

THREE QUESTIONS ABOUT COSTS AND CANCER CLINICAL TRIALS

Thomas N. Chirikos, PhD

From the Department of Cancer Control at the H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida.

Introduction

The recent literature on cancer clinical trials has wrestled with three interrelated, yet distinct, questions about costs:

1. Do treatment costs increase significantly when cancer patients are enrolled on clinical trials and, by implication, should these extra costs be reimbursed by third-party payers?

2. Are the research-related costs of actually conducting clinical trials, especially costs arising from more complex and extensive workloads of clinical research coordinators (CRCs), rising rapidly over time and, by implication, are funds provided by sponsors keeping appropriate pace with these work demands?

3. Should treatment costs be incorporated as endpoints in cancer clinical trials and, thus, should trials appraise the cost effectiveness as well as the efficacy of new therapeutic options?

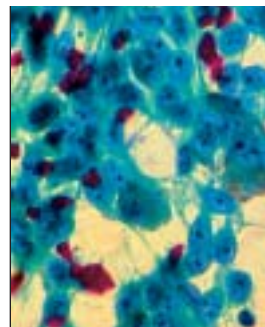
Although typically taken up in separate fashion, these questions have many common elements, particularly when viewed from the economic perspective of how cancer care is valued and financed. The incremental cost of novel therapy relative to standard care is of central importance in appraising the economic worth of a new cancer treatment; it would be the main constituent element of the numerator term in any cost-effectiveness analysis of that therapy. Incorporating cost-effectiveness

analysis in trials provides a means of valuing the economic impact of new therapies in a timely manner, thus ensuring that they pass economic muster before being widely diffused throughout clinical practice. In so doing, cost-effectiveness analysis also provides critical data on whether trial enrollees warrant higher reimbursements from third-party payers because, among others, it forces more precise accounting of standard and protocol-driven treatment patterns. In contrast, the research costs of conducting a trial, especially the costs of the infrastructure needed to test or document the effects of a new therapy, do *not* figure into the economic worth of that therapy; in principle, these research-related costs would be *excluded* from cost-effectiveness analysis numerator terms and calculations of the incremental cost of patient care between trial enrollees and non-enrollees. Nonetheless, research infrastructure costs are important because they influence the level of funding, a key determinant of whether trials are conducted and/or what analytic and data components they encompass, including cost endpoints themselves.

Given the interrelationships, the juxtaposition of brief reviews of these three strands of the recent literature may yield worthwhile insights. This is the primary goal of the present article. I first examine the empirical studies that have been carried out over the past 3 to 4 years to test whether the incremental or extra cost of enrolling patients on clinical trials is zero. Then I examine the somewhat

Oncology practice and economic realities are inexorably linked today. Developments in cancer economics are explored in this feature.

No significant relationship exists between the author and the companies/organizations whose products or services may be referenced in this article.



more meager empirical evidence on the research costs of trials, focusing particularly on recent studies of the workloads of CRCs at different investigative sites. Finally, I review some recent papers on cost endpoints in trials, mostly methodological work that evaluates how best to collect good cost data in trials. In order to appraise the relative economic importance of these interrelated issues, I make several rough, back-of-the-envelope estimates of the costs of patient care and research-related infrastructure in cancer trials at present. The final section draws some general inferences from the review on future research priorities.

Patient Care Costs in Cancer Clinical Trials

There is little reason to suppose that the incremental cost of patient care in treatment trials is zero, even when by convention the cost of the investigational drug or procedure is netted out. Novel therapies may be cost *saving* or cost *augmenting*, and a cost-effectiveness analysis of the new therapy would turn on whether, if cost saving, it was as effective as the standard therapy or whether, if cost augmenting, effectiveness increased commensurately with costs. Recent studies on differences between the costs of enrolled and non-enrolled patients have not tested whether costs are lower or higher in this sense; rather they have focused on the hypothesis that the cost streams of enrolled patients and comparable but non-enrolled patients are equal, irrespective of the net effec-

tiveness of the experimental therapy. Failure to reject this null hypothesis has important policy implications, especially with respect to insurance coverage for patients enrolled on trials. As it happens, available US studies have indeed failed to reject the null hypothesis, ie, they have generally found that the marginal cost of patient care attributable to trial enrollment to be statistically indistinguishable from zero. This literature subset includes several small-scale analyses presented mostly at scientific meetings and four peer-reviewed articles published more recently. The early papers, which were stimulated by a Government Accounting Office analysis suggesting that cancer clinical trials added approximately 25% to the costs of care, are reviewed elsewhere.^{1,2} The four peer-reviewed papers³⁻⁶ are the central focus here.

