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NCI Bid For New Clinical Review Panel Rejected; But Invites Researchers To 'Submit Best Ideas'

NCI has been stymied in its campaign for the creation of a new study section for clinical research and therefore is urging clinical investigators to flood the institute with research applications in an effort to force changes in an existing study section.

(Continued to page 2)

In Brief

NSABP Proposal Selected For Tamoxifen Trial; NIH Building To Be Named After Silvio Conte

NCI EXECUTIVE Committee has selected the proposal of the National Surgical Adjuvant Breast & Bowel Project for the breast cancer prevention trial using tamoxifen. NSABP's proposal was selected over one competitor, and now the actual protocol and funding will be hammered out, according to NCI sources. The trial will be conducted through the Community Clinical Oncology Program. The National Heart, Lung & Blood Institute recently committed funding for heart disease endpoints in the study (see story, page 6). . . . **NIH's CHILD HEALTH** & Neurosciences Building, expected to be completed in July 1992, is being named for the late **Rep. Silvio Conte**, ranking Republican on the House Labor, HHS, Education Appropriations Subcommittee. Conte spoke at a groundbreaking ceremony for the building in 1988. **Other buildings** to be named for former congressman include NIH Bldg. 37, to be named after former Sen. Lowell Weicker, now governor of Connecticut, and the Fogarty International Center, also known as the Stone House, to be named after former Sen. Lawton Chiles (D-FL). . . . **LUTHER BRADY,** chairman of the Dept. of Radiation Oncology & Nuclear Medicine at Hahnemann Univ., has received the Distinguished Alumni Achievement Award at the winter commencement of George Washington Univ. The citation recognizes Brady as "one of the world's foremost oncologists." . . . **CARROLL TEMPLE** has been appointed director of the Organic Chemistry Research Department at Southern Research Institute. He has been at the institute for 35 years. Other promotions: **Dennis McCarthy** to head the Xenobiotics Metabolism Section. **Robert Buckheit** to head the Retrovirus Research Section. **Jim Tucker** to head of the Nondestructive Characterization Section. **Sharon Pinson** to manager of contract administration. . . . **MARTIN MURPHY,** president and CEO, Hipple Cancer Research Center, has been named to the International Advisory Board of the "International Journal of Hematology." . . . **SHELTON EARP** was appointed deputy director of the Lineberger Cancer Center. He was the center's associate director.

'Please Submit Your Best Ideas' For Clinical Research, NCI Says

(Continued from page 1)

Since last fall, NCI officials have complained that clinical research project grant applications do not seem to get a "fair shake" in NIH study sections. Only one in four applications submitted are approved, despite the increasing dollar amounts available in the RPG pool.

NCI officials say they believe this is happening because the study section that reviews most clinical applications also reviews basic science applications, and clinical investigations may not appear to be as scientifically rigorous as basic research.

NCI officials earlier this year asked the NIH Div. of Research Grants to create a new study section specifically for clinical research. Failing that approach, NCI wants the membership of the Experimental Therapeutics 2 (ET2) study section to be changed to reflect a greater emphasis on clinical research.

Creation of a new study section was endorsed by NCI's Boards of Scientific Counselors, as well as the clinical cooperative group chairmen.

According to Cancer Therapy Evaluation Program Director Michael Friedman, DRG has responded by pointing out that ET2, which was created specifically for clinical research, is presently "underutilized."

"Never in its eight year history have there been enough clinical applications for ET2 to deal with," Friedman told the Div. of Cancer Treatment Board of Scientific Counselors at its recent meeting. "Their [DRG's] position is, 'First show us you can utilize it."

NCI plans to talk to the study section members about the problem in an attempt "to reorient them toward a single focus," Friedman said.

Meanwhile, it will be up to investigators to flood ET2 with enough applications to hasten the process.

"We're going to ask everyone to please submit their best ideas," Friedman said. "I realize how thin the trust is," since only one out of four clinical applications are approved. But even one out of four of a larger number of applications "would be two to three fold better than the situation we have now."

A larger number of clinical applications would force ET2 to focus on clinical research and avoid comparison with basic research.

"I don't know whether it's going to work," Friedman said. DRG's argument about the underutilization of ET2 leaves clinical investigators with "very little room to complain."

Criticism Of ET2

"Say the volume of applications increases; can we influence the addition of ad hoc members to the committee?" asked board Chairman John Niederhuber.

Friedman said that's possible, but noted that "sometimes its the clinicians on the panel who have been the most critical," as if they have to prove that clinical research is just as scientifically valid as basic research.

