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Part five in a six-part series that explores cancer program development in the 1990s.

The Challenge for Clinical Research in Community Oncology Programs

by Lloyd K. Everson, M.D.

Oncology practices and cancer programs are facing a multitude of financial and program challenges in their local communities, which will affect the infrastructure necessary for clinical trials research. Clinical trials are a critical component of any mature, quality cancer program. Without continued emphasis and support of clinical trials research for cancer in this country, we are in danger of losing a major resource for all of our cancer patients and their families.

As oncologists and cancer program administrators develop and enhance their clinical trials research program, they face two key questions:

- Why does accrual to clinical trials continue to be low at a time when there is a virtual explosion of new drug development?
- Why shouldn't their institution be involved in cancer clinical trials research?

Answers to these questions lie with understanding 1) the drug approval process, 2) how clinical trials are coordinated, and 3) the strategic value of clinical research in cancer programs.

THE APPROVAL PROCESS

In the United States new drug development research and new drug applications are regulated by the Food and Drug Administration's (FDA's) approval process (see Table 1).

It is interesting to note the prolonged period of time required in the various phases of FDA approval for a new drug. It can take as long as 10 to 12 years from the time of preclinical testing to the time of a drug's actual final review process and release to the health care market. The National Cancer Institute (NCI) and the FDA have collaborated in recent years to expedite review processes combining the Phase II and Phase III periods of clinical trials. Their goal is to shorten the approval process on new medicines for serious and life-threatening diseases such as cancer and AIDS.

An investigational new drug application (IND) is filed after a preclinical testing in the laboratory and after animal studies reveal that there is biological activity in cancer test systems. A general safety assessment is made at that time as well. Subsequent to filing the IND, the drug is approved for Phase I trials in humans. The purpose of this phase of investigation is to determine safety, dosage, and pharmacokinetics of the experimental drug. Following Phase I trials, the drug enters Phase II evaluation in which its effectiveness in a number of different cancer types is determined and its adverse side effects are assessed.

If a drug is deemed to be active in a certain type of cancer, it is then used in a Phase III trial where it is compared to current standards of therapy. Following successful completion of preclinical testing and the three phases of clinical trials, a new drug application (NDA) is filed. The FDA may then take in excess of two years to review and finalize approval for that drug's entrance into the health care market. Most university-based and community-based oncologists participate in Phase II and Phase III clinical trials research.

Under the accelerated approval process, the FDA is permitted to accelerate the approval of new drugs and biologicals for serious or life-threatening diseases such as cancer or AIDS. Zalcitabine, Paclitaxel, and Interferon Beta-1B are examples of drugs that have recently received this approval.

As our understanding of the genetic basis of neoplastic disease has matured, the importance of biotechnology and the molecules manufactured from this industry have become increasingly important. Indeed, biotechnology is one of the fastest growing frontiers of the pharmaceutical industry. More than 140 biotechnology molecules are under development or awaiting FDA approval. More than 50 of these are products for treating cancer or cancer-related conditions.

Understanding the approval process is important since many innovative approaches to cancer treatment are derived from new drugs or new drug applications.

COORDINATION OF CLINICAL TRIALS

Both the pharmaceutical industry and the National Cancer Institute sponsor clinical trials research. Over the last 20 years, the NCI has developed a series of strategies and agencies to coordinate and monitor experimental trials in the United States. Clinical trials in cancer research are conducted through a number of mechanisms that include NCI-designated comprehensive cancer centers, university-based research groups, clinical cooperative oncology groups, the Community Group Outreach Program (CGOP), and the Community Clinical Oncology Program (CCOP).

