THE PRESENT STATUS AND FUTURE OUTLOOK OF CLINICAL RESEARCH IN THE COMMUNITY

This article presents the perspectives of three cooperative group chairmen on the present status of community involvement in clinical research, from barriers that impede increased participation to changes that must be made to ensure continued success.

The Eastern Cooperative Oncology Group

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Before 1960, most of the progress in clinical cancer research appeared to come from relatively few cancer centers, and the therapy approaches were defined by a few investigators at those centers. These investigators basically reported their sequential series and attempted to define progress through historical retrospective comparisons. Over the past two decades, we have seen enormous progress, with most of the advances in the non-hematologic malignancies coming not from single centers, but from large cooperative group trials. A good example relates to changes in breast cancer management that involve surgery, radiation and chemotherapy—all of which have evolved as the result of large trials both in America and in Europe.

In America, the success of these trials has been significantly enhanced by the participation of community cancer physicians and their patients in the studies. It is very appropriate, therefore, to look at the role of the Eastern Cooperative Oncology Group (ECOG), as well as other groups involved in community clinical cancer research.

The History of ECOG

The ECOG was one of the original regional groups established in 1954 to study the treatment of cancer with drugs. Today, the ECOG consists of 29 member institutions that have developed affiliate networks comprising more than 180 community hospitals. These networks are referred to as the Community Group Outreach Program (CGOP). In addition, the ECOG has designated 26 community hospitals as participants in the Community Cancer Oncology Program (CCOP) of the National Cancer Institute (NCI).

In the early 1970s, the NCI had a line budget item for cancer control research. This led to the formation of NCI's Division of Cancer Control. In 1974, the ECOG submitted an unsolicited grant proposal to this division. The principal goal of the proposal was to fund the participation of community hospitals so that their patients could be entered on ECOG protocols. At that time, community hospitals received less than one percent of ECOG funding. An ad hoc review committee disapproved the grant proposal, calling it "unrealistic." Nevertheless, a dialogue continued that finally led to the creation of a community cancer control program for cooperative groups, which was the predecessor of the current CGOP and CCOP programs. The ECOG received its funding for this program in late 1976. In the first year, ECOG registered 652 patients from community hospitals onto protocol studies. In 1989, it is estimated that more than 3,000 community hospital-based patients will be enrolled in ECOG protocols.

ECOG's Community Cancer Program

The ECOG Community Cancer Program is overseen by the Community Cancer Committee, which has 15 elected members who are selected equally from the member, CCOP and CGOP institutions' Principal Investigators (PIs). There is also ex-officio participation by representatives of the Operations Office Statistical Center, Data Managers, and Nurse Oncology Committees. This Community Cancer Committee reviews the program and makes recommendations for funding to the Executive Committee for CGOP support. The CGOP funding is distributed on the basis of these recommendations through a grant to ECOG.

In contrast, the CCOP monies go directly to community hospitals. Involvement in ECOG by community or member institutions does not depend on funding, and each of the various components have unfunded, active members. It is ECOG's policy that CCOP members can be freestanding, but all CGOP hospitals must be associated with a member institution. The member institution is ultimately responsible for the quality of the data. Any deviation in quality, eligibility, or lack of follow-up is considered a demerit against the member institution.

Involvement in ECOG science programs is not restricted to any type of institution, and community members can serve on the Executive Committee as protocol chairs and as committee leaders. Community physicians participate in all ECOG activities, and CCOP members of the ECOG can have affiliations with more than one cooperative group.

The usual ECOG quality control activities, including annual review for quality, accrual, data submission, audits, and IRB approvals, are applied to all community participants. An absolute requirement has been that all CGOP affiliates must contribute at least seven patients per year to ECOG studies over a three-year period. For CCOP members, the requirement is 30 patients per year for those who

TABLE 1

ACCRUAL BY COMMUNITY HOSPITALS

	1984	1985	1986	1987	1988
CGOP	1,619	1,757	1,251	1,385	2,252
CCOP	1,064	970	839	1,035	1,914
% ECOG Accrual From Community Hospitals	60	65	64	60	63

TABLE 2

PERCENTAGE OF PATIENTS FROM COMMUNITY HOSPITALS AND MEMBER INSTITUTIONS ENTERED ON ADJUVANT, MULTIMODAL, CHEMOTHERAPY, AND ANCILLARY STUDIES*

Study Type	CGOP	CCOP	Member
Adjuvant	19	18	16
Multimodal	17	21	18
Chemotherapy	62	57	63
Ancillary	2	4	3

* Adjuvant refers to patients receiving potentially curative therapy. Multimodal refers to mor than one treatment modality. Ancillary refers to non-therapeutic studies.

use ECOG as a primary research base, and 10 patients per year for those who use ECOG as an auxiliary research base. Annually, the total pool of dollars for CGOP institutions is reallocated by the Executive Committee, based on up-to-date accrual and participation by each community hospital. This flexibility has allowed new affiliates to be brought on board and others to be dropped without tying up resources.

