Special Report

The Role of Cancer Cooperative Groups
Within the Spectrum of Cancer Care

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Introduction

This article describes the scope of research activities of the Clinical Trial Cooperative Group Program of the National Cancer Institute (NCI). In addition to providing the vital “backbone” of the clinical cancer research — specifically, the demonstration of efficacy for a given treatment strategy via the highest standard of evidence, the randomized controlled trial (RCT) — the research activities of cooperative groups are increasingly engaged directly in the many facets of cancer care that assist in the transition from treatment efficacy to treatment effectiveness. Areas where these contributions could be expanded are also identified.

Cancer Cooperative Groups

Development and Current Status

In the mid 1950s, pioneering researchers in the use of chemotherapy for cancer requested from the United States Congress increased financial support for a research program focused on further development of this promising new approach. From the initial appropriation, a small network of institutions was formed to test new anticancer agents arising from the NCI’s Drug Development Program. Success in this approach led to continued expansion of the program, forming the NCI Clinical Trial Cooperative Group Program and the development of what are known as cooperative groups.1 Currently active NCI-funded cooperative groups are shown in the Table. Most groups address numerous cancer sites, with some concentrating primarily on certain interventions, such as radiation therapy, surgery, or imaging technology. Some groups focus on specific cancer patient populations or cancer sites (eg, pediatric cancers, gynecologic cancers). Participating institutions in the NCI Cooperative Group Program number over 1,900 and include sites worldwide, with primary recruitment from North America.1 Similarly structured groups exist in other countries, many of which have multinational leadership and recruitment participation. Currently in the United States, more than 60% of patients who participate in publicly or privately funded cancer clinical trials are enrolled through cooperative groups.1 Unfortunately, the total number of adult cancer patients who participate in clinical trials represents a small fraction (1% to 3%) of all cancer patients.2-4

The principal charge of the cooperative group is to evaluate potentially efficacious cancer therapies, primarily through the conduct of RCTs. Such studies remain the recognized highest standard of evidence for treatment efficacy, and they have also been advocated as a cornerstone of the evidence required for other research concerning treatment policies.5,6 In the simplest instance, trials determine whether a new treatment is superior to the current standard therapy in a well-defined patient population. Alternatively, some trials are designed to establish the equivalence of new treatment regimens to current standards and other advantages, such as lower incidence of adverse events or minimized extent of surgery. The cooperative groups have also become increasingly active in cancer prevention, using randomized trials to investigate agents with potential to reduce disease incidence in individuals at increased risk for specific cancers. Primarily for feasibility and rapid ascertainment of results, cooperative group trials are carried out...
through a multi-institution network of investigators who have applied for and are qualified to participate. These participating centers directly oversee enrollment of participants, their treatment course and ancillary care, and their long-term outcomes, and they report the information to a central trial coordinating center.

**Structure and Function**

The development of cooperative group clinical trials is a collaborative effort among many parties, including the principal investigators, academic and pharmaceutical industry researchers, and government research and regulatory agencies. The trial development process is as follows: cooperative group investigators with expertise in the disease in question develop and submit a study concept for review by the NCI Clinical Trials Evaluation Program (CTEP) branch. After approval, a designated study chair develops a full study protocol that undergoes review by multiple internal and external parties, including cooperative group investigators, other experts, the NCI, and, if applicable, the Food and Drug Administration (FDA). Finally, prior to activation, the protocol must undergo full Institutional Review Board (IRB) review and approval at institutions where patients are to be enrolled.

While cooperative groups use large networks in order to carry out studies that require many more patients than could be obtained in single-institution studies, the groups also frequently work together in so-called intergroup trials to achieve trial aims more rapidly or to address research questions in cancers where even single groups cannot recruit enough participants. These collaborations foster exchange of information and serve the greater mission of progress in cancer treatment. They may also extend beyond the NCI-sponsored cooperative groups to clinical trials groups outside North America, further promoting exchange of ideas.

