# WISCONSIN STATE LEGISLATURE COMMITTEE HEARING RECORDS

## 2005-06
(session year)

## Assembly
(Assembly, Senate or joint)

## Committee on Insurance (AC-In)

(Form Updated: 11/20/2008)

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UW Health

TO: MEMBERS OF THE INSURANCE COMMITTEE

FROM: LISA MARONEY, UW HEALTH

DATE: NOVEMBER 3, 2005

RE: ASSEMBLY BILL 617

Attached please find copies of cost studies completed throughout the country on the cost of coverage for routine care costs for cancer clinical trials. None of the studies conducted show any significant increase in health care costs. In fact, some studies actually show a slight decrease.

To date, 22 other states have similar laws/regulations in place. We urge your support for Assembly Bill 617. Thank you.

# Clinical Trials Appear Not to Drive Up Cost of Cancer Treatment

Posted: 01/27/2003

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Cost of Clinical Trials

Some health insurers, concerned that participation in a clinical trial drives up the cost of cancer care, decline coverage to patients enrolled in cancer trials. However, the results of a study by Thomas N. Chirikos, Ph.D. and others at the H. Lee Moffitt Cancer Center in Tampa, Florida, offer no basis for such a policy.

The study, which was published in the April 2001 issue of the journal Medical Care, supports findings from previous research showing that cancer patients enrolled in clinical trials incur no significant increase in treatment costs.

Participants in cancer treatment trials "do not receive more, nor more expensive, services than similarly situated patients who do not enter trials," the researchers concluded. The researchers controlled for variables such as age, extent of disease, initial treatment, and ultimate outcome so as to identify cost differences between the in-trial and out-of-trial patients that were due to trial participation alone.

## Isolating the Effect of Trial Participation

Chirikos and his colleagues examined hospital billing records for about 1,900 cancer patients who were diagnosed and treated at the Moffitt Cancer Center between August 1995 and February 1998. About 380 of these patients were enrolled in clinical trials of cancer treatment. Most of the patients studied were treated for breast cancer; the others, for lung cancer, ovarian cancer, or lymphoma.

The researchers looked for differences in the costs of care given to patients who took part in clinical trials compared with patients with the same type of cancer who did not enroll in trials. They also analyzed differences among patients that could affect the cost of care, such as age, stage of disease, initial treatment received, and treatment outcome. Finally, they used statistical techniques to adjust for such variation among patients in order to isolate cost increases that could be tied only to participation in a clinical trial.

Unadjusted costs did indeed tend to be higher for patients enrolled in trials. The investigators found that patients enrolled in trials tended to receive more complex, aggressive initial treatment; were more likely to have recurrent disease; and were more likely to be followed for a longer time. For example, the average unadjusted cost of care for a patient with ovarian cancer who enrolled in a Phase I or II clinical trial was about double that of a patient with ovarian cancer who did not enroll in a trial ($140,300 vs. $69,100).

However, when the researchers adjusted the data to isolate the effect of trial participation alone, the investigators found that in all but one case, there was no statistically significant differences in the costs of care for patients who were enrolled in trials compared with those who were not.

## Study Limited, But Consistent With Others

Martin Brown, Ph.D., of the National Cancer Institute's Health Services and Economics Branch, noted that the study does have several limitations. First, the study excluded physician fees, looking only at in-patient and out-patient hospital care.

Second, the study used data on charges from hospital billing records. "It is well known that charges can differ markedly from actual payments and underlying resource costs," said Brown.

Third, costs were adjusted for the type and complexity of the initial therapy. "This may be appropriate for cases where the trial involves therapy following initial treatment failure or for recurrent disease," said Brown. But it would tend to result in an underestimation of costs associated with those clinical trials that are designed to compare more complex therapies (such as one that uses multiple modalities) with a simpler therapy for initial treatment.

Though the results of this study may not be applicable to all settings, said Brown, the basic conclusions are nonetheless consistent with several others that also looked at this question.

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# Clinical Trials Not Costly

Posted: 02/09/2000

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Medical care costs for patients enrolled in cancer clinical trials are about the same as costs for patients not enrolled in trials, concludes a report from the January 19, 2000, issue of the Journal of the National Cancer Institute. The study, based at Kaiser Permanente of Northern California, a large health maintenance organization, supports earlier studies and helps the cause of advocates calling for health plans to cover the medical care costs of clinical trials.

Related Pages

Cost of Clinical Trials

To compare costs, the researchers matched 135 patients enrolled in cancer clinical trials to 135 non-enrolled patients, based on type of cancer, age, sex, and trial eligibility. They then examined expenses incurred during a year of treatment, including costs for office visits, lab tests, chemotherapy and other drugs, and any other cancer-related treatments. The average outlay for each trial participant was $17,003; for non-participants it was $15,516, a difference of 10 percent.

Much of this difference was accounted for by 11 patients who underwent high-dose chemotherapy and bone marrow transplants for breast cancer. Excluding these 11 patients reduces the average outlay to $15,041 for each clinical trial participant, almost identical to the costs for non-participants.

The authors argue that besides not costing more, clinical trials could make HMOs more appealing to patients and physicians by giving them access to the latest treatments. In addition, clinical trials are crucial for the development of new treatments, but if managed care organizations continue their reluctance to pay for them, fewer patients may be enrolled in clinical studies.

The Kaiser report follows a 1999 Mayo Clinic study which also found that costs for clinical trials participants are almost identical to those incurred by non-participants

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# Evidence Mounts That Clinical Trials Are Not Costly

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Evidence continues to mount that caring for patients on cancer clinical trials is no more costly than providing standard care, despite claims by insurance companies and other health care providers to the contrary, experts said Saturday at the 2000 annual meeting of the American Society of Clinical Oncology.

The latest evidence, from two studies that analyzed treatment costs at large cancer centers, backs up research published earlier this year. The new studies also lend credence to calls by patient advocates, cancer researchers, and others for insurance companies and Medicare to pay for routine care costs for patients enrolled in clinical trials.

*Dr. Joseph Bailes. (Photo courtesy ASCO.)*

"For years we have advocated coverage of clinical trials because they are state of the art care," said Joseph Bailes, M.D., president of ASCO.

However, many insurers assume that patients in clinical trials will cost more because they require extra care or more tests, said Charles Bennett, M.D., from Northwestern University, who helped conduct one of the studies, run by the American Association of Cancer Institutes.

"One concern is that it is difficult to obtain reimbursement from insurers, limiting the chances people have to enroll in trials. If it's not paid for, how can they do it?" said Bennett.

The AACI study, which is serving as a pilot for a much larger project involving several large cancer centers, found that charges for patients in clinical trials were about the same, or even a little lower, than those for patients receiving standard care. The study tracked 35 patients in phase II cancer clinical trials and 35 patients receiving standard care who were similar, or matched, to the clinical trials patients.

The amount patients or insurers actually paid for six months of treatment was $57,500 for the clinical trials group and $63,700 for the non-clinical trials group. Because the study had so few patients, though, the cost difference was not statistically significant. Bennett said that AACI will use the study as a basis for a project involving 1200 or more patients that will track costs for up to two years.

The second report, from Memorial Sloan-Kettering Cancer Center in New York, also found costs to be similar or lower for clinical trials participants in phase II or phase III trials. The study looked back at costs for 77 clinical trials patients and 75 standard care patients treated at Sloan-Kettering. The total costs, which included inpatient and outpatient costs for six months of treatment, was $30,800 in the clinical trials group and $37,000 in the standard group. [Editor's note: As of Nov. 6, 2002, this study remains unpublished.]

