2/19/91

CER
LETTER

P.O. Box 15189 Washington, D.C. 20003 Telephone 202-543-7665

Vol. 17 No. 7
Feb. 15, 1991

Price $205 Per Year US, Canada.
$230 Per Year Elsewhere

NCI Would Fund 3,164 Research Project Grants, 897 Competing, Under FY92 White House Budget

NCI would fund 3,164 research project grants in FY 1992 under the President's budget released last week, 88 more grants than the institute expects to fund in FY 1991, or a 2.9 percent increase.

(Continued to page 2)

In Brief

Pursell Most Likely To Replace Conte, Friend Of Cancer Program; DeVita Names Associate

SILVIO CONTE, the Massachusetts Republican member of the House of Representatives who died last week of complications from prostate cancer, was one of the best friends of the National Cancer Program in Congress. Conte was the top ranking Republican on the House Appropriations Committee and its Labor-HHS-Education Subcommittee and always expressed strong support for NCI budget increases, frequently taking the White House to task for inadequate requests. Carl Pursell of Michigan probably will move up to top ranking position on the subcommittee; John McDade of Pennsylvania is next in line on the parent committee. . . . **RAYMOND WARRELL** has been appointed to the newly created position of associate physician in chief of Memorial Sloan-Kettering Cancer Center. Warrell will assist Vincent DeVita, physician in chief, with management of the hospital's research program in clinical trials. He will assume responsibility for the Institutional Review Board office and other related duties. . . . **MACE ROTHENBERG**, special assistant for clinical affairs to Div. of Cancer Treatment Director Bruce Chabner, will leave that position in July for the Univ. of Texas Health Science Center (San Antonio). He will become the new executive officer of the Southwest Oncology Group, and will participate in drug development in the Div. of Oncology at the Health Science Center. . . . **"ONCOLOGY REIMBURSEMENT: 1991,"** a joint symposium of Assn. of Community Cancer Centers and Assn. of Northern California Oncologists, Feb. 23 at the Parc Fifty-Five Hotel in San Francisco. This will be the first of 10 regional meetings on reimbursement planned by ACCC. Contact ACCC, 11600 Nebel St., Rockville, MD 20892, phone 301/984-1242. . . . **ONCOLOGY NURSING** Society was one of 16 nursing organizations which joined in drafting a plan for national health care reform. The proposal includes a "standard package" of essential benefits, including primary care and prevention, available to everyone, provided and financed through a mix of public and private sources; steps to promote self care and disease prevention, and "reduce fragmentation of the present systems and its orientation toward high cost acute care."

8 Centers Awarded Comprehensive Designation . . . Page 3

DCPC Advisors OK 16 Year Trial Of Screening Methods . . . Page 4

DCPC Faces Huge Out Year Costs Of Four Trials . . . Page 6

RFA Available . . . Page 8

NCI To Fund 3,164 Grants In FY92, Highest Level In Institute History

(Continued from page 1)

That number of research project grants (RPGs) is the "highest number in the history of the institute," according to NCI Director Samuel Broder.

Of the total grants, 897 would be competing, representing an increase of 57 competitive grants from the FY91 level of 840, a 6.8 percent increase. The award rate for competing grants would be 29 percent, as compared to an expected 27 percent in FY91.

NCI would fund 2,267 noncompeting grants, 31 more than the FY91 level of 2,236.

The President's budget recommends $1.81 billion for NCI in FY92, a $96.47 million increase, or 5.6 percent, over the FY91 level of $1.7 billion.

The average length of awards will be 4.0 years, both in FY91 and FY92, to comply with Congress's mandate last year to lower the average length of awards. The average award length at NCI in FY90 was 4.1.

"We will have to be very careful in some of our mechanisms" to comply with the Congressional mandate on award length, Broder told the Div. of Cancer Prevention & Control Board of Scientific Counselors at its recent meeting. "We will have to seriously review our Outstanding Investigator program, and it will become more and more difficult for individuals to obtain awards, in view of competing applications. We are not going to terminate that program, but it will become more and more difficult. Every seven year award we give will have to be counterbalanced" by shorter awards.

The OIG was begun in 1984 at the recommendation of the President's Cancer Panel. "The OIG was emblematic of the special considerations of NCI in the 1980s," Broder told the National Cancer Advisory Board at its recent meeting. "But this is the '90s." The out-year costs and the burden of maintaining the 4 year average necessitate holding the line on OIG awards.