At the member sites, patients who meet trial eligibility requirements for a given trial are offered participation by the site investigators and are formally entered upon providing informed consent. All aspects of treatment and follow-up care are carried out in accordance with a detailed prescribed plan, with mechanisms for monitoring of adverse events and treatment compliance. Participating institutions are periodically evaluated through data and study conduct audits and regular assessment of the timeliness of data flow to the central coordinating center. These quality assurance practices not only ensure the integrity of trial findings, but also identify practical problems in delivery of regimens and execution of the study in diverse clinical settings. Particular attention is given to reporting of adverse side effects resulting from treatment, and clear guidelines are provided for timely adverse event reporting. At the central coordinating center, monitoring of adverse events occurs on an ongoing basis, with reporting to regulatory agencies as required, and also through regular review by an independent Data and Safety Monitoring Committee (DSMC), which further assures patient safety. These DSMCs also review efficacy data at intervals prescribed in the study design in order to allow for early study termination and dissemination of findings if superiority or futility of a treatment is established.

An important aim of the Cooperative Group Program is to extend trial participation beyond the research-oriented care facility environment and thus provide evaluation of treatments more similar to the “real-life” settings representative of patient care in the community at large. To this end, the Community Clinical Oncology Program (CCOP) was founded in the 1980s to enhance the ability of community physicians and their patients to participate in cooperative group clinical trials. The CCOP links independent physicians and hospitals to institutions participating in the cooperative groups, thereby offering trial participation to a broader patient base and playing an important role in increasing the extent to which trial findings can be generalized to the population at large. Evaluation of this program’s initial progress identified participation barriers for traditionally underrepresented patient populations,7,9 and recent enhancements of the program are intended to further improve attractiveness and access to cooperative group trials.10

**Principal Role of the Cancer Cooperative Groups: Definitive Evaluation of Therapeutic Strategies**

The signifying role of the cooperative group in cancer research is the evaluation of new treatment concepts for therapeutic efficacy through large-scale randomized trials. Many new treatment regimens that show promise in phase II trials (noncomparative, historically controlled trials, or small comparative trials) do not demonstrate unequivocal benefit when subjected to the unbiased assessment inherent in phase III trials (large, comparative, randomized trials). Only through well-designed trials of this type, where treatment allocation is dissociated from selection factors that might unduly favor a given therapy, can apparent improvements in outcomes attributed to a new treatment be substantiated. While the primacy of the RCT has been regularly questioned since its advent in medical research, it has repeatedly been demonstrated to be the most reliable means by which treatment progress can be documented, with some particularly illustrative examples provided specifically in cancer research.11-13 Furthermore, it has been argued that the clinical trial framework provides high-quality care that might otherwise not be obtained.5,14 While studies in the early therapy development cycle (eg, phase I and II trials) are also undertaken, the majority of patients who participate in cooperative group research are enrolled in phase III trials (over 20,000 patients annually).

Numerous advances in cancer treatment and prevention are attributable to cooperative groups. For infor-
mation on cancer treatment development during 1986–2001 arising from NCI cooperative group research efforts, documentation is available at the CTEP Web site (http://ctep.cancer.gov/resources/coop2.html). The cooperative group Web sites can also be consulted for listings of publications. Several examples of progress in cancer treatment from cooperative group research are briefly summarized:

**Childhood Cancers**

Among the greatest success stories for cooperative groups are the achievements in the development of successful treatments for childhood cancers, including Wilms’ tumor, leukemia, and rhabdomyosarcoma. Overall, 5-year survival for pediatric cancers has increased from under 30% to over 75% in the last 4 decades.15 This success is due in no small part to the high participation rate of children in cancer clinical trials, leading to rapid development and evaluation of successful avenues of treatment.16-18

**Surgery and Adjuvant Therapy for Breast Cancer**

Clinical trials evaluating types of curative operation for breast cancer have led to a revolutionary change in the surgical management of this disease. The landmark surgical trials conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) in the 1970s and 1980s (which were recently updated) — first demonstrating equivalent survival between patients undergoing radical mastectomy and total mastectomy19 and then establishing the equivalence to lumpectomy to total mastectomy with respect to survival and the equivalence of these two procedures with respect to in-breast recurrence when lumpectomy is followed by radiation therapy20 — have firmly established less disfiguring and biologically more rational surgical management of this disease. They have also paved the way for a shift of focus to adjuvant therapy.21 Several NCI cooperative groups and international cooperative groups have contributed to the development of adjuvant endocrine therapy and chemotherapy for early breast cancer, developing an increasingly patient-tailored treatment scheme.22 Trials evaluating a new generation of agents across the spectrum of modalities (hormonal, cytotoxic, targeted biologic) are now in progress.

