Clinical Research by Community Oncologists

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ABSTRACT Practicing and hospital-based community oncologists are increasingly recognized as sources for clinical research activity. Although surveys have documented patients’ and physicians’ willingness to consider participation in clinical research studies, accrual to clinical trials by adults in cancer research studies remains embarrassingly low. This may be due in part to a lack of knowledge about available studies by community oncologists, a lack of time or interest, or a lack of resources to support the cost of performing clinical trials. This article addresses these issues as an instructional module for community physicians interested in increasing their activity in clinical trials or improving their abilities to facilitate patient accrual to cancer research studies. (CA Cancer J Clin 2003;53:73-81.) © American Cancer Society, 2003.

INTRODUCTION

A major mechanism to facilitate involvement of community physicians is the Cooperative Group Outreach Program (CGOP), which was established in 1977. As initially conceived, any oncologist could accrue to Cooperative Group studies by affiliating with a main institution of the group. This system does not require a specific target for accruals to any particular study type (e.g., prevention, treatment, etc.), but does require a minimum number of accruals per year to remain active as a group affiliate. Since data management for affiliates is still the primary responsibility of the main institution, reimbursement for the cost of patient accrual and data collection at the affiliate has been variable and often not enough to cover the cost of participation in clinical trials.1,2,3,4

The National Cancer Institute (NCI) recognized the opportunity for increased involvement of cancer specialists in clinical trials accrual with the initiation of the Community Clinical Oncology Program (CCOP) in 1983.1 In this program, community hospitals may compete for independent funding to support their clinical trials program through a recognized research base such as the Eastern Cooperative Oncology Group (ECOG), Southwest Oncology Group (SWOG), Cancer and Leukemia Group B (CALGB), etc. This model of grant support for research by community investigators has been highly successful, quelling the doubters who believed that research belonged only in the arena of academic institutions.1,2,3 Practicing physicians proved to be eager and capable participants in cancer clinical trials, providing useful data quality, appropriate adherence to eligibility criteria, effective observance of treatment protocols, and successful long-term follow-up. However, the number of physicians who could contribute to studies through...
CCOPs is still limited. Participating physicians must be affiliated with a hospital (or group of hospitals/clinics) that can successfully compete for a grant requiring documentation of the ability to accrue substantial numbers of patients to both treatment and prevention cancer research studies.1

The Clinical Trials Support Unit (CTSU) is a new program designed to broaden the base of community clinical investigators. After registering online (www.ctsu.org), individual oncologists who do not have any CCOP or CGOP affiliation can participate in high-priority cooperative group studies. The CTSU mechanism also offers the option of using a central Institutional Review Board (IRB) to facilitate use in community hospitals. A reasonable reimbursement is provided for each patient accrued to help defray administrative costs of the treating oncologist.

The CCOP and CGOP programs have been highly successful in promoting involvement by community physicians in cancer clinical trials. Currently, contributions by CCOP and CGOP participants represent about two-thirds of accrual to Phase III cooperative group studies.1 More importantly, practicing oncologists have become a valued part of the research team, providing input on everything from initial study design to data collection, follow-up issues, consent documents, etc. Identifying the “standard of care” is essential for clinical trials, especially as it relates to coverage of treatment-related costs for patient care by third party payers. This appreciation is the special contribution of practicing physicians during the development of new Phase III clinical studies.

THE CHALLENGE OF CLINICAL TRIALS FOR COMMUNITY INVESTIGATORS

Despite the promise of enhanced accrual to clinical trials by forging a partnership among community oncologists and academic physicians, the overall participation of adult cancer patients in research studies is still abysmal, involving only about three percent of newly diagnosed patients nationally. Accrual is somewhat better at programs that have a commitment to clinical trials such as those at academic institutions or CCOPs with one-third of eligible patients agreeing to participate. However, the involvement of adults in clinical trials is still far less than the 60 percent of pediatric patients who are recruited onto studies. Numerous surveys have explored the barriers to involvement, focusing both on patients and on the treating physicians. Patients profess the interest and desire to participate in trials, if only they knew beforehand about available studies! Physicians claim that the cost of doing studies is not primarily a limiting factor, since they recognize the importance of clinical trials and wish to contribute. So what’s the problem?