NCI is in the process of revising its OIG guidelines.

In addition, the MERIT awards and MERIT extensions, which are five years each, "will have to have very careful scientific review," Broder said. He noted that the issue length of awards is important to the DCPC board because, "I can't envision doing large scale clinical trials without having to have a commitment that is longer than four years."

OIGs account for 8.1 percent of NCI's RPG dollars in FY91 and are expected to remain at the same level in FY92. MERITs would receive 6.5 percent of RPG dollars in FY92 under the President's budget; currently they receive 5.6 percent of RPG dollars.

The average cost of a noncompeting grant would be $274,000 in FY92; it is expected to be $263,000 in FY91. For competing grants the average would be $252,000, and is expected to be $238,000 in FY91.

Under the President's budget, NCI would allocate $846 million to RPGs in FY92, a $57 million or 7.2 percent increase over FY91. Funding for competing grants would be $225.7 million, a 12.6 percent increase over FY91. RPG funding has increased 30 percent (not 20 percent as reported in last week's **Cancer Letter**; intramural funding has increased 20 percent) in real terms since 1980, as measured in 1980 constant dollars.

That fact has prompted NCI to begin a campaign to improve access to resources for clinical oncology research and prevention and control research. Broder submitted a request to the NIH Div. of Research Grants for a study section on prevention and control, and is discussing the possibility of a new study section for clinical oncology, or the rejuvenation of Experimental Therapeutics-2 (ET-2), an existing study section (**The Cancer Letter**, Nov. 23, 1990).

"We need to make sure that we are using our research project grant line to do research in basic and clinical programs, and in prevention and control," Broder told the DCPC board.

"We need to think about innovative new ways of using that research project grant pool to do investigator initiated research" in prevention, Broder said.

Broder told the NCAB that he is "most concerned" about funding for clinical research in the transitional stages, where there is a need to move quickly from the laboratory to the patient.

THE CANCER LETTER

Editor: **Kirsten Boyd Goldberg**
Associate Editor: **Lisa M. O'Rourke**
Contributing Editor: Jerry D. Boyd

Editorial/Subscriptions Office
PO Box 15189, Washington, DC 20003
Tel: (202) 543-7665 Fax: (202) 543-6879
Subscription rate $205 per year North America, $230 elsewhere. ISSN 0096-3917. Published 48 times a year by The Cancer Letter Inc., also publisher of The Clinical Cancer Letter and AIDS Update.

Other Research Grants: Clinical cooperative groups would receive $66 million under the Administration's FY92 budget for NCI, an increase of $3.75 million, or 6 percent, over FY91.

In contrast to the increases for other mechanisms, the budgets for some training grant mechanisms are flat. NCI's research careers mechanism would remain at $8.78 million in the President's budget. Cancer education also would remain at its level of $3.1 million. However, funding for minority biomedical research would increase by 5.4 percent, from $2.8 million this year to $2.98 million in FY92.

Cancer centers would receive $112.7 million in FY92, nearly a $2.7 million increase.

Altogether, the total funding for RPGs, cancer centers and other research, which includes clinical cooperative groups, training, and other grants, would exceed $1 billion under the Administration's budget proposal.

Construction funding update: NCI plans to use $5.35 million in NCI extramural cancer construction funds from the FY91 appropriation to make four construction grant awards. The awardees are Massachusetts Institute of Technology, Univ. of Michigan, Univ. of Pittsburgh, and the Fred Hutchinson Cancer Research Center.

"These awards resulted from applications submitted directly to our construction program in recent years," Broder told the NCAB at its recent meeting. "All of our approved applications will receive awards."

NCI received about 20 applications for construction grants on Feb. 1, Broder said. These will be reviewed and funded with FY91 money, "if available," he said.

Construction funding in the President's FY92 budget is $2 million, and most of that will go toward maintenance of the Frederick Cancer Research & Development Center, Broder said.

Last December, NIH transferred $4.8 million to NCI to award construction grants to two NCI centers, Univ. of Colorado and Univ. of Kansas. This was the result of an RFA competition conducted by NIH last summer. Last August, NIH gave NCI $13.6 million (most of which was NCI's own money) to make five construction awards to the Jackson Laboratory, Purdue Univ., Univ. of Michigan, Univ. of Southern California, and Univ. of Wisconsin.