"This result was not a surprise to us," said Sloan-Kettering's George Bosl, M.D., "because we've consciously tried to not order extra tests for clinical trials patients." Bosl added that many of the drugs used in the clinical trials group were donated, a standard practice for experimental drugs.

During a discussion session, Virginia Commonwealth University's Thomas Smith, M.D., said that these results are beginning to change insurers' attitudes toward clinical trials -- and in fact, several states, including Maryland and Arizona, have mandated coverage of clinical trials -- but added that the process will be slow.

"We need to put these studies in a packet and mail them to every insurance director in all of the states," said Smith. "Then we need to call them up and ask them if they get the message."

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**Related Pages**

Highlights from ASCO 2000
A roundup of news highlights from the 2000 annual meeting of the American Society of Clinical Oncology.

Cost of Clinical Trials
A collection of material about studies showing that patient care costs for clinical trials are not appreciably higher than costs for patients not enrolled in trials.

# Clinical Trials: Are They a Good Buy?

By Charles L. Bennett, Jared R. Adams, Kirstin S. Knox, Andrew M. Kelahan, Samuel M. Silver, and Joseph S. Bailes

***Purpose:*** **Concern that clinical trials may be too costly has been used to justify traditionally restrictive insurer policies regarding clinical trials. Additionally, fear of insurer reimbursement denial can be a significant barrier to clinical trial participation. In this study, we reviewed the empirical data on costs of clinical trials versus standard care and summarized the current status of policy initiatives related to clinical trial insurance reimbursement.**

***Methods:*** **Electronic and print data sources were searched for studies on the costs of oncology clinical trials. Information on policy initiatives for clinical trial reimbursement was obtained from the American Society of Clinical Oncology, the American Society of Hematology, and the Coalition of National Cancer Cooperative Groups and from searches of World Wide Web sites.**

***Results:*** **Five pilot studies provided information for 377 patients on phase II/III clinical trials matched with controls on standard care. Cost estimates ranged from 10% lower to 23% higher costs/charges for clinical trials in comparison to standard medical care. Medicare, 14 states, and several private insurers now cover the costs of patient care in "qualifying" clinical trials.**

***Conclusion:*** **Findings from small pilot studies suggest that phase II and III clinical trials result in at most modest increases in cost over standard treatment costs. Also, an increasing number of policy makers have decided to support clinical trial reimbursement initiatives. It is hoped that economic data from large observational studies will facilitate widespread and permanent decisions that support reimbursement for phase I, II, and III clinical trial participation.**

***J Clin Oncol 19:4330-4339. © 2001 by American Society of Clinical Oncology.***

IT IS ESTIMATED THAT fewer than 5% of adult cancer patients participate in clinical trials.[1] In a recent Harris Interactive survey of 5,980 cancer patients, 60% of patients who were aware of clinical trials (14% of survey sample) and elected not to participate (71% of aware patients) cited concerns about insurance denial as a primary barrier to participation.[2] However, a United States General Accounting Office report found that many insurers already pay for many patients who participate in clinical trials, despite policies excluding payment for "experimental" therapies.[3] As policy makers have become aware that patient concerns over potential reimbursement denial may be a barrier to clinical trial accrual, legislators and insurers have begun to address clinical trial reimbursement policies. The Medicare Cancer Clinical Trial Coverage Act of 1997 sought to authorize a $750 million demonstration project which would reimburse routine patient care costs alongside approved clinical trials. The act also commissioned a report on the actual costs of the funded clinical trials. This legislation was not passed, primarily because of concerns over actual study costs. In 2000, the Institute of Medicine released its report, "Extending Medicare Reimbursement in Clinical Trials," which recommended that the Health Care Financing Administration (HCFA), the former administrator of the Medicare program, reimburse "routine care for patients in clinical trials in the same way it reimburses for routine care for patients not in clinical trials."[3] The report projected that the financial impact of clinical trial reimbursement would be small, based on the findings of pilot studies in 1998 and 1999 from the Group Health Cooperative of Puget Sound, the Mayo Clinic, and Kaiser Permanente.[4-6] Nonetheless, as health care costs rise, the questions related to reimbursement for clinical trials become increasingly relevant. After the favorable reports on the cost of clinical trials from pilot studies, federal policy makers, private insurers, and several state legislatures have introduced policies or laws that support reimbursement of routine medical care in clinical trials. In this article, we address the current status of reimbursement for clinical trials by reviewing the methodologies, results, and future plans for studies on the costs of clinical trials and reviewing the content of federal, state, and private sector clinical trial reimbursement initiatives.

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*Submitted December 28, 2000; accepted August 20, 2001.*

*The opinions expressed herein are solely those of the authors and are not meant to represent those of the committees and departments at the American Society of Clinical Oncology or the American Society of Hematology, where some of the background information was obtained.*

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*0732-183X/01/1923-4330/$20.00*

Table 1. Comparison of Estimates of Incremental Costs/Charges of Clinical Trials From Five Studies

| | Memorial Sloan-Kettering | AACI/ Northwestern | Kaiser Permanente | CBO/Mayo Clinic | Group Health Cooperative |
|---|---|---|---|---|---|
| Reference no. | 8 | 7 | 5 | 4 | 6 |
| Clinical trial patients | 77 | 35 | 135 | 61 | 49 breast/20 colorectal |
| Study years | 1995 | 1996-1998 | 1994-1996 | 1988-1994 | 1990-1996 |
| Phase | II/III | II | III | II/III | II/III |
| Cost Data | | | | | |
| Units used to measure costs | Costs | Charges | Costs | Costs | Costs |
| At 6 months | | | | | |
| Control patients (C) | $30,775 | $63,721 | $9,930 | $10,073 | |
| Clinical trial patients (T) | $37,055 | $57,542 | $12,242 | $12,200 | |
| % Difference (T-C) | 17 | (−10) | 23 | 21 | |
| At 12 months | | | | | |
| Control patients (C) | | | $15,516 | $14,762 | |
| Clinical trial patients (T) | | | $17,003 | $16,819 | |
| % Difference | | | 10 | 14 | |
| At 24 months | | | | | |
| Control patients (C) | | | | | $25,000* |
| Clinical trial patients (T) | | | | | $30,000 |
| % Difference | | | | | 20 |
| At 60 months | | | | | |
| Control patients (C) | | | | $26,797 | |
| Clinical trial patients (T) | | | | $27,090 | |
| % Difference | | | | 1 | |

Abbreviation: AACI, American Association of Cancer Institutes; CBO, Congressional Budget Office.

*Twenty-six closely matched breast cancer patients only; other diseases did not show a remarkable cost difference.

## METHODS

MEDLINE, EMBASE, HEALTHSTAR, and abstracts from the *Proceedings of the American Society of Clinical Oncology* from the years 1995 to 2001 were searched for reports on costs of clinical trials. Key words included cancer costs, clinical trial costs, and clinical trial participation. Leaders at the Department of Public Policy of the American Society of Clinical Oncology, the Committee on Practice of the American Society of Hematology, the Coalition of National Cancer Cooperative Groups, the Department of Defense, and the National Cancer Institute were also queried about ongoing policy initiatives related to clinical trial reimbursement. Individual bills pertaining to mandated insurance reimbursement of clinical trials were found through searches of the legislative history on the Web site of the respective legislative bodies. Web sites of health care insurers and managed care organizations operating on a national basis were reviewed to identify programs that voluntarily reimbursed medical care costs incurred on clinical trials.