It is likely that surveys which ask simple questions about patient and physician attitudes do not reflect the true difficulties in matching patients with appropriate clinical trials. On a superficial level, patients may be enthusiastic about the altruistic concept of helping to find a “cure” for cancer. They may expect “research studies” to provide a treatment that is “better” than the current standard of care. Patients who are evaluated at academic centers may be self-selected and more receptive to the possibility of entering a clinical trial, but many patients at community hospitals are less sophisticated and do not expect to hear a discussion about “research” from the oncologist at their local hospital. Coupled with occasional “negative” media reports about the motivation of physicians performing clinical trials, patients may become very skeptical about participation (Table 1). However, despite some initial reluctance to agree to randomization, patients who are properly educated and counseled may subsequently agree to participate.

Another subset of patients is far more
sophisticated, often identifying potential clinical trial opportunities on the Internet even before their first encounter with a cancer specialist. These patients may already have formed an opinion that one particular study offers better treatment than another. They may be disappointed that the choice of studies at one institution is limited, and that they may not be able to simply enroll in any study that piques their interest. Reading lengthy consent forms may further disillusion prospective participants, especially if the study design introduces concepts such as randomization, placebos, etc., which may not be fully understood after the initial description of these procedures by their physician or the research assistant. Therefore, although patients ideally express enthusiasm about clinical trials, their interest is often tempered after an enlightened discussion with the oncologist.

Physicians themselves may also have a naive view on clinical trials. Although during surveys many oncologists express interest in participation, few actually accrue patients. The rolls of potential affiliated CGOP investigators within cooperative groups are large, but 80 percent of patients enrolled from community hospitals are entered by only 10 percent of active investigators. Not infrequently, a single institution will have one or two effective contributors and several others who rarely accrue patients even though the resources for those physicians (nurses, study coordinators, protocol availability, reimbursement opportunities, etc.) should be equivalent. The difference may then reflect the comfort level or skill of the physician in imparting the importance, value, and benefits of clinical trial participation to their patients.

THE COST OF PERFORMING CLINICAL TRIALS RESEARCH

Most oncologists deny that financial incentives are the primary motivation in the decision to participate in clinical trials. Nevertheless, inadequate reimbursement for costs of trials certainly creates a barrier to participation, either directly or indirectly (Table 2). The availability of a dedicated research nurse or (certified) research associate (CRA) is essential. Effective data management cannot be performed by secretarial or office staff who are not properly trained. Therefore, the commitment to clinical trials research involves a commitment to expand the office (hospital) payroll to facilitate the research study. The role of the CRA may also include: completing exhaustive paperwork related to IRB requirements; assuring that test procedures are performed on schedule; monitoring test results for appropriate treatment adjustments; reviewing physician notes to assure proper documentation of responses or side effects, etc. Even when the assigned study treatment is “standard of care,” the complexity of caring for a patient “on study” may be much more time consuming (and therefore “costly”) for the treating physician than caring for similar patients not on study. The overall work efficiency of oncologists caring for patients on clinical trials may decrease if “the protocol” must be consulted each time a dose adjustment is required or to ensure compliance with recommended testing parameters rather than

| TABLE 1                                      |
|-----------------------------------------------|
| Patients’ Concerns Regarding Clinical Trials   |
| • Getting an “inferior” treatment.            |
| • Excess tests.                               |
| • Uncertain/unknown side effects of the “experimental” arm. |
| • Randomization: getting “placebo.”            |
| • Investigator motivation: being a “guinea pig.” |
| • Costs not covered by insurance.             |
| • Overwhelming information/consent form.      |
| • Lack of flexibility in treatment schedule.  |
| • Travel distance to a “treatment center.”    |
simply using “good judgment” to address those issues.

Other hidden costs might include office overhead such as workspace, computer services, telephone, fax, etc., and secretarial support. Some studies might require test procedures that cannot be billed to third party payers because they relate purely to a research question rather than being standard of care. For example, the cost of a second radiographic study performed one month after achieving remission, simply to document stability of the response, should be covered by the study sponsor. Claims that might be rejected by insurance must be anticipated in advance and paid by a separate accounting system through the clinical trials budget.

