DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE

Memorandum of Understanding (MOU)

AHRQ No 04-459MO-04
NCI No. 86076

This MOU sets forth the terms of agreement between:

Agency for Healthcare Research and Quality
Department of Health and Human Services

and:

National Cancer Institute
National Institutes of Health
Department of Health and Human Services

I. Purpose

The purpose of this agreement between the Agency for Healthcare Research and Quality (AHRQ) and the National Cancer Institute (NCI) is for the two agencies to cooperatively support research projects initiated by the NCI extramural research grant program through the Breast Cancer Surveillance Consortium (BCSC). Under this agreement, AHRQ will provide expert advice and consultation to BCSC research projects through, or with the agreement of, the NCI BCSC Program Director. The purpose of this agreement is to establish the arrangements between NCI and AHRQ and set forth the responsibilities, contributions, and understandings of the parties.

II. Background

The purpose of the BCSC is to enhance the understanding of breast cancer screening in the United States and support collaborative breast cancer research among mammography facilities and health care provider organizations that (1) are oriented to community care; (2) have access to large, diverse patient populations; and (3) can link data on mammography with subsequent diagnoses and outcomes.

The BCSC is a collaborative network of mammography facilities linked in a registry with further linkages to tumor registries and pathology data. A major component of BCSC research relies on pooled databases, obtained from all of these organizations, that contain surveys completed with patients, health care providers, and administrators of these facilities and organizations. Many of the research topics of the BCSC involve measures of screening performance and cancer care services delivered by these and other organizations. The scope of relevant data and level of detailed analysis that could be conducted on these topics would be enhanced by assurances to the participants that the identity of organizations and facilities, as well as individuals, would be protected and not disclosed in any reports, analyses, or any research data that are generated for publication or release by BCSC projects.

The collaboration of AHRQ and NCI on the BCSC project reflects AHRQ's and NCI's mutual commitment to improving quality of care. Both are part of the U.S. Department of Health and Human Services (DHHS) and have statutory responsibilities to collect, study, and disseminate information on certain aspects of the nation's health care. AHRQ and NCI also are currently collaborating on issues involving quality of cancer care through the HHS Quality of Cancer Care Committee and research initiatives such as the NCI-sponsored Cancer Research Network (CRN) and Cancer Care Outcomes Research and Surveillance (CanCORS) Consortium. Data collected for AHRQ's collaborative research projects are subject to the confidentiality provisions of 42 U.S.C. 299c-3(c) [also cited as 924(c) of the U.S. Public Health Service (PHS) Act]. This statute requires, in effect, that no identifying information obtained in the course of the AHRQ-supported BCSC projects may be used for any purpose other than that for which it is provided to the BCSC, and that such information may not be published or released unless the individual data subject(s) or person(s) or organization(s) providing the information has or have consented to such uses or disclosures. All those supplying or providing information will be informed as to restricted categories of users who will have access to identifiable data; that is, only authorized BCSC NCI and AHRQ staff or their respective agents will have access to any of the identifiable information collected. Any unauthorized use or disclosure of the protected confidential information is punishable under 42 U.S.C. 299c-3(d) [924(d) of the PHS Act].

III. Contributions of the Parties to the Project

The BCSC represents an important component of NCI's efforts to assess and improve the quality of cancer care and to evaluate the performance of screening mammography in community settings. AHRQ, with its broad mission to improve health care and its focus on measuring the quality of health care, also has an interest in working to measure and improve breast cancer screening and treatment services. Data generated by the BCSC will be valuable in carrying out AHRQ's mission of improving outcomes and quality of care through research, and, in particular, by providing insights into cancer care for its statutorily mandated National Healthcare Quality Report and the National Healthcare Disparities Report.

AHRQ will contribute in kind support to the BCSC project in the form of AHRQ research staff time and expertise in evaluation of breast cancer control service delivery and in assessment of related breast cancer outcomes. NCI will be responsible for providing funding and guidance to the BCSC. Future proposals for funding stemming from BCSC work may be submitted to AHRQ for consideration for grant funding through the usual AHRQ research grant mechanisms. There also might be some transfer of funds between NCI and AHRQ for related future research; however, such transfers currently are not planned.

IV. Responsibilities of the Partners

1. AHRQ research staff will be invited to review and comment on the ongoing BCSC collaborative research projects in their areas of expertise and will be invited to work with the BCSC staff responsible for maintaining the BCSC data infrastructure to develop collaborative BCSC-AHRQ projects to advance AHRQ research objectives, including, although not necessarily limited to, analyses for the National Healthcare Quality Report and the National Healthcare Disparities Report. NCI will be invited to review and comment on AHRQ projects related to the BCSC and to work with AHRQ staff to develop collaborative projects. AHRQ is

responsible for continued funding of its related research, evaluation, and dissemination projects, but NCI may opt to contribute towards projects of mutual interest.

2. The BCSC collaborative research projects covered under this agreement will be conducted through NCI grants U01CA86082, U01CA86076, U01CA70040, U01CA70013, U01CA69976, U01CA63740, U0163736, and U01CA63731. (A copy of the BCSC Request for Applications is attached as Appendix A.) Responsibilities associated with the administration of these grants will be carried out by the NCI BCSC Program Director and the NCI Grants Management Office. NCI will appoint an individual who AHRQ designates or recommends as the AHRQ BCSC collaboration advisor to serve as a member of the BCSC steering committee. AHRQ will provide additional experts to attend the BCSC meetings and to advise the BCSC Program Director, or the grantees as deemed appropriate by the AHRQ BCSC collaboration advisor in consultation with the BCSC Program Director.

3. The NCI BCSC Program Director, in cooperation with the AHRQ BCSC collaboration advisor, will monitor the status of collaborative research projects as they progress. The NCI BCSC Program Director will provide the AHRQ BCSC collaboration advisor and AHRQ's legal advisor in the Office of General Counsel, when needed, with an advance copy and an opportunity to comment within 3 weeks, on any substantive communication with the grantees pertaining to the statutory confidentiality protections applicable to identifiable collaboration data described in this agreement. The AHRQ BCSC collaboration advisor, with advanced consultation with the NCI BCSC Program Director, may communicate directly with the grantees on scientific matters. All grantees and NCI and AHRQ agency staff who work with the BCSC data will be given copies of the AHRQ confidentiality provision, 42 U.S.C. 299c-3 (c) and (d) [section 924 (c) and (d) of the PHS Act]. Agency staff and grantee staff with access to identifiable data will be asked to sign an acknowledgment, which will be retained by the AHRQ BCSC collaboration advisor. A copy of the confidentiality agreement is attached as Appendix B.

4. During the period of this MOU, the AHRQ BCSC collaboration advisor will be involved in the development and progress of BCSC collaborative research in breast cancer control service delivery. The NCI BCSC Program Director will provide the AHRQ BCSC collaboration advisor with copies of the annual grant progress reports and any publication citations or reprints submitted by the grantees. The AHRQ BCSC collaboration advisor will have an opportunity to comment on these materials.

5. The AHRQ BCSC collaboration advisor and other AHRQ staff the advisor designates as having related expertise or research interests will be invited to attend bi-annual meetings convened for the project. The AHRQ BCSC collaboration advisor will be provided with copies of all meeting-related materials.

V. Duration of this Agreement

This MOU shall be in effect from the date of joint signatures by AHRQ and NCI for breast cancer control service delivery projects beginning immediately and to continue through the end of the next grant cycle, estimated to end August 2010**.** This agreement may be modified at any time based on mutual agreement and duly authorized signatures. It also may be cancelled if either party so notifies the other in writing with 90 days advance notice or if a Federal statute is enacted or regulation promulgated that materially affects the agreement. While the agreement may be cancelled, the applicable statutory confidentiality restrictions cited above continue to protect all the identifying data collected while the MOU was in effect.

VI. Statutory Authorities

Both agencies have general authority to enter into MOUs to carry out and jointly support their respectively authorized programmatic activities. The NCI's authority to support research studies on cancer control and cancer-related population studies is provided in 42 U.S.C. 285a-1 [Section 412 of the PHS Act]. The legal authority of AHRQ to support research studies on breast cancer control and subsequent health outcomes is provided in 42 U.S.C. 299(b), 299a-1(a), and 299b(b) [sections 901(b), 902(a), and 911(b) of the PHS Act]. All identifiable information collected, maintained, or generated under this AHRQ-supported project is subject to the protective confidentiality terms of 42 U.S.C. 299c-3(c) [section 924(c) of the PHS Act] without limitation, and the penalty provisions of 42 U.S.C. 299c-3(d) [924(d) of the PHS Act] apply to any violations of the protective confidentiality restrictions by anyone with access to these data.