**Adjuvant Chemotherapy and Radiotherapy for Colorectal Cancer**

Investigations from the North Central Cancer Treatment Group pioneered the application of adjuvant chemotherapy and radiotherapy for colon and rectal cancer.23 Subsequent trials conducted by several of the cooperative groups have confirmed and refined these early advances, but additional major improvements had been at an impasse until recent years, when several new promising chemotherapy regimens reached criteria for phase III evaluation. Trials with potential to shift standard treatment to a new more effective platform are ongoing.

**Combined Chemotherapy and Radiation Therapy for Cervical Cancer**

Cooperative group trials have demonstrated that women with cervical cancer that was locally or regionally advanced or localized with poor prognostic indicators obtain significant benefit from combined radiotherapy and platinum-based chemotherapy, compared with radiation therapy alone. Five independent trials conducted by three of the US-based groups (Gynecologic Oncology Group, Radiation Therapy Oncology Group, Southwest Oncology Group)24-28 indicated mortality reductions of 30% to 50% for the combined modality approach, prompting the NCI to issue a clinical announcement supporting adoption of this treatment strategy.29

**Paclitaxel for Ovarian Cancer**

Although progress in treating ovarian cancer has been difficult, efforts by the Gynecologic Oncology Group and several other groups resulted in the development of cisplatin and carboplatin as active adjuncts to surgery in the 1980s. Subsequently, paclitaxel was demonstrated to add further benefit to platinum based regimens. The landmark paclitaxel-cisplatin trial by the Gynecologic Oncology Group30 and an important confirmatory trial by European and Canadian investigators31 have provided the current basis on which to pursue further improvements.

**Immunotherapy for Melanoma**

Through a series of trials undertaken jointly by the Eastern Cooperative Oncology Group, Cancer and Leukemia Group B, Southwest Oncology Group, and others, immunologic therapy using interferon has been shown to extend the recurrence-free survival interval and possibly result in longer survival time for patients with high-risk melanoma.32-34

**Cancer Chemoprevention**

In recent years, cooperative groups have crossed the boundary from treatment to cancer chemoprevention, most notably with the completion of the NSABP’s Breast Cancer Prevention Trial in 1998 demonstrating that tamoxifen could reduce breast cancer incidence by nearly 50% in women identified as having increased risk,35 the Southwest Oncology Group’s Prostate Cancer Prevention Trial showing that finasteride could significantly alter risk of prostate cancer in men over 55 years of age,36 and the Cancer and Leukemia Group B trial showing that aspirin can reduce colorectal adenoma in patients with prior history of colon cancer.37 A follow-up trial by the NSABP comparing tamoxifen to raloxifene (Study of Tamoxifen and Raloxifene [STAR]) is nearing completion of accrual of nearly 20,000 women. The Selenium and Vitamin E Cancer Prevention Trial (SELECT) coordinated by the Southwest Oncology Group to further investigate prostate cancer prevention has begun accrual toward a goal of 32,000 participants.
**Adverse Events in Cancer Treatment**

In addition to identifying treatment improvements, large trials play a key role in revealing important secondary effects of therapy. Both the documentation of anticipated adverse effects and the occasionally serendipitous discovery of previously unobserved treatment risks are critical to a full evaluation of any new regimen. Risks for relatively uncommon treatment-related side effects cannot be reliably estimated from smaller studies, or they may be missed entirely with selected patient populations. Some important examples include the increased incidence of leukemia secondary to chemotherapy and endometrial cancer after tamoxifen use for breast cancer. In a recent example, increased mortality observed in large multicenter trials of colon cancer regimens containing the new agent irinotecan led to prompt regimen and study monitoring modifications. In addition, innovations in reporting systems for multicenter trials have been developed to meet NCI and FDA mandates regarding reporting of adverse events.

