Board of Scientific Advisors

Meeting Minutes

March 25-26, 2002

Conference Room 10, C Wing, Building 31
Bethesda, Maryland 20892

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The Board of Scientific Advisors (BSA or Board), National Cancer Institute (NCI), convened for its 20th regular meeting at 10:30 a.m. on Monday, March 25, 2002, in Conference Room 10, Building 31C, National Institutes of Health (NIH), Bethesda, MD. Dr. Frederick Appelbaum, Director, Clinical Research Division, Fred Hutchinson Cancer Research Center, presided as Chair.

The meeting was open to the public until adjournment for opening remarks from the Chairman; ongoing and new business; NCI's decision-making process for grant allocation presentation; Spiral Computed Tomography (Spiral CT) partnership update; a subcommittee report on communicating training opportunities; a report on Requests for Application (RFAs) that involve large initiatives; a status report on clinical trials restructuring initiative and formation of the Cancer Trials Support Unit; a mini-symposium on mammography; and an RFA concept presentation.

Board Members present:
Dr. Frederick R. Appelbaum (Chair)
Dr. David B. Abrams
Dr. David S. Alberts
Dr. Hoda Anton-Culver
Dr. Esther H. Chang
Dr. Thomas Curran
Dr. Suzanne W. Fletcher
Dr. Susan B. Horwitz
Dr. William G. Kaelin, Jr.
Dr. Kenneth W. Kinzler
Dr. Herbert Y. Kressel
Dr. Joseph V. Simone
Dr. Louise C. Strong
Dr. Daniel D.Von Hoff
Dr. Barbara L. Weber
Dr. Alice S. Whittemore
Dr. William C. Wood
Dr. Robert C. Young

Board Members absent:
Dr. Neil J. Clendeninn
Dr. Waun Ki Hong
Ms. Amy S. Langer
Dr. Caryn E. Lerman

Dr. W. Gillies McKenna
Dr. Christine A. Miaskowski
Dr. Enrico Mihich
Dr. John D. Minna
Dr. Nancy E. Mueller
Dr. Franklyn G. Prendergast
Dr. Richard L. Schilsky
Dr. Ellen V. Sigal
Dr. Peter K. Vogt
Dr. Elias A. Zerhouni

NCAB Liaison:
TBN

Others present: Members of NCI's Executive Committee (EC), NCI Staff, Members of the Extramural Community, and Press Representatives.

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I. CALL TO ORDER AND OPENING REMARKS - DR. FREDERICK APPELBAUM

Dr. Appelbaum called to order the 20th regular meeting of the BSA and welcomed members of the Board, NIH and NCI staff, guests, and members of the public. Dr. Appelbaum reminded members of the conflict-of-interest regulations. He informed the Board that he had discussed the future of the BSA with Dr. von Eschenbach, the NCI Director, and had been assured that the BSA had done impressive work and that it would be maintained. Board members were reminded of future Board meeting dates. The 2004 meeting dates were confirmed.

II. CONSIDERATION OF 13-14 November 2001 MEETING MINUTES - DR. FREDERICK APPELBAUM

Motion: The minutes of the 13-14 November 2001 meeting were unanimously approved.

BSA at National Meetings

III. ONGOING AND NEW BUSINESS - DR. FREDERICK APPELBAUM

Dr. Appelbaum noted that Dr. Mary Daly had chaired the "NCI Listens" session at the American Society for Preventive Oncology (ASPO) meeting on 11 November 2001 and that Drs. Greenwald, Rimer, Gray, Lerman, and Mueller were also in attendance. Dr. Daly stated that attendance at the session was good and that ASPO membership exhibited renewed interest in many NCI issues. She stated that there was some discussion at the ASPO meeting about the requirements for the inclusion of population sciences in Specialized Programs of Research Excellence (SPOREs). Clarification of the requirement is needed for both researchers and reviewers. This topic should be discussed at a future BSA meeting. An updated listing of 2002 BSA "NCI Listens" sessions and participants is as follows:

- **American Association of Cancer Research (AACR)** - April 6-10, 2002 - San Francisco, CA; Drs. Mihich (Chair), Anton-Culver, Feigal, Gray, Kalt, Kimes, McKenna, Singer, Strong and von Eschenbach

- **Oncology Nursing Society (ONS)** - April 18-21, 2002 - Washington, DC - Drs. Miaskowski (Chair), Gray and Ms. McCabe

- **Cold Spring Harbor Laboratories Symposium (CSHL)** - August 14-18, 2002 - Cold Spring; Harbor, NY; Drs. Kaelin (Chair), Gray and Singer

- **American Society for Therapeutic Radiology and Oncology (ASTRO)** - October 6-9, 2002 - New Orleans, LA; Drs. McKenna (Chair), Coleman, Gray and Wood (Note: Dr. Dan Sullivan will also participate.)

The **American Society of Clinical Oncology (ASCO)** and the **American Society of Hematology (ASH)** should be contacted to ascertain their interest in holding "NCI Listens" sessions at future meetings.

