Conducting Cancer Control and Survivorship Research via Cooperative Groups: A Report from the American Society of Preventive Oncology

Oxana Palesh¹, Wendy Demark-Wahnefried², Karen Mustian³, Lori Minasian⁴, Julia Rowland⁴, Lisa Sprod³, Michelle Janselins³, Luke Peppone³, Jeff Sloan⁵, Karen Basen Engquist⁶, Lee Jones⁷, Diana Buist⁸, and Electra Paskett⁹

¹Stanford University, Stanford, California; ²University of Alabama at Birmingham, Birmingham, Alabama; ³University of Rochester Cancer Center, Rochester, New York; ⁴National Cancer Institute, Bethesda, Maryland; ⁵Mayo Clinic, Rochester, Minnesota; ⁶University of Texas MD Anderson Cancer Center, Houston, Texas; ⁷Duke University Medical Center, Durham, North Carolina; ⁸University of Washington, Seattle, Washington; and ⁹Ohio State University, Columbus, Ohio

Corresponding author:

Oxana Palesh, Department of Psychiatry & Behavioral Sciences, 401 Quarry Rd, office 2318 Stanford, CA 94305-5718. Phone: 650-725-7011; Fax: 650-498-6678; E-mail: opalesh@stanford.edu

Short title: ASPO: Cancer Symptoms, Survivorship, and Cooperative Groups
Abstract

As the number of cancer survivors expands, the need for cancer control and survivorship research becomes increasingly important. The National Cancer Institute (NCI) Cooperative Groups may offer a viable platform to perform such research. Observational, preventive, and behavioral research can often be performed within the cooperative group setting, especially if resources needed for evaluation are fairly simple, if protocols are easily implemented within the typical clinical setting, and if interventions are well standardized. Some protocols are better suited to cooperative groups than are others, and there are advantages and disadvantages to conducting survivorship research within the cooperative group setting. Behavioral researchers currently involved in cooperative groups, as well as program staff within the NCI, can serve as sources of information for those wishing to pursue symptom management and survivorship studies within the clinical trial setting. The structure of the cooperative groups is currently changing, but going forward, survivorship is bound to be a topic of interest and one that perhaps may be more easily addressed using the proposed more centralized structure.
Cancer Survivorship Research

The definition of a “cancer survivor” differs depending upon an organization’s interpretation of whether this status begins at the moment of diagnosis or if it instead begins upon completion of primary treatment (e.g., surgery, chemotherapy, or radiation therapy). Using the former less restrictive definition, there are more than 11.7 million cancer survivors in the United States and the number is increasing rapidly (1). Cancer survivors are living longer, but not necessarily better, because they may experience side effects from their illness itself and its treatments. In worse cases, they may also experience secondary cancers stemming from their treatments, recurrence of their primary cancers, and, for those with advanced disease, years or even decades of care that may be palliative but not curative. Common side effects of treatments include conditions such as cardiac toxicity (2), compromised bone health (3–5), immune dysfunction, peripheral neuropathy (6, 7), neurocognitive effects (8–11), sleep disturbance (12), pain, and fatigue (13). Cancer survivors often experience problems that begin during or shortly after treatment (e.g., fatigue, insomnia, and depression). Such side effects can be acute and may decrease within a relatively short period of time, but some side effects become chronic and continue well beyond primary or active treatment. Cancer survivors also experience a host of late effects—problems that arise months or years after treatments are complete and even in the absence of detectable disease.

Several years ago, the National Cancer Institute (NCI) made a pioneering step to recognize the importance of cancer survivorship and its growing constituency by establishing the NCI Office of Cancer Survivorship (OCS). The OCS has served as a liaison among cancer survivors, researchers, and other NCI programs, such as the Cancer Cooperative Groups Program (see following section), to help establish and align research priorities in the area of cancer survivorship. The OCS has served as a voice not only for survivors but also for researchers in terms of aligning priorities for investigation.
Cancer survivorship research, as defined by OCS, encompasses research that addresses the health and well-being of individuals after the end of treatment. This research includes issues related to primary and secondary prevention (screening for and taking known measures to prevent the development of a new cancer that may be unrelated to the original cancer), tertiary prevention (monitoring for and preventing a recurrence of cancer and the adverse medical sequelae of illness), and quaternary prevention (a focus on promoting the health and well-being of survivors following treatment). Also included in this area of science are surveillance studies that track the natural history of cancer and its treatment sequelae.