Each of these four studies used a similar analytic approach or framework. Cumulative cost data were generated on two ostensibly comparable groups of cancer patients, one enrolled on a treatment trial (cases) and the other not enrolled (controls). Then, these cumulative cost streams were compared by statistical means to test the maintained (null) hypothesis that case costs are equal to controls. The studies differed in respect to the delineation and composition of the case/control groups. Case groups were made up mostly of patients with common cancers enrolled in a variety of different types of phase II and phase III treatment trials, though one study³ limited cases just to patients enrolled only on chemotherapy tri-

als and three studies were limited to cases enrolled only at one center or site. In contrast, the control groups differed in several important respects. Three studies used direct matching, but the matching criteria varied from just a few demographic and disease characteristics alone to demographic, disease, and trial eligibility characteristics generated from medical chart review. The fourth study used regression methods to control for a large set of covariates between cases and what is tantamount to the average non-enrolled patient with a given type of cancer.⁶ What is most important here is that the studies using direct matching encountered serious difficulties in finding appropriate comparison subjects and thereby had very small sample sizes: the mean across the three studies was just 75 matched pairs per study. (The study using regression methods had much larger numbers of observations to analyze, eg, more than 1,000 women with breast and more than 600 patients with lung cancer.) The four studies also differed in terms of cost ascertainment and the length of follow-up. In most, costs encompassed just direct medical care provided at the site or center, though one attempted to measure the costs of care patients received in the community after treatment, or at least as much of that care as was available in a community claims database.³ Two studies followed patient costs for upwards of 4 to 5 years, while the other two tracked cost streams for only 6 to 12 months.

Despite these differences in detail, the results yielded by these studies were quite similar. Three of

them produced reasonably convincing evidence that the cost streams generated by patient groups enrolled in cancer clinical trials did not differ significantly from the comparison groups. The exceptional study⁴ detected higher costs for cases than controls, but this differential was attributable entirely to higher chemotherapy costs for trial enrollees; moreover, the difference shows up over a relatively short follow-up period of 1 year. Since the two studies with the longest follow-up periods found equal costs between groups, extending follow-up time might negate the exceptional finding. The convergent evidence of the entire set of empirical studies is thus that costs do not differ significantly between groups.

Notwithstanding the formal tests of statistical significance, the mean differential between case and comparison groups tended in magnitude to be just small percentages of cumulative costs at each of the benchmark time points. Even the differential that was statistically significant was only on the order of 10% of the cumulative cost at 1 year — the equivalent of approximately \$1,975 in (inflation-adjusted) 2001 dollars. (Note: All dollar amounts presented in this review have been inflation-adjusted to the year 2001 by means of the All Items Consumer Price Index or, where appropriate, the Medical Care component of that Index.) The two studies with longer follow-up periods found differences of only 1% to 2% of cumulative costs. To generalize these findings, the cumulative costs of early-stage breast and lung cancer patients at 5 years was

gauged by a recent US analysis⁷ to be (in inflation-adjusted terms) on the order of \$35,000 and \$60,000, respectively. The proportional differences observed in the longer-term studies of 1% to 2% would thus translate into rough amounts of \$350 to \$700 for breast and \$600 to \$1,200 for these longer-run survivors of lung cancer. All things considered, these are not appreciable amounts, certainly not as large as those sometimes presented in the popular press.

Yet, because of lingering concerns about sample size and various other selection and censoring biases in the findings of available studies, the National Cancer Institute (NCI) has sponsored a larger, more extensive study of patient costs attributable to clinical trial enrollment.⁸ The Cost of Cancer Treatment Study (CCTS) is being conducted at the present time by the RAND Corporation. Its main design features highlight the gaps in the current literature that it hopes to overcome. It is a nationally representative study based on a large sample of institutions involved in cancer trial research. The CCTS has enrolled 1,500 cancer patients from a broad cross-section of trials and institutions around the country, including academic health centers and community providers. It is using a retrospective cohort design, with patients accrued to NCI-sponsored trials in 1998 asked to participate roughly 1 year after their trial enrollment. The study will gauge the costs of all health-care utilization of this cohort. Similar data will be collected from a comparable group of cancer