Patient Accrual

The participation in ECOG by community hospitals has now reached about 60 percent of total patient accrual (see table 1). We have found that community hospitals have the same quality of data that member institutions do, as measured by eligibility (90 percent), evaluable (95 percent) toxicity and response rates, during the period of 1984 through 1987. Because community hospitals tend to consider themselves as primary care centers, it is of interest to look at the distribution by type of protocols: namely, adjuvant, chemotherapy, or ancillary (non-therapeutic). Table 2, which summarizes this analysis, shows no difference among the various types of participating hospitals.

The ECOG data base is sufficiently mature to permit survival comparisons between patients treated at community hospitals versus major treatment centers. The analysis was based on matching community hospital patients with patients from major cancer treatment centers. (Both patients were on the same protocol, receiving the same treatment, and were of the same sex.) We found that for every 100 patient deaths at community hospitals, there were 96 patient deaths at major cancer treatment centers. This analysis covered all ECOG protocols over a 10-year period. The difference of four deaths per 100 is principally attributed to patients enrolled on melanoma and lymphoma protocols.

Reimbursement Issues

The problem with reimbursement is not a community hospital issue alone. ECOG's member institutions have the same problems with third-party payers, pre-hospitalization review, non-compensation for experimental protocols, etc. The issues are complex and relate to changes in the health care environment and cost containment. HMOs impose restrictions on who can see the patient, what treatment can be offered, and what resources can be used to follow the patient. Third-party payers are increasingly setting up barriers to hospitalization for experimental therapies, particularly when new biologic treatments are involved.

Another problem relates to compensation for physicians' time and data management costs involved in enrolling patients on studies, and collecting data and follow-up information. The need to explain studies and to obtain informed consent takes physicians away from their private practices. While these costs may legitimately be charged against the NCI, the total dollars allocated by NCI have been flat; in fact, they have not even kept up with inflation rates. And while the NCI is attempting to restrict costs, protocols are becoming more complex, follow-up is being extended, reporting requirements are increasing, and both institutions and physicians are having to provide more services.

Unlike trials sponsored by drug companies, the Heart Institute of the National Institutes of Health (NIH), or the National Institute of Allergy & Infectious Diseases (NIAID), physician and patient costs are not included in the dollar base allocated to cooperative groups, such as the ECOG. This is a national issue that must be addressed by all cancer clinical investigators and discussed at the highest levels with federal health agencies, industry leaders, unions, and private insurers.

The Future of Community Clinical Research

The very nature of research demands change as new findings become available. On the other hand, treatment advances, more often than not, are more expensive and require more sophisticated technology (e.g., ER measurements, cell flow studies, and oncogene expression determinations). Therapy itself is changing as more and more treatment involves biologics that are expensive and need to be given by infusion. Some trials involve intensive therapy, such as autologous marrow transfusions or transplantation technology (which is now being considered as a treatment for metastatic disease to the liver). Higher technology and increasingly expensive treatments exacerbate the problems of compensation, patient acceptability, and access to care. In addition, cancer therapy is only one aspect of total care. Cancer physicians must become involved in research and such applications as screening, prevention, and health promotion. As a specialty, oncologists, no matter were they work, must adapt and be involved or others will step in. Unless oncologists do adapt, they may be in danger of becoming the outmoded polio, syphilis or tuberculosis specialists of earlier years. The challenge for us all is flexibility, and to be able to refocus our emphasis from cancer treatment research to such areas as prevention and screening. In the future, we may rely less on killing cancer cells and more on regulating cell growth by differentiating factors.