More specifically, cancer control and survivorship research seeks to identify, examine, and enhance our understanding of the pathophysiology and mechanisms of early and late adverse cancer- and treatment-related outcomes, such as pain, peripheral neuropathies, fatigue, neurocognitive problems, sleep disorders, compromised bone health, cardiac toxicity, immune dysfunction, depression, lymphedema, sexual dysfunction, second cancers, recurrence, comorbidity, and poor quality of life. Cancer survivorship research also seeks to develop effective interventions for the prevention, control, and remediation of early and late adverse cancer- and treatment-related outcomes. Finally, cancer control and survivorship research aims to provide a knowledge base regarding optimal follow-up care and surveillance of cancer survivors and to optimize health during and after cancer treatment.

**Cancer Survivorship Priority Research Areas**

Cancer-specific and treatment-specific sequelae

The OCS has prioritized the need to enhance our understanding of the prevalence of early and late side effects experienced by cancer survivors. Another priority articulated by the OCS is to increase our understanding of the biopsychosocial mechanisms that result in cancer- and treatment-specific sequelae. Relatively little is known about the biological basis or risk
Cancer Symptoms, Survivorship and Cooperative Groups

Factors for developing toxicities and side effects (early or late); why they become chronic; why second cancers develop; how they can be prevented; and who is at increased risk. An understanding of the mechanisms behind the development of side effects and second cancers has the potential to affect primary treatment decision-making, development of more efficacious and effective interventions to manage these adverse effects, and promotion of long-term health.

Needs of patient familial and social networks

It is acknowledged that cancer not only affects the diagnosed individual but also touches the individual’s family, caregivers, and friends. To address this, OCS has called for survivorship research that not only improves the length and quality of life of individuals diagnosed with cancer but also examines and meets the unique needs of survivors’ larger familial and social networks.

Cancer in diverse populations

A better understanding is needed about how cancer and aging interface and how survivorship outcomes may vary among disparate populations (socioeconomically and ethnoculturally diverse groups and various types of cancer). This area of research includes the study of populations that have barriers to travel, such as those who reside in rural regions, and those who are poor, elderly, or unable to receive care at major tertiary cancer centers.

Economics of cancer

There is a need on a broader level to study the economic consequences of cancer and begin developing models of care and better cancer communication strategies designed to lead to cost-effective, appropriate, equitable, and efficient post-treatment follow-up care of survivors.

Cancer-specific instruments and interventions
More cancer-specific instruments and assessments must be developed to ensure that research is able to capture cancer-specific effects and symptoms over the long term.

Cancer Cooperative Groups

The NCI Cooperative Groups Program has a long history of conducting research in the area of cancer survivorship. Building upon the rich success this program has had in identifying promising pharmacologic interventions to treat cancer and its side effects, the Cooperative Groups Program provides an excellent resource for studying many of the challenging cancer control and survivorship issues delineated above. While the Cooperative Groups are often recognized as leaders in conducting large multicenter clinical trials that have significantly improved the landscape of treatment options for primary cancers, they also have fostered efforts in cancer control through programs such as the Community Clinical Oncology Program and have been used to conduct symptom management as well as cancer survivorship studies for several decades. These groups include researchers, cancer centers, and community physicians in the United States, Canada, and Europe. In total, the Cooperative Groups are responsible for placing nearly 25,000 new patients on cancer trials each year. Table 1 provides examples of such studies.