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IV. NCI'S DECISION-MAKING PROCESS FOR GRANT ALLOCATION - MR. STEPHEN HAZEN

Mr. Stephen Hazen, Chief, Extramural Financial Data Branch, Office of Budget and Financial Management (OBFM), Office of the Director (OD), presented an overview of the process used to allocate research project grant funds and to develop paylines. Specifically, Mr. Hazen described how the annual NCI appropriation is first allocated to pay the small business program set-aside, as mandated by law, and the tap for program evaluation. Money is then allocated to pay non-competing commitments (Type-5 awards) and administrative supplements. The remaining money is used to pay competing awards - traditional grants (R01s), program project grants (P01s), exploratory/developmental grants (R21 and R33), requests for applications (RFAs), other smaller grant mechanisms and grants which are exceptions to the paylines.

The process used to set a payline was outlined and the trade-off decisions which need to be made when the EC sets the paylines were highlighted. At the conclusion of the presentation, Mr. Hazen

reviewed the fiscal year (FY) 2002 paylines for several grant mechanisms.

In discussion, the following points were made:

- The number of grant applications has been increasing faster than the size of the NCI budget, leading to a more stringent payline.
- Funding for the various award mechanisms represents both a commitment to continuity and an effort to drive discovery.
- The EC has set a numeric target this year to bolster the number of first time R01 investigators (*R01s) that will be awarded.
- Increases in the funding of *R01 investigators seeking to establish themselves should be prioritized over excessive support of a few senior investigators who are involved in numerous projects.
- Congress mandates a certain percentage of research money to be allocated to small business research. This percentage has remained constant for approximately 10 years.

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V. SPIRAL CT PARTNERSHIP UPDATE - DRS. PETER GREENWALD AND ELLEN FEIGAL

Dr. Peter Greenwald, Director, Division of Cancer Prevention, reported on the progress regarding the Spiral CT Lung Cancer Screening Trial. Dr. Greenwald noted that since the trial's launch, collaborative efforts have been efficient and productive. Biweekly conference calls are being held, and harmonization of forms is nearing completion. Quality assurance programs have been developed. Collaborations are being established with the Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial. Associations are planned with the SPOREs in terms of blood collection for molecular and genetic analyses. Image analysis will be the focus of collaboration with the special studies of the

American College of Radiology Imaging Network (ACRIN) to refine the ability to characterize lesions and develop standards for interpretation.

Dr. Ellen Feigal, Acting Director, Division of Cancer Treatment and Diagnosis (DCTD), stated that three types of partnerships are being sought for the Spiral CT Lung Cancer Screening Trial: scientific and funding partners; international investigators involved in randomized Spiral CT clinical trials; and a biospecimen repository as a national resource for future research.

Scientific and funding partners include device manufacturers, health care insurers, the National Institute on Drug Abuse (NIDA), the American Cancer Society (ACS), and the American Legacy Foundation (ALF). Device manufactures, i.e., General Electric and Siemens, have agreed to provide equipment, software, and technical assistance for the trial. Three health care insurers (the American Association of Health Plans, Blue Cross/Blue Shield [BCBS] Association, and Centers for Medicare and Medicaid Services [CMS]) were contacted and specifically requested to reimburse the NCI for screening costs, i.e., prevalent screens and two annual incident screens.

The American Association of Health Plans, which includes health maintenance organizations, preferred provider organizations, and other similar health plans covering 150 million Americans nationwide, has expressed interest in collaborating with the trial but has not offered any commitment. Dr. Feigal indicated that she is maintaining a continuing dialogue with the Association's Board to pursue the partnership. Regarding BCBS, Dr. Feigal explained that she met with its National Council of Physician Executives, which is BCBS's advisory group. This group provides strategic advice on emerging business and policy issues and assists in the identification of potential partnerships. Dr. Feigal indicated that while she is pursuing ongoing dialogue with BCBS's individual member plans, no commitment has been received. CMS has expressed interest in the trial and has provided appropriate contact information for NCI to open dialogue with other health care providers across the country.

A more scientific, rather than financial, commitment is being sought from NIDA and the ACS. Dialogue with NIDA is ongoing and the ACS has committed to supporting the trial; however, the

specific dollar amount has not been defined.

The ALF is a national independent public health foundation dedicated to decreasing tobacco use in the United States. NCI staff has met with the Foundation's president and CEO. Collaborative studies are being designed to address both the Foundation's goals and NCI's mission. Spiral CT trial participants will be referred to the Foundation's smoking cessation program. A randomized trial involving up to 2,000 patients will assess the difference in smoking cessation rates between patients enrolled in a delayed screen and those enrolled in an immediate screen, using chest x-ray versus Spiral CT. A questionnaire about the use of tobacco products is being proposed to correlate these products with differential risk for disease. The proposal for these collaborative efforts is being finalized and will be reviewed by the Foundation's Board in April 2002. Other foundations being considered by NCI for potential partnerships include the Robert Wood Johnson Foundation and the Aetna Foundation.