The National Surgical Adjuvant Breast and Bowel Project

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These remarks are directed to community-based oncologists who already participate in randomized clinical trials or who are planning on taking that course of action in the near future. The term "community-based," in our view, has no pejorative connotation which implies that a community-based oncologist differs from the oncologist who practices and conducts research in another setting. The term "oncologist" includes not only medical, but surgical and radiation oncologists, as well as oncology nurses. We emphasize that clinical trials are mechanisms to be used for conducting clinical research and, consequently, physicians or nurses who take part in clinical trials are participating in the conduct of clinical investigation. Clinical trials do not make discoveries any more than word processing equipment is capable of producing creative manuscripts. The output of both relates entirely to the capabilities of the individuals who use them, regardless of where they are located.

Since its inception, the National Surgical Adjuvant Breast and Bowel Project (NSABP) has played a seminal role in altering the therapy of patients with primary breast cancer. In more recent years, that group has made similar contributions in the management of colon and rectal cancers. In no small part due to results obtained from NSABP clinical trials, we have witnessed:

- The alteration of standard breast cancer surgical treatment from radical mastectomy to lumpectomy,
- The utilization in the adjuvant setting of chemotherapy regimens previously employed only for metastatic disease,
- The recognition of the importance of markers for determining prognosis and for selecting therapy,
- The worth of combining hormonal therapy (tamoxifen) with chemotherapy for more effective treatment of certain subsets of patients, and
- The emergence of patients with sufficient awareness of the importance of clinical trials to enable them to question their physicians regarding participation in such trials.

When the NSABP was founded in 1958, membership was limited to university-based physicians, because it was believed that they alone possessed the capabilities necessary to carry out clinical trials. At that time, it was thought that community physicians had either a limited interest in clinical investigation or were too occupied with providing primary patient care to become involved in such efforts. It soon became apparent, however, that these perceptions were incorrect, and that the only way in which clinical trials could flourish was if community physicians were invited to participate in NSABP studies.

In the early 1970s, the NSABP became the first cooperative group to 1) make a concerted effort to include community-based oncologists as members, 2) seek methods of funding for them which differed from traditional, often hard-to-obtain research grants, and 3) utilize their talents for the design and implementation of NSABP studies. In fact, it was the success of this early effort which provided the model that was used by the National Cancer Institute to establish its Cooperative Group Outreach Program (CGOP) and, subsequently, the Community Clinical Oncology Program (CCOP). For almost two decades, the NSABP has recruited and welcomed community-oriented investigators whose commitment, enthusiasm, and quality of participation have consistently disproved the prevailing idea that only university-based investigators could fulfill the clinical and data management requirements of cooperative group trials. Whatever success the NSABP has had in the past or is likely to have in the future relates in no small part to the contributions of community oncologists.

While the challenge of the past two decades has been to instruct community oncologists in the operation of the clinical trial system and to convince them to enter patients in trials, the challenge of the next decade will be to convince community oncologists that they are capable of carrying out more sophisticated research. Concerned skeptics who feared that community oncologists could not participate in simple studies (e.g., a protocol comparing L-PAM with L-PAM + 5-FU or CMF with FAC) now admit that such trials can be implemented successfully in the community setting. The NSABP has also demonstrated that community oncologists can participate successfully in more rigorous trials, such as those designed to evaluate 5-FU + leucovorin therapy in colon and rectal cancers.

The NSABP has recently implemented a series of new protocols for evaluating various therapeutic regimens in breast cancer patients with negative axillary nodes. Although these studies may still bear the label, "simple protocols, readily do-able in the community setting," the NSABP has also begun, or will shortly implement, new protocols that will give rise to another group of "doubters," who will question whether these studies can be carried out in the community setting. One of these new studies is a trial to evaluate the worth of preoperative versus postoperative chemotherapy for the treatment of breast cancer using different techniques for diagnosis (fine needle aspiration cytology), immunocytochemical assay for ER determination, flow cytometry for determining tumor characteristics, and the worth of other promising markers. Another new study has been designed to evaluate the worth of dose intensification and increased cumulative dose of chemotherapy employing colony-stimulating factor (GM-CSF). The NSABP is firmly convinced that community oncologists will make major contributions to these studies.

Community investigators, having demonstrated their capabilities over the past two decades in the conduct of increasingly more complex studies, should not be intimidated by the more sophisticated protocols described above or by those planned for the future; nor should they demand that the treatment strategies they test be simple, nontoxic, and non-time-consuming. Such demands would be antithetical to the conduct of exciting, important and innovative clinical research in this country.

