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FDA Softening Its Stance On CME Guidelines; New Version To Be More In Line With ACCME

The Food & Drug Administration appears to be softening its proposal to impose strict guidelines on the types of continuing medical education the agency will allow drug companies to support without the activity being considered promotional. The agency received more than 200 letters objecting to the guidelines proposed in a "draft concept paper" released last fall. The concept described FDA's intent to establish "a category of educational activities that may continue to be funded by drug companies, yet avoid regulation as advertising or promotional labeling" (**The Cancer**

(Continued to page 2)

In Brief

Robert Cooper, Regional Cancer Center Director, Dead At 59; NCI Critic Epstein Invited To NCAB

ROBERT COOPER, director of the Univ. of Rochester Cancer Center, died suddenly March 19 at Strong Memorial Hospital of a heart attack. He was 59. Cooper was instrumental in establishing the cancer center in 1974, one of the first regional cancer centers created as a result of the National Cancer Act of 1971. He organized the system which provides cancer care through five community hospitals, a model that has been adopted by other cancer centers. Last year, Rochester successfully competed for renewal of its cancer center support grant. He also served on many advisory panels including the NCI Div. of Cancer Prevention & Control Board of Scientific Counselors, the Cancer Center Support Grant Review Committee, and the awards jury of the Albert & Mary Lasker Foundation. Cooper is survived by his wife, Stephanie, three sons from a previous marriage, daughter in law, granddaughter, his mother, two sisters, a brother, and five stepchildren. His first wife died in 1989. Memorials may be made to the Univ. of Rochester Cancer Center, Box 704, 601 Elmwood Ave., Rochester, NY 14642. . . . **SAMUEL EPSTEIN,** prof. of epidemiology at Univ. of Illinois and a critic of NCI's cancer causation, prevention and control efforts, has been invited to address the National Cancer Advisory Board at an upcoming meeting. The invitation was hotly debated among NCI executives, but the idea, one said, is to "get some facts on the record" to dispute Epstein's claim, at a recent Washington media blitz, that "We're losing the war on cancer" (**The Cancer Letter,** Feb. 14). . . . **ALFRED KNUDSON,** senior member of Fox Chase Cancer Center, was named a Fox Chase Distinguished Scientist and advisor to the president by the center's board of directors. The sole previous recipient of the award is Nobel laureate Baruch Blumberg.

FDA Softening Stance On CME Funded By Drug Companies

(Continued from page 1)

Cancer Letter, Jan. 3). The concept established a series of tests to determine whether an activity is promotional. Some of those tests were widely criticized as being burdensome and bearing little relationship to clinical practice.

Ann Witt, acting director (as of April 1) of FDA's Div. of Advertising, Marketing & Communications, the division that released the concept paper, told the annual meeting of the Assn. of Community Cancer Centers in Washington that FDA remains concerned that clinicians receive balanced information about drug products.

However, FDA is working more closely with accrediting organizations such as the Chicago-based Accrediting Council for Continuing Medical Education to develop less onerous guidelines.

The rewrite might come too late for some medical education activities that have been hurt by the initial concept, sources told **The Cancer Letter.** "There is an impact already," one cancer center executive said. "Pharmaceutical houses are running scared, even though the guidelines are not in final form. I've had three companies turn down our request for meeting support. I don't know how much of it is a gimmick to avoid spending money, but there really is no reason for a company to hold back support until final guidelines come through."

FDA intends to circulate a new draft of the concept paper by the end of April, and it promises to be less legalistic and more general, sources told **The Cancer Letter.**

In her address, Witt said the medical community has to make sense of a staggering amount of information coming from a wide variety of sources. Information that is distorted by firms promoting their products can impair the sources health professionals rely upon for their independence and impartiality.

"People say FDA has no right to regulate medical education. They're right, we don't," Witt said. "We have the right to regulate prescription drug promotion."

In recent years, drug companies have been using novel methods of promotion that serve to lower a health professional's natural skepticism of advertising, Witt said. These practices include:

▶Promotion in the guise of news. Video news releases sent to local television stations that look like regular TV news reports but serve only to provide information on a particular product.

▶Promotion in the guise of market research, in which a company invites health professionals to "focus groups," but instead of asking the professional for information, the company provides information on its products.

▶Promotion in the guise of medical education. "We recognize that pharmaceutical firms support much medical education that is legitimate and important for scientific exchange," Witt said. "But it doesn't mean companies should have free reign to distort medical education."

FDA is particularly concerned about the following types of activities, Witt said:

--Symposia in which a drug company is the sole supporter, selects the speakers, the studies that are presented, and the slides shown.