Dr. Feigal stated that the European Union Early Lung Cancer Detection Group and its European Union Spiral CT Subgroup are interested in the value of Spiral CT as a screening tool to decrease lung cancer deaths. These groups have met with interested U.S. investigators and organizations to try to harmonize key features of studies involving evaluation of Spiral CT as a screen for lung cancer. Four joint meetings have been held since July 2001. NCI plans to send one or two representatives to the June 2002 meeting. The European groups are focusing on three areas of harmonization: core data elements, radiology protocols, and pathology protocols, including biomolecular marker studies. Dr. Feigal noted that the purpose of this partnership is not to conduct one global trial, but, rather, to harmonize the key elements among the U.S. definitive trial and the small European trials.

The biospecimen repository partnership involves collaborations with investigators who are trying to identify predictors of lung cancer development. The Spiral CT trial represents a great opportunity to collect samples to better characterize the molecular events that correlate with lung carcinogenesis. The trial will implement tissue and specimen banking of serum, sputum, and urine from both arms of the study. Analysis of biomolecular marker data has two goals: to characterize the pathogenesis, clinical, genetic, imaging, and epidemiologic profiles of individuals in the

study, cross-sectionally and longitudinally; and to assess the potential usefulness of biomolecular profiles as predictors of lung cancer. The repository has an oversight committee. A review and evaluation panel will review incoming proposals. Standard operating procedures have been established for the collection, preparation, and storage of specimens and for data that need to be annotated.

In discussion, the following points were made:

- Two potential Spiral CT trial partners include major corporations offering Spiral CT screening to their employees and companies performing Spiral CT scans.

- The proposed Spiral CT trial budget is $197M over eight years. The first two to three years, which involve patient accrual, are the most expensive, with a $30M to $40M per year cost estimate. Costs then drop significantly because the trial will mainly involve follow-up visits.

- One foreseen Spiral CT trial challenge is that the initial negative screen results expected in the majority of participants may have an unintended iatrogenic effect on risk perception, encouraging smokers to continue smoking with future impunity. However, with the assistance of behavioral science on risk perception, the screening outcome messages could be appropriately framed.

- It is critical that the questionnaires used for collecting environmental exposure data with respect to tobacco, as well as lung cancer susceptibility data, be state-of-the-art tools for informing genetic and molecular studies. The Spiral CT trial should also provide an opportunity for behavioral scientists to combine epidemiologic screening instruments with biomarker data to assess susceptibility genes for tobacco addiction.

- A follow-up report on the ongoing dialogues to establish partnerships for the Spiral CT trial should be presented at the June 2002 BSA meeting.

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VI. WORKING LUNCH

Subcommittee on Training Report: Communicating Training Opportunities

Dr. Robert Young, President, Fox Chase Cancer Center, and Chair, Subcommittee on Training, BSA, presented an update on the effort being made to disseminate information regarding NCI-sponsored training opportunities in cancer research. Dr. Young noted that this effort was initiated approximately 12 to 18 months ago in response to concerns expressed by the research community about the lack of information regarding the various NCI training grant mechanisms. The subcommittee's charge was to focus on increasing academic institutions and cancer-related organizations level of awareness of K awards and other training information. Among the targeted institutions and organizations were those that have mechanisms that NCI could utilize to publish articles regarding its training opportunities, with the aim of reaching a larger audience.

Dr. Young acknowledged Dr. Paulette Gray for her hard work and personal commitment to this undertaking. He then reported that the dissemination effort has been a tremendous success, exceeding all expectations. He informed members that 225 responses had been received from institutions across the country, including approximately 36 organizations, expressing interest in receiving written materials and access to Internet or e-mail mechanisms. Most of the 36 responding organizations expressed interest in publishing the NCI written materials. Dr. Gray indicated that the Cancer Training Branch (CTB) was finalizing the training packet that will be mailed to the responding institutions. She also stated that CTB staff are very grateful for the initiative undertaken by the Board. This effort will generate a contacts database so that the CTB staff can disseminate NCI's training grants opportunities in a timely manner.

In discussion, the following points were made:

- The NCI training opportunities packet should be mailed to all institutions and organizations in the database every 3 years.

- A follow-up letter will be mailed to all institutions and organizations that did not respond to the initial BSA letter about the need to communicate information on NCI's training opportunities. Board members were urged to review the list of responding institutions and organizations and to identify additional names, if needed.

- Comments on the draft Career Development and Training Grants marketing letter should be sent to the BSA Executive Secretary.

Report on RFAs That Involve Large Initiatives

Dr. Marvin Kalt, Director, Division of Extramural Activities (DEA), presented background information regarding the BSA's involvement in the review of RFAs. Dr. Kalt stated that the BSA is responsible for concept review of new Request for Applications (RFAs). BSA approved RFAs are generally issued for a period of three to five years and currently can be reissued without Board oversight. A summary of all approved concepts is, however, provided to Board members at each November BSA meeting. This summary provides an overview of the number of awards issued per RFA and the affiliations that received those awards. The report does not give any indication of the outcome of large RFA initiatives.