VII. Data Protection

With AHRQ's support for the BCSC research projects, NCI and its grantees who collect and provide data for this project become subject to the above-described confidentiality statute and related penalty provision that protect identifiable data collected as part of activities supported by AHRQ. Accordingly, NCI and its BCSC grantees must adhere to the statute's restrictions and should cite it and rely upon it in declining to release identifying data gathered solely for cancer control health care research purposes. Termination of AHRQ support does not extinguish the statutorily based confidentiality obligations of anyone who holds data collected as part of activities that AHRQ supported.

VIII. NCI BCSC Program Director/AHRQ BCSC Collaboration Advisor

NCI BCSC Program Director:
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IX. Signatures of Acceptance

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Carolyn Clancy, M.D. Date
Director, AHRQ

Robert Croyle, Ph.D. Director, DCCPS, NCI	Date

Appendix A. RFA

BREAST CANCER SURVEILLANCE CONSORTIUM EXPANSION

Release Date: January 22, 1999

RFA: CA-98-025

P.T.

National Cancer Institute

Letter of Intent Receipt Date: June 15, 1999
Application Receipt Date: July 15, 1999

PURPOSE

The Division of Cancer Control and Population Sciences (DCCPS), National Cancer Institute (NCI), invites applications from domestic institutions for cooperative agreements to support collaborative research within the Breast Cancer Surveillance Consortium (BCSC), established by the Cancer Surveillance Research Program (CSRP) in 1994. This is a follow up to RFAs (cooperative agreements) awarded in 1994 and 1995 and coming to an end in 1999 and 2000. This RFA is intended to include recompetitions from existing centers and applications from new centers. Strengthening surveillance activities has been identified as an NCI priority, particularly in order to allow more definitive statements to be made regarding factors influencing cancer incidence, mortality, and survival at the national level. The Breast Cancer Surveillance Consortium has led to the development of data linkages between radiologic practices, pathology laboratories, and cancer registries to obtain data on screening mammography, recommended and subsequent work up, diagnosis, treatment, and mortality. Some limited risk factor data thought to be most relevant to screening and diagnosis are being collected and data on benign breast disease pathology for biopsied non-cancer cases are being collected at some sites. This initiative will broaden the current Breast Cancer Surveillance Consortium research effort in several key aspects, while continuing to support the central goals and objectives. In addition to funding sites to collect data relevant to mammography performance, this RFA will also support a Statistical Coordinating Center (SCC) to develop data comparability processes, to serve as the central repository for pooled data and to provide the research expertise on complex statistical issues for analysis of these pooled data.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national activity for setting priority areas. This RFA, BCSC Expansion, is related to the Priority area of cancer surveillance and data systems. Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0 or Summary Report: Stock No. 017-001-00473-1) through the

Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325 (telephone 202-512-1800), or at http://www.crisny.org/health/us/health7.html.

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic for-profit and non-profit organizations, public and private, such as universities, colleges, cancer centers, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Applications from minority and women investigators are encouraged. Since this RFA concerns breast cancer surveillance research in the United States, a domestic application may not include an international component. New applicants and those with currently funded programs are eligible as described below. A BCSC applicant may be, but is not limited to, a hospital, a clinic, a group of practicing physicians, a health maintenance organization (HMO), or a consortium of hospitals and/or clinics and/or physicians and/or HMOs that agree to work together with a Principal Investigator and a single administrative focus. If the expertise required does not reside within one institution, an applicant may put together a group with the necessary expertise, which may involve the use of several institutions and/or organizations. Each primary data collection and research center applicant must have access to a resource unit that supports research data management and statistical analyses locally.

MECHANISM OF SUPPORT

The administrative and funding instrument to be used for this program will be a cooperative agreement (U01), an "assistance" mechanism (rather than an "acquisition" mechanism), in which substantial NIH scientific and/or programmatic involvement with the awardee is anticipated during performance of the activity. Under the cooperative agreement, the NIH purpose is to support and/or stimulate the recipient's activity by involvement in and otherwise working jointly with the award recipient in a partner role, but it is not to assume direction, prime responsibility, or a dominant role in the activity. Details of the responsibilities, relationships and governance of the study to be funded under cooperative agreement(s) are discussed later in this document under the section "Terms and Conditions of Award". The total project period for applications submitted in response to the RFA may not exceed five years. Because the nature and scope of the research proposed in response to this RFA may vary, it is anticipated that the sizes of awards will vary also. Awards will be administered under PHS grants policy as stated in the NIH Grants Policy Statement, dated October 1998.

This RFA is a one-time solicitation. If the NCI determines that there is a sufficient continuing program need, a request for new and competitive continuation applications will be announced.

FUNDS AVAILABLE

In fiscal year 2000, the NCI plans to make 9-11 awards for primary data collection and research centers and one award for a SCC. Approximately

$5,000,000 total cost (total cost = direct plus facilities and administrative costs) is expected to be available for the first year of support under this RFA and the research effort will be renewable for up to 5 years. It is anticipated that the award for each primary data collection and research center will be between $400,000 - $550,000 total cost for the first year and the award for the SCC will be about $550,000 total cost for the first year. While it is possible that one institution may apply for a primary data collection and research center and the SCC, separate applications must be submitted. It is anticipated that the relevant expertise necessary to lead these two efforts would result in different PIs for the two applications efforts should a single institution apply for both.

The number of awards to be made is dependent on the receipt of a sufficient number of applications of high scientific merit and availability of funds. Although this program is provided for in the financial plans of the NCI, awards pursuant to this RFA are contingent upon the availability of funds for this purpose. The anticipated date of award is March 2000.

First year costs may include development of computer systems dedicated to this research, if needed. For purposes of budgeting, funds should be requested for up to five persons to attend semi-annual BCSC meetings at alternating BCSC sites or the NCI during each of the five years of award. Funds should also be requested for up to 2 persons to attend up to 2 smaller working group meetings at alternating BCSC sites or the NCI during each of the five years of award. The SCC applicant should budget for up to 11 site visits (one to each potential primary data collection and research center awardee) per year for the purposes of improving data collection, formatting and transfer procedures for pooled data analyses.

RESEARCH OBJECTIVES

Background

A more complete summary of the existing BCSC (16) can be obtained from the American Journal of Roentgenology, October 1997; 169:1001-1008. Excerpts from that summary are included in this background.

Mammography is the primary method of detecting early stage breast cancer and has been shown in randomized clinical trials to reduce breast cancer mortality, especially among women 50 years old and older [1-5]. Authorities in cancer screening have long recognized that the level of efficacy of screening demonstrated in randomized clinical trials may not pertain to community practice for several reasons [6]. These include possible differences in the population groups receiving screening, lower accuracy of screening mammography in the community, or lower compliance with diagnostic follow-up and treatment in community practice, which may not lead to optimal outcomes. On the other hand, screening effectiveness in community practice today could exceed that estimated in trials because the technical and interpretative quality of mammography has improved since the trials were performed. Furthermore, clinical trial efficacy has been estimated based on assignment to receive screening; to the extent that women assigned to

screening were not screened or that women in the control groups were screened, efficacy in trials may have been underestimated.

To optimally evaluate the performance of mammography in a community setting, the screening prevalence and patterns, and the associated sensitivity, specificity and predictive value of mammography in community screening programs should be determined by linkage with cancer outcomes [7,8]. A program of monitoring should also provide data on specific populations, such as rural and minority subgroups, that are traditionally underserved by screening programs and may have different breast cancer mortality rates [9]. Before the Mammography Quality Standards Act (MQSA) of 1992, most mammography facilities in the United States did not maintain record systems that could provide reliable and comprehensive data to evaluate the performance of screening mammography [10]. The concept of a medical audit of outcomes data had been proposed [11] but has not been routinely practiced in the community. The interim regulations of the MQSA mandated the maintenance of mammography data and the performance of a medical outcomes audit [12]. In practical terms the medical audit requirement of the MQSA was limited to an analysis of patients with tests interpreted as "suspicious abnormality" or "highly suggestive for malignancy, " which permits evaluation of the positive predictive value of such interpretations. However, the MQSA does not require linkage to population-based cancer registry data or other source of pathology data, without which it is impossible to accurately assess the outcomes of patients with mammographic examinations interpreted as normal. To understand the full effect of breast cancer screening on cancer outcomes, data on breast cancer screening practices should be linked to data from population-based cancer registries. Moreover, data on pathologic or biologic characteristics of tumors, together with patient demographic and risk factor information, can be linked to population-based registries in order to better understand staging and survival of mammographically-detected compared to non-mammographically-detected breast cancers.