"We believe that NIH will make additional construction grant awards in 1991," Broder told the NCAB at its recent meeting.

Enrico Mihich, in his final meeting as a member of the NCAB, gave another pitch, as he has for the past several years, for the usefulness of the bypass budget, NCI's professional needs budget. Noting that the NCI director must support the President's budget once it is released, Mihich said the bypass budget "still can be a source of inspiration" to members of Congress.

Mihich encouraged the NCAB members individually, as well as other scientists, to bring the bypass budget to the attention of key members of Congress and their staff.

Now is the time to do that, since the Senate Labor, HHS, Education Appropriations Subcommittee is expected to hold hearings on the NIH budget in mid-March. The House subcommittee is tentatively expected to hold its hearing in early April.

Will the new NIH director use her (assuming Bernadine Healy is confirmed, as seems likely) authority, as given to her by Congress last year, to transfer 1 percent of funds from any budget category to any other category? That question makes NCI officials nervous, because they could lose 1 percent of their FY91 budget at any time.

"We have made the case that there are some very high priority needs of the institute," Broder said. Given the fact that it is now well into the fiscal year, perhaps the director will not choose to use this mechanism, which was designed to give the NIH director more funding control and flexibility. "Right now, there's nobody to negotiate with," Broder said.

NIH budget would be $8.77 billion under the Administration's FY92 plan, $498 million more than the FY91 level of $8.276 billion, for a 6 percent increase.

Comprehensive Designation Awarded To 8 Centers Through Peer Review

Eight cancer centers have been approved for comprehensive status through the peer review process under NCI's new guidelines.

The eight were favorably recommended to receive the title "NCI-Designated Comprehensive Cancer Center" by the Cancer Center Support Grant committee. The National Cancer Advisory Board last week approved the recommendation.

The eight institutions had been comprehensive cancer centers under designation guidelines issued in the 1970s. The institutions and their directors are:

▸Univ. of Alabama at Birmingham Comprehensive Cancer Center, Albert LoBuglio.

▸Dana-Farber Cancer Institute, Baruj Benacerraf.

▸Fred Hutchinson Cancer Research Center, Robert Day.

▸Mayo Comprehensive Cancer Center, John Kovach.

▸Memorial Sloan-Kettering Cancer Center, Paul Marks.

▸Kenneth Norris Comprehensive Cancer Center, Univ. of Southern California, Brian Henderson.

▸Meyer Prentis Comprehensive Cancer Center of Metropolitan Detroit, Laurence Baker.

▸Univ. of Wisconsin Clinical Cancer Center, Paul Carbone.

The designation of these eight bring the total number of comprehensive cancer centers to 24. Five centers received comprehensive status through administrative review last year. They are:

Arizona Cancer Center, Norris Cotton Cancer Center, Lineberger Cancer Research Center, Cancer Center of Wake Forest Univ./Bowman Gray School of Medicine, and Pittsburgh Cancer Institute.

Three centers last year received comprehensive status through peer review and NCAB approval. They are:

Yale Comprehensive Cancer Center, Roswell Park Cancer Institute, and Fox Chase Cancer Center.

Eight comprehensive centers that were designated as such in the 1970s have yet to be reviewed for that status under the new guidelines. These centers will retain their status until they are "redesignated," according to an NCI press release. They are:

Jonsson Comprehensive Cancer Center, Sylvester Comprehensive Cancer Center, Illinois Cancer Council, Johns Hopkins Oncology Center, Columbia Univ. Comprehensive Cancer Center, Duke Comprehensive Cancer Center, Ohio State Univ. Comprehensive Cancer Center, and M.D. Anderson Cancer Center.

In addition, the Univ. of Pennsylvania Cancer Center, which received comprehensive designation in conjunction with Fox Chase in 1976, continues to be listed as comprehensive pending the submission and approval of a separate application under the new guidelines.

Under NCI's new guidelines, comprehensive status remains in effect for the duration of a center's core grant, and centers must submit an application for the designation again when the core grant next comes up for renewal.