--Supplements to symposia proceedings. Witt gave a recent example: An Italian drug company submitted an IND for an oncology drug describing studies done in lung cancer. There was one positive study and other negative studies. Then, at an international congress in 1990, the company sponsored a symposium and invited only the investigators who conducted the positive study. The proceedings of the symposium were published as a supplement to the congress proceedings in a respected, peer reviewed journal. FDA asked the firm what plans it had to disseminate the negative results: none. FDA took no action, and the company closed accrual on those trials.

--Peer influence groups. Here's how Witt described this practice: Local sales representatives will invite health professionals to dinner meetings ostensibly to provide information on its products. The company reps will ask for comments, and call on certain participants whom they know to be high prescribers of their product. This is designed to influence other participants to use the product, Witt said.

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These activities "degrade and reduce the credibility of sources of information," Witt said. "When you read an ad, or get a visit from a detail person, you have some skepticism. But if you attend an educational symposium you may be more likely to be swayed."

Drug companies are not allowed to promote their products for unapproved, off-label uses. However, Witt said, FDA does not want to eliminate medical education or discussion of unapproved uses. "Those uses are often essential, particularly in oncology and pediatricts," she said.

"Therefore, our goal is to create a category of medical education that drug companies can fund, but we won't hold them responsible for discussion of unapproved uses," she said.

FDA would allow companies to fund independent programs, or programs for which they have chosen the topic, but have not chosen the speakers or the papers presented. These programs should be "objective and balanced," Witt said.

Items To Be Removed From Concept

Witt listed the items that were strongly opposed in the first concept paper and will not be included in the next draft:

▶Repetition of presentations ("traveling road shows") will not be considered a factor that determines whether a presentation is promotional. "We heard that there are many programs that deserve to be repeated, so we no longer will say that a repeat is evidence that a program is promotional," Will said.

▶Programs about a single drug product will not necessarily be considered promotional but, "We may look closely at it," Witt said. That provision had drawn fire from FDA's own oncology division.

▶A widely criticized provision in the first draft would have held sponsoring drug companies responsible for the information presented in a program even if the company had no control over the material. "If a program is truly independent, we will not hold the drug company responsible for that information," Witt said.

▶Many of those who commented on the draft paper suggested that FDA defer to accrediting organizations such as ACCME to determine whether programs are promotional. "Their guidelines are not as strong as ours, but we are working with them," Witt said.

"What we need to see from the accrediting organizations is the capability to monitor the programs they accredit. If they can monitor programs, then we will have a provision that sponsors should rely on ACCME guidelines," she said. "We're also open to proposals from other accrediting organizations, associations, and nursing organizations."

Robert Temple, director of FDA's Office of Drug Evaluation 1, told the ACCC meeting participants that the agency is following up its crackdown on promotion of unapproved uses with more aggressive efforts to approve the most common secondary uses of oncology drugs.

FDA and NCI officials have met to identify some of the most widespread off-label uses, and FDA is beginning to meet with some drug sponsors.

"It is the drug company's responsibility to file claims for new indications," Temple said, noting that in the past, companies have considered the process onerous and expensive. However, FDA has reduced the time it takes to approve new uses for oncology drugs to a year, Temple said. Since there are no new uses under consideration at the moment, "we have plenty of room to deal with new uses if anyone would submit them," he said.

Companies will be asked to do a literature search documenting their claim for a new indication. "In many cases, the literature will be sufficiently detailed to support the indication," Temple said. "In other cases, we know we will require information from data tapes, with no need to conduct further studies." In some cases, NCI and the companies will be encouraged to support further studies.

"I'm optimistic, but cautiously so," about the attempt to speed secondary approvals, Temple said. "Some of the uses are not supported by data that could be called controlled."

Temple emphasized that FDA has often stated that physicians can decide how to use an approved drug. In an effort to control costs, insurance companies began refusing to reimburse for drug uses they termed "investigational."

The General Accounting Office survey released last fall (**Cancer Economics,** October 1991) showing that at least a third of all cancer drugs administered to patients are for off-label indications, demonstrated that most reimbursement problems arise "in areas where it is not clear what is the definitive treatment," Temple said.

"Reimbursement is an irritant," Temple said. "We have no position as an agency on reimbursement for off-label uses. We have supported remibursment for NCI Group C and Treatment IND drugs, and our position is that investigational uses may represent the best available therapy."

Not every use that is listed in the drug compendia can be included on the label, Temple said. "We're comfortable with the fact that the physician will base a treatment decision on more than what's on the label."