Dr. Young indicated that a central issue to the discussion is: How can the BSA provide appropriate oversight of RFA-based awards that would be useful to the NCI without interfering with the Institute's close management of activities? The current process allows for the Board's involvement in the review of RFAs, but a quality review of large-scale RFAs has not been performed. He wondered whether conducting a thorough review would be a worthwhile undertaking and whether it would help the NCI program staff prepare better RFAs.

In discussion, the following points were made:

- A historical review of approved RFAs would be useful to identify the positive and negative aspects of the RFAs

- An evaluation of approved RFAs is critical to both BSA members and NCI staff. The BSA wants to better

understand what accounts for the success or failure of RFAs, and the NCI could use this evaluation to justify the budget allocated for RFAs.

- The review of an RFA could occur at the time a decision is made whether to reissue the RFA. If the RFA is not going to be reissued, staff could share its opinions with the BSA.

- The BSA needs to know which RFAs have been successful and which ones are not meeting the expected outcomes.

- The reviews should be limited to RFA renewals that involve large infrastructures; these reviews could include both BSA members and NCI staff.

- Each Division could perform a review of its RFAs, and then inform the BSA as to how the assessment of each RFA was made.

- Discussions to reissue an RFA occur at the NCI Executive Committee. A common "report card" could be developed and used when deciding whether an RFA should be reissued.

A Working Group was established to formulate a BSA process to review large RFAs prior to reissuance. A report should be given to the full Board in June. Working group members are Drs. Appelbaum, Anton-Culver, Gray, Mihich, McKenna, Rimer, Singer and Young. Discussions will be via teleconference and/or e-mail. Dr. von Eschenbach should be invited to participate. BSA members should send comments and suggestions to the BSA Chair and/or Executive Secretary.

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VII. STATUS REPORT: CLINICAL TRIALS RESTRUCTURING INITIATIVE AND FORMATION OF THE CANCER TRIALS SUPPORT UNIT - DRS. MICHAELE CHRISTIAN AND JEFFREY ABRAMS

Dr. Michaele Christian, Associate Director, Cancer Therapy

Evaluation Program (CTEP), DCTD, provided a brief overview of the clinical trials program. Dr. Christian stated that the Clinical Trials Restructuring Initiative (CTRI) underwent one of the most inclusive reviews she has seen. The external review committee, called the Clinical Trials Review Committee or the "Armitage Committee," met between 1996 and 1997 and was broadly composed of 28 members representing the BSA, the National Cancer Advisory Board (NCAB), Cancer Center directors, physicians, and advocates. An Implementation Committee followed the Armitage Committee and was composed of 35 members, similarly broad-based.

The Armitage Committee provided seven major recommendations. The recommendations and NCI's response are as follows: 1) Increase Cooperative Group funding to full levels (an increase of $60M over three to four years). Funding for the current year is not complete, but the $58M increase that has been allocated represents a 60 percent increase in the overall Cooperative Group budget; 2) Reduce data collection in large clinical trials to only those data pertinent to study endpoints and safety. Preliminary data indicate that a substantial reduction in the number of data fields has been achieved, but further evaluation is required; 3) Keep data collection uniform. The common data elements project has led to common case report forms, and two data systems, the Common Toxicity Criteria and the Adverse Event Expedited Reporting System (AdEERS), which are now uniform across the Clinical Trials program; 4) Provide the Cooperative Groups with access to all relevant databases; moreover, these groups should be the primary participants in developing and testing NCI's informatics system. Cooperative Groups have been extensively involved, as exemplified by the work on the AdEERS. In addition, considerable time has been spent working with other groups, both within and outside NIH, to promote broader use of these data systems; 5) Streamline concept review and protocol development. Concept Evaluation Panels (CEPs) have been created to review Phase III clinical trial proposals, and an expedited proposal development process has been initiated; 6) Integrate patients into the decision-making process. Patients or advocates serve on most CTEP committees; and 7) Recruit and retain minorities and underserved populations in clinical trials. Clinical trial units have been established at two historically black medical schools, and these units have been instrumental in accruing patients to clinical trials. An ongoing program announcement with the National Institute on

Aging promotes cancer treatment research in the elderly. Meetings with Cooperative Groups also aid in addressing underserved populations and clinical trial related issues.