NCI has sent letters to the cancer centers asking for nominations of ad hoc members to the study section.

Board member Ronald Levy said he was an ad hoc member of ET2. "It isn't a body out to fund the best clinical research." The study section should have a more homogenous membership, he said.

"That was the argument that [Centers, Training & Resources Program Director] Brian Kimes and I made," Friedman said. "If ET2 is to be successful [in approving clinical research] it will have to focus on a single thing."

However, Friedman said, "we have to let the body refocus themselves."

"If there are enough applications, they [DRG] will change ET2," DCT Director Bruce Chabner said. "It's hard for bodies that see basic and clinical applications to give clinical applications a fair shake."

"All your skepticism is well founded," Friedman told the board. "We have to try this experiment of refocusing ET2."

Decline Of Clinical Investigator

The lack of grant approval is seen as the "central element" of the larger problem of "the decline of the clinical investigator in cancer research," Chabner said.

That decline includes "inadequate support for clinical training, the declining numbers of clinically trained oncologists entering the field of cancer research, the very poor track record of clinical grants in R01 study sections and the general perception that clinical investigation has a lowly status in departments

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of medicine in this country," Chabner told the BSC.

Funding for the clinical cooperative groups has declined 30 percent in constant dollars since 1980, compared to a 25 percent funding increase in the research project grant pool during the same time.

"In the ET2 study section that reviews R01 applications in clinical trials and experimental therapeutics, only 50 clinical grants were received last year, and of these only 17 percent were funded," Chabner said.

While the P01 pool funds clinically related grants, these are mainly for very large projects lead by well established investigators, he said.

"The current situation reflects limited opportunity for the young clinical investigator to get funding for new ideas. There is a perception that the individual grant application for clinical research will fare poorly in review."

But, Chabner said, there are good ideas that need funding. "It is my feeling that there has never been as much opportunity for innovative clinical research."

His view is supported, he said, by the tremendous response to a recent RFA for small grants in clinical trials research--160 applications.

"While the small grants programs are a start, they cannot be a solution to the problem, because their funding is not derived from the grants pool, but comes from that portion of the budget that has steadily declined over the past 10 years," Chabner said. "The only meaningful solution is to actively encourage an expansion of clinical research activity in the RPG pool."

Chabner said DCT planned to accomplish this by proposing a program announcement to support clinical investigations and new RFAs to encourage development of U01 type clinical trials. He sought the BSC's approval for these programs. (See following story.)

DCT Advisors OK 2 Grant Programs, Disapprove One, In Clinical Research

NCI advisors recently gave concept approval to grant programs in prostate cancer and pediatric cancer and a program announcement, all of which are designed to encourage clinical investigator initiated research.

But the Div. of Cancer Treatment Board of Scientific Counselors also voted down a concept for a new grant program in central nervous system malignancies, and forced the withdrawal of a new grant program in lung cancer.

The four RFA concepts and program announcement are part of DCT's effort to "encourage the expansion of clinical research activity in the research project grant pool," which would increase the amount of money available for clinical research, according to DCT Director Bruce Chabner.

Had all four grant programs been approved, the board would have set aside a total of $4.75 million in first year funding to the RFAs.

However, board members were reluctant to carve such a large amount out of the RPG pool for the specific programs and repeatedly asked Cancer Therapy Evaluation Program Director Michael Friedman to justify the set asides.

Following are the concept statements and board discussion:

New therapeutic approaches to the treatment of prostate cancer. Concept for a new RFA, proposed first year award $750,000, three years.

When prostate cancer is diagnosed early and when still confined to the prostate, the disease can be cured with radical prostatectomy or radiation therapy. For patients with more advanced stages of the neoplasm, treatment is based on the hormonal dependence of the prostatic cancer cell growth. Leuprolide and goserelin (Zoladex) are two LH-RH analogs recently approved for clinical use that obviate the need for surgical castration. Flutamide is a synthetic nonsteroidal anti-androgen that has also shown promise in clinical trials. However, these new therapeutic techniques do no prevent the common development of therapeutically resistant cells. Almost all advanced prostate cancers ultimately fail to respond to androgen deprivation and the mechanisms involved in the development of androgen resistance are not understood.