Advisors OK 16 Year, $60 Million Trial Of Cancer Screening Methods

NCI advisors have given concept approval to a $60 million, 16 year trial of cancer screening modalities in prostate, lung, colorectal, and ovarian cancer.

The trial proposes to involve 148,000 men and women aged 60-74, randomized between a control arm and a screening arm, to test whether six screening methods reduce mortality from the four cancers. The Div. of Cancer Prevention & Control Board of Scientific Counselors recently approved the concept for the trial, which would be funded out of the division's prevention and control budget line.

The PLCO Screening Trial is the new version of a $42 million trial of prostate, lung, and colorectal cancer screening that NCI was preparing to begin last year, but decided to stop because it did not include women. DCPC staff rewrote the concept to add ovarian cancer, and presented a preliminary version to the BSC last October (**The Cancer Letter,** Nov. 2, 1990).

The trial will begin with a two year pilot phase; after that time a policy advisory board will decide whether the trial should continue.

Following are excerpts from the 23-page concept statement:

Prostate, lung, colorectal and ovarian cancer screening trial. Concept for a new RFP, estimated total cost $60,145,250 over 16 years; awards to one data center, up to 15 screening centers, and one laboratory.

The screening trial is designed to determine in persons aged 60-74 at entry whether:

A. In females and males, screening with flexible sigmoidoscopy (60cm sigmoidoscope) can reduce mortality from colorectal cancer, and screening with chest x-ray can reduce mortality from lung cancer.

B. In males, screening with digital rectal examination plus serum prostate specific antigen (PSA) can reduce mortality from prostate cancer.

C. In females, screening with pelvic examination plus CA 125 and transvaginal ultrasound can reduce mortality from ovarian cancer.

The secondary objectives are:

1) to assess screening variables other than morality for each of the interventions including sensitivity, specificity, and positive predictive value.

2) to assess incidence, stage, and survival experience of cancer cases.

3) to investigate the mortality predictive value of biologic and or prognostic characterizations of tumor tissue as intermediate endpoints.

Project description: The design is a two armed trial with 37,000 females and 37,000 males, aged 60-74 at entry, in each of the two arms. Men would be screened for prostate, lung, and colorectal cancer. Women would be screened for ovarian, lung, and colorectal cancer. The design is as follows:

--Control arm: (37,000 women and 37,000 men) usual medical care.

--Screened arm: 37,000 men receive digital rectal exam, PSA, flexible sigmoidoscopy, and chest x-ray. The 37,000 women receive pelvic exam, CA 125, transvaginal ultrasound, flexible sigmoidoscopy and chest x-ray.

The frequency and duration of screening will be as follows: TVS, initial then annual x 3; CA 125, initial, then annual x 3; pelvic, initial then annual x 3; DRE, initial, then annual x 3; PSA, initial then annual x 3; x-ray, initial then annual x 3; sigmoidoscopy, initial then annual x 3.

It will be necessary to conduct screening examinations in a defined screening center to accelerate the examination process, eliminate confusion and anxiety among screenees, facilitate patient education, and enhance compliance. Screens for all sites should be completed within a two hour period for each screenee.

Acceptability of the screening process by screenees is essential. Technologists of the same sex as the screenee should perform DRE, sigmoidoscopic, pelvic and TVS exams.

The trial is designed to have appropriate statistical power for detecting decreases in mortality separately for each site. Subjects with positive findings on the ovarian screen would receive further work up according to the protocol developed in the pilot phase. Subjects with lesions suspicious for lung cancer on x-ray would receive further work up according to a protocol to be developed during the pilot phase. Subjects with colorectal polyps or suspected cancer detected by DRE or flexible sigmoidoscopy would undergo biopsy and removal of the polyps followed by further work up possibly including barium enema studies and/or colonoscopy according to the protocol worked out in the pilot phase.

Although transrectal ultrasound would not be used as an initial screening modality for prostate cancer, we would propose using it in the diagnostic work up of subjects with discordant results on DRE and PSA according to the following schema where all biopsies are to be ultrasonically guided:

--Rectal +, PSA -, then biopsy.

--Rectal +, PSA -, or rectal -, PSA +, then ultrasound. If ultrasound +, then biopsy. If ultrasound -, then no biopsy.

--Rectal -, PSA -, then no biopsy.