patients — patients who presumptively meet the eligibility criteria for a given trial but who did not enroll in it. In each case, a combination of billing records, medical charts, and information obtained from interview surveys will be used to estimate and then compare the cost streams of these two groups, each in turn subdivided between academic and community health centers. The RAND research team intends to minimize the impact of the preference for trial participation by assessing characteristics that might account for them, eg, measured differences in “locus of control” scores, and then adjust for these differences in multivariate statistical analysis. The data collection phase of the CCTS is now complete, and initial results are expected shortly (D. Goldman, Principal Investigator of the CCTS, personal communication, 2002).

Research-Related Costs of Conducting Cancer Clinical Trials

From the perspective of sponsors and administrators at investigative sites, the trial-related costs of accruing and registering patients as well as of managing and analyzing data may be more important than the routine costs of treating those patients per se. Yet, the cost of the research infrastructure needed to conduct clinical trials has not been studied extensively or comprehensively in the recent literature. Available studies, while valuable, have examined only selected aspects or determinants of these infrastructure/administrative costs, often in

isolation from other factors that drive the overall expense of trials.

A recent study of the costs of conducting a phase II lung cancer trial is a case in point.⁹ The aim of the investigators was to measure the costs of two phase II chemotherapy trials for small-cell lung cancer comparing docetaxel or gemcitabine to standard therapy (etoposide-cisplatin), including the costs of data management. In regard to these data-related costs, the investigators obtained estimates from a small number of data managers of the time they spent carrying out various tasks, especially the time involved in study activation. The investigators then used the medians of these time distributions and mean hourly wage rates of relevant personnel to estimate the monetary costs of data management. Although retrospective in nature, this method of estimating costs is acceptable, provided that the inventory of tasks is sufficiently inclusive or representative of the research-related work to be costed-out. Regrettably, this study failed to account completely for data-related work, omitting tasks related to adverse event reporting as well as those carried out by the central office. Moreover, it omitted overhead costs and failed to gauge cost variations in standard therapy fully. Thus, the conclusion that data management costs are between 13% and 21% of the total patient care costs of the two arms of the study is not easily interpreted.⁹ These estimates, which translate into (inflation-adjusted US \$) amounts of approximately \$180 to \$215 per enrolled patient must be

considered a lower bound on estimates of data management costs in chemotherapy trials.

Several studies have focused more narrowly on the workloads of CRCs and other personnel with similar job functions, the major ingredient of the research infrastructure supporting trial activity.¹⁰⁻¹³ Workload data, in fact, have been used historically by cooperative groups to establish budgetary allocations to participating institutions.¹⁰ Points were awarded for various tasks, eg, 0.25 point for each subject followed after treatment, 0.5 for a phase I study, 1.0 point for a phase II or phase III study, and so forth. It was assumed that a total of 40 points constituted full-time equivalent [FTE] work for a CRC assigned to the trial. Thus, for a given protocol, points would be totaled for a given 12-month period and then divided by 40 to calculate annual FTE funding requirements for that protocol. Not surprisingly, recent studies have been predicated on the concern that these workload algorithms may not adequately gauge CRC time inputs/costs and, correspondingly, that additional research is needed to derive more precise estimates of the funding needs for the management of trial data. For instance, Gwede and colleagues^{10,11} measured various aspects of the workloads of a national sample of CRCs registered with the Radiation Therapy Oncology Group (RTOG), a national cooperative oncology group. Among other things, they found that total workload "credits" or points as described above, which in principle should add up

to approximately 40 per year, averaged more than 57 for full-time CRCs. This finding suggests that the actual work activities of coordinators are significantly higher and more complex than the established funding norm. However, this inference clearly depends on how the methodology of workload is measured per se as well as how clinical research services are organized.^{11,12}