NCI Advisors Ok Etiology Trial In Farmers, Agricultural Workers

Advisors to NCI's Div. of Cancer Etiology have given concept approval to a long-term prospective study of cancer among farmers, their families, and other agricultural workers.

The DCE Board of Scientific Counselors last week committed $6.63 million to fund the study through contracts over the next five years. The Environmental Protection Agency will collaborate and has promised $6.24 million, while the National Institute of Environmental Health Sciences will provide $1 million. NCI is also approaching other agencies.

"The questions about the carcinogenicity of pesticides just don't go away," said board member Pelayo Correa, chairman of the ad hoc advisory committee for the proposed study. "You can do case-control study after case-control study, but you can never be sure. Our committee concluded that this is needed, and this is in response to what this board has been telling DCE: to conduct a study with a nationwide impact."

The agricultural study has been in development for some time at NCI, according to Joseph Fraumeni, director of DCE's Epideiomiology & Biostatistics Program. After conducting case-control epidemiology studies in agricultural workers, "we were at a dead end until we proceeded in this direction," he told the board.

Board member James Felton, co-chairman of the ad hoc advisory panel, said the study is a 10-year commitment, since it is likely that after five years, investigators would make the case for continuing to follow the cohort of farmers. The trial also proposes to study the diet of farmers and its relationship to cancer risk. "It could turn out to be the best prospective dietary study to date," Felton said.

Board members indicated concern about review of the large and complex study. Besides receiving ad hoc extramural review, the study has had rigorous internal review, and will continue to receive annual review from Correa's committee, according to Michael Alavanja, the study's project officer.

The division released an RFP for the study prior to the board's concept approval in order to enable the initial funding to take place in FY92. The RFP was published in the March 13 issue of **The Cancer Letter.**

"It's scientifically viable and it will answer political questions also," DCE Director Richard Adamson said. He noted that previous studies have shown that agricultural workers who took protective measures, such as wearing overalls, gloves and masks, and washing the protective clothing frequently, had the same relative risk for cancer as the general population. In addition, farmers who owned machinery with enclosed cabs did not have increased risk. However, these studies were done in the Midwest in mainly white, middle-class farmers. Risks could be greater for poorer, minority farmers in the South and West, whom this study proposes to include. "At the least, if this group with high pesticide exposure shows no outcome, then you can say that the occupational exposure levels approved by regulatory agencies are not contributing to increased cancer risk," Adamson said.

Following are excerpts from the unanimously approved concept statement:

A Prospective Study of Cancer Among Men and Women in Agriculture.

This investigation will establish a large cohort that can be followed prospectively for 10 years or more to obtain detailed information on agricultural exposures, diet, cooking practices and other factors of etiologic interest for cancer and other diseases. It is designed so that we can also investigate biomarkers of exposure and disease. The cohort will include men and women, who are either farm owners/operators, their spouses and dependents, or commercial pesticide applicators.

The stimulus for this investigation comes from the growing evidence from retrospective epidemiologic studies of agricultural workers in several countries that despite a low overall mortality, farmers experience an excess of several cancers: lymphatic and hematopoietic systems, connective tissue, brain, prostate, skin, stomach and lip. Several cancers (brain, non-Hodgkin's lymphoma, multiple myeloma, and prostate) are also increasing in the general population in many of these countries, suggesting that a common set of exposures may be involved. The occurrence of cancer excesses in several developed countries among a large and important occupational group and the rising incidence for several of these same tumors in the general population underscore the need to identify and clarify exposures that may be involved. Explanations for rising rates for one of these tumors (NHL) was evaluated at an NCI-sponsored workshop. The participants concluded that the increase of NHL among men and women was not an artifact of reporting practices and that the increased use of pesticides over the past several decades could play an important role in the rising incidence. The need to study both cancer and noncancer diseases among agricultural populations has also been noted in the NIH Strategic Plan and at the recent Surgeon General's Conference on Agricultural Safety and Health.

Both men and women on farms may have contact with pesticides, animal viruses, mycotoxins, dusts, fuels, oils, engine exhausts and fertilizers, and there is epidemiologic and experimental evidence that some of these exposures may pose a carcinogenic hazard to humans. Only recently, however, have studies been designed to focus on risks posed by specific agricultural exposures. The major focus to date has been on pesticides and lymphatic and hematopoietic cancer. Phenoxyacetic acid herbicides have been linked to NHL in several studies. NHL was also elevated in a cohort of grain milling workers routinely exposed to fumigants and other insecticides. Insecticides and fungicides have been associated with farmers' risk of NHL, leukemia, and multiple myeloma. NHL has been

linked to fuels in a Canadian study. In studies of other tumors, lung cancer has been associated with duration of exposure to pesticides among applicators in Florida and Germany, while soft tissue sarcoma and brain cancer have been associated with insecticides. Studies of other tumors that are excessive among farmers are needed to develop new hypotheses and evaluate current leads. For example, there is a growing contamination of drinking water in agricultural areas by nitrate fertilizer runoff, which may play a role in the observed excess of stomach cancer.