In recent years, basic researchers have made promising new advances in understanding the mechanisms of growth control in the human prostate cell. The growth and differentiation of benign and malignant prostatic epithelial cells are regulated by androgens which in turn are modulated by growth factors and other hormones. A number of growth factor activities, including basic fibroblast growth factor, insulin growth factor 2, transforming growth factor beta, and transforming growth factor alpha, have been isolated from prostate cancer cell lines. Clinical trials utilizing suramin, which interferes with heparin binding growth factors, have recently shown responses in advanced prostate cancer. The mechanism of action of suramin is still not completely understood, and ancillary laboratory studies need to be done. In addition, biological response modifiers in combination with chemotherapy have achieved promising results in other tumor models but have not been adequately explored in prostate cancer. Many opportunities exist to develop new treatment strategies in prostate cancer utilizing laboratory advances in understanding tumor growth and hormonal control.

While there is limited funding of research on the etiology, diagnosis, and cell biology of prostate cancer, there are no R01 grants on prostate cancer in the Cancer Therapy Evaluation Program. NCI wishes to support clinical research in the R01 grant pool on prostate cancer.

The purpose of the project is to provide funding for clinical trials in prostate cancer that take advantage of new developments in the laboratory or correlative laboratory studies that are relevant to therapeutic clinical trials. Applications should be focused on integrating clinical goals with laboratory research areas. Clinical studies should be designed to improve cancer treatment.

Examples of new clinical trials include 1) hormone therapies

utilizing new agents, 2) treatment therapies for overcoming hormone, drug, or radiation resistance, 3) treatment therapies based on novel mechanisms of action, 4) biologics in combination with drug or radiation regimens, 5) immunotherapies including monoclonal antibody therapy, radioimmunobiology, and the use of new immunotoxins, 6) new therapies combining endocrine manipulations with chemotherapeutic agents, and 7) radiation modifiers to enhance cell kill or protect normal tissue.

Examples of therapeutic correlates that would be measured in patients or tumors include 1) hormone or receptor alterations that correlate with the development of hormone resistance, 2) studies of phenotypic or genotypic alterations correlated with drug or radiation resistance, 3) correlation of tumor growth factors or oncogenes with response to growth factor targeted therapies, 4) pharmacokinetic and pharmacodynamic measurements, and 5) biochemical pharmacologic parameters. Analysis of racial differences in clinical and laboratory parameters should be considered.

Four to five grants would be funded through the prostate RFA. "This is the most effective way of stimulating research," CTEP Director Friedman said. "It assures that the money is out there. This is priming the pump."

However, board members noted that this program calls for a special review committee. Given DCT's effort to encourage clinical applications to the regular NIH clinical study sections (see previous story), some board members wondered why DCT would draw these applications away from that pool. "When I proposed this [program] to Experimental Therapeutics 2, they suggested a special study section," Friedman replied.

"I have trouble with special study sections," said JoAnne Stubbe, Massachusetts Institute of Technology. "We'd all like our grants to go to special study sections."

"But we have a problem that they're not approving grants," said Board Chairman John Niederhuber, Johns Hopkins Univ.

"[Members of] ET2 are very intelligent people, but they don't see this as a priority," said Victor Ling, Ontario Cancer Institute.

"There's no criticism intended for ET2, but it's going to take months if not years to reorient them," said Friedman. "The question is what do we do in the meantime?" He promised to report to the board on the progress of the grants.

"Prostate cancer is an underserved area," said Paul Carbone, Univ. Of Wisconsin Clinical Cancer Center. "I'm all in favor of this--I'm getting older."

The concept was approved, with Stubbe opposed.

New therapeutic approaches to the treatment of localized (early stage) lung cancer. Concept for a new RFA, proposed first year funding $2 million, multiple awards, three years. (This concept was withdrawn). The concept statement said CTEP is proposing to stimulate research in lung cancer through the financial support of multidisciplinary teams of talented and experienced individuals who will determine team approaches to improving the cure rate of patients with lung cancer according to their own perceptions of scientific opportunities. Clinical trials would be conducted that take advantage of new developments in the laboratory, or that attempt innovative approaches to treatment. Some possible areas the concept listed for clinical research included 1) oncogenes, tumor suppressor genes, and chromosomal abnormalities, 2) growth factors, 3) drug resistance, 4) chemotherapeutic agents with new or unusual mechanisms of action, 5) immunotherapies, 6) chemoprevention, and 7) early detection.

"Once again, when you take money out of the RPG pool, you can't fund R01s," said board member Ronald Levy, Stanford Univ.

But Friedman pointed out that there are no R01 grants in this area. "Are there no good ideas? Are there no good investigators? Our analysis is that there are good ideas and there are good investigators, but the system hasn't supported them," he said. "Even if the system were friendly, you'd need a multicenter R01. There's even less chance of supporting that than clinical R01s."