This article addresses routine care costs in clinical trials. For most of the research articles and legislative bills, routine care costs (often referred to as patient care costs in legislation) include conventional care, items or services that are typically provided absent a clinical trial; administrative items, items or services required solely for the provision of the investigational item or service (such as the administration of a noncovered chemotherapeutic agent) and for clinically appropriate monitoring related to complications and treatment effects; and reasonable and necessary care, items or services arising from the provision of an investigational item or service, including the diagnosis or treatment of complications. Routine patient care costs do not include items and services that are customarily provided by the research sponsors free of charge for individuals participating in the trial (such as investigational drugs or items); tests or measurements conducted primarily for the purpose of the clinical trial involved; or the administrative costs associated with collecting research data.

## RESULTS

### *Pilot Studies on Costs and Charges of Clinical Trials*

Three published studies[4,5,7] and two preliminary reports[6,8] conducted an economic evaluation of the routine medical care costs of clinical trials. These studies included information on patients enrolled onto phase II (one study), phase III (one study), and phase II and III clinical trials (three studies). (Table 1) A total of 377 patients on clinical trials were included in the five studies (range, 35 to 165 patients per study). Three studies included information on patients treated in the mid-1990s, one study covered the years 1988 to 1994, and one covered the years 1990 to 1996. Two studies were for patients who received care at managed care organizations (Kaiser Permanente and Group Health Cooperative), two were single-site studies from tertiary cancer centers (Memorial Sloan-Kettering Cancer Center and the Mayo Clinic Cancer Center), and one was from five tertiary cancer centers that belong to the Association of

Table 2. Comparison of Methodologies Among the Five Economic Assessment of Clinical Trials

| Study | No. of Cancer Centers | Payment System | No. of Cancer Types | Case Selection | BMT Cases | Control Selection Matching | Excluded Resources | Costs | Analysis |
|---|---|---|---|---|---|---|---|---|---|
| CBO and Mayo Clinic | 1 | Fee-for-service | 9 | All possible cases | No | Performance status | Outpatient prescription drugs | Costs, 5 years | Paired *t* test |
| Kaiser Permanente | 17 | Managed care | 9 | All possible cases | Yes | Eligibility for trial | None | Costs, 1 year | Univariate regression |
| Memorial Sloan-Kettering | 1 | Medicare | 7 | Patients treated primarily at the cancer center | No | Survival | Resources used outside of MSKCC | Costs, 6 months | Unpaired *t* test |
| AACI/Northwestern | 5 | Fee-for-service | 5 | Patients treated primarily at the cancer center | Yes | Eligibility for trial | Resources used outside of the AACI center | Charges, 6 months | Paired *t* test |
| Group Health Cooperative | NA | Managed care | 2 | GH members on SWOG studies | Not stated | Comorbidity, (eligibility for trial: 26 breast cancer patients) | Not stated | Costs, 2 years | Not stated |

Abbreviations: BMT, bone marrow transplantation; GH, Group Health; MSKCC, Memorial Sloan-Kettering Cancer Center; NA, not applicable; SWOG, Southwest Oncology Group.

American Cancer Institutes (AACI). Control groups included patients with the same diagnosis and tumor stage and similar comorbidity levels who received similar treatments in the setting of standard cancer care.

The studies found that the differences in costs (four studies) or charges (one study) ranged from a 10% savings to a 23% increment for clinical trial participation at 6 months' follow-up, a 10% to 14% increment at 12 months' follow-up, a 20% increment at 24 months, and a 1% increment at 60 months' follow-up (Table 1). There was a wide variation in costs/charges for individual patients and controls, with some clinical trial patients differing by more than $200,000 in costs/charges from matched controls. For breast cancer patients who underwent autologous stem-cell transplantation, mean costs were 120% greater than costs for controls who received standard chemotherapy, while charge estimates were 15% lower in comparison to charge estimates for controls who received autologous stem-cell transplantation outside of a clinical trial.

In evaluating the findings of these studies, several methodologic considerations related to selection of cases and controls, identification of resources, estimation of costs, and statistical analyses should be discussed (Table 2). These areas represent the most important features of economic analyses of cancer care.[9-11]

The studies included patients with between two and nine different types of cancer diagnoses, with breast cancer being the most common diagnosis. Two studies identified cases by reviewing logs from cancer registries at the managed care organization, two studies identified patients through searches of electronic and paper files, and one study included a random sample of a specified number of clinical trial participants at each of five tertiary cancer centers. In some cases, the same patient participated in more than one clinical trial during the study period. The AACI/Northwestern University and the Memorial Sloan-Kettering Cancer Center studies included only those patients who received the majority of their care at the participating cancer center because of the operational difficulties associated with cost identification for medical care provided in multiple settings.

Identification of appropriate controls was the most challenging aspect of study design. Controls were matched for diagnosis, stage, and age in all five studies. Matching was based on eligibility for the clinical trial in two studies, on survival in one study, and on performance status or comorbidity in two studies. However, the type of comparative treatment varied and in all cases differed from that used for case patients who participated in the clinical trials. For example, three studies included breast cancer patients who received an autologous stem-cell transplant, but two of these identified controls who received standard-dose chemotherapy and one included controls who underwent transplantation outside of the clinical trial setting. For the four published studies, control patients who had similar clinical and demographic characteristics but differed with respect to the specific treatment regimen could be identified for two thirds to three quarters of the clinical trial patients.

Measurement of the resources to be included in the economic analyses varied. These data were obtained from electronic claims files in all studies, which facilitated data collection efforts. In the Kaiser Permanente and Group Health Cooperative studies, almost all of the resources associated with cancer care were captured in the electronic data files. The Mayo Clinic study excluded outpatient prescription drugs, durable medical equipment, ambulance and other transportation services, outpatient services provided by allied health professionals, and nursing home care. The other two studies excluded resource use that occurred outside of the tertiary cancer center.

The methodology for deriving economic inputs was unique to each study. The Mayo Clinic study assigned a value for each unit of service that was adjusted to national cost norms using Medicare fee-schedule rates for physician and outpatient ancillary services. Hospital charges were converted to costs by applying department-level cost-to-charge ratios obtained from Medicare reports. Unit costs were normalized to national 1995 values by use of regional hospital market-basket indexes obtained from annual Prospective Payment Assessment Commission reports. The Kaiser Permanente study used a proprietary system that assigned a value to each unit of pharmacy, laboratory, imaging, and home health services, with additional allocation of building and administrative overhead rates that were specific to the Kaiser system. Unit costs reflected average annual costs throughout Kaiser Permanente in Northern California. For out-of-network services, provider charges were used as the estimate for costs. Copayments by patients, representing out-of-pocket costs to patients, were also included. Costs in the Memorial Sloan-Kettering Cancer Center study included hospital costs and physician charges, based on estimates derived from Medicare cost-to-charge ratios for the relevant resources. The Group Health Cooperative Study is currently revising its cost estimation effort. The AACI/Northwestern University pilot study used charges, not costs, in the analyses, primarily because the five-site study would have required a different cost estimation effort for data from each tertiary cancer center. In most cases, the preferred method for economic analyses is based on estimates of costs, not charges, because of marked discrepancies that exist between billed charges and opportunity costs in health care.[12] These differences vary by type of resource, among physicians, and over time, resulting in a distorted estimate of economic differences between groups of patients treated with a variety of medical resources.