Few reports on women in agriculture are available, but ovarian cancer has been linked with triazine herbicide exposure in one study, and breast cancer to insecticide exposure in another. Specific agents that might be responsible for this latter finding, however, were not identified.

In addition to occupational exposures from direct agricultural practices, there is also a need to assess the cancer risk of pesticide exposures from spray drift, dust, contaminated clothing and other objects, and ground water. The farmer's spouse and children may encounter exposures from these sources. Biologic effects from indirect (non-occupational) pesticide exposure have infrequently been studied, but childhood forms of leukemia, brain cancer, and NHL have been associated with indirect pesticide exposures. In addition, malignant lymphoma in dogs has been associated with the owners' use of herbicides on their lawns. Biomarker studies also suggest that bystander exposure can have biologic consequences. For example, long-term depression in white blood cell counts and neurological effects have been observed not only in farmers who use pesticides, but also in people who do not directly handle pesticides but live near orchards and occasionally harvest or grade fruit. Cholinesterase inhibition poisoning was reported in housewives as a result of pesticide spraying in fields 150 meters from their homes and rural wells have repeatedly been found to be contaminated with pesticides in surveys in the United States and Canada. The EPA has a major effort underway to survey pesticides in drinking water wells. Non-occupational exposure to pesticides from applications to lawns, gardens, parks, aerial spraying of residential areas and indoor pesticide applications may occur for many Americans. The cancer risks associated with these exposures are difficult to estimate epidemiologically and few studies have been attempted. In this study, use of prospectivelY collected pesticide application data from farms and measurements of pesticide residues in the homes of farmers will make it possible to more accurately assess the risk of nonoccupational exposures to farm families and permit a better extrapolation to the general population.

We also propose a dietary component to this study. The dietary information is needed because it is important to control for potential dietary effects when evaluating agricultural chemical associations. Dietary factors have not been linked to some cancers excessive among farmers (e.g., cancers of the lymphatic and hematopoietic system), but for other cancers (e.g., stomach, prostate) diet is strongly suspected to play an etiologic role. Consumption of milk, however, has been associated with lymphatic and hematopoietic cancer in a recent study. While not occurring excessively among farmers, several of the more common cancers (e.g., lung, colon) are diet-related. The collection of dietary information to control for confounding in this study will provide an opportunity to cost effectively assess the contribution of diet to cancer occurrence among men and women in agriculture. In addition to examining established dietary risk factors for several cancers, emerging dietary hypotheses can also be explored. Colon cancer risk, for example, has been linked to increased consumption of red meat. This association, while generally attributed to intake of animal fat, might be due to ingestion of potent carcinogens in cooked meat, notably heterocyclic amines.

Analysis of mutagens in major sources of cooked protein in the U.S. diet have shown significant mutagen content in fried or broiled beef, pork, chicken and fish. Seventeen heterocyclic amine mutagens have been identified from cooked meats. The biological activities that have been demonstrated for these compounds include bacterial mutations chromosomal aberrations, transformation and mutation of mammalian cells in culture, mutations in mice and Drosophila and tumors in rats and mice following feeding. Laboratory studies have shown that cooking temperature is important because an increase in temperature causes a large increase in total mutagen production in foods.

In this project, NCI investigators will initially focus on the ten or so cancers that have been associated with agriculture, but once the cohort is established it would be relatively easy to study other cancers, reproductive outcomes, and neurologic diseases, since exposure information has already been assembled. The EPA, and possibly NIEHS, plan to focus on reproductive and neurologic outcomes.

Objectives: A long-term prospective study of men and women and dependent children in agricultural areas is proposed with the following objectives:

1) to identify and quantify cancer risks among men and women associated with specific agricultural exposures and practices;

2) to evaluate the cancer risks among women and children that may arise from indirect (i.e., non-occupational) exposures to agricultural chemicals (e.g., ambient air drifts, handling contaminated clothing, residues on rugs and children's toys, residues in drinking water and food);

3) to identify and quantify cancer risks associated with diet, cooking practices, and the chemicals resulting from the cooking process;

4) to develop an integrated prospective exposure assessment strategy concerning agricultural exposures (both occupational and nonoccupational) which includes periodic interviews, environmental and biological monitoring and biomarker techniques;

5) to study the relationship between agricultural and dietary exposures and biomarkers of exposure, biologic effects, and genetic susceptibility factors relevant to mechanisms of carcinogenesis; and

6) to provide a resource population for the research on health outcomes other than cancer among agricultural populations, including neurotoxicity, reproductive hazards and agricultural safety issues.

