Total funding as well as allowable physician compensation may be increased proportionately for participating in future NCI initiated cancer control activities. Initial funding is to be for three years.
- J. The following administrative requirements prior to award will apply to all CCOP programs.

- 1. Management of Federal Funds

This ability includes the following basic requirements:

- o A formal organizational structure capable of managing the project and safeguarding the disposition of federal funds;
    - o Adequate cost accounting and bookkeeping procedures including the capacity to separately monitor federal funds;
    - o Time and effort policies to account for personnel costs; and
    - o Accountability for all equipment, supplies and other necessary project expenditures.

- 2. Mandated Assurances

These may be found in the Grant Application Form 398 (Rev. 5/80):

- o Civil Rights (page 4)
    - o Handicapped Individuals (page 4)
    - o Sex Discrimination (page 4)
    - o Protection of Human Subjects (pages 3 and 14)

### 3. Cost Sharing

The Appropriation Act for the DHHS requires that grantee institutions share in the cost of activities supported by research grants. Some direct or indirect contribution should be made to the project.

### 4. Indirect Costs

Unless directed otherwise, successful applicants who have not negotiated an indirect cost rate must do so. The negotiation of the indirect cost rate may begin just prior to, or immediately following, notification of grant award. Guidance on this requirement will be made available by the NCI upon approval of the application.

### 5. Payment Procedures

Payments for grants awarded by the NIH are made through the Departmental Federal Assistance Financing System (DFAFS). Guidance for payment will be made by the NCI to successful applicants at the time of award. Under no circumstances will pre-award costs, (i.e., expenses incurred prior to actual funding) be allowed.

## K. The following operational prerequisites are expected:

1. A list of protocols which will be used by the CCOP to meet patient accrual requirements must be stated in the initial application. Protocols initiated after the initial award must be filed with DRCCA staff. Protocol review and approval procedures for the CCOP will be consistent with that of the research base.
2. Each CCOP agrees to maintain a new patient log or minimal registry to include age, sex, primary site of cancer, stage of disease, and treatment disposition for the potentially eligible patient pool.
3. Radiotherapy equipment must have its calibration verified by the Radiological Physics Center (RPC) or one of the regional Centers for Radiological Physics (CRP) in order for institutions to participate in this program. Information is available upon request. Prior to award, a letter of compliance will be provided.
4. Each CCOP agrees to accept periodic on-site monitoring by representatives of its research base(s) or NCI or an NCI designee. The purpose of such on-site monitoring may include monitoring of use of investigational drugs, accuracy of data recording, completeness of reporting adverse drug reactions, protocol accrual and quality control analysis, fiscal and administrative review.
5. Each CCOP agrees to an annual review of its progress by the executive committee of its research base(s) and DRCCA staff. This review will include, but not be limited to, overall case accrual, accrual to high priority protocols, patient eligibility, patient evaluability, and timeliness and quality of data reporting. This annual review may be the basis for probationary status or adjustment in funding.



#### V. CCOP AND RESEARCH BASE(S)--COOPERATIVE ACTIVITIES

In preparation for submission of the application, negotiations between the CCOP and the research base should result in agreement about protocol participation, method of support for the research base (for data management) and the expected cost to the research base as a result of case accrual. Cooperation is anticipated in:

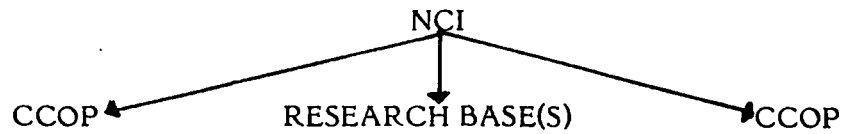
- A. Planning for program development and training of support personnel (e.g., data managers, study assistants, oncology nurses, etc.).
- B. Developing and/or making available appropriate clinical research protocols.
- C. Establishing standards for surgery and pathology reporting procedures of the research base, community members and affiliates.
- D. Holding regular meetings of the research base, community members and affiliates for review of ongoing research activities, planning of future activities, and relate professional education.
- E. Instituting quality control procedures for data recording, protocol compliance, and reporting of adverse reactions.
- F. Instituting control procedures for treatment planning such as standardization of radiation equipment, doses and fields.
- G. Establishing an organizational mechanism for the relationship between the CCOP and research base(s) and the reimbursement of research base costs. Circumstances may vary from CCOP to CCOP.

