Challenges to National Cancer Institute–Supported Cooperative Group Clinical Trial Participation: An ASCO Survey of Cooperative Group Sites

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A necdotal evidence has accumulated that research sites, both academic and community based, are limiting their participation in National Cancer Institute (NCI)–funded cooperative group clinical trials. On the basis of the importance of clinical trials conducted by cooperative groups, ASCO was motivated to conduct a survey evaluating cooperative group site participation in clinical trials. NCI-funded clinical trials have made important contributions to current evidence-based guidelines, which in turn have influenced the practice of oncology. The growing focus on comparative-effectiveness research will make these trials even more influential as they address issues that have major impact on the field. A robust federally funded clinical trials infrastructure promotes the translation of basic scientific discoveries into clinical practice. The vast infrastructure of the cooperative groups facilitates access to trials in every community in which cancer care is delivered, promotes accrual to trials involving small populations and rare cancers, and often provides epidemiologic and biospecimen data, which may not be attainable through pharmaceutical industry–sponsored trials.

Cooperative group trials make invaluable contributions to the evidence base for cancer treatment because they include:

- Head-to-head trials studying comparative efficacy and quality-of-life outcomes of agents or combinations of agents with similar indications, which pharmaceutical sponsors may have no interest in studying
- Studies of rare cancers and small subpopulations
- Studies to expand evidence-based treatments using previously approved methods, which commercial sponsors may not wish to support
- International collaborations that facilitate trial accrual and population diversity
- Large-scale chemoprevention trials.

Practice-Changing Trials

Several cooperative groups have conducted head-to-head trials that not only determine the comparative efficacy of treatments but also evaluate quality-of-life issues and survivorship outcomes. For example, an Eastern Cooperative Oncology Group trial studying advanced non–small-cell lung cancer compared survival and quality-of-life outcomes between two chemotherapy regimens. Because one arm experienced less toxicity and

equal efficaciousness, this trial led to a practice-changing outcome.¹ Head-to-head trials like this are unlikely to be conducted by industry.

Cooperative groups also conduct trials of diseases and agents that may otherwise go unstudied. The cooperative group infrastructure promotes funding and adequate accrual for studies that affect small cohorts of individuals, a need that is intensifying as treatments increasingly target highly characterized molecular subpopulations. In addition, important correlative studies enhance these efforts and increase the knowledge gained from such studies. Cooperative groups conducted such a study in patients with rare cancers with a phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma.² The chemotherapy plus radiation arm had better progression-free survival but more toxicity. The trial included chromosomal analysis resulting in the discovery that missing chromosomal arms 1p and 19q are strong predictors of response to therapy compared with tumors with only one or neither of the lost alleles.² This finding has defined a new prognostic indicator, allowing physicians to more accurately predict response to therapy. Because of limited return on financial investment, the pharmaceutical industry is less likely to fund studies like this outside of federal partnerships.

The cooperative group network also makes it possible to accrue highly specific subpopulations. Women with human epidermal growth factor receptor 2–positive breast cancer represent only 25% of women diagnosed with breast cancer. Cooperative group trials evaluated the effectiveness of adjuvant trastuzumab (Herceptin; Genentech, South San Francisco, CA) after standard treatment in women with human epidermal growth factor receptor 2–positive breast cancer. Women with tumors that expressed the receptor who received trastuzumab had a 52% lower risk of recurrence.^{3,4} The extensive cooperative group outreach and infrastructure facilitated the conducting of this trial in this narrow subset of patients.

By studying additional uses of US Food and Drug Administration–approved agents, cooperative groups have also greatly increased evidence-based therapeutic options for individuals with other cancers. NCI Cooperative Group trials expanded indications for treatment with imatinib mesylate (Gleevec; Novartis, East Hanover, NJ) beyond patients with Philadelphia chromosome–positive chronic myelogenous leukemia to in-

clude patients with gastrointestinal stromal tumors.⁵ Oral therapy with imatinib mesylate for 1 year after surgical removal of the tumor prevented recurrence in 98% of study patients at 1 year.⁶ Imatinib mesylate is now the standard of care in patients with gastrointestinal stromal tumors.

Cooperative group trials are also expanding evidence-based uses of bevacizumab (Avastin; Genentech), a targeted therapy that inhibits the action of vascular endothelial growth factor. Bevacizumab was originally approved by the US Food and Drug Administration for treatment of metastatic colorectal cancer based on industry-sponsored phase III studies.⁷ Cooperative groups have since conducted numerous trials to expand the clinical use of this agent, including evaluating its use in renal cell carcinoma and cancers of the breast, lung, pancreas, and ovaries.⁸ It is important to note that outcomes from some of these NCI-supported trials did not support expanded use of the agent for all of these indications.

