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ORIGINAL ARTICLE

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The Cooperative Groups: Past and future

Abstract The Cooperative Group system of the National Cancer Institute (NCI) has been in existence since the 1950s and has evolved to comprise 11 groups, the membership of which includes universities, Community Clinical Oncology Programs, and Cooperative Group Outreach Programs. The Cooperative Groups serve as models for cancer clinical trials throughout the world. However, in today's changing healthcare environment in the USA the Cooperative Groups need to adjust how they operate to ensure the continuation of their leadership role in cancer clinical trials. Government funds, the main source of support for the Cooperative Groups' activities, are shrinking and currently funding is only 50% of the recommended level. If the Cooperative Groups are to remain at the forefront, adjustments must be made in several areas: the Cooperative Groups need to provide an efficient and rapid scientific and legal mechanism to execute large phase III studies of the increasingly important portfolio of compounds being developed by industry more effectively. Industry has come to rely on contract research organizations for expedited testing of their products due to perceived inefficiency in these areas in the Cooperative Group mechanism. The Cooperative Groups are uniquely situated to provide in-depth evaluation of the newest therapies for regulatory agencies and interested health insurers, as well as provide health outcomes data, which are now much sought after by the healthcare industry. Managed care is shaping medical practice, including cancer care, throughout the USA. Finally, the Cooperative Groups need to foster greater international cooperation to speed technology transfers. The leaders of the Cooperative Groups are discussing new approaches to address these deficiencies, while complementing the existing NCI structure and recognizing the independence of each group. The objectives of these new approaches would be: to establish a structure whereby better contracts with industry for conducting trials can be established; to enhance international cooperation in clinical trials; to encourage greater involvement of third-party payers in clinical trials; to build on the scientific breadth of the members; to identify the most appropriate therapies to consider for reimbursement; to establish a framework which builds on the strengths of each of the members; and to integrate health outcomes and economic measures into the protocol activities. The Cooperative Groups are making changes to ensure they remain the leaders in cancer clinical trials well into the 21st century. The benefits of these adjustments will be realized not only by patients, but also by health professionals and the healthcare industry.

Key words Cooperative Groups · National Cancer Institute · Cancer clinical trials · Contract research organizations · Managed care

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Introduction

The success of the clinical trials system is vital to the progress of standard cancer practice. Most of the major advances in cancer therapy over the past 30 years have been accomplished through clinical trials. The Cooperative Group system in the USA has become the model for cancer clinical trials throughout the world. Begun in the 1950s as consortia of university medical centers and academic physicians, the Cooperative Groups have grown and expanded. Today they include 11 groups which comprise not only well-known academic centers, but also community hospi-

tals, clinics, and practices. The membership of the Cooperative Groups includes physicians, statisticians, nurses, clinical research associates, and pharmacists. All of these healthcare professionals are working together toward the study, prevention, and cure of all forms of adult and pediatric cancers.

The National Cancer Institute (NCI), a division of the National Institutes of Health, provides public funds to the Cooperative Groups through a peer review process; this represents essentially the sole support of the Cooperative Groups. Government funds have been shrinking each year, with the groups currently being funded at approximately 50% of the recommended level. To continue to expand upon the types of research activities in which the Cooperative Groups are involved, a more diversified source of funding is needed.

Cooperative Group strengths and essential adaptations

The Cooperative Group clinical trial process in the USA has been responsible for most of the major advances in cancer treatment over almost four decades. New therapies and new drug compounds are extensively tested and evaluated in the large phase III trials conducted by the Cooperative Groups, leading to major improvements in survival in patients with cancers at a variety of different sites. Some examples of the major advances credited to the Cooperative Group clinical trial system include:

1) discovery of the activity of cisplatin in early studies of a curative therapy for testicular cancer;
2) recognition of the effectiveness of combination doxorubicin + high-dose methotrexate therapy in young adults with osteogenic sarcoma;
3) a 30% reduction in mortality rate due to adjuvant therapy for localized breast cancer; and
4) improved survival of individuals with localized colorectal cancer through treatment with a regimen of 5-fluorouracil (5FU) + levamisole, 5FU + leucovorin, or 5FU + radiotherapy.

In the past decade, the Cooperative Groups have made many important findings in new cancer therapies such as hormone therapies, biologics, and new cytotoxic approaches, among others. Some examples of recent Cooperative Group study findings include:

1) Tamoxifen taken for 5 years rather than one year after breast surgery is more effective in preventing breast cancer recurrence.
2) Treatment of malignant melanoma with less deforming surgery and using interferon alpha can delay the time to recurrence after surgery.
3) An effective treatment program for early-stage lung cancer has been established involving a combination of chemotherapy and radiation.
4) Taxol has been shown to be effective in treating stage IV non-small cell lung cancer (NSCLC), as well as having significant activity in head and neck cancers.

Over the decades, relationships with industry have played an important role in these studies, resulting in the establishment of new approaches to treatment. For example, the Cooperative Groups, in partnership with Bristol-Myers Squibb, were the first to show the importance of Taxol in ovarian cancer. Additionally, as a result of the Eastern Cooperative Oncology Group (ECOG)-coordinated studies of Taxol, the world is now changing its view of up-front treatment for NSCLC and primary treatment of breast cancer. Clinical trials operated outside of the Cooperative Group system lack such a record of major accomplishments and the organizations coordinating them do not have the experience, expertise, or broad base of scientific resources to carry out such landmark studies effectively.