#### VI. RESEARCH BASE PARTICIPATION

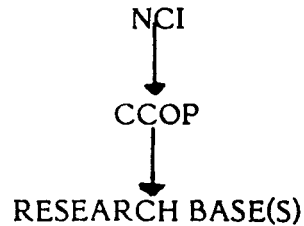
The general function of a research base is to collaborate to a degree appropriate to the applicant CCOP, providing protocol access, assistance in data quality control and feedback information on clinical trial performance. The CCOP-Research Base Agreement should define mechanism for community participants to have input as active research base members.

Each research base will need to develop a plan to support additional administrative and data management functions and to provide annual reports on protocol accrual and quality control analysis for review by DRCCA staff.

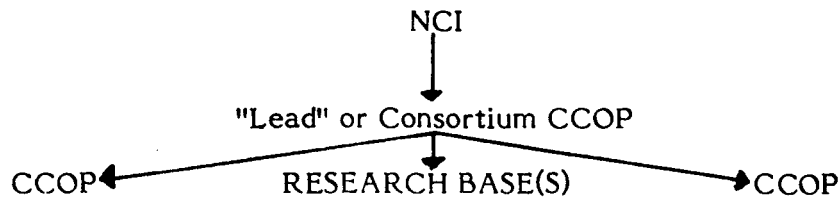
Three options for research support are available. The research base(s) participating with approved CCOPs may receive appropriate support through a supplement to their existing primary grant which will be subject to appropriate review and approval processes. Costs will be based on anticipated protocol participation and data management expectations, negotiated by NCI staff after appropriate review. (See Example 1)

Example 1.

An alternative method of fiscal support for the research bases may come through a single CCOP (See Example 2);

Example 2.

or a lead CCOP (See Example 3);

Example 3.Research Base Options

## A. A Multi-disease Research Base

(may choose one or two)

1. NCI-funded comprehensive and clinical cancer centers
2. Cooperative Groups
  - a. Cancer and Leukemia Group B (CALGB)
  - b. Eastern Cooperative Oncology Group (ECOG)
  - c. North Central Cancer Treatment Group (NCCTG)
  - d. Northern California Oncology Group (NCOG)
  - e. Southeastern Cancer Study Group (SEG)
  - f. Southwest Oncology Group (SWOG)
  - g. Mid-Atlantic Oncology Group-Georgetown University
  - h. Piedmont Oncology Group

B. Special Category Research Bases (maximum three)

1. Pediatric Oncology Research Base (may choose one)

- a. Childrens Cancer Study Group (CCSG)
- b. Pediatric Oncology Group (POG)

2. Other Research Bases (may choose more than one)

- a. Gynecologic Oncology Group (GOG)
- b. Radiation Therapy Oncology Group (RTOG) - Must clarify patient allocation if protocols overlap with category A choices.
- c. National Surgical Adjuvant Breast and Bowel Project (NSABP) - participation in surgical protocols (B-06 is an example) falls in this category. Participation in the adjuvant protocols of this group may be a potential conflict with the protocols of a category A research base and allocation of patients must be clarified and both NSABP and the category A research base must concur in this allocation plan.
- d. Gastro-Intestinal Tumor Study Group (GITSG) - participation in the protocols of this group may conflict with protocol of a category A research base and allocation of patients must be clarified and both GITSG and the category A research base must concur in this allocation plan.
- e. Lung Cancer Study Group (LCSG) - participation in the protocols of this group may conflict with protocols of a category A research base and allocation of patients must be clarified and both LCSG and the category A research base must concur in this allocation plan.