**“Negative” Findings**

While clinical trials that fail to find in favor of new treatments under consideration may be disappointing and do not garner as much attention than positive studies, such trials are equally valuable in directing treatment policy and furthering research, provided that the trial in question had adequate statistical power to find a specified difference in treatments had one existed. A classic example involves the use of high-dose chemotherapy with stem cell support for breast cancer. This complex, high-risk treatment regimen was increasingly used prior to the availability of evidence from RCTs. As results of several trials, including those conducted by cooperative groups, have become available and matured, the value of this regimen has been called into question as there remains no clear benefit for the more aggressive therapy.

**Additional Research Questions Investigated by Cancer Cooperative Groups**

In addition to treatment efficacy evaluation, a wide variety of secondary hypotheses may be evaluated in cooperative group clinical trials. Those that touch on broader cancer care issues are described here.

**Prospective Studies in Outcomes Research and Cancer Control**

The National Library of Medicine describes outcome assessment (the listed term closest to outcomes research) as “research aimed at assessing the quality and effectiveness of health care as measured by the attainment of a specified end result or outcome. Measures include parameters such as improved health, lowered morbidity or mortality, and improvement of abnormal states (such as elevated blood pressure).” With respect to disease treatment, this definition implies that outcomes research addresses questions beyond the demonstration of efficacy narrowly defined as disease-specific response in a given evaluative setting. It may encompass the study of (1) dissemination and use of medical knowledge about treatments, (2) access to and delivery of those treatments and ancillary care in diverse healthcare settings, (3) benefits and consequences of the treatment, using alternative metrics to the usual efficacy measures, and (4) the sum impact of these treatments on morbidity and mortality burden in the total patient community. Because outcomes research is necessarily multifaceted and multidisciplinary, it is difficult to fully partition its goals, methods, and endpoints from clinical cancer research as a whole. However, as the field matures, it is evolving into recognizably distinct disciplines, perhaps supplanting a general notion of outcomes research. This pattern is well described in a recent review circumscribing the past and current state of outcomes research as it pertains to cancer.

Prospective studies of secondary endpoints relevant to cancer care may be embedded in the clinical trial protocol. The rigorous collection of clinical and pathologic characteristics, demographic information, and treatment course history in clinical trials provides a high-quality environment for the study of quality of life, psychological effects, physical function, and other aspects of cancer and its treatment.

**Quality of Life (QOL) Studies:** QOL studies have become an integral component of most cooperative group clinical trials. The scope of such studies is wide, including well-planned, hypothesis-driven assessments of how cancer treatment affects physical function, psychological well-being, sexuality, cognition, and daily life activities and lifestyle. In recent years, cooperative groups are also increasingly involved in conducting prospective trials of symptom management agents and other interventions to improve cancer care. A review of QOL studies, as well as additional behavioral science research carried out by cooperative groups, can be found in a review by Gotay and colleagues.

**Economic Analysis:** The feasibility of incorporating health economic evaluations into cooperative group trials has been investigated, and such studies are likely to become an important component of future trials. Indeed, several of the approaches to economic analysis in oncology as defined by Schulman and Yabroff are already being used to retrospectively evaluate results from cooperative group trials. For example, cost minimization concepts (appropriate when treatment efficacy of various choices is equivalent) have been applied to an Eastern Cooperative Oncology Group trial of chemotherapy regimens for advanced non–small-cell lung cancer. Cost-util-ity analysis (which takes into account survival extension and the quality of the additional survival time attributable to treatment) has been applied to a glioma trial conducted.
by the Radiation Therapy Oncology Group. These investigators have argued for the merits using multicenter cooperative group trials as a basis for economic analysis of cancer treatments.

Cooperative groups have served and will continue to serve a key role in outcomes research by providing high-quality evidence of genuine treatment advances and through the judicious incorporation of prospective outcomes-oriented studies into RCTs. Indeed, some have argued that large-scale RCTs of the cooperative groups in their current form are outcomes research, while others suggest that while RCTs do not fulfill the criteria for outcomes research, these studies are nonetheless a key component in this broader perspective of cancer care (Figure).