"What are the ideas?" Carbone asked. Friedman listed prospects for stage 3A disease, use of chemotherapy and radiation in combination, increased local control of the disease, and radiosensitizers.

Stubbe asked why Friedman had chosen lung cancer for an RFA concept, as well as the topics of the other three RFA concepts.

"By how little is going on in these areas. They are undersubscribed," he said. There are 150,000 new lung cancer cases each year.

"The amount of basic information about non-small cell lung cancer is lacking compared to other areas; there's certainly less information than in breast cancer and information about determinants of drug response is minimal," said DCT Director Chabner. "We'd like to do [this type of research] through the [cooperative] groups, but we haven't been successful in the past."

"Perhaps the reason this is not done is because there is little to be done--there are more exciting areas," said Loretta Itri, RW Johnson Pharmaceutical Research Institute.

"Lung cancer in terms of therapy has been a disaster," said Carbone. "It would be nice to get a group together and say, here are some ideas, these are some pilot studies that need to be done. But for this disease, prevention is the way to go. My bias is to get a few good pilot ideas, and then get resources to do it. I'm reluctant to say here are the resources and now look for ideas."

"Who's going to support pilot studies?" asked Chabner.

Friedman withdrew the concept, and Chabner

suggested that CTEP develop a program announcement on biologic activity in lung cancer.

Clinical cancer therapy research. Concept for a program announcement.

NCI supports an extensive network of clinical and laboratory research studies through contracts, grants, and cooperative agreements. The primary means by which new clinical concepts and basic research ideas evolve is through investigator initiated research, supported through research project grants (R01, R29, R37) and the larger research program project grants (P01). In 1990, NCI received nearly 2,500 unsolicited R series applications. Of those assigned to the Cancer Therapy Evaluation Program, only 103 proposed clinical therapeutic studies of cancer. This is a startlingly low submission rate in view of the relevant new knowledge available in cancer biology and drug development and the interest in developing new therapies.

In order to reverse this trend in clinical therapeutic grant submissions, NCI proposes two steps be taken: 1) a program announcement for clinical cancer therapy research to attract new grant proposals should be published, 2) the Experimental Therapeutics 2 study section in the Div. of Research Grants should be designated specifically for the review of clinical research grant proposals. This would demonstrate NCI's commitment to identify and fund outstanding clinical research proposals.

The Div. of Cancer Treatment encourages qualified investigators to develop new grant applications (R01, R29) involving clinical therapeutic studies of neoplastic diseases. Clinical studies should be designed to improve cancer treatment. The applications should include single or multi-institution patient driven research studies (clinical trials) with appropriate biological correlates linked to these studies. New clinical therapeutic studies employing drugs, biologics, radiation, or surgery--whether used as a single agent/modality or in combination--are appropriate.

Some examples of clinical research areas include 1) mechanism of action and metabolic studies of chemotherapeutic agents, 2) studies of mechanism of drug toxicity, drug resistance and reversal, 3) mechanism of action of biologic response modifiers in the treatment of cancer, e.g., cancer immunotherapy (monoclonal antibodies, cytokines, vaccines) alone or in combination with chemotherapeutic agents, 4) new radiation or surgical therapies in combination with therapeutic agents. Investigators are not limited to the above areas of potential studies. Clinical research, by definition, must involve and clinician-patient subject interaction with a therapeutic intent.

The concept was approved unanimously.

Phase 1 trials of new cytotoxic and biologic agents in children with cancer. Concept for a new RFA, cooperative agreements, proposed first year award $1 million (multiple awards), four years.

A large body of evidence supports the concept that childhood malignancies differ remarkably from adult malignancies in their biology as well as their response to therapy. In addition, children tolerate chemotherapeutic agents to a greater or lesser extent than adults, making the direct application of adult phase 1 data inappropriate. Pediatric phase 1 trials thus are becoming increasingly difficult to perform, thereby jeopardizing timely evaluation of promising new agents for children with cancer. An intrinsic problem of performing pediatric phase 1 trials is the relatively small number of children with cancer, compared with adults with cancer. The number of pediatric patients available for phase 1 trials has been reduced even further in recent years by increasingly intensive initial therapy which makes many children ineligible for entry into subsequent clinical trials.