The timeframe within which the clinical trial initiatives have developed has been fairly quick. The Armitage Committee provided its report in August 1997; the Implementation Committee presented its report to the BSA a year later. The contract for the Cancer Trials Support Unit (CTSU) was approved by the DCTD in February 1999 and awarded to Westat Corporation in September of the same year. The first patient was enrolled in November 2000. Dr. Jeffrey Abrams, Medical Officer, Clinical Investigations Branch, CTEP, DCTD, provided details about the operational characteristics of the pilot endeavors. Dr. Abrams noted that the Cancer Clinical Trials Web site (http://cancertrials.nci.nih.gov/system) uses a picture of a puzzle to illustrate how different components make up NCI's clinical trial endeavors. To improve enrollment in clinical trials, new ideas need to be generated, access to trials broadened, procedures streamlined, data systems automated, and emphasis placed on communication with and education of patients and physicians. Clinical trials support initiatives for accomplishing these tasks are as follows:

State of the Science Meetings are small meetings attended by representatives from industry as well as U.S. and international researchers and patient advocates. These meetings focus on new leads and gaps in research to identify the Phase I and II studies needed for development of Phase III clinical trials. Dr. Abrams listed the types of meetings held in the past and those currently planned. A Web site, http://www.webtie.org/sots/index.htm, allows general access to the information from these meetings. A brief overview of the State of the Science Meetings evaluation plan was given. Several important outcomes of the State of the Science Meetings include the establishment of a national tumor bank for small-cell lung cancers, an international consortium for new agents and approaches for chronic lymphocytic leukemia, and a North American Leukemia Alliance to develop large Phase III intergroup trials.

Clinical Evaluation Plans (CEPs): The Implementation Committee recommended adding outside experts to complement NCI reviewers but indicated that these additions should not slow

the activation of new protocols. This latter requirement has been achieved by using a specific template for submission of Phase III concepts and requiring that the sections of the concepts be written so that, upon approval, they can be directly adopted into the final protocol. Two CEPs, Genitourinary and Lung, meet monthly via a Web-supported teleconference mechanism. The results of the 29 months of work from October 1999 to March 2002 include the review of 40 Phase III concepts and approval of 15. An overview of the evaluation plan was given.

Central Institutional Review Board (CIRB): After 2 years of discussions between the NCI and the Office for Human Research Protections (OHRP), 22 representatives of local Institutional Review Boards (IRBs) participated in the initial approval of protocols for selected diseases. The procedure involves CIRB approval of a protocol, communication with the local IRB (and the local investigator), and a decision by the local IRB to use the "facilitated review" process. If the process is accepted, the local IRB allows the CIRB to become the IRB of record. The CIRB then handles all further amendments to the study. The local institution monitors local conduct of the study, specifically, investigator compliance and toxicity events.

The CIRB has reviewed 19 protocols for the current 22 trial sites and has approved all but the last protocol, which is under revision. The CIRB hopes to expand the number of trial sites to 100 in the next several months. A new, protected CIRB Web site will be used to communicate with the local IRBs, Cooperative Groups, investigators, and the Data Safety Monitoring Board (DSMB). The evaluation plan for the CIRB was described.

Cancer Trials Support Unit (CTSU): The CTSU has two main goals: 1) provide access to NCI-sponsored Phase III studies for Cooperative Group members and other investigators, irrespective of group affiliation; and 2) streamline physician credentialing, patient enrollment, and data collection processes (for all trials, Phase I to III). This latter goal addresses a claim by physicians that regulatory processes have been a barrier to clinical trials participation, i.e., CTSU accrual barriers include low reimbursement per case and the IRB burden. The CTSU Web page (www.ctsu.org) includes details on topics such as health insurance coverage and instructions on IRB submissions and the patient enrollment process. In addition to protocols, the site also includes

educational and training materials.

Dr. Abrams devoted the final part of his presentation to the large CTSU, CTEP, and Cooperative Groups' informatics projects. He noted that the goal is to increase the efficiency and streamline amenable tasks, such as regulatory support, remote data capture, and clinical data transfer and randomization. Ongoing efforts for these tasks were presented.

In discussion, the following points were made:

- The progress to date toward clinical trials restructuring meets expectations, except that a brisker accrual rate was anticipated. Broader new patient and intergroup participation is likely once the efficiency of the CIRB improves.

- Competition by large pharmaceutical companies for patient recruitment to clinical trials ultimately ends in per-patient reimbursement issues. Higher per-case reimbursement has resulted in higher levels of accrual and may be the single most important incentive for increasing accrual.

- The CTSU Web site is linked to the NCI's Physician Data Query (PDQ), a search mechanism, making the Web site directly available to interested patients.

- A public media program to increase clinical trials awareness may promote patient interest in and, ultimately, patient accrual to clinical trials. Likewise, stronger connections with patient advocacy groups may be influential in increasing patient recruitment to clinical trials.

- Currently, cancer prevention clinical trials are not on the CTSU menu.

- The U10 budgets of institutions have not received more than cost-of-living increases for the past several years. These institutions contribute 40 to 50 percent of the accrual in the Cooperative Group program and should receive a financial incentive to contribute even more.