Cancer Cooperative Groups are comprised of a consortium of academic sites and their investigators. These groups are designed to develop and conduct multicenter clinical trials for the treatment of cancer as well as to support correlative studies. These groups have a distinct statistical and data management core funded by NCI, an operations core that manages the logistical and regulatory aspects of multicenter clinical trials and community affiliate organizations, and statistical centers that oversee data management and statistical analyses. At the end of 2010, there were 12 NCI Cooperative Groups (see Table 2). These groups vary in their research purpose and focus. For example, the Children’s Oncology Group (COG) focuses exclusively on pediatric cancers, whereas the Gynecological Oncology Group (GOG) studies a
constellation of reproductive cancers in women, and some groups address multiple cancer sites and disciplines [e.g., Eastern Cooperative Oncology Group (ECOG) and Southwest Oncology Group (SWOG)]. Each of the groups has created its own national network of academic and community investigators to conduct multicenter trials. Recently, the NCI proposed a reorganization of its cooperative groups. Among the major changes is the proposal to consolidate the current 9 groups studying adult cancers into 4 groups. However, the Children’s Oncology Group will remain the same and will be the single pediatric cooperative group. (More information about the NCI Cooperative Groups is available at www.cancer.gov/cancertopics/factsheet/NCI/clinical-trials-cooperative-group.)

Furthermore, cooperative groups are eligible to become research bases in the Community Cancer Oncology Program (CCOP). Currently 8 of the 12 funded cooperative groups are funded as CCOP Research Bases. NCI-designated cancer centers can also apply to become a CCOP Research Base. Four of the 66 NCI-designated Cancer Centers are currently funded under this mechanism. As indicative of the name, the primary mission of the CCOPs and Research Bases is to make clinical trials available to the broader public. CCOP Research Bases can use a cooperative group structure and operate via a collaborative network of multiple sites or, in some instances, exist within one comprehensive cancer center with satellite or outreach sites. Similar to cooperative groups, the CCOP Research Bases are funded to design, conduct, analyze, and publish clinical trials in cancer prevention and control. Symptom management and survivorship research falls under the umbrella of cancer control research. To date, interventions have largely focused on reducing acute toxicities (e.g., neuropathy, fatigue, cardiac toxicity, lymphedema, and impaired cognitive function) that are caused by cancer therapy and often inhibit complete delivery of cancer therapy.
Experience with Conducting Research via Cooperative Groups and Research Bases with CCOPs

Participants in a roundtable discussion of the Survivorship Special Interest Group of the American Society of Prevention Oncology, held in March 2010, discussed some of the positive and negative aspects of dealing with cooperative groups to conduct survivorship research. Some of these considerations are listed below:

- Given that cooperative groups were initially established to deliver and test therapeutic treatment trials, such as studies of pharmacologic agents, radiation therapy, or surgical interventions, behavioral interventions serve as a departure from this model. Thus, it is important for investigators to propose interventions and modes of assessment that are feasible and easy to do at multiple sites and that could work in clinical care settings that are set up to deliver cancer care.

- Cooperative studies require plans to assure fidelity to the intervention, ample training, and quality assurance. Studies that have been successful have typically used a standardized intervention that is easy to administer and adhere to, such as a home-based or self-help intervention.

- Because not all study sites have similar resources, there is a need to inventory each site in advance to assess whether appropriate resources, as well as interest, exist prior to launching the study. Investigators could consider conducting the trial at a limited number of sites in order to focus their efforts and increase the chances of success.

- Cooperative studies require a large time commitment. On average, a concept takes approximately 2 years to be developed into a protocol and launched; approximately 2 to 5 years are required to complete a study.
How to Get Started Working with the Cooperative Groups and Research Bases

In most cases, additional funding is required to support survivorship research within the cooperative groups, though some survivorship protocols that involve minimal effort, such as brief survey studies or post-hoc analyses, can be done without such funding if both the investigator and the cooperative group reach agreement. Regardless of the source of funding, successful cooperative group trials are launched via an iterative dialogue between the investigator and various committees within the cooperative group—a dialogue that transpires during group meetings (held 1-4 times per year, depending on the specific group) and through correspondence between these meetings. Investigators endeavoring to conduct trials through cooperative groups should make the inroads necessary before proposing their first study by pursuing the following steps: (i) joining the cooperative group with which their institution is affiliated; (ii) contacting the relevant committee leaders; (iii) attending and then joining the relevant committee that conducts survivorship research within the group; and (iv) regularly attending and contributing to its meetings.