VII. MECHANISM OF SUPPORT

The CCOP awards will be made as Cooperative Agreements. These are assistance relationships supporting projects that require substantial collaboration and involvement with NCI staff. Depending on individual CCOP costs, up to 200 awards with a total not to exceed 10 million dollars per year, will be allocated for this program. NCI anticipates making multiple awards under this request. Awards will be for periods of three years to establish the initial capabilities of the participants. Repetitive RFAs are planned. Renewal of grants after three years will be contingent upon satisfactory review of a competing application by a scientific peer review committee and the National Cancer Advisory Board.

VIII. LETTER OF INTENT

Letters of intent should precede the submission of the grant application and are due August 23, 1982. These are to be detailed documents suitable for review for responsiveness to this Request for Applications. Those judged to be non-responsive will be returned with an explanation and the applicants will be encouraged to respond to future issuances of the RFA for Community Clinical Oncology Programs.

The letter of intent should address the following issues succinctly (about one page per topic):

- A. A description of the CCOP organization (including catchment area and patient availability).
- B. Existing cancer control activities in the area of the CCOP.
- C. Names and type of practice (e.g., medical oncology, internal medicine) of participants.
- D. Research affiliations, planned protocol participation and estimated patient accrual per protocol.

The total pages for the letter should not exceed 15 pages. Applicants whose letter of intent is responsive will be notified and asked to submit full applications.

#### IX. METHOD OF APPLYING

Complete applications are due on or before close-of-business November 9, 1982. Applications must address all requirements as presented in this RFA. Applications for CCOPs and Research Bases should be submitted on Form PHS 398, (revised 5/80), the application form for the traditional research project grant, which is available in the business or grants and contracts office at most academic institutions and research institutions, or from the Division of Research Grants, NIH, Bethesda, Maryland 20205. This CCOP application request has no page limitation; however, applications should be as concise as possible. The words "Community Clinical Oncology Program" should be typed in bold letters on line number 2 of the face page of the application and also on the outside of the mailing package.

Additionally, a brief covering letter should accompany the application indicating that it is being submitted in response to this request. The original and 6 copies of the application should be submitted to the Division of Research Grants, NIH, as directed in the Grant Application Instructions. Two additional copies should be sent to:

Referral Officer, Grants Review Branch  
Division of Extramural Affairs  
National Cancer Institute  
Westwood Building - Room 826  
5333 Westbard Avenue  
Bethesda, Maryland 20205

#### X. REVIEW PROCEDURES AND CRITERIA

##### A. Review Method

Applications responsive to this RFA will be reviewed by an appropriate peer review panel of the National Institutes of Health. Final review is provided by the National Cancer Advisory Board.

**B. Availability of Patients**

Reviewers will assess the ability of the CCOP to meet the requirement for entering a minimum of 50 evaluable patients per year on clinical trials. Evaluable patients are those eligible individuals who have had the appropriate diagnostic work-up, treatment, and follow-up to complete the study as outlined in the protocol. Available patients are those seen by CCOP physicians who may be considered eligible for study. Only the patients available to the CCOP applicants will be counted toward the denominator constituting the 10% minimum requirement. The population referral area should be specified. Information (tumor registry and/or clinic visit data) should be provided which demonstrate the number of cases (by disease category) seen per year by the participating physicians and/or institutions during 1980 and 1981. An explanation of how the numbers were derived should be provided. Special attention should be given to those disease categories for which the CCOP has agreed to enter patients on protocol.

**C. Physicians**

Reviewers will consider the availability, training, experience and commitment of participating physicians as appropriate for the treatment of patients on the protocols in which the CCOP has agreed to participate (e.g., if protocols require radiotherapy, the availability and qualifications of radiation therapists will be considered, etc.). The work experience of participant oncologists gained from residency, fellowship, or post training in the entry and treatment of cancer patients on research trials should be described. A curriculum vitae (not to exceed two pages each) and a signed statement of commitment to enter patients on selected protocols chosen by the CCOP from each participating physician should be provided.

**D. Facilities and Equipment**

Reviewers will appraise the availability of treatment facilities, both inpatient and outpatient; these should be described in the application. If the CCOP plans to enter patients on studies involving radiation therapy, available equipment should be described. A statement of commitment from each participating institution should be provided.