More recently, the results of a larger study conducted under the auspices of the NCI of Canada (NCI-C) has produced more detailed data on workloads of CRCs.¹³ Specifically, 84 CRCs at 24 NCI-C member centers were asked to keep diaries for a 30-day period on the time each spent on various clinical-trial-related tasks. Among others, the tasks encompassed data collection, analysis and monitoring, case management, recruitment and enrollment of human subjects, protection of subjects through informed consent procedures and/or preparation of adverse event reports, maintenance of drug records, grant and budget development, preparation of reports, and so forth. Time estimates for these various tasks were then aggregated into four categories corresponding to stages of the trial process: (1) protocol management (trial-specific), (2) eligibility and entry, (3) treatment, and (4) follow-up and final documentation. The first spans the entire life of the trial, the second is performed once per patient per study, and the third and fourth represent repeated tasks performed multiple times per study patient. The NCI-C investigators then analyzed the distributions of time inputs by stage/task, looking

particularly at whether they differed by phase of trial and/or type of sponsor. They found that time tasks varied significantly by these factors: early-phase studies were significantly more time consuming than phase III trials, and industry studies had significantly higher mean times than did cooperative group or local trials.

Although each of the CRC workload studies described above have clear cost implications, none actually prepared cost estimates from the time/task data. To provide a reference point, I used the mean times of each task reported in the NCI-C study to estimate the cost implications of these workload figures. I weighted the mean times of each stage and all tasks (other than quality-of-life [QoL] data collection and some patient-care activities) by the mean hourly wage rate of registered nurses in the United States in 2001, a plausible, though perhaps upper bound, estimate of CRC pay. (Adjusting for fringe benefits and associated operating expense, this wage rate equals \$35 per hour.) Because scale is important, I estimated the costs of a simple trial that accrues 30 patients for a 1-year study with just one follow-up and an enrollment rate from the eligible pool of 50%. Given these conditions and the assumption that institutional capital expenses would be equal to 50% of CRC costs, the research-related costs of the trial would be on the order of \$14,673, or \$489 per enrollee year. The largest proportion of this total (56%) is accounted for by eligibility and entry tasks, with the remainder split about evenly between proto-

col management and follow-up activities. While this is clearly a rough estimate, it is interesting that research-related costs of trial activity are likely to be at least equal in magnitude to the patient care cost differentials described above, if not substantially greater.

This rough estimate of the per-enrollee cost omitted the time spent by CRCs administering QoL follow-up instruments, a narrowly defined task that would add about \$35 per enrollee year if included in the figure above. As a recent study makes clear, however, this is an underestimate of the actual costs of a QoL trial component because it omits the costs of statistical design and analysis, among others.¹⁴ This study of the full costs of introducing QoL elements in SWOG trials monitored “central office” staff time relating to the processing of QoL materials, including the *design* of QoL instruments in addition to the collection and analysis of QoL data. Staff time encompassed highly trained professionals such as PhD psychologists and biostatisticians as well as computer programmers, clerical workers, and the like; it also encompassed QoL registrations over a number of different SWOG protocols at different stages in the trial process (eg, open vs closed). Averaging estimated monthly costs across the percentage of SWOG enrollees entered on QoL-related protocols, the study found that direct (inflation-adjusted) costs per registrant of \$310 and \$528, respectively. The author observed that the \$528 estimate of “per QoL registration cost is particularly interesting because the

Statistical Center estimates that total cost (direct plus indirect) per patient in a therapeutic trial is very similar.”¹⁴ Moreover, these costs are additive because therapeutic trials are needed alongside QoL studies to drive the QoL hypotheses. Thus, conducting a trial with a QoL component adds substantially to the cost of conducting a trial. The same is true if cost endpoints or an economic component is built into a cancer clinical trial, as discussed below.

Costs as Clinical Trial Endpoints

The primary impetus for including cost endpoints in clinical trials is the continuing rise in healthcare costs and the associated need to promote value for the use of scarce resources in cancer care.^{15,16} This need has been felt throughout the healthcare sector, so many trials have incorporated economic or cost elements, though not always successfully.¹⁷ Some cancer clinical trials have followed suit, but there is an insufficient number of them to warrant a comprehensive review at this time (and in any case is beyond the scope of this article). In greater supply in the recent literature are methodological discussions/probes that presage the pitfalls of adding economic components to cancer trials without due consideration of the analytic and interpretative issues that cost components raise. A brief summary of these issues follows.