In considering the future of commu-

nity clinical research, it would seem that the major obstacle is a lack of sufficient funds. To tailor the type of research that will be conducted in the community setting to the amount of money available would be disastrous. The amount of available funding must be dictated by the cost required to conduct good scientific investigation. Otherwise, the quality of investigation being conducted by community oncologists, or any researchers, is compromised, the effort being expended is wasted, and the results are of less value. Consequently, all community oncologists should make Congress aware of the need for additional funding in the National Cancer Institute budget to support clinical trials research in the community setting.

The Southwest Oncology Group

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Dr. Coltman

The Southwest Oncology Group (SWOG) initiated the Cooperative Group Outreach Program (CGOP) in 1976 to recruit and integrate community physicians into cooperative cancer research trials.

This program was developed in response to the National Cancer Institute's (NCI's) determination that the reduction of cancer mortality was impeded by the lack of both patient resources in the community setting and educational opportunities for private practice physicians. Prior to 1976, SWOG membership, as in other major cooperative groups, was restricted to physicians based at large universities or teaching institutions. However, this limitation greatly reduced the number of patients available for clinical trial research and, concomitantly, deprived wide segments of patients from potentially beneficial or curative treatment and guaranteed the continued naivety of community physicians about current cancer treatment methods. As a result, SWOG elected to commit resources to an outreach program. Objectives for this program include: 1) making state-of-the-art cancer management available to cancer patients in the community; 2) involving a wider segment of the community in clinical research; 3) enhancing the recruitment of patients from community hospitals onto appropriate protocols; and 4) evaluating the transfer of new patient care technology to the community.

Because CGOP affiliates are not directly funded by the NCI via grant awards, the program was developed around SWOG's major contributing members (currently 32 member institutions) to initiate and maintain close communication between experienced participants and new CGOP affiliates. The member institutions receive nominal budgets to support registration and quality control for their affiliates. Affiliates are paid quarterly directly from the operation office on a per case basis. This money is used to assist CGOP physicians with data management and travel to group meetings. The performance of CGOP affiliates, with regard to the quality and quantity of treated patients, has a direct impact on the overall performance evaluation of member institutions, which has provided the necessary incentive to achieve a high level of commitment to the success of the program.

Since the inception of the CGOP program, SWOG has experienced enormous growth in membership. Current membership consists of 520 physicians, representing all cancer specialties, practicing at approximately 215 hospitals, in 32 states across the country. Corresponding with the growth in program membership has been the increase in annual patient accrual, from seven patients in 1976, to an average of 540 patients during 1987 and 1988.

While SWOG leadership strived to increase accrual through the CGOP program, it recognized that its success also hinged on the participation of community physicians in SWOG's scientific and educational programs.

The integration of community physicians into SWOG research is apparent from their membership in virtually all of the group's scientific committees. This involvement includes participation in the development of research trials, coordination of studies, and authorship of publications. Members of the CGOP program have also been encouraged to attend SWOG's semi-annual meetings, which provide continuing educational forums and detailed reviews of past, present, and future clinical trials.

A final component essential to the success of the CGOP program is the quality of data obtained from outreach physicians. Obviously, poor-quality data will result in ineligible and non-evaluable research subjects, which negates the potential accrual contributions to be made by CGOP participants. SWOG's efforts to educate members about the importance of accurate data collection practices, particularly through semi-annual data manager training courses, continuous updates of the data management manual, and maintenance of the SWOG policy and procedure manual, are validated by current data. Group statistics have confirmed that data collected by CGOP affiliates is equal to, and in fact superior to, the quality of data received from experienced clinicians in the university setting (see the table on next page).

The integration of community/private practice physicians has proven invaluable and, certainly, indicates the need for increased participation by this subset of clinicians. Furthermore, these data are compatible with our hypothesis that SWOG physicians and data management teams are without peer in the clinical trials area.

SWOG has recognized that continued participation by community physicians is integral to the rapid completion of important trials that will address a multitude of timely questions. Also critical is the ability to develop new, successful cancer treatment methods that can be readily transferred to the community setting. Because many of these trials are complex in nature, it is important to prove that community physicians are capable of providing identical treatment programs that duplicate previous successes. Obviously, cancer treatments that cannot be administered by community physicians greatly reduce the number of future patients that could be cured, and compromise cooperative groups' efforts to increase cancer survival.