Analytic approaches also differed. The Mayo Clinic reported costs over a 5-year time period, the Group Health Cooperative reported costs over a 2-year time period, the Kaiser Permanente study reported on costs over a 1-year time period, and the Memorial Sloan-Kettering Cancer Center and the AACI/Northwestern University studies reported costs over a 6-month time period. Censoring of patients with incomplete follow-up was done only in the Mayo Clinic study because of the long follow-up period. Statistical differences were determined using paired *t* tests based on matched samples in the studies from the Mayo Clinic and the AACI/Northwestern University, a one-covariate (Charlson comorbidity score) ordinary least squares regression model in the Kaiser Permanente study, and unpaired *t* tests in the Memorial Sloan-Kettering Cancer Center study.

There are two ongoing large-scale efforts designed to develop valid and reliable estimates of the incremental costs of clinical trials carried out in diverse academic and community settings. The RAND/National Cancer Institute (NCI) Costs of Clinical Trials Study is evaluating the costs of 750 individuals enrolled onto phase II/III clinical trials from multiple community and tertiary cancer centers and 750 matched controls.[10] The AACI/Northwestern University Clinical Trials Costs and Charges Project has proposed a complementary study that will evaluate and compare the costs of 100 patients enrolled onto phase I clinical trials conducted at tertiary cancer centers with those of an equal number of matched controls. These studies are warranted for several reasons. First, the five pilot studies had sample sizes that were insufficient to detect cost differences that may be important for policy purposes. Second, treatment patterns differ across institutions, and four of these studies were conducted within a single institution or health system, which makes it difficult to generalize. Third, cases and controls matched at a single institution may differ in unobserved but important ways that affect treatment costs, as a result of self-selection into trials. Fourth, the pilot studies excluded some potential important dimensions of treatment, such as clinicians outside the delivery system. Finally, single-institution studies may underestimate the financial impact of transferring care from a community setting in order to participate in some clinical trials.[10]

### *Federal, State, and Private Sector Policy Initiatives Related to Reimbursement of Clinical Trials*

*Federal efforts.* Federal policy initiatives related to clinical trial reimbursement began in 1994 when the Department of Defense (DOD) initiated a demonstration project that covered the costs of bone marrow transplantation in clinical trials (Table 3). In 1996, this demonstration project was expanded to include all phase II and III cancer treatment trials funded by the NCI. The DOD demonstration project was limited to NCI trials because the imprimatur of the NCI is only given to cancer trials that have demonstrated

Table 3. Federal Cancer Clinical Trial Legislative Efforts

| Cancer Clinical Trial Reimbursement Legislation | | | | |
|---|---|---|---|---|
| Federal Efforts | | | | |
| Federal Agency | Year | Trial Purpose | Phase | Qualified Trials |
| DOD/TRICARE | 1996,1999* | Prevention,* early detection,* screening,* treatment | II, III | DOD/NCI Cancer Clinical Trials Demonstration Project; NCI (NIH) trials only** |
| DVA | 1997 | Prevention, diagnosis, treatment | I, II, III, IV | NCI and DVA cost-sharing agreement; NCI (NIH) trials in DVA hospitals |
| Medicare/Medicaid | 2000 | Diagnosis, treatment | Any trial undertaken with therapeutic intent | All clinical trials, not just cancer, NIH, CDC, AHRQ, HCFA, DOD, DVA, FDA; other qualified trials |

Abbreviations: NIH, National Institutes of Health; DVA, Department of Veteran's Affairs; AHRQ, Agency for Healthcare Research and Quality; CDC, Centers for Disease Control; FDA, Food and Drug Administration.

*Expanded benefits added at the later date.

themselves to be addressing a critical public need with rigorous scientific methodology. In 1997, the Department of Veterans Affairs (VA) joined the federal demonstration project effort. In 1999, the DOD expanded their NCI cancer trials demonstration project to include coverage of prevention, early detection, and screening trials. Enrollment onto the program has increased three-fold since the beginning of the project in 1996. Of the approximately 11,700 patients diagnosed with cancer annually under the DOD (TRICARE) health coverage umbrella, 51 enrolled in 1996 (0.5%) and 131 enrolled in 2000 (1.5%). In 2001, an estimated 240 cancer patients (2.0%) are expected to enroll onto the DOD/NCI trial program.

Medicare policies were not supportive of clinical trials during the 1990s.[13] The HCFA excluded coverage of routine care costs associated with clinical trial participation for Medicare enrollees, on the basis that the treatment was experimental or investigational.[1] However, the United States General Accounting Office found that less than 4% of claims for clinical trial costs incurred by Medicare beneficiaries were denied.[2] Furthermore, they found that oncologists frequently submitted bills for components of complex treatments, without specifying the procedure itself. HCFA is estimated to have paid 50% to 90% of routine patient care costs in clinical trials, after taking into account both costs for which no reimbursement was sought and claims that were submitted and rejected. In 1993, the Office of the Inspector General of the Department of Health and Human Services found that Medicare was being billed millions of dollars for surgical procedures involving unapproved medical devices. Almost all of the 130 hospitals under investigation had billed for clinical trials. However, quickly passed legislation prevented HCFA from collecting from the hospitals.[1]

In addition, no federal clinical trials legislation has been passed. One 1993 bill, the Cancer Treatment Improvement Act, addressed the issue of clinical trial coverage but never made it past committee. In 1996, the Medicare Cancer Clinical Trial Coverage Act was introduced in the Senate and the Medicare Cancer Clinical Trial Demonstration Act in the House. The bill, which applied to the 44 million individuals whose coverage was regulated by Employee Retirement Security Act plans, would allocate $750 million to cover cancer clinical trials sponsored by the National Institutes of Health (NIH), DOD, and the DVA, would require development of federal regulations that would define routine patient care costs, and would study the impact of clinical trials reimbursement on group health insurance plans. The Medicare Cancer Clinical Trial Coverage Act was reintroduced in 1997, 1998, and 1999, without success. The Health Insurance Bill of Rights Act of 1997 introduced mandated coverage by all group health plans of federally funded clinical trials for "seriously ill patients with no standard treatment alternative." The language regarding clinical trials was folded verbatim in 1998 into the Patient Bill of Rights Act. The Sydney E. Salmon Access to Cancer Clinical Trials Act of 1999 was among the 90% of bills that never make it past committee. The Bipartisan Consensus Managed Care Improvement Act, introduced by Representatives Charlie Norwood (R-Georgia) and John Dingell (D-Michigan) in 1999, was passed by the House in 2000 but tabled by the Senate. The bill would have mandated group health plan coverage of all phases of federally funded prevention, early detection, and treatment trials for patients with serious or life-threatening illnesses.