Development and Purpose of the NCI Breast Cancer Surveillance Consortium

A section of the MQSA authorized the Secretary of the Department of Health and Human Services to fund research establishing a breast cancer screening surveillance system. In response to this legislative mandate, the NCI established the BCSC in 1994. The three major objectives of the BCSC are: 1) to enhance our understanding of breast cancer screening practices in the United States through an assessment of the accuracy, cost, and quality of screening programs and the relation of these practices to changes in breast cancer mortality or other shorter term outcomes, such as stage at diagnosis or survival; 2) to foster collaborative research among BCSC participants to examine issues such as regional and health care system differences in the provision of screening services and subsequent diagnostic evaluation; and 3) to provide a foundation for the conduct of clinical and basic science research, especially basic research on biological mechanisms, that can improve understanding of the natural history of breast cancer. The intent of the third objective is to ensure that a core set of pathologic data on established prognostic indicators is collected and to provide the capability to examine the prognostic potential of other more investigational indicators. The NCI

developed a Consortium of research sites in order to address issues that can be adequately examined only in a very large sample drawn from diverse geographic and practice settings. The first major effort of the Consortium was to create a standard set of carefully defined variables in order to facilitate pooling of data with sample sizes sufficient to examine issues in subgroups for which the number of cancers is relatively low, such as among younger women, women with a family history of breast cancer, or some ethnic or racial groups. This latter, critical objective of national pooled data analyses necessitated the development of a SCC and is the rationale for the involvement of NCI surveillance research staff in this project through a cooperative agreement mechanism.

In order to address these research objectives, the BCSC has developed standardized data collection and linkage mechanisms for mammography practice data and population-based cancer registry data. This linkage can provide cancer characteristics and follow-up of patients for vital status and cause of death and will allow an assessment of the performance of screening mammography in diverse community settings. Furthermore, the linkage of these data will provide a unique opportunity, in the short term, to determine whether differences in the practice of screening mammography and subsequent diagnostic evaluation influence breast cancer detection rates and stage at diagnosis. In the long term, such linked data may have the potential to provide information on whether differences in practice patterns influence breast cancer mortality. The original 5 years duration of funding does not allow for evaluating this long term objective. By the year 2000 the database will contain information on nearly 3.2 million mammographic examinations and over 24,000 cases of breast cancer. The estimated racial and ethnic distribution of women receiving mammography reflects that of the geographic catchment areas for the nine sites. The age distribution of women currently receiving mammography within the database is 8%, 31%, 26%, 19%, and 16% for ages less than 40, 40-49, 50-59, 60-69, and 70 and older, respectively.

In addition to its intended purpose of evaluating population-based screening mammography in the United States, the database will be a valuable resource for future research. For example, with continued collection of data in these populations and follow up for outcomes, BCSC data will allow assessment of the effect of community mammography screening on stage distribution of breast cancer. Current BCSC pilot studies are examining the hypothesis that the performance of screening mammographic examinations varies by biologic characteristics, stage, and rate of growth of breast tumors. Furthermore, the BCSC database will provide information on demographic, risk factor, clinical characteristics, and treatment for women who subsequently develop breast cancer. It will also provide data on a large population-based sample of women at high risk for breast cancer, including those with a family history of breast cancer or benign breast disease. Therefore, this resource may be particularly useful for identifying patients relevant for research into the population prevalence of genetic and other biological markers for breast cancer risk and prognosis and potential associations of these markers with other known breast cancer risk factors. Data from the BCSC will provide estimates of the prevalence of subsequent diagnostic follow-up and information relevant to improving the communication of risks and benefits related to

screening. The mammography registry may also serve as a resource for intervention trials to study ways to improve screening compliance.

A second use of the database will be to permit the comparison of regional data across the United States. The process of identifying a uniform set of data at the BCSC sites has improved consistency in data collection and provides a model for the development of linkages between mammography and cancer registries. Other entities, such as states that are establishing mammography registries, have sought information from the BCSC on how to set up comparable systems. Dissemination of such information should foster uniformity in data collection among emerging software packages and at other facilities trying to create linkages between mammography data and cancer registries, thereby further improving the ability to compare the performance of mammography across regions. These efforts should also improve quality of data and, through publication and feedback of the data to radiologists in the community, improve mammography screening quality.

Accomplishments

In addition to the above background, some of the accomplishments of the BCSC merit further discussion because they are distinctive to the needs and future directions of national surveillance research. These are chronologically described and relate to the development of standardized, high quality methods for data collection, ensuring confidentiality of data and research subjects, novel approaches to data collection within the context of routine clinical care, and, finally, the research productivity of the BCSC database.

Development of standardized, high quality data:

A data dictionary has been developed which details the standardized format created to allow analysis of data pooled from multiple sites. Unlike multi-center clinical trials that use a common protocol and common data collection instruments, the research projects within the BCSC rely on data collected within the context of routine medical care. Variability in practices at diverse sites presents a challenge to the collaborative research effort in which all sites must collect the same core variables. Core variables are being collected to build three databases which can be linked: patient demographic and health history, radiologic history, and follow-up. Research using the database will demonstrate the specific variables and level of detail that are most valuable in assessing the performance of screening mammography in community practice. The results of this research effort (and details of level of specificity required) are likely to be central to future FDA revision of the MQSA. The data dictionary has been a valuable resource to researchers considering the development of similar systems in their own regions.

Ensuring confidentiality of data and research subjects:

Data confidentiality and protection of research subjects has become an increasingly important issue with the development of large, linked computerized databases with potential access by a variety of individuals. The absence of adequate legislative protection of the data during interstate

electronic transit and while at the SCC was a major issue influencing the ability of the BCSC to perform pooled data analyses. The concern was raised because data contributed to the SCC are exceedingly sensitive in nature. Data from health care providers reflect their practice and their accuracy in performing mammography, while data from patients pertain to their cancer status. Third party payers might have an interest in obtaining both types of data. Although state legislative statutes, institutional quality assurance (QA) statutes, or both may (depending on state laws or institutional policies) protect research databases and QA data from either litigation or access, once the data cross state lines or institutional borders they may not be protected. The BCSC addressed this concern by applying for and receiving federal Certificates of Confidentiality for each member site, including the NCI and the SCC, in accordance with the provisions of Section 301(d) of the Public Health Service Act (42 U.S.C. 241 (d)). The Certificate is issued to protect the privacy of research subjects by withholding their identities from all persons not connected with the research. This federal level of protection of BCSC and SCC databases is the highest level of protection available in the United States and represents the first Public Health Service Certificate of Confidentiality that has included health care providers as research subjects. The Certificates provide protection to research data irrespective of location, whether at the originating site, in transit to the SCC, or at the SCC. Such protection may become increasingly important to the conduct of research involving community practice and patients. To further protect data confidentiality, common confidentiality procedures were detailed in a manual and are followed at each site [17].

Novel approaches to data collection within the context of routine clinical care:

The sources of data for this national mammography surveillance research effort are diverse and range from solo practitioners in rural settings to multi-specialty groups within large, structured managed care organizations in urban settings. The complexity of integrating data from these multiple sources and the increasing use of computerized medical record systems for clinical care necessitated the development of novel data collection and editing systems within the BCSC. Two examples of very different systems developed by BCSC investigators to accommodate their study populations are illustrative of the innovation required. The Carolina Mammography Data System collects data from over 70 sites providing mammography to women in 24 largely rural counties in the state of North Carolina. Data collection methods initially included a high proportion of paper data collection and transfer but now are primarily accomplished via electronic systems. Conversely, in the San Francisco Mammography Registry data collection and transfer were developed as electronic clinical practice systems and implemented in the largely urban, large multi-specialty practices included in that registry.