To gain insight to the current problems and benefits of community physician participation in cooperative group trials, SWOG surveyed members of the CGOP program about what they perceive as impediments to cancer research. A total of 54 participants responded to the questionnaire. Surprisingly, a relatively

ELIGIBLE/EVALUABLE PATIENTS AT MEMBER INSTITUTIONS AND CGOP PARTICIPANTS

Membership Type	% Eligible	% Evaluable	% Eligible / % Evaluable
Member Institutions (University)	94	94	88
CGOP Affiliates (Private)	94	97	91

small number of respondents think that regulatory requirements pose insurmountable barriers to their participation. Only 22 percent believe that the required institutional review board approval of cancer trials is time consuming and a potential inhibitor to accrual, and only 16 percent indicate that obtaining patient informed consent is difficult and obstructive to their participation.

A second surprising conclusion is that, in spite of relatively nominal reimbursement per each accrued case, only 37 percent of investigators think that the current payment scale is inadequate for funding of data management and other support needs. The majority indicate that their participation is based on access to innovative and state-of-the-art trials rather than financial rewards. In addition, 70 percent of respondents indicate that, in spite of the relative absence of funding, the data management workload is not inhibiting and is, in most cases, manageable. The obvious exception to this conclusion is the need for long-term follow-up (all patients entered on SWOG trials must be followed until death), which is a time consuming and frustrating exercise that requires considerable additional personnel hours.

The primary obstacle to increased participation on clinical trials by community physicians is SWOG's inability to provide a constant cadre of trials to meet the needs of their patient populations. These include studies in metastatic lung, colon, prostate, and breast cancers; refractory lymphomas; and carcinomas from an unknown primary. In addition, the majority of patients seen in the community are elderly and have concurrent diseases—a factor that excludes patients from many clinical studies because of the stringent eligibility requirements. These factors, in addition to the actual cost to patients who participate in clinical trials, limit SWOG's ability to increase participation by community physicians.

A final important conclusion obtained from the survey was that the provision of continued educational opportunities influences both the initial interest of community-based physicians in SWOG and their ongoing membership.

Continuing education has been particularly relevant over the past four to five years, because of SWOG's increased participation in cancer control research and basic science research. CGOP participants have access to current trials utilizing flow cytometry (bladder cancer, sarcoma, breast cancer and lymphoma), leukemia biology studies (FAB classification, cytogenetics, surface marker analysis and proto-oncogene expression), lymphoma immunophenotyping and cancer control research (i.e., evaluation of reproductive function in testicular cancer patients, pain control, and quality of life evaluations). CGOP investigators have also gained considerable experience in the administration of new investigational agents. All of these research initiatives have been clearly identified as activities that will likely accompany state-of-the-art cancer research.

A successful outreach program hinges on several factors, all of which have been identified in the past as major inhibitors to increased participation. Of primary concern is the inevitable stagnation of the CGOP program if increased funding sources cannot be identified.

We are convinced that, without adequate financial compensation, an increase in accrual by outreach affiliates will not be possible, because of the complexity of current and planned trials, which involve stringent follow-up for patient monitoring, and an increased number of components per trial, such as basic science research in addition to the use of multiple treatment modalities. In addition, the identification of successful cancer treatment regimens will hopefully correspond with an increase in long-term follow-up cases, both in the total number of cases and the life expectancy of each. As stated previously, however, current requirements for long-term follow-up are cumbersome given the established payment system.

Another impediment to increased participation is the requirement of multiple laboratory and radiographic exams to monitor each patient's clinical condition and response to therapy while on study. The increased cost to the cancer patient has discouraged private practice physicians from participating in many past cancer trials. To address this issue, SWOG has established a Cost Containment Committee, whose primary charge is to review trials and eliminate both unnecessary study parameters and duplication of tests. Although the repetition of certain exams is required to confirm study results, the Committee's review will hopefully guarantee that only essential tests to evaluate new treatment regimens/methods are required.

Finally, we believe that educating the cancer patient is critical to successfully recruiting an increased number of cooperative group subjects. To this end, SWOG has initiated a publicity program. Press releases are sent to members' local newspapers to publicize individual investigator/hospital performance within SWOG (e.g., recognition of excellent performance, awarding of honors or research funds, new available research trials). Hopefully, this program will increase community awareness of SWOG activities and trigger greater patient participation in community-based clinical trials.

Significant strides have been made over the past 12 years toward the integration of community practitioners in cooperative group research. However, the potential for increasing participation and escalating successful cancer research is limitless. The future success of outreach programs is contingent on the commitment of the NCI, each cooperative group, and the community physicians themselves. Efforts to address problems faced in the community setting must be recognized and resolved if we are to guarantee major reductions in the national cancer mortality rate. ■