It is difficult to get reliable estimates for acceptable workloads for CRAs. The Society of Clinical Research Associates (SoCRA) estimates that one CRA could effectively manage approximately 30 new patient accruals per year. However, as a program matures, the increased workload due to follow-up reporting requirements on previously treated patients may significantly alter the equation. In addition, the number of new patient accruals may not always accurately reflect the work of the CRAs who must check participant eligibility, test results, informed consent, and other items for all potential study patients regardless of whether they ultimately agree to participate or not.

Figure 1 shows the number of patients who were evaluated for inclusion in clinical trials at Greater Baltimore Medical Center (GBMC) and the number of patients actually accrued, grouped in six-month intervals from 1997 through 2001. There is significant variation in activity by physicians, nurses, CRAs, and support staff in any time period. The fluctuation is due in part to differences in the number of studies available for common malignancies and physician enthusiasm for those studies.

The physician encounter with a potential candidate for a clinical trial is very time consuming. The additional time could total four hours. To practicing physicians in the community, this extra time (which is now unavailable for seeing other patients who ultimately help cover the overhead costs of office expenses) represents a cost as well. Although personal remuneration for time spent may not be a requirement by most physicians participating in clinical trials, the reimbursement should at least cover expenses (Table 3). The NCI has estimated that the cost of performing government-sponsored clinical trials averages approximately $3,000/patient (ranging from

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**TABLE 2**

Costs Associated with Clinical Trials by Community Physicians

| Personnel                      |
|-------------------------------|
| Nurse, Certified Research Associate (CRA). |
| Secretarial.                  |
| Pharmacist services.          |

| Office Overhead               |
|-------------------------------|
| Workspace.                    |
| Computer access.              |
| Phone, fax, mail, etc.        |

| Physician Time                |
|-------------------------------|
| Review of study feasibility.  |
| Institutional Review Board (IRB) involvement. |
| Discussions with patient.     |
| Assuring compliance with protocol parameters. |

| Meeting Time                  |
|-------------------------------|
| Loss of productivity.         |
| Physicians, Nurses, CRA.      |
| Travel expenses.              |

| Often overlooked expenses/time. |
|--------------------------------|
| Assessing insurance issues.    |
| Paying for non-covered protocol requirements. |
| IRB fees.                      |
| Audits.                        |
| Chart storage fees.            |
| Legal advice for contracts with study sponsor. |

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$600 to $5,000). While studies initiated by pharmaceutical companies usually provide reimbursements that meet or exceed the cost of performing such trials, the more challenging and scientifically important cooperative group trials often do not. Oncologists are therefore forced to choose whether to participate in clinical trials based on the amount of reimbursement by the study sponsor, even though payment for study involvement may be a low priority for them overall.

At GBMC in 2001, the clinical trials budget was $330,000. Our mature clinical trials program had 60 active studies, accrued 125 patients to various studies, and had five full-time non-physician staff members. The revenues obtained from various contracts and research affiliations in 2001 were $330,000. Therefore, although a financial commitment would be required for a new program (perhaps for two to three years), it is likely that with good management, clinical trials can eventually become available to patients in community hospitals with no additional expenses to the sponsoring institutions.

### Oncologists Benefit from Performing Clinical Trials

Although cancer physicians may incur costs because of clinical trials activity (both real expenses and the “cost” of time spent without additional remuneration), the benefits are also considerable. Oncologists performing clinical trials will be more aware of current treatment options and available experimental therapeutics. Participation in national group meetings with ECOG, SWOG, CALGB, etc., represents an excellent source of continuing med-
-ical education. Furthermore, the personal interaction among community oncologists and experts in the field enhances the opportunity for subsequent consultations with world-renowned physicians via phone or e-mail in a judicious manner. With their enhanced knowledge and “connections,” local oncologists may then become a resource to both patients and other physicians as a “second opinion” in the community. Their expertise may be recognized regionally and could justify a part-time faculty appointment at an academic center, which may further enhance their credentials. More importantly, participation in clinical trials provides specialists with the self-satisfaction that they are contributing to a body of knowledge that every oncologist needs to continue providing patients with the best possible care. Expressed in that way, oncologists should feel a moral obligation to donate some of their time to clinical trials.