In 2000, after years of lobbying of HCFA leadership by individuals, patient groups, health care workers, and organizations who were concerned about reimbursement denials of clinical trial costs and the low rates of accrual to clinical trials, former President Clinton issued a memorandum stating that HCFA was authorized to cover the costs of cancer clinical trials. This decision was supported by the

Table 4. Pending Federal Legislative Initiatives for Cancer Clinical Trials

| On the Horizon in Congress | | | | |
|---|---|---|---|---|
| Legislative Body | Year | Trial Purpose | Phase | Qualified Trials |
| House of Representatives by Pryce (R-Ohio), HR 967 | 2001 | Treatment | Not restricted | The Access to Cancer Clinical Trials Act of 2001 would mandate group health plans to cover all federally supported cancer trials (NIH, CDC, AHRQ, HCFA, DOD, DVA, DOE, NIH COOP groups, NIH-supported centers) and trials of IND-exempt drugs |
| Senate by Snowe (D-Washington), S 257 | 2001 | Treatment | Not restricted | The Improved Patient Access to Clinical Studies Act of 2001 would mandate all ERISA and group health plans to cover care received in all trials sponsored by HHS, NIH, FDA, VA, DOD, or NIH-qualified nongovernment research entity |
| Senate by McCain (R-Arizona), Edwards (D-North Carolina), Kennedy (D-Massachusetts), (S 1052) | 2001 | Not specified | Not restricted | The Bipartisan Patient Protection Act would mandate group health plans to cover trials approved and sponsored by NIH, NIH COOP group or center, FDA, DOD, or VA |
| House of Representatives by Ganske (R-Iowa), Dingell (D-Michigan), Norwood (R-Georgia), (HR 2563); Norwood (House Amendment 303) | 2001 | Not specified | Not restricted | The Bipartisan Patient Protection Act would mandate group health plans to cover trials approved and sponsored by NIH, NIH COOP group or center, FDA, DOD, VA, or NIH-qualified nongovernment entity |

Abbreviations: DOE, Department of Energy; COOP, cooperatives; ERISA, Employee Retirement Security Act; DHHS, Department of Health and Human Services

empirical evidence on the cost of clinical trials from the Group Health, Kaiser, and Mayo Clinic studies, the Institute of Medicine's report recommending Medicare coverage of routine patient costs on clinical trials, and the growing body of state legislation and voluntary initiatives from private insurers. This benefit included a broad definition of "qualified" clinical trials. The Final National Coverage Determination issued by HCFA extended the definition of qualified clinical trials beyond those funded or conducted by government bodies to trials that satisfied qualifying criteria. Certain trials were deemed to be qualified and automatically covered: those funded by the NIH, the Centers for Disease Control and Prevention, the Agency for Health Research and Quality, HCFA, the DOD, and the DVA; trials supported by centers or cooperative groups that are funded by these organizations; and trials conducted under an investigational new drug (IND) application reviewed by the Food and Drug Administration. The Agency for Healthcare Research and Quality has, in conjunction with other federal agencies and input from interested specialty groups and other stakeholders, developed additional criteria to identify high-quality trials that would be qualified. These criteria await approval from the new administrator of the Center for Medicare and Medicaid Services (formerly the HCFA). Until these qualifying criteria are available, trials that are exempt from having an IND will be automatically considered to be qualified trials if the study evaluates an already defined Medicare benefit, is designed with a therapeutic intent (not to evaluate toxicity), and enrolls beneficiaries with a diagnosed disease if the study is for a therapeutic intervention (but it may enroll healthy beneficiaries if the trial is for a diagnostic intervention). Medicare will cover reasonable and necessary care required to diagnose and treat complications arising from participation in clinical trials, as well as items and services required for the provision of the investigational item. All clinical trials submitted for Medicare coverage will be entered onto a national registry. Medicare will cover all routine costs of automatically qualifying and investigator-certified trials. However, if the Center's chief clinical officer subsequently finds that a clinical trial was misrepresented, the provider may be held liable for the costs.

Efforts to pass broad clinical trial legislation have moved forward in 2001 (Table 4). The recently approved Patient Protection Act legislation led by Senators McCain (R-Arizona), Edwards (D- North Carolina), and Kennedy (D-Massachusetts) in the Senate (S. 1052) and Congressman Ganske (R-Iowa), Dingell (D-Michigan), and Norwood (R-Georgia) in the House (H.R. 2563) includes a section mandating coverage of all phases of federally funded treatment trials for the seriously ill. However, after incorporation of an amendment related to financial and administrative considerations for lawsuits by Representative Norwood (House Amendment 303) that was negotiated with President Bush, the Senate and House bills differ markedly in their language regarding other aspects of managed care and will need to be reconciled in the conference process of the Congress. A bill dealing specifically with coverage of patient care costs of cancer clinical trials was introduced in the House by Representative Deborah Pryce (R-Ohio) as the Access to Cancer Clinical Trials Act of 2001 (H.R. 967). This bill is in line with the Medicare National Coverage Decision and mandates coverage of all phases of federally funded cancer prevention, diagnostic, and treatment trials,

trials approved and funded by "qualified nongovernmental research entity identified in the guidelines issued by the National Institutes of Health for center support grants," and IND-exempt investigator-initiated trials. During debate over the McCain-Kennedy-Edwards legislation, the Senate approved a nonbinding "Sense of the Senate" amendment on clinical trials by an 89 to 1 vote. The amendment, offered by Senator McCain, expresses the sense of the Senate that individuals with life-threatening diseases should have the opportunity to participate in federally approved or funded clinical trials. All versions of the proposed legislations state that qualified individuals have life-threatening or serious illnesses "for which no standard treatment is effective" and that participation in the trial offers "meaningful potential for significant clinical benefit." This language raises concern that patients might be excluded from clinical trials if the standard therapies are a reasonable option. Attempts to clarify this language are ongoing. President Bush has also voiced support for coverage of patient care costs for treatment in qualified clinical trials in a February 2001 statement sent to Congress related to "principles" for a patient's bill of rights. Thus, the prospects for passage of comprehensive federal legislation supporting clinical trial reimbursement are good, although the exact details remain uncertain.

*State legislative efforts.* As of August 2001, 14 states have passed laws mandating coverage of patient care costs associated with treatment provided on specified categories of cancer clinical trials (Table 5). The question put before state legislatures has been whether the insurance barrier to clinical research is best removed through the voluntary action of health insurers or if formal legislation is needed. Rhode Island was the first state to legislate insurance coverage for clinical trials in 1995. The bill originally supported coverage of phase III and IV cancer treatment trials but was amended in 1997 to cover phase II, prevention, screening, and phase III trials. Qualifying trials were those that were funded by the NIH, DVA, or DOD or conducted in an NCI-affiliated cancer center. Georgia mandated insurance for selected pediatric cancer trials in 1998. Maryland and Virginia expanded on the idea in 1999, mandating insurance for cancer trials conducted in in-state academic institutions. Also in 1999, Maine passed a law requiring coverage of NIH-sponsored trials in cooperative groups or NCI-designated cancer centers. The same year, Louisiana passed a law including these trials as well as trials sponsored by the Food and Drug Administration, DOD, DVA, and the Coalition of National Cancer Cooperative Groups. Several other states followed suit in 2000 and 2001. Illinois extended its guarantee of coverage to all "seriously ill patients for which no standard therapy is available." This ambiguous clause defined the qualified patient as necessarily lacking "standard care," phrasing echoed in the Patient Bill of Rights. Furthermore, it only required that insurers had to offer this as an option, not that employers had to buy the benefit as part of their employee health coverage package. Most of the state-level legislation does not define a qualified patient but instead defines qualified trials. Similar legislation is pending in a number of other states. Many of the current coverage initiatives exclude phase I trials partly because no data exist on costs, little data exist on the investigative treatment, and the treatments have little chance of being therapeutic. Other initiatives limit their scope to trials with a therapeutic intent. Most initiatives limit coverage to cancer clinical trials, in part because the national infrastructure surrounding cancer trials is the most established and comprehensive of all diseases and cancer clinical trials are subject to high levels of controls, monitoring, and oversight. State legislative efforts do not pertain to employees of self-insured corporations as defined under the Employee Retirement Security Act of 1974. Lastly, concern over variable scientific quality has led many state legislatures to limit reimbursement to trials funded by federal agencies. Although institutional review boards ensure that a trial is designed and conducted ethically, they do not assess scientific validity. However, this policy excludes a great many high-quality clinical trials that are funded by sources other than the federal government.