VIII. MINI-SYMPOSIUM: MAMMOGRAPHY - A CONTINUING CONTROVERSY - DRS. PETER GREENWALD, STEVEN WOOLF, RACHEL BALLARD-BARBASH, AND ERIC FEUER

Overview

Dr. Greenwald stated that the recent mammography controversy was prompted by an article published by Olsen and Gotzsche, two Danish investigators, in the 20 October 2001 issue of *Lancet*, which was then reported in the *New York Times*. The authors criticized the 1960s, '70s, and '80s mammography randomized trials by questioning whether the randomization methods were balanced as well as other issues. Dr. Greenwald stated that an inconclusive PDQ Screening and Editorial Board discussion about the *Lancet* article was also reported by the media. The PDQ Board subsequently issued a brief, revised statement; a full statement will be published later. Members were told that the PDQ, U.S. Preventive Services Task Force (USPSTF), supported by the Agency for Healthcare Research and Quality (AHRQ), Department of Health and Human Services (DHHS); and an update of some Swedish trials published in the March 16, 2002, issue of the *Lancet*, all reaffirmed that screening by mammography, with or without clinical breast examination, may decrease breast cancer mortality. He stated that NCI also reaffirmed its recommendation that women have a mammogram every one to two years, beginning in their 40s. Also, a working group (24 experts from 11 countries) convened by the International Agency for Research on Cancer (IARC), World Health Organization, concluded at its March 5-12 , 2002, meeting that trials have provided sufficient evidence for the efficacy of mammography screening for women between 50 and 69 years of age. But for women 40 to 49 years of age, the group felt there is only limited evidence of a reduction in mortality.

Dr. Greenwald informed members that Drs. Stephen Woolf, Rachel Ballard-Barbash, and Eric Feuer would present the USPSTF's findings; statistical modeling of the effect of screening on stage-specific incidence of breast cancer; and emerging data from the Breast Cancer Surveillance Consortium (BCSC).

U.S. Preventive Services Task Force: New Recommendations on Screening for Breast Cancer

Dr. Steven Woolf, Professor of Family Medicine, Virginia Commonwealth University, presented a synopsis of the USPSTF's new recommendations on screening for breast cancer. As background information, Dr. Woolf indicated that the USPSTF was established in 1984 by the Public Health Service (PHS) and is staffed by AHRQ. The USPSTF periodically publishes a book called *The Guide to Clinical Preventive Services* and develops recommendations on hundreds of clinical preventive services covering the full range of screening tests, counseling, interventions, immunizations, and chemoprophylaxis. The recommendations are rigidly based on the quality of the supporting evidence. Randomized controlled trials typically carry the greatest importance. Dr. Woolf explained that the USPSTF has a new grading scheme for making recommendations. The new scheme includes grades from *A* to *D*, plus *I*, arranged in a matrix in which one axis refers to the quality of evidence, and the second axis represents the estimate of net benefit. An *A* recommendation is given when an intervention has good evidence and substantial benefit. A *C* recommendation is made when the net benefit is small, and an *I* grade is given when there is insufficient evidence.

Dr. Woolf stated that the breast cancer screening guidelines recently announced by the USPSTF are the product of an update initiated in 1999, not a response to the Danish review. The systematic review of the trials and other evidence related to the mammography issue, as well as a meta-analysis commissioned to help integrate the latest follow-up data from the mammography trials, was performed by the Oregon Health and Sciences University. The new USPSTF recommendations are as follows:

A *B* recommendation is given to mammography screening, indicating that the Task Force recommends screening mammography, with or without clinical breast examination, every 1 or 2 years for women aged 40 and older. Mammography screening was previously graded *A*, Dr. Woolf explained, but this is not a downgrading; it is only because of the change in the grading scheme. Based on the recent examination of the latest follow-up data from eight clinical trials that indicated that relative risk reductions ranged from 2 to 32 percent, the USPSTF changed its longstanding policy of not recommending screening for women in

their 40s, a policy based on the lack of sufficient evidence to recommend for or against mammography for this age group. The meta-analysis that included the follow-up data showed that there is about 25 percent risk reduction of death from breast cancer for women who undergo mammography screening. The USPSTF changed its position and recommended starting screening at age 40 rather than 50, because five of seven trials suggested a benefit with longer follow-up data, and the USPSTF finds that the relative risk reduction for women in their 40s is similar to that of the older age groups. Clinical breast examination and breast self-examination have an *I* grade, indicating that there is insufficient evidence to make a recommendation.

Regarding the Gotzsche and Olsen article, Dr. Woolf stated that his group carefully studied the criticisms and attempted to estimate whether the biases introduced by the flaws in the trial design would likely be of sufficient magnitude and duration to account for the mortality reductions observed in those trials. He noted that although there are imperfections in the trials, his group does not view them as fatal flaws and does not agree with the conclusions reached by Gotzsche and Olsen. Dr. Woolf stated that his group will soon publish an article containing its own systematic review and a review of the methodologic issues raised by the Danish authors.