Research productivity:

A major mandate within the MQSA called for the Secretary of DHHS to establish

research projects testing the feasibility of establishing population-based linked databases for evaluating the performance of screening mammography in community practice. The mandate for this research effort was assigned to the Cancer Surveillance Research Program within NCI. A number of sites and the BCSC have published baseline manuscripts describing the development of these systems [13-16]. Ensuring confidentiality of data and research subjects is a critical component of feasibility and has been described in a BCSC manuscript [17]. Research at individual sites has addressed the performance of screening mammography in diverse settings [18-20], the effect of patient characteristics, such as family history for breast cancer, use of hormone replacement, and breast density on screening performance [21-23], and the accuracy and reliability of breast pathologic diagnosis in community practice [24]. Data from one site have been used to estimate the cost and benefit of screening mammography [25], and pooled data will allow these issues to be examined in greater detail for population subgroups. Results from one research project within a large managed care organization, which has complete ascertainment of mammography utilization in its population, have provided the first community-based data demonstrating a decline in late stage breast cancer associated with increasing screening mammography [20]. A facility survey on technical quality assurance practices in Colorado has demonstrated continued improvement in quality assurance practices (26); the effect of these improved practices on mammography performance is being examined. Initial collaborative research within the BCSC includes methodologic analyses to examine which parameters have the greatest influence on performance measures, and analyses of whether the actual use of the recommended American College of Radiology lexicon for classifying screening mammography interpretations are consistent with follow-up recommendations for diagnostic evaluation. The later has important implications for assumptions currently used to estimate cost-effectiveness and benefit of mammography screening.

Current Research Objectives and Scope

The original and continued objectives of the BCSC are: 1) to enhance understanding of breast cancer screening practices in the United States through an assessment of the accuracy, cost, and quality of screening programs and the relation of these practices to changes in breast cancer mortality or other shorter term outcomes, such as stage at diagnosis or survival; 2) to foster collaborative research among BCSC participants to examine issues such as regional and health care system differences in the provision of screening services and subsequent diagnostic evaluation; and 3) to provide a foundation for the conduct of clinical and basic science research, especially basic research on biological mechanisms, that can improve understanding of the natural history of breast cancer.

These objectives remain as priorities, although additional research priorities detailed below have been identified since the first issuance of this RFA in 1993. The BCSC has demonstrated that creating mammography registries with data linked to pathology and cancer registry data is feasible. Now longer term research objectives can be accomplished. Furthermore, significant progress has been achieved in establishing a core set of data, and efforts to move towards more standardized sets of questions for data collection have

begun. Building future research capacity and continued collection of core data remain priorities.

In addition to core data collection, each site will propose special projects. These special research projects may address a diversity of issues, including but not limited to the following:

- innovative approaches for collecting more detailed risk factor data in mammography registry areas, - utilization of state-of-the-art and emerging new technologies in breast cancer screening and diagnosis, or
- the examination of differences in clinical management, biology, or outcome of screen detected versus interval (non-screened detected) cancer.
The complex statistical issues, development of methods, and coordination of data comparability for pooled analyses will be supported by a single SCC.

One purpose of this RFA is to stimulate multidisciplinary collaborative research to enhance understanding of mammography screening in community practice. The backgrounds of current members of the BCSC reflects the diversity of research expertise that is needed: epidemiology, health services and economics, clinical practice related to screening mammography and subsequent diagnostic evaluation (nurses, internists, family physicians, radiologists, pathologists), behavior (psychology, sociology, and health education), statistics and computer modeling, and data management.

Continued collection of core data remains a priority

o Longer term data are needed to evaluate whether the community practice of mammography affects outcomes, such as breast cancer mortality.

o Large sample sizes in diverse population subgroups are needed to track the performance of mammography in diverse populations, and to track the diffusion of new technologies into clinical practice.

o Similarly, large sample sizes over time are needed to track changes in the accuracy of mammography because of introduction of new technology or increased adherence to quality assurance standards, and to assess whether these changes influence cancer mortality.

Continued efforts to increase data comparability and standardization

o Substantial progress has been made and efforts should be continued to ensure comparability of data across sites. This includes the development of a standardized set of questions for collection of core data elements. All responses to this RFA must indicate familiarity with the core data elements identified by the BCSC [16]. The NCI Program Director can be contacted for documents which describe these data elements in detail. The purpose of this research effort is to evaluate the translation of mammography screening into community practice within existing health care systems.

o One objective in the next stage of this effort will be to clarify the most critical data elements for evaluating the performance of mammography screening

in populations and improve standardization and to collect those elements within routine clinical practice.

o A second objective will be to identify innovative approaches to the collection of data elements which may not be easily obtained within the context of the routine clinical practice of mammography screening, such as more detailed risk factor data. There is a particular interest to collect established risk factor data among both screened and nonscreened populations in regions covered with both mammography and cancer registries. Innovative approaches could be developed and tested within the context of special research projects carried out at individual primary data collection and research sites. The innovative approaches proposed may vary by site.

o These objectives require that all sites 1) provide core data elements to the SCC for the purpose of conducting collaborative pooled data analyses, and 2) participate fully in the cooperative organization unit, referred to as the BCSC, including collaborative biannual research meetings and working groups identified to address specific research issues. The BCSC has been formed for the purpose of planning, developing, and conducting collaborative research projects which share common protocols, study designs, research objectives, and comparable data collection procedures.

Building future research capacity

Some research objectives, such as tracking the diffusion of new technology, are likely to be best accomplished by adding items, such as use of MRI and Nuclear Medicine to core data. The BCSC has revised the core data elements to anticipate the need for collecting these new data elements. Information on standardized questions and data format for core data elements are available from the NCI Program Director.

Other research objectives are best accomplished by special research projects, which will be proposed by each site. Data collection and research center applicants are encouraged to consider special research projects that might include but are not limited to the following areas: (Because this RFA is intended to build surveillance research capacity, these research projects cannot address interventions to change patient or provider behavior.)

- innovative approaches for collecting more detailed risk factor data in mammography registry areas. While some limited risk factor data are collected through core data collection at all sites, it is anticipated that much of the expanded data collection effort on risk factors may be accomplished through innovative special research projects at different sites. Core data collection provides information on the screened populations, while special research projects may address both screened and nonscreened populations. Special research projects that address collecting more detailed risk factor data through general population surveys, targeted samples of the population, or other methods are encouraged. Efforts to partner with existing risk factor surveillance efforts in the defined region of the mammography registry and the use of geographic information systems are encouraged but not required.

- utilization of state-of-the-art and emerging new technologies in breast cancer screening and diagnosis. Research is needed to improve the ability to track the diffusion of new technology and emerging technology not yet included in routine clinical practice. Relevant radiologic procedures currently under study for their utility in screening include but are not limited to the following: digital mammography, computer aided diagnosis, transmission of radiologic images with information technology for remote interpretation, central review and other purposes, MRI for women with dense breasts, stereotactic or ultrasound guided final needle aspiration and biopsy. Tracking potential biologic or pathologic modalities, such as pathologic diagnostic testing of breast biopsy specimens or nipple aspirates for evaluation of risk and prognosis, is also of interest. Some aspects of these objectives may require the addition of data elements to core data collection, while special research projects may be needed to explore hypotheses that cannot be examined with core data.

- examination of the reliability and validity of specific terms used in the clinical practice of screening mammography. Terms, such as breast density and ACR BiRADs Lexicon codes, are based in part on subjective interpretation and may be used differently across radiologists. Studies to examine the reliability and validity of these terms are encouraged.

- the examination of differences in clinical management, biology, or outcome of screen detected versus interval (non-screened detected) cancer or basic clinical studies of prognostic markers for screen detected vs interval cancer. Because this research effort is examining issues at the community level, basic clinical studies of well-established prognostic markers are encouraged. Studies of less established markers are also of interest.

- development of statistical modeling. There are a limited number of data sets available that have information on entire mammography screening histories for women. This type of data could be used to develop models for patterns of mammography utilization in the community and among sub-populations. These models could specifically address characteristics such as age of first mammography exam and repeat screening behavior. There would be a number of uses for comprehensive models of lifetime screening behavior, including looking at issues of compliance to recommended guidelines, identifying how actual utilization differs from guidelines, and prediction of how targeted interventions may influence long term mammography use. These issues are clearly of interest to both the primary data collection and research centers as well as the SCC.

- surveys of psychological and social consequences of screening mammography. While the core data of the BCSC will provide invaluable data on the extent and outcomes of medical evaluation following screening mammography, data are also needed on the psychological and social consequences of this increasing common practice.

- better understanding of the mammographic characteristics of ductal carcinoma in situ (DCIS). The detection of DCIS has increased markedly with the advent of ever more sensitive screening mammography. The uncertainty of the clinical

consequences of this diagnosis drives the need to better understand whether distinctive subcategories of DCIS in terms of clinical outcomes can be identified in terms of unique mammographic characteristics, biological markers or other parameters. Special studies in this area are encouraged.