The problem of the small pool of patients eligible for phase 1 trials mandates that these trials be performed in multi-institutional settings, since single institutions do not accrue adequate patients to complete trials in a timely fashion. However, the ability of the pediatric cooperative groups to perform phase 1 trials is restricted by the limited resources available to the cooperative groups. The cooperative groups have operated under level budgets since 1987, which when combined with inflation in medical costs has meant a decrease in actual resources available. At the same time that group resources have dwindled, the complexity of laboratory correlative studies associated with phase 1 clinical trials has increased dramatically. For example, many of the most interesting new agents are biological, which require laboratory evaluation of the modulating effects of the agents on the patients' immune and hematopoietic systems. Additionally, phase 1 trials of cytotoxic agents require increasingly sophisticated pharmacokinetic studies of the agents, their metabolites, and their intracellular disposition. Without additional sources of support for the evaluation of new agents in children with cancer, the timely evaluation of these promising agents will be severely compromised.

NCI is seeking a consortia of institutions who will interact with extramural program staff to perform phase 1 trials of anticancer agents in pediatric cancer patients. Scientific approaches should reflect the creativity and capabilities of participants. Objectives and approaches will be investigator originated, with participants funded via cooperative agreements.

Integrated packages of individual applications are encouraged, with the lead institution of a proposed consortium indicating which participating institutions will provide organizational support, scientific leadership, laboratory capabilities, and/or patient resources. Institutions will be evaluated with regard to their proposed roles in the consortium and those deemed meritorious will receive individual cooperative agreements.

The cooperative agreements are not intended to support those costs associated with the maintenance or establishment of laboratory or other facilities, which should be supported by other mechanisms. These cooperative agreements are intended to support the additional costs of clinical research associated with phase 1 studies, such as data collection, sample handling, additional professional time, and the like.

Proposed consortia must have the following capabilities: 1) documented numbers of eligible patients with a history of adequate accrual to perform 5-6 phase 1 trials in a two year period, 2) laboratory support within the consortium to perform pharmacokinetic studies of both cytotoxic and biologic agents, including monitoring of metabolites and intracellular products when appropriate, or other relevant laboratory correlative studies, 3) laboratory support within the consortium to measure relevant indicators of biologic response and 4) adequate central data collection and processing capabilities including documented ability to comply with required phase 1 reporting guidelines as well as biostatistical expertise.

The number of participating institutions to perform phase 1 trials within each applying consortium must be limited to 12-15 because of limitations related to regulatory and quality assurance monitoring requirements.

Institutions associated with a consortium should meet the following requirements: 1) at least two full time physician investigators with demonstrated expertise in phase 1 and 2 studies, with at least one of these available at all times via a 24 hour phone number, 2) intensive care and blood bank facilities on site and functioning 24 hours per day, 3) adequate physician, nursing, and data management resources to comply with all data reporting requirements of NCI sponsored phase 1 trials, 4)

adequate physician, nursing and laboratory resources to collect, process, and ship required specimens in a timely fashion for pharmacokinetic and other laboratory correlative studies, 5) appropriate drug control procedures as required for utilization of NCI supplied experimental agents, and 6) adequate patient accrual with annual monitoring to ensure continued enrollment of patients on phase 1 trials.

It is anticipated that one or two consortia will be supported to provide the capability of performing five or six pediatric phase 1 trials annually.

The $1 million set aside will fund two grants, Friedman said. Board member Donald Kufe, Dana-Farber Cancer Institute, asked why this program could not be done through contracts. Chabner and Friedman said contract funds are "being squeezed" every year.

Again, the board was reluctant to set aside funds from the R01 pool for RFAs. Chabner suggested the amount be cut to $500,000. Carbone moved approval of the concept at that amount. "This is a new area--it would be reasonable to move slowly," he said. But the board defeated the motion 4-6, with two members not voting.

William Hryniuk, Ontario Cancer Foundation, moved the board approve the concept at the level requested, $1 million. But that motion was defeated 5-7.

Carbone then moved approval of the concept at $750,000. That motion was approved, with eight board members in favor.

Treatment of central nervous system malignancies in adults. Concept for a new RFA (cooperative agreements), first year funding $1 million, three years. (This concept was disapproved).

The concept proposed to support one or two teams of investigators to conduct clinical trials that take advantage of new developments in laboratory science, imaging procedures, therapeutic irradiation techniques, or other innovative approaches. Clinical research could include phase 2 and phase 3 evaluation of cytotoxic drugs, interstitial irradiation, three dimensional conformal irradiation, hyperthermia, immunotherapy, or other techniques of systemic or local-regional treatment.