Quantifying the Population Effect of Mammography: Performance and Outcomes

Breast Cancer Surveillance Consortium. Dr. Rachel Ballard-Barbash's, Chief, Applied Research Programs (ARP), DCCPS, presentation focused on the ongoing efforts of the NCI to enhance population-level data and research on screening and cancer outcomes through the BCSC and the International Breast Cancer Surveillance Network (IBSN). The BCSC began as a series of pilot studies within the Surveillance, Epidemiology, and End Results (SEER) registry program in the early 1990s. It now has seven research centers collecting data across the United States, and a statistical coordinating center at Group Health Cooperative. The IBSN is a group of 25 volunteer organizations around the world, each from a different country. The BCSC was established to determine whether the benefit estimated by randomized controlled trials was actually occurring in practice. Its objective was to evaluate the performance of screening in practice through standard

measures of performance, such as sensitivity, specificity, and recall rates, as well as look at other measures, both at the individual patient level and at the health care professional and systems levels, in terms of effects on performance. The BCSC database contains about 4 million mammography records, mostly for women 40 to 49 years of age. She explained that the high number of mammograms among this population is a reflection of the larger proportion of women in this age group in the general population.

Dr. Ballard-Barbash informed members that, more recently, there has been an interest in quantifying the population effect on the stage shift from screening to mortality outcomes. She noted that this effort was designed deliberately to allow investigators to track new technologies in screening, including imaging, tissue and molecular markers, and proteomics. Partnership with collaborators such as the Food and Drug Administration (FDA), Centers for Disease Prevention and Control (CDC), American College of Radiology (ACR), and individual communities is important to better understand what is happening in practice.

In brief comments regarding the IBSN, Dr. Ballard-Barbash stated that they have published six papers. A reflection of the number of countries that have had screening in place for a sufficient length of time to evaluate stage-shift and other surrogate endpoints for mortality reduction. All of the papers have demonstrated a shift to lower-stage disease among screened women. Dr. Ballard-Barbash emphasized that enhancing the accuracy of screening and decreasing false-positive results is crucial so that fewer women will need to undergo biopsy procedures. Data from the BCSC indicate that women who undergo biopsy procedures develop a lower sensitivity for subsequent screening mammography. She noted that there is a critical need for new statistical methodologies for evaluating ways to manipulate these complex population data and account for individual-level data as well as health professional, facility, or system-level data. The BCSC has increased its attention on quantifying the population effect on mammography in terms of updating analyses on stage shift and exploring the degree of mortality in defined populations. The IBSN will meet in May 2002, and this issue will be a major focus of that meeting.

Statistical Modeling: Dr. Eric Feuer, Statistical Research and Application Branch, Surveillance Research Program, DCCPS, discussed statistical modeling and the impact of mammography on

population trends from the perspective of: ecologic regression; "back of the envelope" calculation of the impact of the observed stage shift seen in the SEER data on breast cancer mortality; and a cooperative group of modelers, i.e., the Cancer Intervention and Surveillance Modeling Network (CISNET). Dr. Feuer indicated that via *"ecologic regression"* there is a potential bias in analyzing trends in breast cancer mortality by state versus mammography rates because adjuvant therapy, multi-agent chemotherapy, and hormonal therapy began at approximately the same time as mammography was becoming widely disseminated in the United States. A direct adjustment for these factors cannot be made due to the lack of sufficient data for every state.

Another type of analysis is by trends in breast cancer mortality by the SEER Health Service Area (groups of counties in which people tend to stay to get their health care). This analysis is a proxy measure of the amount of screening that takes place, it is possible to adjust for the percentage receiving adjuvant therapy, based on the SEER patterns-of-care studies. International comparisons are also possible. Data show that 1) in many Western European countries, breast cancer mortality has declined; 2) between 1992 and 1999, almost every state in the United States has had a breast cancer mortality decline; and 3) the higher the rate of mammography, the larger the percentage of decline in mortality. The analysis also shows a statistically significant decline in mortality, even after adjusting for hormone or adjuvant therapy.

"Back of the envelope" calculation - Dr. Feuer explained that as mammography use was disseminated in the United States in the mid-1980s, a decline in large localized and regional breast cancers was seen. In their analysis, investigators referred to this decline as "avoided cases." At the same time, large increases in small localized and *in situ* breast cancers were observed. These were dubbed "excess cases." These are cases detected through mammography that might otherwise have gone undetected, and it partly represents a shift from "avoided cases" to "excess cases." To study this shift's impact on mortality, Dr. Feuer and colleagues first projected the incidence in the absence of the stage shift. For "avoided cases," the difference between the observed and the projected trend, plotted on an appropriate stage-specific survival curve, reads as a decline in mortality. The same analysis for the "excess cases" shows a rise in mortality. Dr. Feuer explained that these two forces compete against each other, and the net effect is a

beneficial impact on mortality, mostly due to the decline in regional disease.

Efforts by *"CISNET"* are underway to obtain a more systematic partitioning of the cancer mortality rates into stage shift and other causes, including treatment and changes in background risk, among others. The overall purpose of CISNET is to model the impact of cancer control interventions, such as screening, treatment, and primary prevention, on current and future trends. A secondary goal is optimal cancer control planning, related to analyzing trends. Dr. Feuer noted that CISNET is a Cooperative Agreement RFA. The first round of awards was for FY2000 for a 4-year period. NCI awarded seven applications in breast, one in prostate, and one in colorectal cancer. The second round will be funded during the summer of 2002. Breast cancer has been excluded and lung cancer added to this round.