Research objectives and scope of the Statistical Coordinating Center (SCC)

It is essential that a SCC applicant show evidence of the ability

- to establish and evaluate data collection and formatting procedures to create comparable data files for the type of pooled data analyzed within the BCSC. The SCC applicant should demonstrate good understanding about the elements of the data dictionary which has been developed within the BCSC for the purposes of pooled data analysis. The NCI Program Director can be contacted for documents which describe these data elements in detail. Unlike controlled clinical trials, data used by the BCSC is collected within the context of routine clinical practice and is therefore not completely standardized across all sites. The SCC applicant should demonstrate good understanding of how to create comparable data files from these diverse sources and how to link the various subcategories of data being collected for this research effort.

- to develop a standardized set of questions for data collection at primary data collection and research centers. The SCC applicant should demonstrate good understanding of the data elements and questions which the BCSC have determined should be included as core items within all primary data collection and research centers. The NCI Program Director can be contacted for documents which describe these data elements in detail. Some evidence to support the standardized set of questions proposed should be provided.

- to work with primary data collection and research centers to develop quality control procedures for data collection, storage and transmission of data to the SCC. While primary data collection and research centers are responsible for developing site specific quality control procedures for data collection and storage at their sites, the SCC should present a process for working across all centers to ensure that a minimum level of data quality is practiced at all sites.

- to develop a process for transferring all data to a central repository using file transfer protocols. The SCC applicant should provide evidence of understanding and experience in creating a central data repository, developing procedures for primary data collection and research centers to transfer data.

- The SCC applicant should develop and describe a process that ensures data security, privacy and confidentiality in the transfer process and while the data resides at the SCC.

The above criteria for the SCC are essential to ensuring data quality and comparability in order to accomplish pooled data analysis. In addition to its central role in moving the BCSC towards comparable data collection, the SCC is intended to accomplish several other research objectives with this initiative.

Advancing statistical methodology for breast cancer surveillance research

- Increased focus on the development of novel statistical methods and models for the analysis of these complex population data. Statistical methods to address multiple measures over time, variability across populations, facilities and providers are needed. Incorporation of statistical experts developing new methodologies is encouraged. Processes for facilitating understanding and further development of these methods among statisticians at individual sites should be addressed.

- Statistical methods for creating standardized parameters, such as those that adjust for underlying population characteristics in assessing the impact of mammography on outcomes, such as late stage disease and mortality, are needed and should be addressed by the SCC.

Data management for pooled data analysis

- In addition to its research role the SCC has a central responsibility for:
o Data management, including data comparability, formatting, and standardization of data elements;
o Reporting out status of data submitted for pooled data analysis in terms of completeness and utility for pooled analysis;
o Creating an electronic system for disseminating information regarding submitting core data elements and facilitating pooled data analysis; and
o Review and assistance with prioritizing pooled data analysis based on data available for proposed analysis and statistical methods available to address proposed hypothesis.

Definitions of population-based mammography registries

Finally, clarification is needed on the definition of population-based mammography registries for the purposes of this RFA. Two distinct categories of population-based mammography registries are included in the current Breast Cancer Surveillance Research Consortium. One category captures data on the population receiving mammography in community practice within a defined geographic region and links these mammography data with complete ascertainment of all cancer outcomes (and in some cases of all pathologic evaluations, including those for benign disease). The second category captures screening and risk data on a defined population, which may not be geographically defined, such as members of health plans or managed care organizations, and links these mammography data with complete ascertainment of all pathologic evaluations, both benign and malignant. This latter category provides the opportunity to collect data on women who participate in screening and those who do not. This latter category allows tracking the diffusion of screening mammography and directly evaluating the impact of diffusion on early and late outcomes, such as declines in late stage disease and death, respectively. Both categories are critical for future research needs, but may not always be available in a single site.

SPECIAL REQUIREMENTS

The NCI will convene the first of the semi-annual meetings for award recipients to join the NCI's BCSC. This BCSC consists of all investigators and research staff participating in this research effort. The BCSC Steering Committee consists of one voting member from each award recipient (the Principal Investigator or designee) from the primary data collection and research centers and the SCC and one voting member from the NCI (the Program Director or designee). The awardees to this Consortium will review the established group procedures and goals, and work with other investigators to plan and set priorities for cooperative group studies. The NCI Program Director will coordinate and facilitate the interactions of the BCSC institutions and will review their activities for relevance to the objectives of the RFA and programmatic considerations.

The BCSC will convene as needed to discuss collaborative study progress and address scientific and technical aspects of implementation. At BCSC meetings, members will strive to develop collaborative protocols and comparable standards for data collection and management, examine the areas of commonality, and discuss progress toward the agreed upon goals in all of the RFA scope of activities. These range from development of data collection instruments to more complex procedures such as the study protocol required to answer research questions in the collaborative studies proposed by the BCSC. Time lines will be established, revised and refined; BCSC members will collectively address and solve problems within the project; outstanding research questions will be defined and existing ones will be prioritized; data will be analyzed and prepared for "pooled" statistical analyses to answer agreed upon research questions requiring pooled analyses.

At these meetings, information relevant to collaborative studies will be reviewed and discussed, including such issues as overall BCSC performance and the science of current or proposed collaborative studies. Data will be analyzed and the outstanding research questions established and prioritized into national research goals by the BCSC investigators and the NCI Program Director. The Principal Investigators will have the primary responsibility for analyzing and prioritizing the research questions to be developed into collaborative studies. The NCI Program Director will provide assistance and guidance as needed, for example, in developing shared study protocols, selecting data elements, obtaining cooperation from the three types of facilities, linking databases, and analyzing pooled data on the operational aspects of screening. Communication among PIs at the various stages of protocol development is encouraged and communication systems have been developed by NCI to facilitate this communication.

Terms and Conditions of Award

Under the cooperative agreement, a partnership will exist between the recipient of the award and the NCI, with assistance from the NCI in carrying out the planned activity. The following terms and conditions pertaining to the scope and nature of the interaction between the NCI and the investigators

will be incorporated in the Notice of Grant Award. These terms are in addition to, and not in lieu of, otherwise applicable OMB administrative guidelines; HHS Grant Administration Regulations at 45 CFR Parts 74 and 92, and other HHS, PHS, and NIH Grant Administration policy statements.

The inability of an awardee to meet the performance requirements set forth in the Terms and Conditions of Award in this RFA, or significant changes in the level of performance, may result in an adjustment of funding, withholding of support, suspension or termination of award.

1. Awardee Rights and Responsibilities

a. Nature of Involvement with BCSC

The award recipients must join the NCI BCSC for the purpose of planning, developing, and conducting collaborative projects which share a common protocol, study design and research objectives, and comparable data collection procedures. Within this framework, the awardees will have primary and lead responsibility for the project as a whole, including research design and protocol development, and the planning, conduct, analysis, publication and interpretation of their studies. Data from these collaborative projects will be pooled for joint analysis, interpretation and publication of results in accord with policies and procedures established by the BCSC. The BCSC will convene as needed to discuss collaborative study progress and address scientific and technical aspects of implementation. In addition, when relevant, the award recipients will provide reports on progress of other funded projects external to the collaborative activities.

Awardees will be required to accept and implement the common processes and procedures approved by the Steering Committee and the processes and procedures established by the Statistical Coordinating Center.

Each primary data collection and research awardee must access three different kinds of facilities for the purpose of data collection and analysis regarding breast cancer screening practices. Access to existing records and collection of new information is required for: mammography facilities, pathology laboratories, and a quality-controlled, population-based cancer registry. Since this project includes substantial involvement in the use of the facilities' records and practices, the awardee must ensure collaboration among the three facilities throughout the award for purposes of this research project. Each awardee is required to submit core data elements for pooled data analysis as approved by the Steering Committee.