The main beneficiaries are our patients. At GBMC, we offered paclitaxel to our ovarian and breast cancer patients two years before it was approved by the Food and Drug Administration (FDA). Dozens of other therapies have been available to our patients subsequently, including monoclonal antibodies, radiopharmaceuticals, growth factors, pegylated compounds, biologic response modifiers, Phase I agents, targeted small molecules, novel antiemetics, antisense compounds, hormonal agents, prevention strategies, cancer vaccines and angiogenesis inhibitors. These new therapies provided treatment interventions for patients who had little hope with their advanced or aggressive malignancies. As these agents gain FDA approval, the physicians who have used them in clinical trials become a resource to area oncologists.

Another useful benefit of physician involvement in clinical trials is the carryover to nursing services. Our nurses share the desire for excellence, and have participated in nursing clinical trials directed at patient support, symptom control, quality of life, etc., resulting in regional and national recognition for our nurses and enhanced care for our cancer patients.

**TALKING POINTS FOR PATIENTS**

Physicians must budget additional time for patients who may be candidates for clinical trials. The discussion should begin with a conceptual framework about “Here’s where we are today,” for treating the malignancy in question. This discussion involves a historical approach to “Here’s what has changed in our treatment over the past 10 to 20 years.” The inference is that we have improved the treatment (survival?) over that time period because of the lessons learned from previous clinical trials. Now, “Here’s where we need to go,” is a natural evolution of the process of

| TABLE 3
Institutional Compensation for Clinical Trials Activity | Per Patient* |
|--------------------------------------------------|--------------|
| **Cooperative Groups**                            |              |
| ECOG, RTOG, NSABP, GOG                           | $1,000 - $2,400 |
| **Pharmaceutical Studies**                        |              |
| Post marketing                                   | $500 - $2,000 |
| Phase III                                       | $2,500 - $8,000 |
| Phase I/II                                      | $6,000 - >$20,000 |
| **Other**                                        |              |
| Nursing studies                                  | none/grants  |
| Quality of life                                  | none         |
| Tissue bank/genetics                             | none/variable |
| Compassionate use                                | none         |
| Investigator initiated                           | none/grants  |

*Values based on Greater Baltimore Medical Center (GBMC) experience.
ECOG = Eastern Cooperative Oncology Group.
RTOG = Radiation Therapy Oncology Group.
NSABP = National Surgical Adjuvant Breast and Bowel Project.
GOG = Gynecologic Oncology Group.
scientific discovery, which will lead us to even better results. We need the participation of our patients to realize the promise of improved treatments for cancer. Some will participate because of the unselfish desire to be helpful, some out of fear that friends or relatives may get the same disease and can benefit from knowledge gained in the future. Some patients will refuse for their own stated or private reasons (Table 1). Such barriers to patient participation have been well described elsewhere and will not be further reviewed here. However, it is clear that while some patients will have a failure of trust, which limits their desire to participate,15 others who eagerly seek involvement in clinical trials will be deemed ineligible because of rigid study entry criteria.3,5,6

Many physicians feel insecure about recommending studies that involve randomization or placebos.3,5,6,11,12 Although they might have had similar discussions with patients during their fellowships at academic institutions, those patients may have been self-selected and more receptive to participation in such studies. In choosing to participate in a clinical trial, the oncologist must first be certain that he/she believes in the integrity of the science, the feasibility of the treatment program, and the benefit for patients. A reasonable “test” is for the investigator to ask himself/herself whether he/she would be personally willing to participate in the study if the tables were reversed and he/she was the patient? The answer to that question must be “yes.” When the patient finally asks, “What would you do if you were me?” the physician must be honestly able to answer, “I would be enrolling myself into this study!” If that is not an honest answer, patients will likely identify hesitation in the physician’s reply, and the trust between physician and patient could be unalterably affected.