Secondary and Retrospective Investigations Using Cooperative Group Trials Databases

Retrospective analyses of both clinical and nonclinical factors in cancer prognosis and survivorship are a second way in which cooperative groups contribute to knowledge in cancer care. Clinical and pathologic data from trials are often a valuable resource for research in cancer biology. With respect to other aspects of cancer, although the trial participant cohorts do not represent random population-based samples of individuals with the disease in question, studies often provide additional information toward applicability of standard and experimental treatments to special populations. Some of the secondary objectives and goals addressed by the studies described in this section may also be considered outcomes research in the broad sense, and a recent review found the majority of cancer outcomes research studies to be retrospective in design. Some examples of this research are as follows:

Role of Cooperative Group Trials in the Synthesis of Cancer Treatment Information

Because of the expense and time required to conduct these studies, cooperative group trials are carefully designed to avoid equivocal findings or, in other words, to provide definitive evidence for whether a current standard therapy should or should not be supplanted. Nonetheless, even clear findings will invariably leave some questions unanswered. If we are to view the RCT as an exercise of the scientific method, as many have, then there is an important role for confirmatory (ie, replicated) trials and synthesis of studies with similar aims into a coherent framework for use by the medical and patient community. This is particularly important for clinical decision-making, where trial results, which reflect a benefit in a sample (hopefully) representative of a population of patients with certain disease characteristics, have to be translated to the individual patient’s utility for various treatment options. While redundancy of large trials may be viewed as costly and inefficient, the value of corroborating evidence can contribute greatly to cancer treatment practice changes, especially when benefits are moderate as is the case in many cancer treatment advances. For this reason, cooperative groups may conduct confirmatory trials to strengthen evidence.

In a similar spirit, meta-analyses have played a key role in advancing acceptance of the worth of local and systemic adjuvant therapy in cancer. The demonstration of consistent treatment effects across numerous trials serves to strengthen the evidence base, particularly when individual studies may have inadequate power for modest yet meaningful benefits. While some limitations and pitfalls exist and there is no substitute for large definitive trials, meta-analyses are a valuable complementary research strategy that has been influential in cancer treatment.

Cooperative groups have played an essential role by providing high-quality trial data and by participating in the meta-analysis synthesis and interpretation process. Relative uniformity in design of data collection instruments used by the groups (often motivated by intergroup trials) also contributes to the standardization of trial data and facilitates meta-analyses.

Consensus development is another means by which information from cooperative groups is incorporated into treatment practice. In the typical consensus development process, current evidence is assessed and unanswered questions are identified. Since large trials remain the most definitive evidence for treatment efficacy, they play a central role in treatment recommendation guidelines. For example, in the recent National Institutes of Health (NIH) Consensus Development Conference on adjuvant therapy for early breast cancer, debate centered on the use of certain tumor markers for preferential selection of agents, the migration to a new baseline “standard” multidrug regimen in node-positive patients, the apparent lack of clear benefit for high-dose chemotherapy, and the impact of all treatment types on transient and long-term quality of life. Despite the effort toward consensus and information dissemination, there has been concern regarding subsequent adoption of the recommendations that arise from such efforts. One study showed little impact on physician practice of guidelines arising from earlier NIH Consensus Development Conferences on breast cancer and other diseases. It has been argued that participation by physicians in cooperative group research will itself standardize and improve treatment uniformity and quality; particularly with regard to surgical and staging procedures. More research focused on quality of care in diverse practice settings is needed to monitor the spread of cancer treatment information and understand the causes of deviations from recommendations.