Robert Holden, Wishard Memorial Hospital, asked what happened to the Brain Tumor Study Group. That group "has had a great deal of difficulty accruing patients," Friedman said. The BTSG will be recompeting in a year and a half and could apply for this program, he said. "We think opening up the field to others would be a good thing to do," he said.

"I like some of the ideas," said Mark Groudine, Fred Hutchinson Cancer Research Center. "There's a lot to be done to come up with better therapies. By putting aside the money you will come up with better approaches to therapy."

Carbone moved approval of the concept, but the anti-set-aside feeling in the board ran strong, and the concept was disapproved 4-6, with two abstentions.

NHLBI Advisors Commit Funding To Women's Health, Tamoxifen Trials

The National Heart, Lung & Blood Institute's Advisory Council recently gave concept approval to two NCI research initiatives to study the incidence and etiology of coronary heart disease in conjunction with breast cancer in postmenopausal women.

The council committed $1.4 million to fund the heart disease endpoints in the Women's Health Trial, and $9.5 million to the tamoxifen chemoprevention trial.

With the involvement of NHLBI, the Women's Health Trial will attempt to determine whether a diet with only 20 percent of calories from fat can reduce the incidence of breast cancer and heart disease. The two institutes will conduct a joint, three year feasibility study of 3,000 postmenopausal women, that will serve as a pilot phase of the full scale trial, which would eventually involve 24,000 women.

William Harlan, director of NHLBI's Div. of Epidemiology & Clinical Applications, told the council that, "As the dietary fat intake increases, the age-adjusted death rate from breast cancer increases as well."

One of the main issues the feasibility study must answer is whether minority groups and low socioeconomic status women can be recruited and adhere to the diet. NCI will fund a coordinating center and three clinical centers for the feasibility phase.

NHLBI will provide $1.4 million over three years to support a cardiovascular center to work with the NCI centers on the feasibility study. The feasibility study will also examine the effect of a low fat diet on blood lipid levels.

If the feasibility study is successful, RFPs will be issued for the main, multicenter trial, which will follow the women for a minimum of 10 years.

Jacqueline Flowers, director of the Office of Minority Affairs for the Associated Medical Schools of New York and a member of the advisory board, cautioned the institutes "to consider cultural factors with the diet," because the focus of the intervention is a lower-income, ethnic population.

Peter Greenwald, director of NCI's Div. of Cancer Prevention & Control, replied that "that was the whole point of this continuing feasibility study."

Other members of the advisory board asked how compliance with the diet will be measured. Greenwald said that the study would employ "state of nutrition surveillance." Earlier studies, he said, had shown the capability to monitor fat intake "as best you can judge

without having a good blood marker."

Following is the NHLBI concept statement for its involvement in the WHT:

Clinical trial to test the hypothesis that a low fat diet prevents heart disease and breast cancer in postmenopausal women--feasibility study. Proposed RFP, 3-year duration; total NHLBI funding $1.4 million; $200,000 in FY 1992, $600,000 in each of FY93 and FY94.

The primary objectives of the feasibility study are: to determine the feasibility of recruitment and dietary intervention in minority and/or low socioeconomic status (SES) postmenopausal women, and to assess the effect of the low fat eating pattern on blood lipids in postmenopausal women.

The feasibility study would further examine the differences among SES and racial/ethnic groups for dietary and blood lipid response. While complete answers are not expected, the feasibility study will also evaluate the risk relationships of CHD with diet, blood lipids, and other risk factors in postmenopausal women.

If the feasibility study is successful, a full scale trial would be implemented which would include feasibility study participants. The primary objectives of the full scale trial are: to determine whether a low fat dietary pattern can reduce the incidence of breast cancer and fatal and nonfatal coronary heart disease (CHD), and to determine the effect of a low fat dietary pattern on total mortality in postmenopausal women.

Secondary objectives of the full scale trial are to assess the safety of a low fat dietary pattern on the incidence of fractures and selected indices, including functional status and quality of life in postmenopausal women.

The major prospective primary prevention clinical trials that demonstrate a reduction of CHD events by lowering of plasma cholesterol levels have been conducted in middle-aged men. Studies in men have shown that restriction of dietary fat and cholesterol can lower plasma total and LDL cholesterol. There have been no trials in women to study the effects of lowering lipids on CHD incidence, either by diet or drugs. Nor have any intervention studies been conducted in postmenopausal women to determine the long-term effect of a low fat diet on lipid levels. There are only a few studies on the efficacy of lipid lowering diets in women; the number of subjects studied has been small, the length of dietary periods relatively short and the results inconsistent. Further, a recent NHLBI Workshop on Cholesterol in the Elderly and Women called for clinical trials to demonstrate that lipid lowering interventions decrease CHD risk in women.