Methods: Farmers and other pesticide applicators will be identified as they their pesticide application licenses. This project has three major components:

1. The main cohort study. Questionnaires will be administered to a cohort of 100,000 pesticide applicators ("Applicator Questionnaire" or Q1A and 56,000 spouses of farmers ("Spouse Questionnaire or Q1B) at multiple times during the length of the study. Cancer incidence and mortality will be monitored through state-wide cancer registries and vital statistics offices. Questionnaires will focus on agriculture and dietary exposures and related occupational and lifestyle variables. Information on children of farmers will also be obtained so that their cancer experience can be determined.

2. Nested case-control studies. Cases of selected cancers from the main cohort study, including stomach, lung, prostate, breast, ovary, colon, NHL, leukemia, and multiple myeloma will be enrolled in the nested case control studies. Cases and controls will receive additional "Specific Disease Questionnaires" which examine important etiologic issues in addition to agricultural and dietary exposures. For selected cancers, tumor tissue, histologic

slides, peripheral blood samples and urine samples will be collected for pathology review and laboratory analysis. Body fluids will also be obtained from controls, to be compared with cases for markers of exposure, disease, and susceptibility.

3. Prospective exposure assessment study. Detailed exposure measurements will be performed on a sample of the cohort. The exposure patterns and combinations of exposure determinants identified through the questionnaires described in the main cohort study will be linked with monitoring data from the sample. Monitoring data on the exposure patterns will then be extrapolated from the sample to the entire cohort, so that quantitative estimates of exposure can be made on everyone in the main cohort. Monitoring diets for nutritional content and byproducts of high-temperature cooking will also be performed and related back to the entire cohort by means of responses to the dietary portion of the questionnaire.

RFPs Available

Requests for proposals described here pertain to contracts planned for award by the National Cancer Institute unless otherwise noted. NCI listings will show the phone number of the Contracting Officer or Contract Specialist who will respond to questions. Address requests for NCI RFPs, citing the RFP number, to the individual named, the Executive Plaza South room number shown, National Cancer Institute, Bethesda MD 20892. Proposals may be hand delivered to the Executive Plaza South Building, 6130 Executive Blvd., Rockville MD. RFP announcements from other agencies will include the complete mailing address at the end of each.

RFP NCI-CM-37815-30
Title: Biochemical Genetic Monitoring of Rodents
Deadline: April 21

The Biological Testing Program, Development Therapeutics Program, NCI Div. of Cancer Treatment, seeks proposals from organizations having the capabilities to provide a genetic monitoring resource for the BTP. Genetic monitoring for quality assurance will accompany the long-standing efforts in microbiological quality, so that each animal produced from derived stock, under BTP production contracts, is as well defined as possible. Genetic monitoring will be accomplished by biochemical means, i.e., testing for loci involved in producing cellular enzyme or protein variants.

It is anticipated that one contract will be awarded for this effort, as a result of this RFP for a period of 60 months. This is a recompetition of a project being performed by Texas A&M Univ.
Contract specialist: Elas Carlton
RCB Executive Plaza South Rm 604
301/496-8620

RFP NCI-CP-33011-21
Title: Continuation of Follow-up of DES-Exposed Cohorts
Deadline: May 14

The Div. of Cancer Etiology, Environmental Epidemiology Branch, Epidemiology & Biostatistics Program of NCI is seeking collaborative investigators to continue follow-up of surviving members of a cohort exposed to DES given in pregnancy, and designated unexposed comparison subjects.

Each cohort shall consist of at least 300 people (mothers, daughters and sons). The combined cohort (inclusive of all collaborative investigators) shall include at least 3,500 people exposed in utero (daughters and sons) and at least 2,600 women exposed during pregnancy (mothers). Unexposed subjects that can be compared to daughters or sons shall be included, but unexposed subjects comparable to mothers shall not.

It is anticipated that outcomes shall be ascertained by questionnaire and record review, not by clinical examination. Clinical examinations shall be conducted only for cohort members who have not been examined before, for example, new entrants. It should be noted that any offeror may propose not to conduct follow-up of the cohort, but to provide the names, addresses and other locating data to NCI.