Limitations of Cooperative Group Trials

While numerous strengths and achievements of cooperative group trials have been identified, a number of limitations and shortcomings of the cooperative group structure and its research need to be mentioned. Clinical trials necessarily have inclusion/exclusion criteria for entry that serves to limit the generalizability of findings, often unnecessarily so. The effect of this lack of a truly representative patient population extends beyond the primary efficacy comparison to any ancillary QOL, economic, or other outcomes-oriented study questions examined. A second problem is slow accrual. When controversy or debate about a given treatment regimen is high (some would argue that
this is a situation where a clinical trial is most needed), participation may fall far short of that needed in order to obtain results in a reasonable time frame. A recent example involves the value of regional radiotherapy in breast cancer where, following results from two earlier studies, an intergroup trial was launched, only to close recently due to insufficient accrual. Even when enthusiasm is high, some cancers are sufficiently rare so that even multigroup trials cannot obtain the necessary number of participants in a timely manner. Regardless of the reasons for slow accrual, these trials run the risk of becoming scientifically and clinically defunct, as the basic science, diagnostic, and therapeutic development landscape will continue to change while the trial is ongoing under its original design and treatment scheme. Finally, the diffused investigator structure, the necessity to deal with large numbers of institutions (and their attendant IRB requirements), and other aspects common to large, complex organizations can make cooperative groups bureaucratic at times and unable to respond and rapidly adapt these trials to changing conditions in oncology.

Areas for an Expanded Role of Cancer Cooperative Groups

There are several areas in which cooperative groups can work to mutually serve their mission and enhance the broader cancer care effort.

Expand Use of the Cooperative Group RCT Database and Structure as a Data Resource for Molecular Marker Studies: The wealth of clinical, pathologic, demographic, and follow-up data already existent in RCT databases has been used in secondary studies as described earlier, but more opportunities exist. New developments in biotechnology offer exciting potential for more informed clinical decision-making, specifically, how to appropriately select patient-tailored treatment from a growing stock of options. For example, the application of genomics may finally allow for preferential selection of existing and future treatment agents according to a patient’s propensity to benefit or susceptibility to toxicity. Because of the randomization mechanism and the mature follow-up with detailed clinical outcomes in RCTs, these databases may ultimately provide the most valuable resource for clinical evaluation of new molecular markers in the near future. As described earlier, collection of materials is being carried out concurrently with most accruing trials, and this material will be of great value for diagnostic and prognostic determinations and the follow-up matures on these studies.

Continue and Expand the Inclusion of Prospective Outcomes Research Studies: Prospective studies that entail thoughtful study designs with adequate statistical power to evaluate precise hypotheses provide the highest level of evidence for questions concerning the totality of impact of cancer treatment, control, and prevention strategies. The cooperative group trial provides the ideal environment for such studies, provided that the additional data collection necessitated by such studies can be carried out without undue burden on participants and researchers. Realistic assessment of additional resource needs and increased support for these activities is needed.

Expand Diversity in Participation: While the demographic constitution (with respect to whites, blacks, and Hispanics) of NCI-sponsored treatment clinical trials have been found to be generally representative of the incident cancer burden in the population in adults and children, increased racial/ethnic diversity in clinical trial participation is needed. More diverse participation will enhance justification for extrapolating from trial results to the population as a whole, will ensure dissemination of quality care in accordance with current treatment guidelines, and will provide the necessary data for continued investigations of the role of ethnic, social, and cultural factors in cancer prognosis and optimal treatment. Recruitment of racial minority participants to cancer trials remains challenging, but research is shedding light on ways to overcome barriers. With regard to age, the National Institute on Aging jointly with the NCI recently appealed to cooperative group researchers to actively study cancer treatment in the elderly. The Cancer and Leukemia Group B has begun a clinical trial specifically for elderly breast cancer patients, while other studies are in development. Studies addressing patient and physician barriers have identified areas for improvement in diversification of clinical trial participants.

Conclusions

This article has described the scope of cooperative group clinical trials and presented the case for the work of these groups broadly serving the cancer care endeavor. Opportunities for even greater contributions exist, and it is hoped that the cooperative group enterprise continues to move in the direction of demonstrating cancer treatment effectiveness. Given the synergy of goals between the cooperative group researchers and the broader cancer care community, contributions to an expanded scope of research by cooperative groups should continue and grow, while maintaining the primary mission of the cooperative groups: the prospective evaluation of interventions that can reduce morbidity and mortality caused by cancer.

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