When an investigator has a potential idea for a protocol (termed a “concept”), he or she must discuss it with the committee leadership. If the idea is deemed worthy, it will be placed on the agenda during a committee meeting. The investigator will then present the concept to the committee and obtain feedback. Once feedback is received and incorporated into the concept, the investigator will seek approval from the committee, from any relevant disease committees (for protocols that focus on specific cancer sites), and ultimately from the larger Cooperative Group Executive Committee. Concepts that receive approval are then forwarded to the NCI for review at the Division of Cancer Prevention (DCP). If the investigator is submitting a grant application to cover study costs, as in most cases, a letter of support from the cooperative group stating their commitment to the study should be obtained at this point. If the NCI approves the concept, DCP will provide a letter of support for the grant application. Successful investigators...
stress that it is essential to receive the letter of support before the grant is submitted, to work
with the cooperative group and its sites to include relevant information in the resource pages for
the grant application, and to discern which costs need to be borne by the investigator’s budget
(in most cases, budgeting is required for the resources that are needed to deliver and assess
the intervention) and which costs need to be borne by the cooperative group (usually staff time
needed to accrue subjects, obtain their consent, and manage data).

On average, the concept’s approval by the cooperative group and the NCI can take up to
12 months, whereupon a formal protocol is then submitted for internal review in the cooperative
group and formal review at the DCP at NCI. Once a protocol is open, it is important to
remember that all trials need to be approved, not only by the Institutional Review Board at the
investigator’s institution but also at each of the sites implementing the protocol. Conducting a
successful multicenter trial via cooperative groups requires a strategic approach by investigators
(for example, to incorporate sites that have the potential to accrue well and provide care to the
target population). Investigators need to develop solid relationships among themselves and with
each of the participating sites if successful completion of the trial is expected. They also need to
spend the time and energy required to cultivate their relationships with other investigators within
the cooperative group if they are to be successful in this venue.

Benefits of Conducting Cancer Control and Survivorship Studies in the Cooperative
Groups and Research Bases

Cooperative groups can provide an avenue for investigators at all stages of their career
to conduct cancer control and survivorship research. Indeed, there are many benefits of
conducting research in the cooperative groups. First, cooperative groups can promise well-
defined cancer populations. In addition, cooperative groups provide access to detailed medical
and cancer treatment–related information and are familiar with collecting data on health
outcomes (adverse events, response to treatment, quality of life, and other treatment-specific outcomes) concerning their patients. This is an advantage given the fact that many cancer patients don’t know or remember their complicated course of care. Finally, and most importantly, the main benefit that cooperative groups offer is access to patients and the potential to accrue large numbers of study participants quickly.

The outcomes of some survivorship research have the potential to inform development of future trials, such as was the case in studies among children with acute lymphocytic leukemia (ALL). Survivorship studies (14, 15) helped change the approach to care of these young ALL patients to spare those deemed to be at low recurrence risk for central nervous system relapse from exposure to cranial irradiation (RT). This research also led to a lower dose of RT being given in those at higher risk. Examples of more recent work include survivorship research by Ganz and colleagues, who examined Southwest Oncology Group (SWOG) trial participants who were treated with trastuzumab for its late cardiac effects (16).

In addition to studying clinical aspects of survivorship, the Cooperative Groups have conducted correlative studies with translational end points designed to measure biological mechanisms of cancer-related symptoms in conjunction with their treatment trials. The Cooperative Groups and the CCOP Research Bases have been encouraged to develop translational end points in conjunction with survivorship studies as well. However, the primary objective of the cooperative group is to deliver therapeutic cancer care. Thus, investigators must remember to propose studies that fit the cooperative group model, rather than vice versa, and to work diligently to simplify not only the intervention delivery but also the means by which it is evaluated. If investigators are able to implement their research successfully in a cooperative group setting, they can feel more confident that the study can be readily implemented in or translated to the practice setting, given that the cooperative group sites are primarily set up to deliver cancer care.
Summary