Subjects are to be randomized into study and control arms. Two randomization and informed consent procedures are acceptable. Post randomization consent is similar to the procedure used in the HIP breast cancer screening trial. Informed consent is sought only from those in the study arm.

For screening modalities directed at each of the four cancer sites, cancer specific mortality for that site is to be the primary endpoint. In addition, cancer incidence, stage shift, and case survival are to be monitored to help understand and explain the results. Biologic and/or basic prognostic characteristics of the cancers will be measured and correlated with mortality to determine the mortality predictive value of these intermediate endpoints.

Tissue specimens from prostate, colon, lung, and ovary biopsies and malignant lesions are required for the intermediate endpoints correlative studies. Although tissue samples from screened subjects will be collected by the screening centers, the analyses of these specimens will be carried out at laboratories participating in a research network under separate contract to NCI for such work. Specimens will be shipped by screening centers to laboratories designated by NCI. Assuming tissue samples from 100% of screened cases and 25% of control cases are collected, tissue will be required from at most about 700 cancers per year, or about 47 cancers per screening center. Samples of all biopsy materials from these subjects are required. Samples of colon polyps are also required. Blood samples from biopsied and polypized patients are also required. Potential molecular and biologic markers of interest would include: chromosome 5q mutations, DNA hypometholation, chromosome 18q deletion, and p53 gene deletion or mutation.

The general timetable of the trial is: protocol development and pilot studies in years 1-2; recruitment and initial screening of subjects in years 3-5; follow up and completion of screening in years 6-8; further follow up in years 9-15; final follow up and data analysis in year 16.

The general plan is to recruit and randomize approximately 10,000 or more subjects to the study at each screening center for a total of 74,000 females and 74,000 males. Proposals are to be solicited from military and veterans' hospitals, HMOs, cancer centers, and university or other groups who are capable of putting together the necessary staff and facilities to recruit subjects, conduct the screening, and follow up all randomized patients for at least 10 years after initial screening.

Minority representation in the aggregate patient population will be sought in appropriate numbers. A single contract is to be awarded for a coordinating center which will be responsible for receiving and processing data in all phases of the study from the screening centers, for quality control, coordinator training, and for logistical support for meetings and other activities required by the project. Laboratory facilities will be contracted to conduct PSA and CA 125 assays.

Certain pilot studies will be necessary in the first two years of the trial. On the basis of these, decisions on the long term commitment to the trial would be made. The major activities to be carried out during the pilot phase are summarized below:

1. Test acceptability of randomization by randomizing 600 subjects per center.
2. Work out the detailed logistics by performing the screening examinations. It is expected that all screening will take place during a single visit lasting not longer than two hours.
3. Assess background level of usage (contamination) of each screening modality by appropriate surveys in each center's population catchment region and among the 600 randomized subjects at each screening center.
4. Assess compliance for each of the screening modalities at each screening center.
5. Test in actual practice all of the data forms and procedures developed during the first year of the pilot phase.
6. Establish procedures to collect, ship, and analyze blood for PSA and CA 125 assays and to collect and ship blood and tissue samples for intermediate endpoint studies.

During the first six months of the pilot phase the study investigators will jointly develop a detailed protocol. Randomization of subjects will begin at six months. Randomization of the first 600 subjects at each screening center and initial screening for those subjects assigned to screening should be accomplished in the second six months. Centers not performing adequately may be dropped and the recruitment load shifted to other centers. Subjects randomized during the pilot phase will be included with the subjects recruited later in the full scale trial. If contamination rates in the aggregate are too high (e.g. routine chest x-rays in asymptomatic smokers) for one or more organ sites, those organ sites may have to be dropped from the trial.

If recruitment during the second six months of the pilot phase is concluded satisfactorily in the opinion of the Policy Advisory and Data Monitoring Panel, then the full scale recruitment will begin in the second year. However, if recruitment is not satisfactory, a second year of pilot studies will be required. Each screening center will be required to randomize a minimum of approximately 10,000 subjects to the trial during the third through fifth year of the study. After recruitment is complete, further screening will be required for three years and annual determination of cancer incidence and of deaths of study subjects will be needed for the remaining years of the study. However, before embarking on this phase of the study, a second decision point will occur at the end of the recruitment phase when the Policy Advisory and Data Monitoring Panel will be requested to evaluate the progress to date including recruitment experience and compliance rates and to recommend whether or not the trial should proceed as planned.