To keep this exchange of science and process of dynamic discovery moving forward, several key areas need to be adjusted. If the Cooperative Groups are to remain at the helm of the clinical trial process the following issues must be addressed.

1) Industry is developing an increasingly important portfolio of compounds. For definitive testing, these active antineoplastic agents require the large phase III trials conducted by the Cooperative Groups. Despite the groups' history of therapeutic discoveries, the current Cooperative Group system does not allow for the efficient and rapid scientific negotiations with pharmaceutical companies required to execute large studies. Additionally, it does not allow for appropriate financial case reimbursements for carrying out the study at Cooperative Group institutions.
2) Competition to place patients on clinical trials is strong. In the USA today, it is estimated that only 2–5% of all adult cancer patients are enrolled in a clinical trial. A larger group of participants is needed to meet the statistical requirements of studies currently in development and of future protocols. Additionally, as industry works to get their compounds through trials and submitted for approval quickly, they often spurn the Cooperative Groups due to the perceived inefficiency of the group mechanism and the incongruity which exists between the stated needs for regulatory control and current Cooperative Group regulatory practices. Therefore industry turns to contract research organizations (CROs) for protocol management. There are few CROs that have the extensive experience in cancer clinical trials or the national network of cancer professionals and none that have the record of accomplishments of the Cooperative Group system.
3) For cancer care to continue to advance at a rapid pace, innovative therapies must continue to be developed. Members of the Cooperative Groups have been successful in developing new treatments from the earliest concepts, and many of these treatments are earmarked for later broad phase III testing within the Cooperative Group system. Regulatory agencies and third-party health insurers are interested in the evaluations of these "emerging treatments," which can ultimately be helpful in shaping standard practice and influencing reimbursement programs.
4) Managed care has affected almost every aspect of healthcare in the USA today. Although managed-care organizations espouse a financially responsible case-man-

agement approach, most managed-care and indemnity organizations do not foster the entry of patients into clinical trials. The Cooperative Group protocol system is the dynamic case-management system of leading treatment alternatives agreed upon by experts in the community and academia, and should be viewed as an attractive feature by the managed-care groups. The reluctance of managed-care groups to reimburse the costs of care administered as part of a Cooperative Group-sponsored trial not only runs counter to their expressed ideals of supporting high-quality care, but may also threaten the continued progress of cancer research. This threat reaches beyond the function of the Cooperative Groups and into the lives of individuals and society.

5) Health outcomes research is a major focus of the healthcare industry today. The Cooperative Groups are essentially medical outcomes programs. Within the Cooperative Groups, there are recognized experts in the collection and evaluation of quality of life data, informatics, and economic outcomes data. In the face of shrinking budgets, the groups are currently struggling to integrate these types of expertise into the operations of the Cooperative Groups.

6) Cooperating with international cancer consortia must become the norm to speed the development and transfer of technology. Some progress has been made in recent years; however, more relationships need to be fostered and the Cooperative Groups must become better able to work with industry partners and international colleagues on the global scale.

Initiatives to drive adaptation

The chairs of the respective Cooperative Groups have developed initiatives within their organizations to address one or more of these deficiencies. Foundations have been established to provide the groups with greater flexibility in funding to achieve these goals.

1) The ECOG began an initiative to open discussions with third-party payers to cover the costs of patient care on Cooperative Group-administered cancer clinical trials. Since the ECOG began these discussions, several other Cooperative Groups have joined this initiative. Ultimately, it is expected that all phase III clinical trials of "leading treatment alternatives" sanctioned by the NCI and conducted by a Cooperative Group-designated institution will be covered for reimbursement. Trials of emerging treatments (phase I studies) will be evaluated on a case-by-case basis.

2) In April 1996, the Pediatric Oncology Group and Children's Cancer Group established a program with the Blue Cross Blue Shield Association (BCBSA) to form the Pediatric Cancer Network. This program provides members of the BCBSA with immediate access to a pediatric oncologist participating with the Cooperative Groups.

3) Cancer and Leukemia Group B has a strong program in health outcomes research. These data are coveted by and useful to regulatory agencies and third-party payers.

4) The Gynecologic Oncology Group has established a mechanism to evaluate phase I therapies. Through such evaluations the Cooperative Groups can provide recommendations to payers on the most efficacious treatments to consider as part of a reimbursement program.

Conclusions

The Cooperative Groups have essentially the same operational systems and similar missions; therefore the next step in achieving success and growth for the Cooperative Groups will be to cooperate in areas of mutual interest. The advantage is in the experience, broad ranges of expertise, wealth of scientific knowledge, and high quality of care that are consistent throughout the Cooperative Group system. A single organization that could bring the strengths of each of the groups together would better be able to address the problems in the system, provide a more flexible and diversified funding source, and ensure continued Cooperative Group advances in cancer treatment, prevention, and control. The organization could be established as a new, not-for-profit foundation that would allow the groups to retain their independence while complementing the work already performed within the NCI structure. Currently, the chairs of the 11 national Cooperative Groups are discussing how best to establish such a collective group to meet their goals most effectively and ensure that the Cooperative Groups lead the way in cancer research well into the next century.