The offerer will participate in all other contract activities, but NCI will provide for the follow-up of cohort members. In addition, any offeror may propose not to conduct tracing of the cohort, but will participate in all other contract activities. NCI will trace the lost cohort members. These variations should be clearly noted in the proposals and the subsequent budgets should be adjusted accordingly. This project is a research effort. The contracts to be awarded will be cost-reimbursement, completion types.
Contract specialist: Barbara Shadrick
RCB Executive Plaza South Rm 620
301/496-8611

RFA Available

RFA CA-92-12
Title: **Clinical Correlative Studies in Solid Tumors**
Letter of Intent Receipt Date: May 29
Application Receipt Date: July 10

The Cancer Therapy Evaluation Program of NCI's Div. of Cancer Treatment and the Cancer Diagnosis Branch of the Div. of Cancer Biology, Diagnosis and Centers invite applications for cooperative agreements from institutions or consortia, such as DCT Clinical Trials Cooperative Groups, capable of and interested in performing clinical correlative studies with new prognostic factors ready for large-scale evaluation. These factors must be relevant to the cancer treatment or clinical outcome of patients with solid tumors. It is essential for institutions to have access to sufficient numbers of patients on phase III clinical protocols to be able to test correlative hypotheses.

Applications may be submitted by domestic nonprofit and for-profit organizations, public and private. Applications may be submitted from one institution or may include arrangements with one or more additional institutions, if appropriate. Applications from minority individuals and women are encouraged.

Support of this program will be through the cooperative agreement (U01). Approximately $2 million in total costs per year for four years will be committed. It is anticipated that 10 to 12 awards will be made. The total project period may not exceed four years. The earliest feasible start date for the initial awards will be April 1993.

The objectives of this RFA are to foster collaborations and interactions between basic researchers and clinical investigators in the advancement of therapeutic clinical research and to conduct correlative studies in solid tumors on new prognostic factors that are ready for large-scale evaluation. CTEP and CDB invite cooperative agreement applications from institutions or consortia, such as the DCT Clinical Trials Cooperative Groups and the NCI Cancer Centers, capable of and interested in performing clinical correlative studies relevant to cancer treatment or clinical outcome in patients with solid tumors.

Solid tumors, e.g., breast, prostate, lung, colorectal, upper aerodigestive, ovary, bladder, pancreas, melanoma, stomach, kidney, and rarer tumors such as pediatric and adult brain and sarcoma, which are relevant to this RFA, account for significant cancer incidence, morbidity and mortality. Special consideration will be given to studies with colorectal, breast, ovarian, lung, and prostate tumors. Institution applications are expected to be focused on a specific solid tumor. Applicants may propose to undertake several correlative studies relevant to the specific solid

tumor during the grant funding period (up to four years). An individual scientist or a consortia of institutions may be included on more than one application.

The correlative studies should be based on strong and testable hypotheses. A clear rationale must be given for the experimental design and technical methodologies selected. The hypotheses tested must relate to potential clinical applications such as development of new treatment strategies or identification of patient subsets for specific treatment approaches. Preliminary data from appropriate tumor models or analysis of patient specimens must be provided to support the feasibility of each study. Assays must have already been demonstrated to be applicable to tissue samples and/or body fluids. The laboratory assays must utilize tumor specimens from patients receiving defined treatments in large clinical trials such as phase III clinical protocols. Applications will be considered responsive only if investigators have access to sufficient numbers of patient specimens. All investigators are encouraged to work with multi-center organizations or form a consortium of institutions in order to access sufficient numbers of patients and clinical information to test the proposed hypotheses. To coordinate the above activities, each institution must have access to a Central Operations Office and Statistical Center as defined in the RFA.

The cooperative approach outlined in this RFA allows for interactions among successful applicants and is designed to optimize use of patient resources, tissues, reagents, and methods.

Copies of the complete RFA available from, and letters of intent may be sent to: Diane Bronzert, Program Director, Cancer Therapy Evaluation Program, NCI, Executive Plaza North Rm 734, Bethesda, MD 20892, phone 301/496-8866, FAX: 301/480-4663.

Program Announcements

PA-92-51

Title: **Effective Dissemination of Health and Clinical Information and Research Findings**

Application Receipt Dates: June 1, Oct. 1, Feb. 1

The Agency for Health Care Policy and Research (AHCPR) invites applications to conduct applied research and demonstrations on effective dissemination of health-related information and clinical practice guidelines, technology assessments, general health services research findings, and research findings used in policy decisions and recommendations.

Applications may be submitted by public and private non-profit institutions, units of state and local government, and individuals. For-profit institutions are not eligible for AHCPR grants.