Prior to the early 1970s, clinical trials in cancer were primarily conducted at universities. However, with the increasing number of well-trained medical oncologists and hematologists entering community practices, more than 80 percent of all cancer patients being treated were in community settings. Because of this shift, Congress and the NCI have

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Table 1 . FDA approval process

	Preclinical Testing		Phase I	Phase II	Phase III		FDA
Time (years)	3.5		1	2	3		2.5
Test Subjects	Laboratory Animals	File IND	Humans	Humans	Humans	File NDA	Review Process
Purpose	Determine Safety & Biological Activity		Determine Safety & Dosage	Determine Efficacy & Side Effects	Verify Efficacy & Compare with Other Therapies		Review Process

proposed firm links and opportunities for cancer patients to access state-of-the-art trials research in the community setting through the CGOP and CCOP funding mechanisms. The Association of Community Cancer Centers, the American Society of Clinical Oncology, and the American Cancer Society were instrumental in making this happen. Currently, 12 clinical cooperative oncology trial groups operate under NCI sponsorship in the United States (see Table 2).

The quality of data is of prime concern in any clinical trial design and execution. Prior to the 1970s, there was a general perception that quality research could only be conducted by university-based oncologists. However, a number of the cooperative groups have conducted internal studies showing that the quality of data contributed by community-based oncologists was equal to and in some cases better than that submitted by university-based oncologists.

The quality of data, protocol development, and accrual to protocols constitute a complex process that challenges the operations office of the cooperative groups, as well as its various university and community-based oncology members. Some of the common elements of a successful cooperative group are outlined in Table 3.

CLINICAL TRIAL GROUP VIABILITY IN THE 1990S

More than 50 percent of all patients accrued to cancer clinical trials are entered by community-based oncologists. However, despite efforts by NCI, cooperative groups, dedicated oncologists, and their staffs to enhance accrual to cancer clinical trials, the percentage of patients enrolled in these trials has never exceeded 5 percent nationally.

Table 2. NCI-sponsored oncology clinical trials groups

Group	Chair	Location	Phone Number
Brain Tumor Cooperative Group (BTCG)	William R. Shapiro, M.D.	Phoenix, Ariz.	602-285-3895
Cancer and Acute Leukemia Group B (CALGB)	O. Ross McIntyre, M.D.	Lebanon, N.H.	603-650-6717
Children's Cancer Study Group (CCSG)	W. Archer Bleyer, M.D.	Houston, Texas	713-792-6604
Eastern Cooperative Oncology Group (ECOG)	Douglass Tormey, M.D.	Denver, Colo.	303-239-3370
Gynecologic Oncology Group (GOG)	Robert C. Park, M.D.	Philadelphia, Penn.	215-854-0770
The Intergroup Rhabdomyosarcoma Study	Harold M. Maurer, M.D.	Omaha, Neb.	402-559-4204
National Surgical Adjuvant Breast and Bowel Project (NSABP)	Ronald B. Herberman, M.D. (Interim Chairman)	Pittsburgh, Penn.	412-692-4670
National Wilms Tumor Study Group (NWTSG)	Daniel M. Green, M.D.	Buffalo, N.Y.	716-845-2334
North Central Cancer Treatment Group (NCCTG)	Michael J. O'Connell, M.D.	Rochester, Minn.	507-284-2080
Pediatric Oncology Group (POG)	Sharon B. Murphy, M.D.	Chicago, Ill.	312-880-4584
Radiation Therapy Oncology Group (RTOG)	James Cox, M.D.	Houston, Texas	713-792-2121
Southwest Oncology Group (SWOG)	Charles A. Coltman, M.D.	San Antonio, Texas	210-677-8808

For example, in 1991 about 4 percent of newly diagnosed breast cancer patients entered clinical trials and only 2 percent of patients with colon/rectal cancer did so. Oncologists and program administrators face enormous challenges in the 1990s, especially with regard to cost containment and federal initiatives that raise the concerns of lower funding levels for cancer research.

In addition, a multitude of factors inhibit clinical trial enrollment (see Table 4).

Ultimately, the oncologist and the cancer program administrator are faced with balancing the pros and cons of involvement in a clinical trials network. On the pro side of the equation, there are several obvious benefits for the cancer program, oncologist, and patient:

- access to state-of-the-art therapeutic innovations with new or approved drugs
- access to an educational milieu of state-of-the-art peer interaction for physicians and nursing staff in the cooperative group trials mechanism
- enhanced community perspective of the oncology practice and program as state of the art.