The structure of the Cooperative Groups is changing, but as the number of cancer survivors expands and the need for survivorship research becomes increasingly important, the NCI Cooperative Groups will continue to offer a viable platform to perform such research. Going forward, survivorship is bound to be a topic of interest and one that perhaps may be more easily addressed using the proposed more centralized structure. Observational, prevention, and behavioral research can often be performed within the cooperative group setting, especially if resources for evaluation are fairly simple, if protocols are easily implemented within the typical clinical setting, and if interventions are well standardized. Some protocols are better suited to cooperative groups than others, and there are advantages and disadvantages to conducting survivorship research within the cooperative group setting. Familiarization with other researchers who currently are involved in the Cooperative Groups, as well as contact with NCI designated program staff, can serve as valuable sources of information.
References


Table 1. Examples of symptom management and survivorship studies accruing through the NCI Cooperative Groups or CCOPS

<table>
<thead>
<tr>
<th>Cooperative group and research base</th>
<th>Study title(s)</th>
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</table>
| Cancer and Leukemia Group B (CALGB) | 1. Phase III double blind trial of oral Duloxetine for treatment of pain associated with chemotherapy-induced peripheral neuropathy (CIPN) CALGB 170601  
2. A randomized study to prevent lymphedema in women treated for breast cancer CALGB 70305  
3. Development of a geriatric assessment measure for older patients with cancer CALGB 360401  
4. Collection of patient reported symptoms and performance status via the Internet CALGB 70501 |
| Children’s Oncology Group (COG) | A group-wide, prospective study of ototoxicity assessment in children receiving cisplatin chemotherapy COG-ACCL05C1 |
| Eastern Cooperative Oncology Group (ECOG) | 1. SOAPP (Symptom Outcomes and Practice Patterns): A survey of disease and treatment-related symptoms in patients with invasive cancer of the breast, prostate, lung, or colon/rectum ECOG-E2Z02  
2. Phase III randomized placebo-controlled trial to determine efficacy of Levocarnitine for fatigue in patients with cancer ECOG-E4Z02  
3. Quality of life in younger breast cancer survivors ECOG-E2Z04 |
<p>| Gynecologic Oncology Group (GOG) | A prospective study of cognitive function during chemotherapy for front-line treatment of ovarian, primary peritoneal or fallopian tube cancer GOG-0256 |</p>
<table>
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<tr>
<th>Cooperative Groups</th>
<th>Studies</th>
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| SunCoast CCOP Research Base at the University of South Florida                    | 1. Stress management therapy for patients undergoing chemotherapy  
|                                                                                 |   SCUSF-0501                                                                                     |
|                                                                                 | 2. Thyroid function and breast cancer: A pilot study to estimate prevalence of thyroid dysfunction in women diagnosed with breast cancer and the magnitude of change in thyroid function post-chemotherapy  
|                                                                                 |   SCUSF-0502                                                                                     |
| North Central Cancer Treatment Group (NCCTG)                                      | 1. The use of topical Baclofen, Amitriptyline, HCl, and Ketamine (BAK) in a PLO gel vs. placebo for the treatment of chemotherapy induced peripheral neuropathy: A phase III randomized double-blind placebo-controlled study  
|                                                                                 |   NCCTG-N06CA                                                                                   |
|                                                                                 | 2. A phase III, randomized, double-blind, placebo-controlled evaluation of Pregabalin for alleviating hot flashes  
|                                                                                 |   NCCTG-N07C1                                                                                   |
|                                                                                 | 3. Pilocarpine for vaginal dryness: a phase III double-blind RCT  
|                                                                                 |   NCCTG-N04CA                                                                                   |
| National Surgical Adjuvant Breast and Bowel Project (NSABP)                       | Patient reported outcomes in long-term survivors with colon and rectal cancer  
|                                                                                 |   NSABP LTS-01                                                                                  |
| Radiation Therapy Oncology Group (RTOG)                                          | 1. A phase III international randomized trial of single vs. multiple fractions for re-irradiation of painful bone metastases  
|                                                                                 |   RTOG-0433                                                                                      |
|                                                                                 | 2. A randomized, double-blinded, placebo-controlled phase III trial to evaluate the effectiveness of a phosphodiesterase 5 inhibitor, Tadalafil, in prevention of erectile dysfunction in patients treated with radiotherapy for prostate cancer  
|                                                                                 |   RTOG-0831                                                                                      |
| Southwest Oncology Group (SWOG) | 1. Randomized placebo-controlled trial of Acetyl-L-Carnitine (ALC) for the prevention of Taxane induced neuropathy phase III SWOG-S0715  
2. Companion long-term follow up study of men diagnosed with prostate cancer SWOG-0437  
3. Phase III trial of LHRH analog admin during chemotherapy to reduce ovarian failure following chemo in early stage hormone-negative breast cancer SWOG-S0230  
4. RCT assessing the effects of exercise on patients with locally advanced lung cancer undergoing curative intent combined modality therapy SWOG-S0229 |
| University of Rochester Cancer Center (URCC) CCOP | 1. Yoga for persistent sleep disturbance in cancer survivors URCC 04-01  
2. A study of the effects of exercise on cancer-related fatigue URCC 08106 |
**Table 2. Listing of cancer cooperative groups and contact information**