*Private insurer efforts.* Private insurers may be concerned that clinical trial costs are excessive, primarily as a result of extensive observation and testing periods. Uncertainty over reimbursement, rather than actual denial of reimbursement, may adversely affect participation in clinical trials. Furthermore, some clinical trials, such as trials of bone marrow transplantation for breast cancer, were undoubtedly expensive. In the early 1990s, private insurers who refused reimbursement for bone marrow transplants for breast cancer paid large jury awards and settlements to families of the affected individuals. Subsequently, many states and private insurers adopted policies to reimburse for the procedure. In 1999, findings of an absence of clinical benefit with bone marrow transplantation for breast cancer were reported. The reports had been delayed by several years because poor clinical trial accrual had led to an extended study period.

At the end of the prior decade, several large private health insurers agreed to reimburse for medical care that occurs with clinical trials. These insurers included the New Jersey Association of Health Plans, OhioMed, United Healthcare, and the Mayo Health Plan[14] (Table 6). The New Jersey Association of Health Plans agreement is unique in that it represents the first instance for which all private insurers in a single state have voluntarily agreed to provide cancer

**Table 5. State Legislative Efforts for Cancer Clinical Reimbursement**

| Cancer Clinical Trial Reimbursement Legislation | | | | |
|---|---|---|---|---|
| State Legislation | | | | |
| State | Year | Trial Purpose | Phase | Qualified Trials and Pending Initiatives |
| Alabama | | | | None |
| Alaska | | | | None |
| Arizona | 2000 | Prevention, palliation, treatment | I, II, III, IV | NIH, NIH COOP group, DVA, FDA, entity meeting NIH grant criteria, academic institutions in Arizona |
| Arkansas | | | | None |
| California | 2001 | | I, II, III, IV | NIH, FDA, DOD, DVA, trials of IND-exempt drugs |
| Colorado | | | | None |
| Connecticut | 2001 | Prevention, treatment | III (prevention); I, II, III, IV (treatment) | NIH, COOP groups, FDA, DOD, DVA |
| Delaware | 2001 | Treatment | Not specified | NIH, COOP group, cancer center, CCOP, DOD, DVA; part of state patients' bill of rights |
| District of Columbia | | | | None |
| Florida | | | | Bill introduced in 2001; did not progress through committee |
| Georgia | 2000 | Treatment | II, III, IV | Bill introduced to amend current law to include adults in NIH, COOP group trials; did not progress through committee |
| | 1998 | Treatment | II, III | Pediatric trials only, NIH, FDA, meets COG standards |
| Hawaii | | | | None |
| Idaho | | | | None |
| Illinois | 2000 | Treatment | II, III, IV | Terminally ill patients with no standard treatment, NIH, DHHS, FDA*, benefit must be offered but employer not required to purchase |
| Indiana | 2001 | Detection, prevention, treatment | I, II, III, IV (detection, prevention); II, III, IV (treatment) | Bill introduced, referred to committee, NIH trials |
| Iowa | 1998 | | | Health Insurance Consumers' Bill of Rights introduced but did not come out of committee |
| Kansas | | | | None |
| Kentucky | | | | None |
| Louisiana | 2000 | Detection, prevention, treatment | II, III, IV | NIH, COOP group, cancer center, FDA, DOD, DVA, Coalition of National Cancer Cooperative Groups |
| Maine | 1999 | Treatment | Not specified | DHHS, NIH, COOP group, cancer center |
| Maryland | 1999 | Prevention, early detection, treatment | I, II, III, IV | NIH, NIH COOP group, DVA, FDA, academic center in Maryland, IRB-approved trials at institution with MPA from OHRP |
| Massachusetts | | | | Bills introduced in House and Senate, referred to committee |
| Michigan | | | | Voluntary agreement, pending final sign-off |
| Minnesota | | | | Voluntary agreement, pending final sign-off |
| Mississippi | | | | None |
| Missouri | | | | Bill introduced in 2001, referred to committee |
| Montana | | | | None |
| Nebraska | | | | None |
| Nevada | | | | None |
| New Hampshire | 2001 | Treatment | I-IV | NCI (COOP groups, centers, CCOPs), FDA, DOD, DVA, IRB-approved trials at institutions that have MPA from OHRP |
| New Jersey | 1999, 2000† | Prevention, early detection, treatment | II†, II†, III | Voluntary agreement covering NIH, FDA, DOD, DVA* |
| New Mexico | 2001 | Prevention, detection, treatment | I, II, III, IV | NIH, COOP group, cancer center, DOD, DVA, NIH-qualified nongovernment agency |
| New York | 2001 | | | Bill introduced for coverage of "experimental drugs" for breast cancer; referred to committee |
| North Carolina | 2001 | | | Two bills introduced, still in committee |
| North Dakota | | | | None |
| Ohio | | | | Coverage of trials on individual case basis |
| Oklahoma | 2001 | | | Bill introduced, but clinical trial clause removed in conference committee |
| Oregon | | | | None |
| Pennsylvania | 2001 | | | Bill reintroduced, still in committee |
| Rhode Island | 1995, 1997† | Treatment | II†, III, IV | NIH, NCI, COOPs, DVA, FDA, NIH-qualified institute following NCI guidelines |
| South Carolina | | | | None |
| South Dakota | | | | Possible coverage through off-label drug provision |
| Tennessee | | | | Possible coverage through off-label drug provision |
| Texas | | | | None |
| Utah | | | | None |
| Vermont | 2001 | Prevention, early detection, treatment | I, II, III, IV | Cancer trials at Norris Cotton Cancer Center and Vermont hospitals |
| Virginia | 1999 | Treatment | II, III, IV | NIH, VA, FDA, academic center in Virginia |
| Washington | | | | Two bills did not progress through committee in 1999 and 2000; not yet reintroduced |
| West Virginia | | | | None |
| Wisconsin | 1999 | | | Voluntary agreements by selected payers associated with UWCCC |
| Wyoming | | | | None |

Abbreviations: CCOP, Community Clinical Oncology Program; COG, Children's Oncology Group; IRB, institutional review board; MPA, Multiple Project Assurance; OHRP, Office of Human Research Protection; UWCCC, University of Wisconsin Comprehensive Cancer Center.

*These projects will include an analysis of the economic impact of clinical trial reimbursement.

†Expanded benefits added at the later date.