The etiology of both breast cancer and coronary heart diseases have been linked through international studies to the consumption of high fat diets. Studies show a strong positive correlation of per capita fat consumption with breast cancer incidence (R=0.79) and mortality (r=0.89) rates. An examination of the relationship between per capita fat consumption and breast cancer rates for women aged 45-69 years in 21 countries suggest that dietary factors explain much of the international variation in breast cancer incidence rates. Migrant studies of Japanese and Italian women show that the incidence of breast cancer has been increasing in successive generations as does the intake of dietary fat.

The proposed project is randomized, controlled, multi-center trial. Minority and/or low SES women, aged 50-69 years and currently consuming >= 38 percent of total calories as fat, would be eligible for randomization to either a control group (minimal information on dietary recommendations to lower fat) or an intervention group (intensive dietary counseling). The feasibility phase will include 3,000 women recruited at three clinical centers, with 60 percent randomized to the control group and 40 percent to the intervention group. These women would form a vanguard group for the full-scale trial. The dietary intervention would be designed to reduce total fat (to 20 percent of calories) and saturated fat and to increase fruits, vegetables, and grain products.

If the feasibility phase of the trial is successful, as judged by successful recruitment and dietary adherence, a full-scale trial would randomize 24,000 women, aged 50-69 years, and follow these women for a minimum of 10 years. Women participating in the feasibility phase would be continued as part of the full-scale trial.

The sample size for the feasibility study is based on funding of three clinical centers to recruit at a rate comparable to the full-scale trial schedule of 500 women per center per year.

NCI proposes to support a coordinating center and three clinical centers for three years in the feasibility phase. The first 6 months of the contract would be for protocol development and training of staff. Recruitment would extend over two years, with the expectation that 500 women will be randomized per clinic per year to reach a total of 3,000 women. The last 6 months of the feasibility phase would be for data collection and analyses and preparation for the full-scale trial. NHLBI proposes to support a Cardiovascular Center to work with the NCI coordinating center and clinical centers.

If as a result of the feasibility study a full-scale trial should be conducted, the full-scale trial would last 15 years; a projected four years for recruitment and a minimum of 10 years for follow-up. Approximately 12 clinical centers would participate in the full-scale trial.

The feasibility study is seen as a vanguard group. If a full-scale trial is conducted, the feasibility study participants would become part of the full-scale trial. Therefore, measurements for the feasibility study participants approximate those planned for the full-scale trial. The measurements and workscope for the trial are as follows:

--surveillance of clinical non-fatal and fatal CHD events in all participants;

--surveillance of fractures and selected indices of safety and quality of life such as mobility and function on all participants;

--electrocardiograms at baseline on all participants to detect subclinical (silent) myocardial infarction.

--lipoproteins on all participants at baseline and 10 percent sample of both control and intervention women at one follow-up;

--total cholesterol and triglycerides in a 90 percent sample of both the control and intervention groups at 12 months.

--blood pressure measurements on total sample at baseline and follow-up visits;

--support of a Coordinating Center for administrative functions, monitoring quality of data, clinical center staff training, verification of endpoints and subcontracts [subcontract for CDC standardized lipid laboratory, subcontract for electrocardiogram readings, and subcontracts to clinical centers for data collection];

--representation of NHLBI Program and Contract Staff on steering and monitoring committees.

Tamoxifen Trial

In his concept presentation, NHLBI's William Harlan said the basis for the second FY 1992 joint initiative is a fundamental conflict of prevention efforts in postmenopausal women: estrogen replacement therapy decreases the incidence of coronary heart disease in these women, but seems to be a risk factor for the development of breast cancer.

"Obviously if one could find an agent that in fact would inhibit the growth of breast cancer and yet

have some estrogenic replacement effect it would be quite beneficial," Harlan said.

The compound tamoxifen, which he described as "an interesting agent, a prototypic estrogen antagonist that has apparently some agonist activities," could be that dual-benefit agent.

NCI has approved a seven year trial to determine the efficacy of tamoxifen therapy in preventing breast cancer. That trial will be conducted through the institute's Community Clinical Oncology Program.

The NHLBI initiative will add a total of $9.5 million for a Cardiovascular Risk and Events Coordinating Center that would oversee the monitoring of cardiovascular factors and the incidence of heart disease in the 16,000 women enrolled in the NCI protocol.

The council approved the concept with little discussion.