In addition to responsibilities of the SCC noted under data collection and management, the SCC awardee must participate actively on all meetings of the NCI BCSC and provide scientific, statistical, and technical input into discussions of pooled and collaborative research projects where relevant.

b. Strategy Sessions and Meeting Attendance

The award recipients (Principal Investigator or designee) must attend semi-

annual BCSC strategy session meetings and cooperate fully as active participants in the development and implementation of collaborative projects. Up to four additional staff will be required to attend as necessary to address the wide range of substantive and methodological discussions conducted during these strategy sessions. In addition, award recipients must attend up to two additional small working group meetings of PI subgroups working to facilitate progress on specific analyses.

c. Data Collection and Management

Award recipients:
- Must cooperate in the establishment of comparable data collection techniques for collaborative studies;
- Ensure that the tripartite multi-institutional group is able to implement the data collection procedures to be developed by the BCSC members;
- Ensure that the population-based registry data are compatible with SEER Program standards;
- Make all data required by any collaborative BCSC study available for pooled analyses within the time frame established by the Steering Committee; and
- Ensure that core data elements are collected to allow pooled data analysis.

Awardees are required to collect prospective detailed data directly from breast cancer screening facilities and from pathology records, and to link these data to population-based cancer registry data. These unique linkages are required in order to conduct research on breast cancer screening programs and to facilitate investigator initiated research on the immunobiology, cell biology, molecular genetics and endocrinology of breast cancer.

The awardee for the SCC is required to:
- Maintain existing data comparability processes developed by the BCSC and improve these processes where needed;
- Serve as the central repository for pooled data by maintaining confidential and secure mechanisms for transmitting electronic files for core data elements to the SCC;
- Examine and report on the quality of submitted data for the purpose of pooled data analysis; and
- Provide the research expertise on complex statistical issues for analysis of these pooled data.

Each awardee will retain custody of and primary rights to their data and is responsible for statistical analysis of local data, computer processing and statistical interpretations. However, for any collaborative studies among the BCSC members, the SCC will provide data analysis and statistical evaluation for pooled analyses. For these collaborative studies, the BCSC members will be responsible for the study design, planning and interpretation of the data. The NCI Program Director or designee will have access to all data generated under collaborative studies conducted under this award consistent with current HHS, PHS, and NIH policies. The NCI Program Director or designee will review periodically data management and analysis procedures approved by the BCSC.

Data must also be available for external monitoring if required by NCI's agreement with other Federal agencies, such as the FDA.

2. NCI Staff Responsibilities

The NCI program director will be responsible for normal stewardship of this award, and will also have substantial scientific/programmatic involvement as described below:

a. Establishment of Consortium
The NCI Program Director will convene the first of the semi-annual meetings for award recipients to join the NCI's BCSC. Principal Investigators from each of the award recipients will meet with the NCI Program Director to build a cooperative organizational unit, referred to as the BCSC Steering Committee. The Program Director may designate a staff person in the Surveillance Program to assume some duties of this role as needed.

b. Strategy Sessions
The NCI Program Director or designee, in cooperation with the Chair of the Steering Committee, will sponsor semi-annual strategy sessions attended by the Principal Investigators of the primary data collection and research centers and the SCC, other appropriate BCSC staff, and appropriate NCI staff.

c. Data Management
The NCI Program Director will have access to all data generated under this award consistent with current HHS, PHS, and NIH policies. The NCI program director or designee will review periodically data management and analysis procedures approved by the BCSC.

d. Monitoring and Program Review
In addition to normally prescribed duties of program and grants staff, an on-site program review will occur as early as 10 months but no later than 18 months after award. The program review will be conducted to evaluate progress of the BCSC, particularly the collaborative projects. The inability of a BCSC member to meet the performance requirements set forth in the Terms and Conditions of Award in the RFA, or significant changes in the level of performance, may result in an adjustment of funding, withholding of support, suspension or termination of the award.

3. Collaborative Responsibilities

This BCSC consists of all investigators and research staff participating in this research effort. The BCSC Steering Committee consists of one voting member from each award recipient (the Principal Investigator or designee) from the primary data collection and research centers and the SCC and one voting member from the NCI (the Program Director or designee). The Steering Committee may form subcommittees or working groups to address specific issues. Members will be identified within the BCSC membership or from other NCI staff suggested by the NCI Program Director and will be approved by the Steering Committee. The Steering Committee will meet separately during the course of the semi-annual BCSC meetings. It will also meet by conference call at least

twice between the semi-annual meetings.

Awardees (primary data collection and research center and SCC) to this request must agree to join the BCSC. The BCSC Principal Investigators from the primary data collection and research centers and the SCC will establish a leader (Steering Committee Chair, chosen from awardees) who, with the NCI program director, will administratively preside at all BCSC meetings. The Steering Committee Chair, other members of the BCSC, and the NCI Program Director (Chief, Applied Research Branch, CSRP, DCCPS) have established administrative procedures (i.e., meeting dates, guidelines for reporting, etc.) and methods by which all scientific/analytic requirements of the RFA will be met. The collaborative protocols will be developed by the Steering Committee. Core data elements will be submitted centrally to the SCC. Information on standardized questions and data format for core data elements are available from the NCI program director. The Steering Committee will define rules regarding access to data and publications. The new awardees will review these procedures and work with the BCSC to determine the need for any changes. Awardees will be required to accept and implement the common protocol and procedures approved by the BCSC Steering Committee. Special research projects occurring only at one site are not required to be approved by the Steering Committee. Collaborative research projects which utilize data from more than one site will be required to be approved by the Steering Committee.

Because the existing BCSC was a feasibility effort and was developed over several years, some members of the BCSC were funded by sources other than the BCSC RFAs, such as NCI funded R01 or grants funded by other agencies. NCI anticipates that this RFA will be the primary source of funding for nearly all centers participating in the BCSC, but other centers with comparable research objectives funded under other sources may be considered for membership into the BCSC. If the NCI and the BCSC Steering Committee determine and approve by vote that such a center can accomplish the BCSC research objectives, including sending required core data elements for pooled data analysis to the SCC, it will participate in the BCSC as a full voting member.

4. Arbitration Process

The Terms and Conditions of Award require that the NCI Program Director make post-award decisions related to program performance and programmatic decisions on scientific-technical matters. Any disagreement that may arise on scientific/programmatic matters (within the scope of the award) between award recipients and the NCI may be brought to arbitration. NCI will establish an arbitration process when a mutually acceptable agreement cannot be obtained between the awardee and the NCI Program Director. An arbitration panel (with appropriate expertise) composed of one member selected by the recipient group, one NCI nominee, and a third member chosen by the other two will be formed to review the NCI decision and recommend a course of action to the Director, NCI. These special arbitration procedures in no way affect the awardee's right to appeal an adverse action in accordance with PHS regulations 42 CFR Part 50, Subpart D, and DHHS regulations 45 CFR Part 16.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

Because screening mammography for breast cancer is only recommended for women, the research issues under study in this RFA are only relevant to women. Therefore, applicants to this RFA are not required to address the inclusion of women in this RFA. However, applicants are required to address the inclusion of members of minority groups.

It is the policy of the NIH that women and members of minority groups and their sub populations must be included in all NIH supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification is provided that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993.

All investigators proposing research involving human subjects should read the "NIH Guidelines For Inclusion of Women and Minorities as Subjects in Clinical Research," which have been published in the Federal Register of March 28, 1994 (FR 59 14508-14513) and in the NIH Guide for Grants and Contracts, Volume 23, Number 11, March 18, 1994, available on the web at the following URL address: http://www.nih.gov.grants/guide/1994/94.03.18/notice-nih-guideline008.html.

Investigators may also obtain copies of the policy from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS

Because screening mammography for breast cancer is not recommended nor practiced for children, the research issues under study in this RFA are not relevant to children. Therefore, applicants to this RFA may use Justification 1, the research topic to be studied is irrelevant to children, from the policy announcement. The following information is provided to ensure that all NIH applicants become aware of this policy.

It is the policy of NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are clear and compelling scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects" that was published in the NIH Guide for Grants and Contracts, March 6, 1998, and is available at the following URL address: http://grants.nih.gov/grants/guide/notice-files/not98-024.html

LETTER OF INTENT

Prospective applicants are asked to submit, by June 15, 1999, a letter of

intent that includes a descriptive title of the proposed research, name, address, and telephone number of the Principal Investigator, identities of other key personnel and participating institutions, and number and title of the RFA in response to which the application may be submitted.

Although a letter of intent is not required, is not binding, and does not enter into the review of subsequent applications, the information allows NCI staff to estimate the potential review workload and to avoid conflict of interest in the review.

The Letter of Intent is to be sent to the program staff listed under INQUIRIES.