Table 6. Private Insurance Plan Agreements for Cancer Clinical Trial Reimbursement

| Private Insurance Plan Agreements | | | | |
|---|---|---|---|---|
| Organization | Year | Trial Purpose | Phase | Qualified Trials |
| New Jersey Association of Health Plans | 1999, 2000* | Prevention, early detection, treatment | I*, II*, III | NIH, FDA, DOD, DVA† |
| Ohio Med | 2000 | Treatment | II, III | NCI (NIH) trials only† |
| United Healthcare | 2000 | Prevention, diagnosis, treatment | I, II, III, IV | Trials of COOP groups participating in Coalition of National Cancer Cooperative Groups and trials of the Coalition† |
| Aetna US Healthcare | 2000 | Not specified | Not specified | FDA, NCI, or similar national cooperative body |

*Expanded benefits added at the later date.
†These projects will include an analysis of the economic impact of clinical trial reimbursement.

clinical trial coverage. The agreement was the result of a collaborative effort of a working group consisting of insurers, consumers, and physicians. In the face of recent expansion in state legislation on health insurance, Michigan and Minnesota have recently followed the New Jersey example by encouraging collaborative task forces to work with private insurers to voluntarily pursue clinical trial coverage. Policy makers in Minnesota felt that a voluntary agreement among insurers avoided the antagonistic nature of mandated health coverage and would more likely lead to a broader definition of qualified clinical trials than piecemeal legislation. Voluntary initiatives might also foster cooperation. However, the task force from New Jersey also warned that oversight of the insurance agencies was still warranted.

## DISCUSSION

A paradox exists in reimbursement policies in which insurers may refuse to cover a promising new therapy because it is available only through clinical trials while covering what is considered standard treatment even though it may often be ineffective and sometimes more expensive. Pilot studies have found that the incremental costs and charges of clinical trial participants are similar or only slightly greater than those incurred by patients not enrolled onto clinical trials. It is expected that the large RAND/NCI Costs of Clinical Trials Study, which addresses phase II and phase III studies, the AACI/Northwestern University Clinical Trials Costs and Charges Project, which addresses phase I studies, and the economic projects built into several of the health policy initiatives will provide empirical data that allow for derivation of generalizable estimates of the costs of clinical trials. The small cost increment observed in pilot studies to date is justified by the additional benefits that clinical trials bring to all patients. If increased clinical trial enrollment could facilitate the completion of a trial that demonstrates an innovative therapy to be effective or a current therapy to be ineffective even a year earlier, thousands of lives could potentially be saved. Moreover, clinical trials remain our best source of information on drug safety. During phase I, II, and III clinical trials, reporting of adverse events is virtually complete, with comprehensive reports of these events as well as assessments of possible or definite causality. Identification of rare but potentially fatal side effects is facilitated in the clinical trial setting.

There are three strategic options for addressing clinical trial reimbursement: litigation, legislation, and voluntary cooperation. Litigation, as might be suggested by the bone marrow transplant studies in breast cancer, may be unlikely to lead to the most coherent, egalitarian, and entirely scientific reimbursement policy. Legislation and voluntary industry initiatives are the most probable paths to rational health policy decisions about clinical trial reimbursement. Initiatives such as the DOD/NCI cancer clinical trials demonstration project have started slowly, but the numbers of participants in the DOD demonstration in 2000 almost doubled from the year before and will most likely double again this year. Several states, several large private insurers, and Medicare have agreed to reimburse for medical care that occurs in the setting of certain clinical trials, although phase I clinical trials are frequently excluded. Medicare has made the largest leap in extending coverage to all clinical trials and drafting criteria to extend the range of qualified clinical trials beyond those sponsored by the NIH, DVA, or DOD. The New Jersey Working Group expects that their health insurance cooperative agreement, which covers 98% of insured patients in New Jersey, will increase the 3.3% rate of New Jersey cancer patients currently on clinical trials to 15% in 3 years.

Most major improvements in cancer treatment have been accomplished through controlled clinical trials. While a Harris Interactive survey found that both the general public as well as persons who participated in cancer trials had a favorable impression of clinical trials,[2] only 4% of cancer patients participate in these studies. If recruitment to clinical

trials continues to be poor, then the generalizability and timeliness of clinical trial findings will be jeopardized. Enrolling large numbers of patients onto clinical trials facilitates translational efforts to identify the most effective medical treatments, enhances comprehensive assessments of drug safety, and helps identify therapies that are likely to be ineffective. Finally, if empirical data continue to show that clinical trials result in only modest increases in costs, and if broad-based policy initiatives continue to occur, then there is no reason that clinical trial coverage should not ultimately be a permanent benefit that is supported by federal, state, and private sector policies.

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# Incremental Costs of Enrolling Cancer Patients in Clinical Trials: a Population-Based Study

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***Background:*** **Payment for care provided as part of clinical research has become less predictable as a result of managed care. Because little is known at present about how entry into cancer trials affects the cost of care for cancer patients, we conducted a matched case–control comparison of the incremental medical costs attributable to participation in cancer treatment trials.** ***Methods:*** **Case patients were residents of Olmsted County, MN, who entered phase II or phase III cancer treatment trials at the Mayo Clinic from 1988 through 1994. Control patients were patients who did not enter trials but who were eligible on the basis of tumor registry matching and medical record review. Sixty-one matched pairs were followed for up to 5 years after the date of trial entry for case patients or from an equivalent date for control patients. Hospital, physician, and ancillary service costs were estimated from a population-based cost database developed at the Mayo Clinic.** ***Results:*** **Trial enrollees incurred modestly (no more than 10%) higher costs over various follow-up periods. The mean cumulative 5-year cost in 1995 inflation-adjusted U.S. dollars among trial enrollees after adjustment for censoring was $46 424 compared with $44 133 for control patients. After 1 year, trial enrollee costs were $24 645 compared with $23 964 for control patients.** ***Conclusions:*** **This study suggests that cancer chemotherapy trials may not imply budget-breaking costs. Cancer itself is a high-cost illness. Clinical protocols may add relatively little to that cost.** [J Natl Cancer Inst 1999;91:847–53]

As health plans have become more adept at reviewing and managing the care received by their covered populations, payment for care provided as part of or incident to clinical research protocols has become less predictable *(1)*. As a matter of federal policy, Medicare does not pay for routine patient care delivered in clinical trials unless that care would be necessary without the trial.

Managed care administrators are understandably concerned that patient enrollment in cancer clinical trials increases medical care cost. Although this concern may be justified in certain well-publicized cases, such as very expensive new treatments for conditions with no currently available therapy, cancer clinical trials span a wide array of interventions and disease stages. Most cancer trials today involve the use of chemotherapy. Little is known at present whether the treatment regimens of cancer trials increase or decrease the costs of care over the remaining lifetimes of cancer patients.

Information on the incremental patient care costs (or cost savings) associated with cancer clinical trials can help put such concerns into proper perspective and, thereby, facilitate arrangements for patients insured by managed care organizations to participate in such studies. To our knowledge, no published study has evaluated the costs associated with participation in cancer trials. Estimates of differences in patient care costs between trial enrollees and equivalent patients receiving conventional cancer care across a wide spectrum of clinical studies can assist in fiscal planning, negotiations for sharing of patient care costs, and financial risk management.

For these reasons, we conducted a matched case–control comparison of the cumulative incremental patient care costs attributable to participation in phase II and phase III cancer treatment trials from the date of trial entry until either death or 60 months after trial entry.

## Subjects and Methods

### Selection of Case Patients

We identified all residents of Olmsted County, MN, who entered cancer clinical trials at the Mayo Clinic Cancer Center from January 1, 1988, through December 31, 1994. This sampling period permitted relatively complete enumeration of the 5-year history of medical services used by trial participants. The Rochester Epidemiology Project, a cooperative effort of the principal sources of medical care in Olmsted County, provides an umbrella for population-based research, including a comprehensive medical care utilization database *(2)*. The year 1988 was chosen as the earliest date for inclusion in the study for the following two reasons: 1) Health care utilization and cost data are available in electronic form for 1987 and later, and 2) changes in medical technology or in the nature of clinical protocols could invalidate earlier data.