Trial of tamoxifen in postmenopausal women to prevent breast cancer, coronary heart disease, and Bone fractures. Proposed RFPs, 7-year duration; total NHLBI funding $9.5 million; first-year NHLBI total: $1.4 million.

The primary aim of this trial is to assess the impact of tamoxifen on the development of breast cancer. The secondary aim of the study is to evaluate the effects of tamoxifen on the development of coronary heart disease and fractures.

Tamoxifen is a non-steroid compound that has anti-estrogenic as well as estrogen-agonist activity. Tamoxifen has proven to increase survival significantly in pre- and postmenopausal women with either node-positive or node-negative breast cancer. This agent is believed to exert its activity against breast cancer by blocking estrogen receptors on breast cancer cells and inhibiting cell growth. Currently, tamoxifen is approved to be used as an adjunctive treatment following breast cancer surgery or radiation. Major toxicity has been very infrequent, and clinical experience with this agent spans 10 to 15 years, during which it has been extensively used in some hundreds of thousands of women. Some studies have confirmed a significant benefit in preventing the development of cancer in the contralateral breast when administered following breast cancer on one side. Several lines of evidence suggest that tamoxifen may prevent coronary heart disease.

A recent overview by the Breast Cancer Collaborative Group of all adjuvant therapies for breast cancer on a total of 100,000 patients followed for 5 to 15 years after initiation of therapy demonstrates an overall improvement in survival of 28 percent in Tamoxifen-treated patients compared to controls. An important component of this advantage was accounted for by a 38 percent reduction in vascular deaths (coronary heart disease and stroke), which was highly significant ($p < 0.005$). Recent studies indicate a possible explanation for the apparent beneficial effect of Tamoxifen on development of cardiovascular disease. This agent in a dose of 10 mg per day lowers total serum cholesterol by about 20 percent. This reduction is principally due to a lowering in LDL-cholesterol.

NCI will conduct a randomized controlled trial of primary prevention of breast cancer in postmenopausal women, the majority of whom will be at increased risk for breast cancer. A study of 16,000 women, half randomized to receive tamoxifen 10 mg daily, will be conducted using the Community Clinical Oncology Program network.

Each hospital may elect to participate or not in a particular protocol. The clinical oncology studies conducted by these facilities are supported by grants that vary by participation in studies. Study protocols are developed by "science base" coordinating centers in concert with NCI. These centers are separately grant-supported for their effects in planning, organizing, conducting, and analyzing trials in which the cooperating community facilities are involved. NCI has obligated funds for a 7-year trial.

NCI has indicated an interest in having NHLBI collaborate by measuring cardiovascular risk factors and events in the cohort. The future utilization of this agent for breast cancer prevention may depend on its ability to prevent coronary heart disease and/or osteopenia, two of the most common conditions of menopause that are often managed by administration of estrogen.

It is proposed that the NHLBI measure serum lipids and lipid fractions as well as other principal cardiovascular risk factors, their changes on tamoxifen therapy and the fatal and nonfatal cardiovascular events (coronary heart diseases, stroke, and thromboembolic disease).

An RFP would be issued for a "Cardiovascular Risk and Events Coordinating Center." This center would develop collaboratively with NHLBI and NCI staff a final protocol for assessment of risk and events. It would be responsible for training of CCOP personnel in collection of data for risk and endpoint assessment, as well as obtaining blood and electro-cardiograms. Payment would be made to clinic staff to collect the additional cardiovascular data. The cardiovascular coordinating center will provide or subcontract for measurement of blood cholesterol and triglycerides in all participants and other lipid fractions as outlined in the annex to this initiative. Data will be managed by the cardiovascular coordinating center and edited tapes merged with data tapes from the NCI center for analysis.

NCI's Cancer Prevention Fellowship Now Offers Master Of Public Health

NCI's Cancer Prevention Fellowship Program now offers fellows an opportunity to attend an accredited school of public health for up to one year to obtain a master of public health degree. The training will constitute the first year of the fellowship.

The enhancement was recently approved by the Div. of Cancer Prevention & Control Director's Committee, the NCI Executive Committee and the NIH Legal Counsel. In the second and third years of the program, the fellows will report to NCI for prevention and control research.

The CPFP is a three year training program designed to prepare oncologists, other physicians, and scientists from a variety of disciplines for a career in cancer prevention research and public health applications. Fellows are expected to stay in the program for twice the amount of training time, or pay the government for the costs of training. The program began in 1987 and has selected 22 fellows.

For more information on the program, contact Douglas Weed or Barbara Redding, 301/496-8640.