APPLICATION PROCEDURES

The research grant application form PHS 398 (rev. 4/98) is to be used in applying for these grants. Applications kits are available at most institutional offices of sponsored research; from the Division of Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone 301/435-0714, E-mail: grantsinfo@nih.gov; and on the web at: http://grants.nih.gov/grants/forms.htm

Additional Materials to Include in the Application

Because the Terms and Conditions of Award will be included in all awards issued as a result of this RFA, it is critical that each applicant include specific plans for responding to these terms. Plans must describe how the applicant will comply with NCI staff involvement as well as how all the responsibilities of awardees will be fulfilled.

Criteria for the primary data collection and research centers

1. In addition to providing a complete research plan based on the kind of resources immediately available to the applicant, each applicant must delineate its catchment area for each of the three facilities (mammography, pathology, and tumor registry).

2. A designated Principal Investigator is required. An associate Principal Investigator should be named to assure continuity in the event of resignation of the Principal Investigator. The qualifications and experience of both must be described.

3. Each applicant must describe the proposed duties and attendant necessary qualifications required for all other proposed personnel, such as project managers, pathology coordinators, statisticians, data managers, computer programmers, and data entry clerks.

4. Multiple research affiliations and related funded research are permitted provided they are not conflicting. The affiliation agreements must state specifically how the problem of competing projects will be resolved.

5. Quality control and assurance procedures for all phases of the research proposed from data collection, storage, transfer and analysis must be described in detail. In addition, it is essential that the level of data quality and quality control of the cancer registry be described. Recent descriptions of data quality within cancer registries in North America have been developed by the North American Association of Central Cancer Registries (NAACCR) and can be obtained from the NCI Program Director.

6. The availability of facilities, including mammography facilities, pathology laboratories, and quality controlled population-based cancer registries, must be described for the primary data collection and research centers. A statement of commitment from each participating institution or organization and/or documentation of collaborative arrangements must be provided. Each applicant must have a defined space for administrative activities and administrative personnel which will serve as a focus for data management, quality control, and communication.

7. Each applicant's capability and expertise to manage the data must be described. Data management includes development of data collection forms, procedures for data transmittal, procedures for data entry, data editing, compilation, and analysis, as well as procedures for quality control and verification of submitted data. Statistical data collection comparability must exist among the tripartite local facilities and the collaborative research project. Each applicant must provide evidence of their willingness to pool statistical data for analysis as required for collaborative studies. Each applicant's ability to manage data from local facilities and to participate in multi-institutional collaborative studies must be described.

8. The applicant must describe how the issue of confidentiality will be addressed, describing how the records of all research subjects will be protected. The applicant must include evidence and knowledge of legal issues pertaining to the collection and analysis of data. When relevant, specific state and/or federal laws and their impact on the project must be fully explained.

9. Applicants need to demonstrate that they can successfully develop a tripartite organization of local facilities (i.e., mammography, pathology and/or registry) and show evidence that they will successfully participate in a BCSC and conduct collaborative studies. This will be the primary mechanism by which the NCI Program Director will relate to all principal award recipients over the duration of the period of the RFA.

10. Each applicant for the primary data collection and research centers must submit at least one and not more than five research plan(s) for special research project(s), separate from the construction of the research database in the application, with an additional five page limit being allowed to describe each additional special research project. In the event several projects or components are proposed, the format of the program project grant should be used in which separate budgets are used.

Criteria for the Statistical Coordinating Center

1. A designated Principal Investigator is required. An associate Principal Investigator should be named to assure continuity in the event of resignation of the Principal Investigator. The qualifications and experience of both must be described.

2. Each applicant must describe the proposed duties and attendant necessary qualifications required for all other proposed personnel, such as statisticians, project coordinators, data managers, computer programmers/analysts, program assistants, and data entry clerks.

3. Multiple research affiliations and related funded research are permitted provided they are not conflicting. The affiliation agreements must state specifically how the problem of competing projects will be resolved.

4. Quality control and assurance procedures for all phases of the research activities carried out by the SCC related to pooled data including data transfer, and storage for pooled data files must be described in detail. The procedures for minimum data quality assurance and control practices at primary data collection and research centers must be described briefly.

5. The applicant must have a defined space for administrative activities and administrative personnel which will serve as a focus for data management, quality control, and communication.

6. Each applicant must submit at least one and not more than 5 research plan(s) for special research projects entailing advances in statistical methodology for this research effort or for specific major analyses of pooled data addressing key questions in mammography surveillance, separate from the description of the data management, coordinating and analysis for pooled data, with an additional five page limit being allowed to describe the research plans for each of these special projects. In the event several projects or components are proposed, the format of the program project grant should be used in which separate budgets are used.

7. The applicant must describe how the issue of confidentiality will be addressed, describing how the records of all research subjects will be protected. The applicant must include evidence and knowledge of legal issues pertaining to the collection and analysis of data. When relevant, specific state and/or federal laws and their impact on the project must be fully explained.

8. Documentation of prior experience in similar studies, in creating a system for the transmission of data to a central facility, and in monitoring the quality and timeliness of such data, should be demonstrated.

9. Knowledge of the potential problems associated with conduct of pooled data analysis for this study, which is collecting data from routine clinical

practice and not controlled clinical trials and possible solutions must be demonstrated.

10. The applicant must describe suitability of proposed data management and analysis plans, and demonstrate the ability to design, implement and maintain a data entry system for pooled data analysis for the primary data collection and research centers.

11. The applicant must demonstrate knowledge and understanding of how to create a standardized set of questions to mammography surveillance within this research effort for data collection at primary data collection and research centers.

12. The applicant must describe the approach to and likelihood of soliciting cooperation from the participating primary data collection and research centers and exercising appropriate leadership in matters of study design and protocol revisions, and data acquisition, management, and analysis. Specific plans for ensuring quality control of data collection for core data elements are required.

The RFA label available in the PHS 398 (rev.4/98) application form must be affixed to the bottom of the face page of the application. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked.

Submit a signed, typewritten original of the application, including the Checklist, and three signed photocopies, in one package to:

CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040 - MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817 (for courier/express service)

At the time of submission, two additional copies of the application must also be sent to:

Ms. Toby Friedberg
Division of Extramural Activities
National Cancer Institute
6130 Executive Boulevard, Room 636
Bethesda, MD 20892
Rockville, MD 20850 (for express/courier service)

Applications must be received by July 15, 1999. If an application is received after that date, it will be returned to the applicant without review. The Center for Scientific Review (CSR) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. The

CSR will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of a substantial revision of an application already reviewed, but such an application must follow the guidance in the PHS Form 398 application instructions for the preparation of revised applications, including an introduction addressing the previous critique.

REVIEW CONSIDERATIONS

Review Method

Upon receipt, applications will be reviewed for completeness by the CSR and responsiveness by the NCI. Incomplete and/or non-responsive applications will be returned to the applicant without further consideration. All applications will be judged on the basis of the scientific merit of the proposed project and the documented ability of the investigators to meet the RESEARCH OBJECTIVES of the RFA. Although the technical merit of the proposed protocol is important, it will not be the sole criterion for evaluation of a study.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by the NCI in accordance with the review criteria stated below. As part of the initial merit review, a process will be used by the initial review group in which applications receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of the applications under review, will be discussed assigned a priority score, and receive a second level review by the National Cancer Advisory Board.

Review Criteria

Applicants from existing BCSC sites and the SCC must include a comprehensive progress report. The BCSC sites must demonstrate successful collaborative activities supported through their site. Applicants who have not had a BCSC site should explain how they will establish successful collaborative efforts.

Primary Data Collection and Research Centers

The following factors will be considered in evaluating the scientific merit of each response of the primary data collection and research centers to the RFA:

1. Scientific, technical, or medical significance and originality of each research project within the application that includes analytic research on breast cancer screening plus one or more of the following: utilization of state-of-the-art and emerging new technologies in breast cancer screening and diagnosis, basic biology and immunobiology of screened detected versus non-screened detected breast cancer, genetic alterations among women with screened detected versus non-screened detected breast cancer, economics of breast cancer screening techniques, development of innovative approaches to collecting risk factor data on screened and non screened populations of women

within the geographic area or among defined populations covered by mammography registry, and other investigator proposed studies.

2. Appropriateness of plans to develop or modify current data collection, formatting and transfer practices to conform to standards set by BCSC members which should include:

o evidence of obtaining cooperation of radiologists, pathologists, surgeons, tumor registrars, etc., necessary for data collection efforts;

o description of how data systems in the area will be linked to cancer registry and plans to solve anticipated problems with data linkage.