The panel will consist of outside experts with experience in mass screening, clinical trials, appropriate medical specialties, medical ethics, biostatistics, and other appropriate disciplines. Termination of any aspect of the trial may occur at any time that it becomes appropriate.

Screening center costs, in addition to screening costs, for years 1-2 of the pilot phase are set at $1.1 million. The budget for the coordinating center has been set at $600,000 per year for years 3-16 and somewhat less during the pilot years.

Barnett Kramer, head of the Early Detection & Community Oncology Program, said the trial would have "very high power to detect medically significant results." The lowest power is for ovarian cancer: .77 power to detect a 30% reduction in mortality, or .88 to detect a 35% reduction. The pilot phase is expected to cost $4 million. If inflation remains constant, the total cost will be $87.7 million after 16 years.

BSC members were concerned about the trial's complexity and cost. Kramer said no money for the trial would be allocated after the first two years without the board's consent.

Carol D'Onofrio said she was worried about the potential morbidity of the screens, the cost, and "patient anxiety." "I just have trouble supporting the whole package. I'm not sure the whole concept is acceptable," she said.

"There is a certain window of opportunity to do these studies," Kramer said. These screens are "pouring out into the community" and their inefficient use might be leading to "overdiagnosis and overtreatment."

"I would urge you to approve the whole thing," he said. If the board approved only the pilot phase, NCI would have to come back to the board with the continuation plan earlier than under the current proposal and might have less information on which to base its decision.

Harmon Eyre said he had a different concern. "Of the four cancers, there are three that we don't know the cause of, and we don't know how to prevent, so our best strategy is to try to find them earlier. But for lung cancer, we know the cause and we know how to prevent it." This trial, he said, "might be sending the wrong message to the public that it's ok to smoke--you just have to get screened."

"I take your point," Kramer said. Even if all smokers quit, "we will have a major problem with lung cancer in the future. We need a several-pronged approach" including prevention, screening, and treatment.

"The basis for the lung screen (chest x-ray) seems very weak," said Charles Hennekens.

"All of them can be called weak," Kramer said. The estimated contamination rate (smokers getting chest x-rays as part of their usual medical care) for the lung screen is 40%. "We might drop lung cancer after two years. Almost anything could happen."

David Byar, chief of the Biometry Branch, said the question of whether chest x-ray can reduce lung cancer mortality has not been answered, and the fact that prevention is possible "is not comforting to the tens of thousands people who smoked."

"The only question is, how many are already getting x-rays?" Byar said. "Lung cancer is by far the biggest killer, but people have stopped talking about lung cancer screening. I think [its inclusion in the trial] would be a very good bargain."

David Alberts asked about attrition, considering the fact that a person who enters the trial at age 74 will be 90 by the time the trial ends. "That's were the action is, where those cancers occur," Kramer said.

James Holland made the motion to approve the concept, and the board voted six in favor, none opposed and one abstention (Donald McCormick). D'Onofrio, who expressed the most concern about the trial, voted in favor of the concept.

DCPC Faces Huge Out-Year Costs Of Four Major Prevention Trials

NCI's Div. of Cancer Prevention & Control is faced with the prospect of supporting four very large, expensive prevention trials whose most expensive years are just around the corner.

The four trials are the Women's Health Trial, the ASSIST smoking prevention trial, the tamoxifen breast cancer prevention trial and the prostate, lung, colorectal and ovarian cancer screening trial (see previous story).

Division Director Peter Greenwald devoted his recent report to the division's Board of Scientific Counselors to the issue of priorities for the division, in the face of the large commitments required for the four trials.

"We need a balance of high priority items; no single item is of such high priority that it should be supported at the expense of all else," Greenwald said.

DCPC received a substantial budget increase in the FY91 budget, from $134.9 million in FY 1990 to $149.2 million. The prevention and control line, which must be used to fund most of the division's large trials, went from $75.4 million to $83.8 million, an $8.4 million increase.

The division's funds for investigator initiated (RO1, PO1) research rose from $43.4 million to $47.7 million, a $4.3 million increase.

Items in the prevention and control line include CCOPs, which had the largest share of funds, smoking prevention, chemoprevention, diet and nutrition, public health, health promotion, and early detection.