To begin with, cancer trials assess the efficacy, not the effec-

tiveness, of new therapies. Control groups may not be representative of real patient populations, and outcomes may be limited in scope and duration, eg, cancer trials often focus on tumor shrinkage or time to recurrence, not lifetime effects of the disease and treatment for it.¹⁸ Using efficacy instead of effectiveness thus threatens the external validity of the cost-effectiveness analysis. Notwithstanding this issue, other technical problems may arise. For one thing, sample size and power considerations will differ between cancer trials with and without a cost-effectiveness component. Since, for example, there is likely to be more statistical noise around a cost-effectiveness ratio than an efficacy-related outcome, cost endpoints that are simply added to an ordinary trial may result in underpowered analysis.¹⁹ For another, cost streams, like other trial outcomes, may be influenced by survival and follow-up losses. While earlier research suggested that standard survival techniques (eg, Kaplan-Meier procedures) might also be employed for censored data on cost streams, the weight of current opinion is that they do not apply because, unlike time, costs cumulate at different rates over the follow-up period. Other methods are therefore warranted.²⁰ For yet another, cost comparisons may be invalid. To illustrate, international trials admit to meaningful comparisons of health effects across subjects, but it is unlikely that cost differences across countries do. The reasons are the wide differences across nations in practice patterns, relative prices driven by different

reimbursement methods, and cost estimation procedures, eg, the treatment of overhead costs and capital depreciation allowances.²¹ Similar interpretive problems are encountered in cost comparisons across centers and patients as well.²² Efforts to finesse these problems by means of, say, modeling costs do not always produce meaningful results.²³

These potential problems suggest that care must be taken when an economic component is incorporated into a trial and, in turn, that adding such a component is itself likely to be costly. Using the operational steps for conducting an economic analysis alongside a cooperative group clinical trial presented in Bennett and Waters,²⁴ I estimate that adding an economic component would cost roughly the same amount as adding a QoL component, assuming that data are collected only by means of questionnaire or interview surveys of patients themselves. However, it is doubtful that data needed on the full range of healthcare services used during cancer treatment can be obtained just from patients; supplemental data from administrative/claims records at the site and/or records of insurance payers may also be needed. Personal experience in working with computerized claims data files suggests to me that collecting these supplemental data will significantly raise the cost of a trial. Coupled with the need for economic expertise, a cost-effectiveness component might well cost twice or even three times what adding a QoL component to a cancer clinical trial costs.

If adding economic components to trials is indeed expensive, then these components must be carefully designed and conducted — they cannot simply be tacked on *ex post facto*. Costly economic components also mean that sufficient funding must be available to investigators. Bennett et al²⁵ have pointed out that attempts to add economic analyses to cooperative group trials have faltered for lack of funding, which they argue is a result of the knowledge gained by such analysis being what economists call a pure public good, ie, the benefits cannot be appropriated by any one party, so everyone has reason to avoid paying for the research. This “free rider” problem is a classic argument in favor of public sector funding to avoid under-investment in research. There is in regard to cancer trials an even more difficult problem: some sponsors, especially industry sponsors, may be able to appropriate benefits if the trial succeeds, so they will be inclined to fund only those trials destined to succeed. Djulbegovic and colleagues²⁶ have adduced convincing evidence that if there is such bias in funding, trial activity may violate the equipoise principle, which diminishes the value of data generated through the trial process. All of this may explain why enthusiasm for incorporating economic components in trials has waned somewhat over the past few years.

Discussion

The recent literature bearing on costs and cancer clinical trials is segmented and incomplete. As we

have seen, studies of patient care cost differentials attributable to trial participation have not taken the costs of research management into account. Studies of workload issues have not considered the additional demands on research management tasks when QoL and/or cost-related endpoints are built into trials. For their part, studies exhorting the need for new or more extensive trial endpoints have not paid sufficient attention to the administrative and patient costs that may result from expanding trials in this way. Although not altogether successful because its cost measures were truncated, the study by Evans et al⁹ that aimed to cost-out an entire trial from beginning to end nonetheless stands out as an exemplar to be replicated and extended to other centers, cancers, and trial phases. The review here suggests in the aggregate that the yearly cost per enrollee (for a typical small-scale trial) might be on the order of \$1,300 to \$2,200, depending on whether QoL and/or economic components are included. This figure does not include arguably the most important resources of all: the research-related time and talents of physician investigators, the direct costs of investigational drugs/procedures, and the indirect costs of the time of enrollees and their family members. Each of these factors would be included in a more broadly gauged cost analysis of cancer clinical trials conducted from a societal perspective.