Prior to CISNET, the modeling was done using observed incidence, survival, and mortality; the impact of intervention was estimated by putting these pieces together. CISNET's novelty is the incorporation of the preclinical natural history of disease into the population planning models. Dr. Feuer added that the central theme for the various groups of grantees working on modeling of breast cancer involves looking at the impact of mammography, adjuvant therapy, and the combination of the two on U.S. breast cancer mortality between 1975 and 2000. All models will use common inputs, because NCI has access to a large quantity of population data that all investigators can use. The uniqueness of each model, however, will be preserved by employing specific inputs and assumptions related to the efficacy of treatment, tumor growth rates, and metastatic spread, among others. Because of the unlikeliness of future launches of randomized trials on screening, alternative approaches must be explored. Population data and modeling represent an imperfect but intriguing approach to evaluating the effectiveness of community interventions and partitioning the population trends. A CISNET project is to make the model differences more transparent using a state-of-the-art interactive Web site called *Model Profiler*.

In discussion, the following points were made:

- CISNET is attempting to conduct statistical modeling for separate racial and ethnic minority groups, in addition to

modeling for the general population.

- SEER data show that breast cancer mortality in African-American women has recently decreased in all age groups for which screening is taking place. Also, screening has now shown similar trends for the African-American and white populations. However, the quality of treatment received by the two populations may still not be equivalent.

- A Cancer Research Network project, the Detect Project, is investigating the reasons for failure to detect breast and cervical cancer at early stages.

- The Institute of Medicine has produced a book entitled *"Beyond Mammography,"* which may provide insight into the potential of new technologies to improve mammography screening.

- The NCI has established a Breast Screening Working Group that has three subcommittees to: 1) deal with mammography and communications, including modeling; 2) review new technologies, and 3) discuss issues related to basic biology. Advisory groups and the Institute of Medicine will review the work of the subcommittees.

- NCI is conducting an omnibus survey to assess women's reactions to the latest controversy on mammography screening. Interestingly, surveys during the 1993 and 1997 controversies and preliminary data from the recent controversy indicate that the overwhelming majority of women do not feel confused. Data show that women in underserved populations are the most confused. Special measures should be taken to address those groups.

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IX. RFA CONCEPT - PRESENTED BY NCI PROGRAM STAFF

Division of Cancer Biology

Molecular Interactions Between Tumor Cells and Bone (RFA). Dr. Suresh Mohla, Chief, Tumor Biology and Metastasis Branch (TBMB), Division of Cancer Biology (DCB), NCI, stated that the purpose of this initiative is to promote a better understanding of the pathophysiology of bone metastasis, especially the mechanism whereby tumor cells interact with a large number of cells in the bone microenvironment. The overall objective is to gain a better understanding of the unique features that render the bone and its microenvironment an attractive destination for tumor cell migration. The bone is a common site of metastasis, especially for breast cancer, prostrate cancer, and myeloma. There are few clinical treatments available, and none has resulted in an increased rate of survival in patients with bone metastases.

The RFA objectives are: 1) the interaction between tumor cells and bone cells, which involves studying the differences between metastatic and nonmetastatic tumor cells, identifying candidate genes, and validating these genes in physiologically relevant models; 2) targeting the study of biological mediators and signaling pathways involved in bone metastasis; 3) focusing on investigating the interactions between tumor cells and endothelial cells; and 4) defining the role of the immune system, including immune modulators. The importance of studying the systematic effects on the host of chemotherapy and/or radiation therapy was emphasized.

Members were told that 8 of 145 grant proposals concerned with tumor metastasis specifically address bone metastasis. A FY 2002 Congressional Area of Emphasis statement emphasized the study of the bone microenvironment as it relates to the metastasis of cancer to the bone. Because of the exploratory nature of some of the studies, the R21 grant mechanism will be included with the standard R01s.

The proposed length of the award for this one-time solicitation is 2 and 5 years, with a first-year set-aside of $3M and a total cost of $12.3M for an estimated four to six R21s and six R01s.

In subsequent discussion, the following points were made:

- There is very little research regarding metastasis, which is a critical phase of cancer progression. There is a need to promote research in this area.

- This RFA provides a good opportunity to tackle the large research question of how tumor cells interact with bone. It should also enable model development of bone metastasis, as there are so few models currently available.

- Obtaining consent for acquiring large amounts of tissue could be a problem because it would involve an invasive procedure.

- The private sector is already focusing on metastasis research, but only in the realm of pain management. There is still a need to study the underlying biology of this pathological process.

Motion: A motion to approve the RFA concept entitled "Molecular Interactions Between Tumor Cells and Bone" was unanimous.

Adjournment: The meeting adjourned at 5:15 p.m. on Monday, March 25, 2002.

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