ECOG 1594 is a good example of a Phase III randomized clinical trial involving four seemingly disparate treatment regimens.20 This well known study compared four different treatments for lung cancer: paclitaxel/cisplatin, gemcitabine/cisplatin, docetaxel/cisplatin, and paclitaxel/carboplatin. In order to participate in this clinical trial, the investigator must earnestly believe that each of the four study regimens truly has potential effectiveness and acceptable toxicity. One treatment arm uses paclitaxel given over 24 hours, although this schedule was no longer “standard” by the mid-1990s and was occasionally rejected by insurance companies. Was the 75 mg dose of docetaxel too low for lung cancer treatment? Was 225 mg of paclitaxel too much? Was three weekly doses of 1,000 mg of gemcitabine too myelotoxic? What was the comfort level with 75 or 100 mg of cisplatin in various arms? Finally, the treatment cycle could be every three weeks or every four, depending on the arm assigned, and might involve treatment three weeks out of four, one week out of three, or hospitalization for 24 hours.
A full discussion about this protocol could quickly swamp the patient with confusion. If the investigator truly believes in the potential equivalency of these treatment arms, the discussion should focus instead on the similarities (Table 4). All of these regimens have proven effectiveness in lung cancer. If there is no response, we can still consider second-line therapy.

After the discussion, which should only broadly review the various experimental treatment arms, the patient should be given the consent form, introduced personally to a research nurse or CRA, asked to take the consent form home to read, and asked to communicate any further questions with the nurse or physician. The CRA can then review the chart for eligibility and recommend any further tests required before starting the study.

A second example is NSABP B-33 for women who have completed five years of adjuvant tamoxifen for breast cancer, and involves randomization to two years of exemestane or placebo. Although the use of “placebo” might disturb some patients, this is an important study, and the placebo-based concept is essential for scientific integrity. Talking points are outlined in Table 5.

### TABLE 5

**Discussion Points for Patients: National Surgical Adjuvant Breast and Bowel Project (NSABP) B-33**

*Exemestane versus placebo after five years adjuvant tamoxifen*

- There is no role for continuing tamoxifen beyond five years.
- The standard of care is “observation” alone.
- There is still some risk of relapse, even after five years.
- In the event of relapse, therapy would likely involve another hormone, such as an aromatase inhibitor.
- Exemestane has little or no toxicity; some patients note arthralgias.
- Osteoporosis may actually be improved by exemestane, but this is not yet certain; osteoporosis can be monitored and treated with medication if needed.
- The medications are provided free; no additional tests or visits beyond the customary follow-ups.

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A mature clinical trials program can offer numerous opportunities for patients and physicians, including interesting new compounds prior to FDA approval. However, such community programs have a high level of complexity coupled with organizational components that rival that of the CCOPs that are funded separately by federal grants. Although achievable, large programs should develop gradually. Here are some guidelines for starting a clinical trials program:

- Begin with no more than four or five Phase III studies that are directed at common malignancies, and which are endorsed by several associated physicians. The effort should be led by one highly committed physician. The endorsement of respected local surgeons is critical.10,13
- Choose studies that have clinical/scientific importance and which will accrue well.
- Employ a dedicated oncology nurse or CRA on a full or part-time basis, but do not divide his or her duties among other office activities.
- Consider participating in a pharmaceutical “Phase IV study” (post-marketing) or Quality of Life/Supportive Care study to get started. These studies are useful to prime the staff for patient eligibility questions, data collection, IRB issues, etc.
- Check out the following Web sites for start-up help: www.clinicaltrials.gov, www.trialcheck.org and www.ctsu.org.21
- Have fun!

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*Clinical Research by Community Oncologists*
FINAL THOUGHTS

The number of new drugs available for cancer patients will continue to escalate through the next decade. Defining the proper combinations and sequences of therapeutics will require careful, well-designed, large randomized studies. The pharmaceutical industry now increasingly partners with community investigators in an effort to complete studies quickly and get the data necessary for FDA approval. However, even after approval, we often do not yet understand the best way to use many of these drugs. Testing various combinations is important, but will never be the primary focus of scientific investigations for our colleagues at academic institutions. Greater involvement in clinical trials by community physicians is an essential element of progress in our battle against cancer. We can win this war.

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