The recent literature has also lagged, rather than led, in the formulation of public and third-party

payer policies. This is best illustrated by the lag between changes in reimbursement policy and the completion of studies addressing the issue of incremental patient costs in trials. Only preliminary results were available when President Clinton's June 2000 Executive Memorandum guaranteeing Medicare reimbursement for patients enrolled on NCI-approved cancer trials was promulgated and when negotiations by the National Institutes of Health designed to achieve the same outcome with managed care organizations were being initiated.^{27,28} More robust empirical findings were still unavailable when debate began in the US Congress on a legislative mandate for insurance coverage of cancer trials under the provisions of what became known as the Bipartisan Patient Protection Act. (More particularly, Section 119 in both the Senate version [S1052] and the House of Representatives version [HR2563] guarantees that third-party payers cannot deny participation of "qualified individuals" in "approved clinical trials," cannot deny, limit, or impose other conditions on the coverage of "routine patient costs" associated with participation in the trial, and may not discriminate against an individual because he or she participated in an approved trial.²⁹) This legislative remedy was drafted before the more definitive NCI/RAND study described above was even near completing its primary data collection. Somewhat ironically, because the Patient Protection legislation is stalled at the present time — negotiations between the Democrats and the White House broke off in late summer of 2002 — there is a

slim chance that the study results will actually become available before final passage of the Act. In the future, policy-relevant research must be carried out in a more timely fashion.

Finally, we must recognize that the cost issues reviewed here are mere symptoms of a deeper and more complex set of problems confronting cancer clinical trials. One is the continuing problem of low enrollment rates. While there is a statistically significant effect of insurance status on the probability of trial enrollment, the magnitude of the effect is small, so expanded and guaranteed coverage may raise enrollment rates but probably not by much.³⁰ More substantial gains in enrollment may be forthcoming by targeting such critical factors as physician "triage"³¹ and eligibility criteria,³² to name just two. An equally significant issue relates to the wide variation in the manner in which many cancers are treated and, correspondingly, the significant variance in the cost of "standard" therapy.³³ More extensive analyses of the costs of cancer care per se are needed in order to judge the narrower issue of the cost of patient care in clinical trials. Perhaps most fundamental of all are the benefits of clinical trials, including the economic value of the knowledge advances yielded by trials. However daunting the technical task, there is no reason in principle why these benefits cannot be quantified. The estimated benefits should then be compared to the cost of generating knowledge by means of the controlled clinical trial mechanism. The cost literature

and the back-of-the-envelope calculations set out in this review of the likely costs per enrollee will doubtless appear well justified when compared to the potential economic value of the knowledge gains arising from cancer trials.

Appreciation is expressed to Clement K. Gwede, PhD, MPH, RN, for very helpful comments on an earlier draft of this paper.