This Program Announcement will use the traditonal research grant (R01). It is anticipated that projects will vary from one to three years in length. Project lengths could be up to five years in rare cases due to the complexity or breadth of the subject area, or in areas proposing to investigate the longer term effects of particular forms of dissemination.

The purpose of the AHCPR is to enhance the quality, appropriateness, and effectiveness of health care services and to imnprove access to that care. AHCPR is the Federal Government's focal point for general health services research, including medical effectiveness research, and has lead responsibility for the Medical Treatment Effectiveness Program (MEDTEP). MEDTEP projects systematically study the relationships between medical treatments and procedures and the outcomes. Patient Outcomes Research Team (PORT) projects focus on variations in clinical practice and outcomes for a particular medical condition. The AHCPR convenes expert non-Federal panels and awards contracts to develop clinical practice guidelines for specific conditions and treatments. The AHCPR Office of Technology Assessment evaluates medical devices, procedures and services and makes coverage recommendations to Federal health programs. The AHCPR intramural research program undertakes health policy research and analysis on National medical expenditures, hospital cost and utilization data, and long-term care. Health services research focuses on a broad range of policy and delivery system issues in the areas of cost and financing, primary care, and technology and quality assessment. In addition, the AHCPR is responsible for increasing the quality and quantity of data for general health services research, including medical effectiveness research.

The AHCPR authorizing legislation requires the AHCPR to disseminate as broadly as possible the products and results of its research. This Program Announcement for demonstrations and applied research is part of the AHCPR dissemination program. The focus on "effective dissemination" is based upon a growing recognition that distribution of information does not not guarantee adoption or use. The definition of effective dissemnation used in this PA goes beyond the traditional concepts of diffusion and distribution of information and encompasses the process through which target groups become aware of, receive, accept, and utilize disseminated information. The test of effective use is the extent to which target audiences become more informed, make decisions, or change behavior patterns as a result of using disseminated information. The goal of effective dissemination is to improve patient care, patient outcomes and quality of life.

Early studies of innovation diffusion in the health arena examined the spread of new information, knowledge or technologies, the characteristics of the diffusion process, and the role that people and organizations played in the adoption of innovations. These studies confirmed that some innovations were not adopted or utilized and that there was a long lag time between availability and widespread use of new scientific information.

Underlying many efforts to provide new clinical information or practice guidelines to practitioners has been the assumption that clinical practice behavior will change if relevant scientific evidence is effectively disseminated to health care providers and patients. The dissemination-related health literature has focused primarily on the introduction of medical technology, the flow of new information into practice, continuing medical education, and more recently on physician behavior change resulting from the diffusion of new information or clinical practice guidelines. Most of this literature has focused on practitioners and health care settings. Pertinent research related to consumers has focused on public health and health education information, the psychology of mass communications and other work related to marketing. Research directed at policy makers has examined the use of data and evaluation studies in legislative and executive settings.

The objective of this Program Announcement is to stimulate new grant applications for demonstrations and applied research projects that examine the most effective means of disseminating a broad range of products (health and clinical information, research findings, clinical practice guidelines, technology assessments, policy recommendations) to a wide variety of target groups (consumers, health care practitioners, the health care industry, researchers, policy makers, and the press). Applied research in effective dissemination should be multi-disciplinary, drawing on the field of communications and information theory, commercial marketing, social and behavioral psychology, education, computer sciences, and policy sciences. The eventual goal is for disseminated information to be assimilated and used in ways that improve the effectiveness and quality of health care services, utilization of and access to those services, and ultimately patient outcomes and quality of life.

A. Audiences, media, and products of dissemination--The audiences, media, and products of dissemination that are of

interest to the AHCPR include:

Audiences: Consumers (individuals or organizations); health care practitioners of all disciplines (physicians, nurses, allied health professionals and professional organizations); the health care industry (organizations, group practices and managed care organizations, third-party payers, medical equipment manufacturers, pharmaceutical manufacturers, Federal health care systems, quality assurance and utilization review organizations); policy makers (Federal, State and local, executive and legislative, and private sector decision makers); researchers (both biomedical and general health services); and the press (popular media and newspapers, general health, trade and scientific journals).

Media: Printed (direct mail, technical and trade journals, popular magazines and newspapers); and electronic (TV, radio, and electronic databases).

Products: General health services research findings; clinical information; clinical practice guidelines; health technology assessments; research-based policy recommendations; and general health information for consumers.

B. Types of projects supported--The AHCPR invites applications on effective dissemination that focus on practical methods to achieve better informed audiences, improved decision making, and behavioral change that improve the delivery of health care and patient outcomes. AHCPR encourages projects that involve dissemination of AHCPR products or other research and information products similar to AHCPR products so that findings can contribute to improving the effectiveness of the dissemination program.