"Since we are an applied division, I believe that over half of our dollars should be allocated to initiatives that have outcomes or endpoints in the 1990s, rather than beyond the year 2000," Greenwald told the BSC at its meeting late last month.

"This has implications for the proportion of the new dollars that we devote to large scale, long term trials. For example, to comply with this strategy for prioritization, in order to fund a very high priority trial that costs $10 million per year and lasts until the year 2005, we would want to see at least a $20 million budget increase in order to be able to balance the long term project with shorter term projects," Greenwald said. He told the BSC that, "Your views on how we can or should accomplish both short and long term gains are most welcome, as such budget increases seem unlikely."

Following is Greenwald's discussion of the major trials and other research areas:

▸**Tamoxifen breast cancer prevention trial**--This trial is being proposed to be conducted as part of the Community Clinical Oncology Program, and Greenwald said he added $2 million to the CCOP budget to begin this trial this year. Two proposals for the trial have been received and reviewed. First year cost of the trial is expected to be $4 million, and $6 million or more in subsequent years.

"In order to do this trial, there will have to be a shift in accruals to CCOP away from therapy trials and into this trial," Greenwald said. "We would like to increase CCOP accrual to both prevention and therapy trials, but just don't see a way to do that. In the long run, we would like to see a balance where approximately half of CCOP accruals relate to prevention and half to therapy. I think that is appropriate for a prevention and control activity."

The two tamoxifen protocols that are under consideration are simple designs, Greenwald said. "I would appreciate advice on second randomization or factoral designs. For example, in high risk women, should we consider a later randomization to 4 hydroxy-phenyl retinamide? There is experimental evidence that this might have an even greater impact on breast cancer risk reduction."

▸**Smoking prevention**--DCPC wants to expand its smoking prevention efforts, Greenwald said. COMMIT and ASSIST are the division's major community intervention projects, and Greenwald added $2 million to the ASSIST budget this year. However, the "big jump in costs" for ASSIST come in FY 1993, when the trial is expected to cost $20.9 million. "In addition to these two flagship community projects, it is important to continue to emphasize networks and coalitions against smoking, and applied, investigator initiated research that will help reduce smoking related cancers."

▸**Women's Health Trial**--As approved by the National Cancer Advisory Board last December, the first phase of the trial (essentially a feasibility study) will begin this year. NCI would establish a WHT policy board, issue an RFP for the coordinating center, develop a final protocol in conjunction with the coordinating center, which would develop and test interventions related to low educational groups and minority populations and gather information on patient compliance. NCI also would issue an RFP for three clinical units including one each in predominantly black and hispanic groups.

"Obviously, experienced and well meaning professionals have divergent opinions about this trial," Greenwald said. "Without some scientific basis for a better consensus, it is difficult to see how we can conduct a trial of such a large scale given the competing priorities. Thus, the next three years will be especially important. It will provide the basis for scale up or for termination.

"An early function of the WHT Policy Board should be to define the criteria for continuing the trial or for terminating after this initial phase," Greenwald said.

"Since it is possible that either for scientific or for fiscal reasons we will be unable to do the full scale trial, alternative research proposals that address the same general scientific issues should be developed. I have asked the DCPC staff to work on that and would appreciate the suggestions of others. As an example, one possibility would be to have an RFA for testing and tracking dietary guidance and its impact on cancer rates in a variety of defined populations."

▸**Early detection trial**--Prostate, Lung, Colon, and Ovary Early Detection Trial, (see story beginning on page 4 for a full discussion) has a two year pilot phase beginning in FY92.

▸**Chemoprevention trials**--"This clinical and public health prevention trials program is showing great promise," Greenwald said. "It has the potential to broaden the practice of oncology to include some aspects of prevention. It also may give us important information about diet and cancer risk reduction. One of the exciting results of the past year has been the report by Hong et al on the chemoprevention of second primary head and neck tumors with 13 cis retinoic acid. We have allocated another $1 million to the chemoprevention budget."

▸**In addition,** DCPC is working on setting up a Biomarker Intramural Prevention Research Branch. "A somewhat larger intramural program is extremely important in helping to build the field of prevention and control both here and across the country," Greenwald said. DCPC at present is 1.8 percent of NCI's intramural program.