References

1. Bennett CL, Adams JR, Knox KS, et al. Clinical trials: are they a good buy? *J Clin Oncol.* 2001;19:4330-4339.
2. Goldman DP. Costs of conducting cancer clinical trials. *Manag Care Cancer.* 2001;3:14-18.
3. Wagner JL, Alberts SR, Sloan JA, et al. Incremental costs of enrolling cancer patients in clinical trials: a population-based study. *J Natl Cancer Inst.* Erratum: *J Natl Cancer Inst.* 2000;92(2):164-165. 1999;91:847-853.
4. Fireman BH, Fehrenbacher L, Gruskin EP, et al. Cost of care for patients in cancer clinical trials. *J Natl Cancer Inst.* 2000;92:136-142.
5. Bennett CL, Stinson TJ, Vogel V, et al. Evaluating the financial impact of clinical trials in oncology: results from a pilot study from the Association of American Cancer Institutes/Northwestern University clinical trials costs and charges project. *J Clin Oncol.* 2000;18:2805-2810.
6. Chirikos TN, Ruckdeschel JC, Krischer JP. Impact of clinical trials on the costs of cancer care. *Med Care.* 2001;39:373-383.
7. Riley GF, Potosky AL, Lubitz JD, et al. Medicare payments from diagnosis to death for elderly cancer patients by stage at diagnosis. *Med Care.* 1995;33:828-841.
8. Goldman DP, Schoenbaum ML, Potosky AL, et al. Measuring the incremental cost of clinical cancer research. *J Clin Oncol.* 2001;19:105-110.
9. Evans WK, Dahrouge S, Stapleton J, et al. An estimate of the cost of conducting phase II trials in lung cancer. *Lung Cancer.* 2000;28:85-95.
10. Gwede CK, Johnson D, Trotti A. Measuring the workload of clinical research coordinators, Part 1. Tools to study workload issues. *Appl Clin Trials.* 2000;9:40-44.
11. Gwede CK, Johnson D, Trotti A. Measuring the workload of clinical research coordinators, Part 2. Workload implications for sites. *Appl Clin Trials.* 2000;9:42-47.
12. Gwede CK, Daniels S, Johnson D. Organization of clinical research services at investigative sites: implications for workload measurement. *Drug Inf J.* 2001;35:695-705.
13. Roche K, Paul N, Smuck B, et al. Factors affecting workload of cancer clinical trials: results of a multicenter study of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol.* 2002;20:545-556.
14. Moinpour CM. Costs of quality-of-life research in Southwest Oncology Group trials. *J Natl Cancer Inst Monogr.* 1996;11-16.
15. Brown M, McCabe M, Schulman KA (eds). Integrating economic analysis into cancer clinical trials: the National Cancer Institute-American Society of Clinical Oncology economics workbook. *J Natl Cancer Inst Monogr.* 1998;24.
16. Lyman GH. Economic analysis of randomized, controlled trials. *Curr Oncol Rep.* 2001;3:396-403.
17. Adams ME, McCall NT, Gray DT, et al. Economic analysis in randomized controlled trials. *Med Care.* 1992;30:231-243.
18. Ramsey SD, McIntosh M, Sullivan SD. Design issues for conducting cost-effectiveness analyses alongside clinical trials. *Annu Rev Public Health.* 2001;22:129-141.
19. Willan AR. Analysis, sample size, and power for estimating incremental net health benefit from clinical trial data. *Control Clin Trials.* 2001;22:228-237.
20. Etzioni R, Riley GF, Ramsey SD, et al. Measuring costs: administrative claims data, clinical trials, and beyond. *Med Care.* 2002;40(6 suppl):III63-III72.
21. Koopmanschap MA, Touw KC, Rutten FF. Analysis of costs and cost-effectiveness in multinational trials. *Health Policy.* 2001;58:175-186.
22. Coyle D, Drummond ME. Analyzing differences in the costs of treatment across centers within economic evaluations. *Int J Technol Assess Health Care.* 2001;17:155-163.
23. Owen JB, Grigsby PW, Caldwell TM, et al. Can costs be measured and predicted by modeling within a cooperative clinical trials group? Economic methodologic pilot studies of the radiation therapy oncology group (RTOG) studies 90-03 and 91-04. *Int J Radiat Oncol Biol Phys.* 2001;49:633-639.
24. Bennett CL, Waters TM. Economic analyses in clinical trials for cooperative groups: operational considerations. *Cancer Invest.* 1997;15:448-453.
25. Bennett CL, Smith TJ, George SL, et al. Free-riding and the prisoner's dilemma: problems in funding economic analyses of phase III cancer clinical trials. *J Clin Oncol.* 1995;13:2457-2463.
26. Djulbegovic B, Lacey M, Cantor A, et al. The uncertainty principle and industry-sponsored research. *Lancet.* 2000;356:635-638.
27. Arnold K, Vastag B. Medicare to cover routine care costs in clinical trials. *J Natl Cancer Inst.* 2000;92:1032.
28. Brown ML. Cancer patient care in clinical trials sponsored by the National Cancer Institute: what does it cost? *J Natl Cancer Inst.* 1999;91:818-819.
29. Library of Congress. Thomas: Legislative Information on the Internet. Available at: <http://thomas.loc.gov/> for a description of this legislation. Accessed December 19, 2002.
30. Lara PN Jr, Higdon R, Lim N, et al. Prospective evaluation of cancer clinical trial accrual patterns: identifying potential barriers to enrollment. *J Clin Oncol.* 2001;19:1728-1733.
31. Taylor KM, Feldstein ML, Skeel RT, et al. Fundamental dilemmas of the randomized clinical trial process: results of a survey of the 1,737 Eastern Cooperative Oncology Group investigators. *J Clin Oncol.* 1994;12:1796-1805.
32. George SL. Reducing patient eligibility criteria in cancer clinical trials. *J Clin Oncol.* 1996;14:1364-1370.
33. Chirikos TN. Cancer economics: on variations in the costs of treating cancer. *Cancer Control.* 2002;9:59-66.