In addition to studies performed in the United States and Canada, cooperative groups have also developed international partnerships and collaborations. A cooperative group trial studying glioblastoma was able to accrue 1,174 patients as a result of the joint efforts of the Radiation Therapy Oncology Group and the European Organisation for Research and Treatment of Cancer. The trial is currently closed to accrual and undergoing data analysis. Joint efforts like this one make trials accessible across continents and decrease the length of time it takes to meet accrual targets.

In addition to treatment trials, cooperative groups successfully completed the first chemoprevention trials, ushering in a new era in cancer prevention and research. The Breast Cancer Prevention Trial was offered at more than 300 sites throughout the United States and Canada and successfully accrued 13,388 women.⁹ The primary outcome of the trial was to determine whether the drug tamoxifen (Nolvadex; AstraZeneca, Wilmington, DE) could prevent breast cancer in a high-risk population. The follow-up cooperative group trial STAR (Study of Tamoxifen and Raloxifene) rapidly enrolled 19,747 women and compared the effects of these two drugs in the prevention setting.^{10,11} This trial confirmed that these agents are equally efficacious in preventing estrogen receptor–positive breast cancers and defined their respective toxicities. These trials are a testament to the vast network established by cooperative groups and their ability to adapt quickly to new trial designs.

A 1999 ASCO survey of clinical trial participation reported strong support of federally funded clinical trials by oncologists, because these trials were perceived to be nonbiased, were peer reviewed, and often resulted in outcomes with the potential to change clinical practice and transform standard care.¹² Research indicates that the actual cost of conducting trials is much higher than the established per-case rate of \$2,000.^{13,14} We hypothesized that per-case reimbursement was an influential factor limiting site participation.

Methods

ASCO authors contacted the headquarters of each NCI-funded US and Canadian cooperative group and asked each office to

forward a participation request to all group members. From August 10, 2009, to September 3, 2009, a representative of each research site was asked to complete a survey via an Internet-based tool. Sites belonging to multiple cooperative groups may have received several links to the tool, but they were asked to complete only one response per site. When multiple responses from the same site were identified, the site was contacted by the ASCO authors, and the response was corrected in an attempt to ensure no overlap or duplication. Respondents were asked to classify themselves according to the following site types: academic medical center, nonacademic hospital, private practice, and other. A small number of respondents indicated they were outside the United States and Canada.

Results

Five hundred sixty-six sites initiated the survey, and 509 complete responses were received. In 2008, approximately 1,800 research sites in the United States enrolled patients onto cooperative group trials.¹⁵ Assuming that every center enrolling patients onto cooperative group trials received a link to the survey, the response rate was slightly more than 25%. Sites classified themselves as follows: 207 (41%), academic medical center; 141 (28%), nonacademic hospital; 78 (15%), private practice; and 19 (4%), other. Sixty-four (13%) did not identify a site type.

Of the 509 sites, 168 (33%) were planning to limit participation in NCI-funded cooperative group trials (Fig 1). The reduced participation would include limits on total number of patients accrued, number of trials open, and number of cooperative group affiliations. An additional 44 sites (9%) were considering—but had not yet decided on—implementation of these limits.

Sites planning to limit participation (Fig 2) were asked to indicate the reason for their decision; choices included insufficient staffing, insufficient NCI per-case reimbursement, and other (which allowed free-text entry). Sites were permitted to select as many of these reasons as appropriate. One hundred twenty-six sites (75%) selected insufficient NCI per-case reimbursement as a reason for their decision; 40 selected per-case reimbursement as the sole reason for limiting participation, whereas 86 sites selected per-case reimbursement along with at least one other reason. An additional 42 sites (25%) limiting participation selected only insufficient staffing or other or selected both staffing and other as the determining influence. Respondents provided free-text comments indicating other rea-

Figure 1. Sites planning or considering limitations in cooperative group trial participation.

Figure 2. Reasons for limiting participation in cooperative group trials.

Figure 3. Increasing industry participation.

sons for limiting participation, which included the following: NCI grant mechanisms provided greater financial incentives for investigator-initiated trials as opposed to cooperative group trials; accrual was capped by community clinical oncology program remuneration and not by patient availability; insufficient funding from reimbursement to support staff salaries; and cancer center leaders placed less emphasis on the importance of cooperative group trials compared with other studies.