These benefits must be reconciled with several potential drawbacks, including:

- the reduction of adequate direct funding for critical infrastructure development, data management, and oncologist leadership in local clinical trials research.
- the shift from hospital-based to ambulatory-care settings for oncology services
- the potential lack of timely reimbursement for services and therapies of patients on clinical trials protocols.

Once the decision has been made to become involved in a clinical trials network, a number of key elements are needed for success. First, the program must have the data management services, personnel, record keeping, and computer systems necessary to identify and randomize potential candidates, as well as to monitor patient entrance onto clinical research protocols.

Interest and dedication by key oncology leadership are critical. There must be oncologist review of protocol efficacy and design as it pertains to the local health care environment. In addition, there must be Institutional Review Board (IRB) approval and protocol activation.

Finally, a skilled clinical research nursing team is required. In some institutions clinical nursing responsibilities are combined in the initial phases of program development. However, as the volume of patients and protocols increases and the program matures, more personnel will be needed to accomplish the dual tracks of clinical coordination and data management.

Table 3. Operational elements of cooperative group clinical trials

Biostatistical functions	Protocol design and monitoring
Data management functions	Randomization procedures and ongoing data monitoring
Disease specific committee functions	Protocol design and follow-up monitoring
Specialty specific functions (medical oncology, surgery, radiation oncology, hematology)	Involvement in virtually every aspect of the cooperative group
Community oncology member functions	Protocol design, monitoring, and accrual success for the group
Fiduciary group functions	Disbursement and monitoring of group and member funding
Ethics functions	Involvement of group member and patient advocacy groups with protocol design and monitoring

Table 4. Potential barriers for patient accrual to clinical trials

- Obtaining informed consent requires too much time and resources from a practice.
- Informed consent documents are too difficult and detailed to understand.
- Data management time and expense are prohibitive.
- The randomizing process is too cumbersome.
- There may be a philosophical aversion to the clinical trials process.
- There may be adverse effects on the doctor/patient relationship.
- The decision-making process of the physician may be affected.
- There may be adverse reimbursement policies by HCFA and third-party payors.

STRATEGIC VALUE OF CANCER CLINICAL RESEARCH IN CANCER PROGRAMS

University-based and NCI-designated comprehensive cancer centers have traditionally focused on research and education as their primary missions. In recent years, however, clinical services have become increasingly important because of the need for supplementing funding sources to support the primary missions of research and education. In community oncology programs where private practice-based oncologists and oncology groups form the backbone of the program, the principal mission has been one of clinical service. Research and education are secondary functions.

Health care market forces today continue the drive for cost containment and more cost-effective approaches to delivery of health care. The challenge for cancer care providers is to set the standards for quality care delivery. This is certainly apparent in oncology, where the multidisciplinary comprehensive and integrated approaches that have become the standard for cancer care in community and university settings are confronted with

budgetary constraints.

As the previous four articles in this series have addressed, there are a number of critical elements in successful cancer program development. These elements, which include organization, programs, and financial strength, are the determinants of ultimate success or failure.

Most oncologists and cancer program administrators acknowledge that it is increasingly difficult, from a financial perspective, to justify nonrevenue-producing program functions in a practice or in a hospital-based cancer program. Given this reality, our challenge will be to find added value for our patients and the community in the clinical trials research programs. Certainly this will involve less costly and more "user-friendly" protocol development.

As we probe and unravel the mysteries of the human genome and understand the complexities of prevention, early detection, and treatment of cancer, clinical research will be the critical element in forging application of these new frontiers. Clinical trials cancer research is a critical component in state-of-the art therapies. Future clinical trials in prevention, early detection, and screening programs will become of increasing importance for our patients and families. More than 80 percent of all patients with cancer in the United States are cared for and treated in community settings. It is a critical challenge for all of us to ensure that in this area of evolving cost containment and health care reform, we do not lose access for our patients and families to state-of-the-art care.

The danger, of course, is that with a decreasing federal emphasis on funding support (coupled with increasing pressures on cost containment in our community hospitals and community group practices), the infrastructure necessary for clinical trials research will be diminished or lost completely. Without continued emphasis and support of clinical trials research for cancer in this country, we are in danger of losing a major resource for all of our cancer patients and their families.

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