<table>
<thead>
<tr>
<th>Cooperative group</th>
<th>Chair</th>
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<tbody>
<tr>
<td>American College of Radiology Imaging (ACRIN)</td>
<td>Mitchell Schnall, MD, PhD</td>
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<tr>
<td><a href="http://www.acrin.org/">http://www.acrin.org/</a></td>
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<tr>
<td>American College of Surgeons Oncology Group (ACOSOG)</td>
<td>David M. Ota, MD</td>
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<tr>
<td><a href="http://www.acosog.org">http://www.acosog.org</a></td>
<td>Heidi Nelson, MD</td>
</tr>
<tr>
<td>Cancer and Leukemia Group B (CALGB)</td>
<td>Monica Bertganoli, MD</td>
</tr>
<tr>
<td><a href="http://www.calgb.org">http://www.calgb.org</a></td>
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<tr>
<td>Children's Oncology Group (COG)</td>
<td>Peter Adamson, MD</td>
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<tr>
<td><a href="http://www.childrensoncologygroup.org">http://www.childrensoncologygroup.org</a></td>
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<tr>
<td>Eastern Cooperative Oncology Group (ECOG)</td>
<td>Robert L. Comis, MD</td>
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<td><a href="http://www.ecog.org">http://www.ecog.org</a></td>
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<tr>
<td>European Organisation for Research and Treatment of Cancer (EORTC)</td>
<td>Françoise Meunier, MD, Director General</td>
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<td><a href="http://www.eortc.be/default.htm">http://www.eortc.be/default.htm</a></td>
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<tr>
<td>Gynecologic Oncology Group (GOG)</td>
<td>Philip J. DiSaia, MD, Chair</td>
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<td><a href="http://www.gog.org">http://www.gog.org</a></td>
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<tr>
<td>Radiation Therapy Oncology Group (RTOG)</td>
<td>Walter J. Curran Jr., MD, Chair</td>
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<td><a href="http://www.rtog.org">http://www.rtog.org</a></td>
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<tr>
<td>Southwest Oncology Group (SWOG)</td>
<td>Laurence H. Baker, DO, Chair</td>
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<td><a href="http://www.swog.org">http://www.swog.org</a></td>
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<tr>
<td>Organization</td>
<td>Contact</td>
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<tr>
<td>National Cancer Institute of Canada, Clinical Trials Group</td>
<td>Ralph Meyer, MD, Director</td>
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<tr>
<td><a href="http://www.ctg.queensu.ca">http://www.ctg.queensu.ca</a></td>
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<tr>
<td>National Surgical Adjuvant Breast and Bowel Project</td>
<td>Norman Wolmark, MD, Chair</td>
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<td><a href="http://www.nsabp.pitt.edu">http://www.nsabp.pitt.edu</a></td>
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<tr>
<td>North Central Cancer Treatment Group (NCCTG)</td>
<td>Jan C. Buckner, MD, Chair</td>
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