Responding sites were also asked about their plans regarding participation in industry-funded trials (Fig 3). Of the 168 sites limiting cooperative group participation, 65 (39%) acknowledged plans to increase participation in industry-sponsored trials. Free-text responses regarding industry-funded trials revealed site loyalty to cooperative group trials, indicating that investigators found the NCI trials more scientifically compelling and less resource intensive compared with industry-funded trials.

There are some known limitations to the survey. The number of recipients who received the survey is unknown, but (as noted above) we believe the response rate to be slightly higher than 25%. It is also unclear whether the 509 responses are truly representative of all cooperative group sites, because recipients were informed of the intent to use the survey outcomes to motivate policy change, which may have created a response bias.

Discussion

NCI-supported cooperative group trials have produced many practice-changing studies, which have resulted in the development

of practice-changing clinical guidelines. The infrastructure that supports these trials may be at risk as a result of sites limiting participation. It is important to acknowledge that the NCI and extramural research community are engaging in several initiatives to address challenges in the initiation, implementation, and conduct of clinical trials. However, we believe the NCI is underestimating the importance of adequate funding as a means of sustaining enrollment and participation in NCI-supported cooperative group trials. For example, funding for the cooperative group system has been virtually flat and declining since federal fiscal year 2003.¹⁶

The per-case reimbursement of \$2,000 has not increased in 10 years. Simply to meet basic inflation, the NCI would have to increase reimbursement to at least \$2,500.¹⁷ More importantly, studies indicate that this compensation is significantly below the cost of conducting clinical trials. An ASCO study¹³ published in 2003 and a C-Change study¹⁴ published in 2005 underscore the fact that the actual cost incurred by a site conducting a trial far exceeds NCI reimbursement. The average study cost per enrollee in publicly sponsored trials in the ASCO and C-Change studies was \$5,000 to \$6,000, indicating the NCI reimburses less than 50% of the actual cost incurred by sites. Although the NCI has created a mechanism to provide an additional \$1,000 for a limited number of complex trials, the amount is still insufficient and only affects a small percentage of studies.

On the basis of the number of participants enrolled onto therapeutic trials, the NCI devotes approximately \$60 million annually on the \$2,000 per-case reimbursement, representing only 1.2% of the NCI fiscal year 2009 budget of \$4.97 billion.¹⁸ Because clinical trials are responsible for translating basic science into evidence-based patient treatments, the NCI should reevaluate its commitment to clinical trials. If the NCI were to reimburse at the more realistic rate of \$6,000 per patient, tripling the current reimbursement amount, this would require an additional \$120 million, yet total funding would still account for only 3.6% of the NCI budget. Without a change in funding for clinical research, federally funded trials will remain underfunded and at risk.

This survey also noted that some sites are limiting participation in NCI-funded trials because of inadequate staffing. This issue is related to the inadequate per-case reimbursement and the inadequate funding received by sites to maintain internal operations to support research and regulatory personnel. It may also be related to the challenges sites experience in recruiting, training, and retaining research staff. In addition to reevaluating per-case reimbursement, the NCI should continue to adequately support research infrastructure and staff. Safe conduct of trials and collection of reliable data depend on trained re-

search staff. The NCI must be committed to this issue to ensure that quality research is maintained.

The cooperative group survey showed that 39% of respondents who indicated they are decreasing participation in NCI-supported clinical trials plan to increase participation in industry-funded trials. This signifies that sites remain committed to clinical trials but for previously stated reasons are limiting participation in federally funded trials. Anecdotal reports indicate that some sites see a necessity to increase industry trials to maintain the staffing, infrastructure, and equipment necessary to safely conduct trials and remain compliant with regulatory requirements. This shift away from federally funded trials could lead to fewer trials of diseases that affect small populations and fewer trials supported by independent sources of funding and could ultimately affect the quality of data guiding clinical practice.

As oncology treatments move into an era of highly characterized molecular subpopulations, the NCI Cooperative Group structure is an important network with the potential to accrue sufficient numbers of patients to trials. Although funding is not the only factor affecting whether sites participate in NCI-funded trials, the significant and growing disparity between actual research costs and the amount provided by the NCI to cover those costs serves as a significant deterrent. Without increased funds, the NCI will not be able to increase the number of trials, increase the number of participants enrolled onto trials, or maintain the current infrastructure to support the safe conduct of clinical trials. As outcomes of this survey indicate, failure to adequately reimburse research costs is jeopardizing the critical infrastructure enabling the conduct of cooperative group trials.

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