Costs Of Long Term Trials

At the optimal levels of funding for the four trials, there will be a large escalation in costs, starting in about FY 1993, as can be seen the chart Greenwald showed the BSC, reprinted below.

DCPC Long-Term Trials And Projects Estimated Costs (Dollars in Millions)

Year	Women's Health Trial	ASSIST	Tamoxifen	PLCO Screening	*Total*
1991	1.7	7.4	4.0	—	13.1
1992	2.5	8.4	8.0	2.2	21.1
1993	2.5	20.9	6.0	2.2	31.6
1994	9.4	22.2	6.0	4.6	42.2
1995	9.3	21.2	6.0	7.5	44.0

Over the next several years, information will become available to help in ranking priorities, Greenwald said. Evaluations will be made of the WHT feasibility study, and COMMIT, which will provide information on whether to continue with ASSIST. The tamoxifen trial would be brought up for review after the first year, and the PLCO trial includes a pilot phase that would require review.

Even with these upcoming evaluations, Greenwald asked the BSC for advice on the following:

"1. At various levels of funding, how should we rank priorities? We would like to be ready to use our full professional judgement (i.e. bypass) budget, should we get it. On the other hand, it is very possible that we will only get a flat budget or modest increases. How do you suggest we budget for a flat budget or for a moderate increase over the next five years?

"2. All four of these long term trials and projects must be done within the cancer prevention and control part of our budget. How do you think we should deal with the fact that it will not be possible to do all of them in the even of modest budget increases?"

BSC Chairman Edward Bresnick suggested that the board plan a smaller meeting or form a committee or several committees to discuss priorities.

RFA Available

RFA CA-91-05

Title: Interventions to promote application of state of the art cancer management in rural areas

Letter of Intent Receipt Date: March 20

Application Receipt Date: May 20

NCI invites applications for research projects aimed at strengthening the application of state of the art cancer diagnosis and management practices in rural areas by enhancing the links between rural health care providers and regional cancer specialists. The researchers are to test methods that enhance the utilization of existing cancer expertise and resources by rural providers. The development and evaluation of interventions that are sensitive to the cancer problems in a selected rural area and are supported by rural practitioners are important. Outcomes should be designed to capture changes in cancer diagnosis and management.

To date, the treatment programs of NCI have been designed to conduct state of the art cancer treatment research through a network of cancer specialists in university centers and community programs. With this initiative, NCI strives to reach practitioners who provide care in rural communities and link them with cancer specialists.

The purpose of this project is to test ways of enhancing links between rural health care providers and cancer specialists. NCI expects the interventions to be designed to strengthen associations between the rural generalist providers and regional cancer specialists, and may include targeted training, visiting specialists, and/or clinical trials participation. Evaluation should address indicators of changes in cancer diagnosis and management practices and efficiency of the intervention.

Based on the characteristics of the health care providers and the patients in the rural area in which the research is to be conducted, the researchers are to test approaches to link rural providers and cancer specialists to enhance state of the art cancer management practices of physicians and nurses in the selected rural area. The interventions should incorporate, as appropriate, established resources of NCI, specifically the Cancer Information Service or the Physicians' Data Query or Cancer FAX. Examples of possible interventions include:

--review of screening and/or biopsy specimens

--computer assisted diagnosis and/or management algorithms

--free telephone consultation between cancer specialist and generalist provider

--PDQ protocols for patient management with specialist consultation available

--telephone hotline service for consultation

The research design should consider both process and health outcome measures as appropriate. The researchers are to focus the intervention on aspects of current cancer patient management that are well described in the baseline data. For example, a pattern of head and neck cancer diagnosis at stages 3 and 4 or the lack of appropriate adjuvant chemotherapy for breast cancer could be the focus. While mortality rate changes may be sought, NCI realizes that the research design may not have the power to discern such changes. An outcome of interest is the stage of cancer at diagnosis and the proportion of patients who receive state of the art cancer management in the target rural area. Changes in practice are extremely important to document, as well as evaluation of the implementation techniques. Numerous direct and indirect indicators are possible.

Inquiries concerning the RFA are encouraged and should be directed to Anne Bavier, Program Director, CORP, EDCOP, DCPC, NCI, Executive Plaza North Rm 300-E, Bethesda, MD 20892, phone 301/496-8541.