**E. Other Existing Cancer Control Activities**

Reviewers will consider the quality and effectiveness of existing cancer control efforts. These include education programs, tumor board conferences, patient management guideline development, formal supportive care efforts, and participation in formal cancer control network, outreach and research programs. Such activities will be regarded as a positive feature in an application and an indication of the institutional commitment to quality cancer care. No one activity will be considered a requirement.

**F. Affiliation Agreements**

Reviewers will appraise the affiliation agreements with research bases provided in the application. The appropriateness of the affiliation and of the

protocols chosen, the adequacy of quality assurance mechanism for both treatment and data, and the adequacy of investigational drug monitoring procedures and data management procedures will be considered.

G. Principal Investigator

Reviewers will consider the qualifications and experience of the principal investigator related to his/her ability to organize and manage a community oncology program.

H. Support Personnel

The qualifications and experience of all proposed non-physician personnel will be assessed by the reviewers. A clear description of the proposed duties for each named and to-be-named position should be provided.

XI. NATURE OF COOPERATION WITH NCI STAFF: TERMS OF AWARD

A. Protocol Review

Protocol review and approval procedures for the CCOP will be consistent with that of the research base.

B. Quality Control

The DRCCA staff will periodically review mechanisms developed to apply clinical trials quality control procedures in the community setting.

C. Data Management

DRCCA staff will have access to all data and will periodically review data management by the group. Data must be available for external monitoring if required by NCI.

D. Investigational Drug Management

DCT staff will advise investigators of specific requirements and changes in requirements concerning investigational drug management that the Food and Drug Administration (FDA) may mandate. Investigators performing trials under Cooperative agreements will be expected, in cooperation with the NCI, to comply with all FDA monitoring and reporting requirements for investigational agents.

E. Program Review and Performance Reporting Requirements

Annual progress reports will be submitted to the DRCCA, NCI. Report format will be provided by the DRCCA staff to the CCOPs. Following the receipt of these reports, the CCOP's progress will be reviewed by the DRCCA staff in collaboration with the affiliated research bases. Reviews will be based on performance criteria presented in this RFA and as outlined in CCOP-Research Base Agreements.

## XII. SOURCES OF FURTHER INFORMATION

Inquiries related to (1) the identification of eligible research base options and (2) general information on CCOPs should be directed to:

Office of Cancer Communications  
Public Inquiries Section  
Building 31 - Room 10A18  
9000 Rockville Pike  
Bethesda, Maryland 20205

Residents of all states but Maryland may call the toll free number:

(800) 638-6694  
(800) 638-6070 Alaska and Hawaii

Maryland residents may call:

(800) 492-6600

Correspondence related directly to application development and letters of intent should be directed to:

Robert W. Frelick, M.D.  
Program Director  
Division of Resources, Centers and  
Community Activities  
National Cancer Institute  
Blair Building - Room 7A01  
8300 Colesville Road  
Silver Spring, Maryland 20910

Telephone: (301) 427-8708

Questions pertaining to business matters should be directed to:

John G. Dell  
Grants Management Specialist  
Grants Administration Branch, OD  
National Cancer Institute  
Westwood Building - Room 854  
5333 Westbard Avenue  
Bethesda, Maryland 20205

Telephone: (301) 496-7444

## V. CCOP AND RESEARCH BASE(S)--COOPERATIVE ACTIVITIES

In preparation for submission of the application, negotiations between the CCOP and the research base should result in agreement about protocol participation, method of support for the research base (for data management) and the expected cost to the research base as a result of case accrual. Cooperation is anticipated in:

- A. Planning for program development and training of support personnel (e.g., data managers, study assistants, oncology nurses, etc.).
- B. Developing an/or making available appropriate clinical research protocols.
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Each research base will need to develop a plan to support additional administrative and data management functions and to provide annual reports on protocol accrual and quality control analysis for review by DRCCA staff.

Three options for research support are available. The research base(s) participating with approved CCOPs may receive appropriate support through an administrative supplement to their existing primary grant which will be subject to the usual approval process. Costs will be based on anticipated protocol participation and data management expectations, negotiated by NCI staff with appropriate consultation.