The following types of projects will be considered responsive to this Program Announcement:

1. Demonstration projects (with appropriate research hypotheses) measuring the effectiveness of dissemination mechanisms (e.g., continuing professional education, opinion leaders, peer review and feedback, computerized systems, incentives, organizational approaches) or combinations of mechanisms in stimulating the use of disseminated information;

2. Studies examining the comparative effectiveness of different dissemination mechanisms using the same information with different audiences or different information with the same audiences;

3. Studies examining the effectiveness of different dissemination mechanisms under conditions in which the target audiences are either economically advantaged or economically disadvantaged by the behavior changes;

4. Studies examining the comparative cost of different methods of stimulating behavior change (e.g., cost measures may be calculated by cost per thousand population, magnitude of changes);

5. Longitudinal studies of sustained change in knowledge, skills, attitudes, and behavior as a result of dissemination of health and clinical information;

6. Projects designed either to improve health services research methods as applied to effective dissemination or to overcome dissemination research problems, especially projects that focus on multi-disciplinary research methods (e.g., the use of behavioral change models in health information dissemination campaigns); and

7. Innovative research on unique methods of reaching particular audiences (e.g., informing consumers to stimulate and effect practitioner behavioral change and multi-faceted dissemination campaigns).

Direct inquiries regarding programmatic issues to: Margaret VanAmringe, Director, Center for Research Dissemination and Liaison, Agency for Health Care Policy and Research, 2101 East Jefferson Drive, Suite 501, Rockville, MD 20892, phone 301/227-8362.

PA-92-45

Title: **Novel Non-Ionizing Radiation Technologies for Breast Cancer Imaging**

Application Receipt Dates: June 1, Oct. 1, Feb. 1

NCI, through the Diagnostic Imaging Research Branch of the Radiation Research Program seeks grant applications to conduct multidisciplinary research in the area of novel non-x-ray technology development and evaluation for improved breast cancer imaging. This Program Announcement encompasses a full range of studies from basic technology and instrumentation development through pre-clinical and clinical evaluation.

Applications may be submitted by foreign and domestic, public and private, nonprofit and for-profit organizations.

This program will be supported by the individual research grant (R01) and the First Independent Research Support and Transition (FIRST) Award mechanisms.

The goal of this Program Announcement is to stimulate development and validation of novel non-ionizing radiation technologies and imaging methodologies for the improved diagnosis and characterization of breast cancer.

Current data indicate that conventional mammography is a mature imaging technology producing high-quality images in the majority of patients. Indeed, conventional mammography has been shown to be an accepted problem-solving and an effective screening tool in older women (age category over 50 years), resulting in a 30 percent mortality reduction in these patients. However, recent data indicate that novel technologies, such as conventional magnetic resonance imaging (MRI) and ultrasound, may provide important additional diagnostic information if the detected lesions need to be characterized (e.g., cystic vs. solid mass) and/or in younger women and patients with radiodense breast tissue. Further clinical studies are required to define the comparative role and analyze the cost-effectiveness of MRI and ultrasound in breast cancer diagnosis and characterization.

Dynamic contrast-enhanced MRI has been shown to be a promising adjunctive diagnostic tool in the following clinical situations: (1) conventional mammography and physical examination fail to provide diagnosis; (2) the differentiation of dysplasia vs. cancer; (3) dense breast; and (4) small lesions.

Advanced MRI and ultrasound technologies appear to have an important potential for quantitative characterization of tumor biology. Novel ultrasound technologies, such as high frequency systems, modern pulse echo/color flow, and 2D/3D imaging, may improve image quality and provide improved anatomic and physiologic information. Novel MR techniques, such as magnetization transfer approach, diffusion/perfusion imaging, magnetic resonance spectroscopy and electron spin resonance, will provide additional quantitative biochemical, biophysical, and physiologic parameters for breast cancer characterization in order to optimize treatment planning.

Further, a number of novel imaging techniques (e.g., optical, microwave, thermal) are currently under development. Indeed, recent reports indicate that the ballistic optical imaging technique, while highly experimental at this stage, can detect structures in vitro as small as 200 microns. Further studies are required to advance this technology for in vivo use.

Written and telephone inquires concerning the objectives and scope of this Program Announcement and inquiries about whether or not specific proposed research would be responsive are encouraged and are to be directed to: Faina Shtern, M.D., Chief, Diagnostic Imaging Research Branch, Radiation Research Program, NCI, Executive Plaza North, Suite 800, Bethesda, MD 20892, phone 301/496-9531.