The development of a database linking breast cancer screening facilities to registries and pathology laboratories will be considered as a basic requirement of the application. The establishment of this database is necessary for the research priorities for this RFA to be completed. Establishment of this database must be described succinctly so that reviewers can determine its viability. However, the mere establishment of the database is not equivalent to responsiveness to the RFA.

o description of how systems for data collection, formatting and transfer will be developed to incorporate standardized sets of questions approved by the BCSC members.

The BCSC has already established sets of standardized data elements and a set of standardized questions for self-report of a limited set of core data elements for patient history. The NCI program director can be contacted for documents which describe these data elements and the standardized set of questions for self report information in detail.

o description of confidentiality and quality assurance and control practices will be established to ensure the records and data of all research subjects will be protected.

3. Appropriateness and adequacy of the experimental approach and methodology proposed to carry out the research.

4. Qualifications and research experience of the Principal Investigator and staff, particularly, but not exclusively, in the area of the proposed research should include:

o demonstration of a track record of interdisciplinary activity;
o experience in the management of large data sets;

o personnel with credentials and experience in cancer registration, breast cancer pathology, mammography and other breast cancer screening technology, breast cancer biology, biostatistics, data management and computer programming.

5. Adequacy of time (effort) that the Principal Investigator and staff would

devote to establishing the database and conducting the proposed studies.

6. Availability of resources necessary to perform the research.

7. Commitment to conduct pooled analyses of combined data across cooperative agreements in the BCSC for research objectives that require pooled analyses of data.

8. Availability of a population for surveillance coverage and research which complements the proposed research. Surveillance of men and children is not relevant to this research effort. Adequacy of plans to include minorities and their subgroups, as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated.

In addition, applications from existing BCSC awardees must include a comprehensive progress report and demonstrate successful collaborative activities supported through their CRC. Applicants who have not had an BCSC award should explain how they will establish successful collaborative efforts.

Statistical Coordinating Center

The following factors will be considered in evaluating the scientific merit of each response of the statistical coordinating center to the RFA:

1. Scientific and technical merit of each research plan within the application that includes advances in statistical methodology and analytic research on the evaluation of breast cancer screening within analysis of the pooled BCSC data.

2. Appropriateness of plans to develop or modify current data collection, formatting and transfer practices to conform to standards set by BCSC members for pooled data analysis which should include:

o description of how data formatting and transfer systems will be set up to ensure conformation to standards set by the BCSC and to facilitate pooled data analysis.

o description of procedures used at the SCC to protect data and research subject confidentiality.

o description of elements of a standardized set of questions for self-reported data on patient history, and core data elements and sources of such data for mammography, follow-up and pathologic diagnosis following mammography screening and the potential problems with key core data elements.

3. Appropriateness of plans to solicit cooperation from the participating primary data collection and research centers, including a description of plans for site visits to primary data collection and research centers to facilitate the conduct of pooled analytic research.

4. Scientific and technical significance and originality of the proposed

statistical methodologic research to advance methods in breast cancer surveillance.

5. Qualifications and research experience of the Principal Investigator and staff, particularly, but not exclusively, in the area of the proposed research should include:

o demonstration of a track record of interdisciplinary activity, particularly in terms of conducting pooled data analysis;

o experience in the management of large data sets;

o personnel with credentials and experience in supporting the activities of the SCC, including biostatistics, computer systems programmer/analyst, and project coordinating and data entry.

6. Adequacy of time (effort) that the Principal Investigator and staff would devote to establishing the database and conducting the proposed studies.

7. Availability of resources necessary to perform the research.

In addition, applications from existing BCSC awardees must include a comprehensive progress report and demonstrate successful collaborative activities supported through their CRC. Applicants who have not had an BCSC award should explain how they will establish successful collaborative efforts.

AWARD CRITERIA

The anticipated date of award is March 2000. In the final funding selection process of peer-reviewed and scored applications, NCI program staff will make funding decisions on the basis of scientific and technical merit as determined by peer review, appropriateness and duration of the proposed budget in relation to the proposed research, appropriate minority representation in the BCSC as a whole, and rural/urban and geographic balance among primary data collection and research centers.

Applications recommended by the National Cancer Advisory Board will be considered for award based upon (a) scientific and technical merit; (b) program balance, including in this instance, sufficient compatibility of features to make a successful collaborative program a reasonable likelihood; and (c) availability of funds.

SCHEDULE

Letter of Intent Receipt Date: June 15, 1999
Application Receipt Date: July 15, 1999
Review by NCAB Advisory Board: February 2000
Anticipated Award Date: March 2000

INQUIRIES

Written and telephone inquiries concerning this RFA are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome. Information on standardized questions and data format for core data elements are available from the NCI program director.

Direct inquiries regarding programmatic issues to:

Rachel Ballard-Barbash, M.D., M.P.H.
Division of Cancer Control and Population Sciences
National Cancer Institute
6130 Executive Boulevard, Room 313, MSC 7344
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Direct inquiries regarding fiscal matters to:

Bill Wells
Grants Administration Branch
National Cancer Institute
Executive Plaza South, Room 243
Bethesda, MD 20892
Telephone: (301) 496-7800, Ext.250
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Direct inquiries regarding review matters to:

Ms. Toby Friedberg
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6130 Executive Boulevard, Room 636, MSC 7399
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AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.399. Awards are made under authorization of the Public Health Service Act, Title IV, Part A (Public Law 78-410, as amended by Public Law 99-158, 42 USC 241 and 285) and administered under PHS grants policies and Federal Regulations 42 CFR Parts 52 and 45 CFR Part 74 and Part 92.

This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. The PHS strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-

227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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Appendix B. Breast Cancer Surveillance Consortium Confidentiality Agreement

Under 42 U.S.C. 299c-3(c) [also cited as Section 924 (c) of the Public Health Service Act], set out below, data that identify individuals or establishments collected as part of activities supported by the Agency for Healthcare Research and Quality (AHRQ) may be used only for the purposes for which they were supplied. Thus, under this statute, the intent and understanding of the supplier controls and limits what may be disclosed from identifiable data. Therefore, it is particularly important to secure and document agreement and consent from each supplier of data (or data subject) to a statement of the purposes for which the identifiable data are supplied that is broad enough to allow all of the anticipated and intended uses as well as other reasonable potential uses. Disclosures or releases of identifiable information about individuals are specifically restricted by the statute and require consents. To protect against being forced to make disclosures about identifiable establishments, an appropriately restrictive and exclusive statement of intended uses, including the specification of permissible groups or types of users, should be carefully prepared for data suppliers or data subjects so that their agreement to any such disclosures can be documented, or they can clearly indicate their understanding there will be none. Unauthorized disclosure of confidential identifying information protected under this provision is subject to penalty under 42 U.S.C. 299c-3(d) [Section 924(d) of the Public Health Service Act] (see text below).

> (c) No information, if an establishment or person supplying the information or described in it is identifiable, obtained in the course of activities undertaken or supported under this subchapter may be used for any purpose other than the purpose for which it was supplied unless such establishment or person has consented (as determined under regulations of the Director) to its use for such other purpose. Such information may not be published or released in other form if the person who supplied the information or who is described in it is identifiable unless such person has consented (as determined under regulations of the Director) to its publication or release in other form.
>
> (d) Any person who violates subsection (c) shall be subject to a civil monetary penalty of not more than $10,000 for each such violation involved. Such penalty shall be imposed and collected in the same manner as civil money penalties under subsection (a) of section 1320a-7a of this title are imposed and collected.

EACH INDIVIDUAL WITH ACCESS TO IDENTIFIABLE DATA ABOUT INDIVIDUALS OR ESTABLISHMENTS IS TO SIGN A COPY OF THE ATTACHED ACKNOWLEDGEMENT AND SEND THE DOCUMENTS WITH ORIGINAL SIGNATURES TO:

Susan Meikle, M.D., M.S.P.H.
AHRQ BCSC Collaboration Advisor
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality
540 Gaither Road
Rockville, MD 20850

I acknowledge that I have received and reviewed a copy of 42 U.S.C. 299c-3(c) and (d) [Section 924 (c) and (d) of the Public Health Service Act], described and set forth above. I understand that establishment- and person-level data collected as part of the Breast Cancer Surveillance

Consortium are subject to the confidentiality protections of Section 924 (c) and (d) of the Public Health Service Act described above.

Typed/Printed Name	Signature	Date
_____	_____	_____

Breast Cancer Surveillance Consortium Site

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