Identification of case patients began with an inventory of all clinical protocols at the Mayo Clinic Cancer Center that were accruing patients during the sampling period. All of the protocols were funded by the National Cancer Institute either through the North Central Cancer Treatment Group or directly to the Mayo Clinic Cancer Center, and all were chemotherapy trials. Selected data on each protocol and on each patient enrolled during the study period were obtained from electronic and paper files maintained at the Mayo Clinic Cancer Center.

All protocols were screened to eliminate nonclinical or ancillary studies, such as those involving only record reviews or secondary analyses of laboratory specimens. The remaining protocols fell into one of the following five trial types: 1) pilot trials, 2) phase I treatment trials, 3) phase II treatment trials, 4) phase III treatment trials, or 5) cancer control trials. We merged the lists of participants in each protocol into a master list of unique patients enrolled in one or more cancer clinical trials, and we further restricted the sample to those who had enrolled in at least one phase II or phase III study.

Many patients participated in more than one cancer trial. Although no patients participated simultaneously in more than one treatment trial, some entered two or more treatment trials sequentially during the study period or participated simultaneously in a treatment and a cancer control study. Approximately 10% of all case patients participated in more than one trial during the study period. We regard multiple trial enrollments partly as consequences of the familiarization of patients with the clinical research environment and the frequent contact between trial participants and clinical research teams. Thus, entering one trial may pre-

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*See* "Notes" following "References."

dispose individuals to enter other trials, with their accompanying cascade of cost impacts. Therefore, we did not exclude case patients from the sample if they were enrolled in more than one cancer trial over the study period, provided that the first trial entered was a qualified phase II or phase III treatment trial.

We excluded all trial participants who were not residents of Olmsted County on the date of trial enrollment. Of 2466 individuals enrolled at Mayo Clinic Cancer Center in phase II or phase III cancer treatment trials in the study period, 176 (7%) were Olmsted County residents on the date of trial enrollment.

## Selection of Control Patients

The selection of control patients occurred in a two-stage process designed to maximize similarity between case patients and their matched control patients on demographic and clinical characteristics likely to affect both trial eligibility and prognosis independent of the trial. We balanced the goal of achieving demographic and clinical equivalence between case patients and control patients against the constraints on the number of available control patients.

In the first stage, we identified all potential control patients through a review of the Mayo Clinic Tumor Registry. We matched the characteristics of the 176 case patients with those of all cancer patients recorded in the registry. Potential control patients were Olmsted County residents who between 1988 and 1996 were classified as having malignant disease diagnosed before autopsy and as having a date and place of treatment recorded in the Mayo Clinic Tumor Registry. Registry data elements in the first-stage matching criteria included age, sex, site of the primary cancer, stage of cancer, and year of diagnosis. Year of diagnosis pertained either to the initial diagnosis of cancer or to the initial diagnosis of metastatic disease as discussed below. An age range of up to 17 years was allowed in matching the control patient with a case patient. Patients were matched for the site of their primary tumor by use of the three-digit code as described in the International Classification of Diseases for Oncology (ICD-O) *(3)*, with additional groupings to minimize the number of case patients for whom no match would be found.

We developed an algorithm to match the date of diagnosis of each potential control patient with that of the case patient. Treatment protocols were divided into those for metastatic and those for nonmetastatic disease. Using this separation, we matched potential control patients with nonmetastatic disease on their initial date of diagnosis of cancer. Potential control patients whose diagnosis date was within 3 years of the case patient's diagnosis date were accepted, except for patients with colorectal cancer. Because surgical adjuvant therapy became standard medical practice in 1990 for treatment of colorectal cancer, case patients diagnosed in 1989 and earlier were matched only with potential control patients also diagnosed within 3 years of the case patient in 1989 or earlier. Case patients whose colorectal cancers were diagnosed in 1990 or later were matched only with potential control patients diagnosed in that later period. Case patients entered into protocols for treatment of metastatic disease were matched in the same way, except that the relevant diagnosis date was the date of diagnosis of metastatic disease as recorded in the Mayo Clinic Tumor Registry. Patients with colorectal cancer were again divided into those diagnosed before 1990 and those diagnosed in 1990 or later.

Through the above process, we identified 617 unique potential control patients for 133 case patients undergoing treatment on protocol. Thus, 43 (24%) of the 176 case patients could not be matched in the first stage.

In the second stage, the medical records of potential control patients identified in the first stage were reviewed to further ascertain their appropriateness as matches. Review of the medical records began with the potential control patients for those case patients with the fewest available potential control patients. Potential control patients for each case patient were randomly assigned a rank order for medical record review. If a potential control patient met the eligibility criteria for a case patient's clinical protocol, his or her record was selected and was ineligible for selection as a control patient for any other case patient. In the interests of time, we further elected to restrict the number of potential control patients for any case patient to no more than 10, when a case patient had more than 10 potential control patients.

The matching criteria used in the medical record review were the eligibility criteria specific to the relevant treatment protocol and an assessment of the patient's performance status. We considered performance status to be an important predictor of both longevity and ability to tolerate therapy. Trial eligibility criteria generally included type and stage of cancer, specific laboratory parameters, and performance status as measured by the criteria of the Eastern Cooperative Oncology Group *(4)*. To be considered eligible for the trial, the potential control patient's medical record could have no mention of a condition or finding violating protocol eligibility at any time from diagnosis date to an assigned trial entry-equivalent date. The trial entry-equivalent date for the control patient was chosen so that the period between the date of diagnosis and the date of entry (or entry-equivalent date) in the trial would be the same for both patients in a matched case and control pair. (For example, if the case patient was diagnosed with cancer of the cervix on January 1, 1990, and entered a phase II or phase III trial for cervical cancer on January 1, 1991, then the matched control patient who was diagnosed with cervical cancer on January 1, 1992, would be assigned a trial entry-equivalent date of January 1, 1993.) The second stage yielded matches for 61 (46%) of the 133 case patients surviving the first-stage matching process.

## Cost Measurement

The primary end point of the study was the cumulative 5-year incremental medical care cost. This cost was defined as the total excess cost for case patients compared with that of equivalent control patients incurred from trial entry date or trial entry-equivalent date until the date of death or the end of the 60th 30-day month, whichever came first. The follow-up period was limited to 5 years because too few observations would be available to provide stable cost estimates beyond this period. Secondary end points were the excess cost incurred by participants from the date of enrollment in the trial to the end of the 12th month and the average monthly cost incurred throughout the follow-up period.

The Olmsted County utilization database, an archived source of provider billing data for Olmsted County medical care providers, was the basis for cost estimation. This database is available in electronic format starting with 1987 data and presently containing data through the end of 1995. It captures 90%–95% of all physician and hospital services used by Olmsted County residents *(2)*. The proportion may be even higher for cancer patients.

Although complete capture of all categories of health care costs was the goal, certain categories were excluded, notably outpatient prescription drugs, durable medical equipment, ambulance and other transportation services, outpatient services provided by allied health professionals (such as physical and occupational therapists or clinical psychologists), and nursing home care. The utilization database includes services in these categories provided by the medical facilities participating in the Rochester Epidemiology Project, but it does not include items provided by drugstores, dispensers, distributors, and independent allied health professionals. In the interests of consistency, therefore, we eliminated all such services from the cost estimates. We also did not capture services provided to study subjects outside Olmsted County, such as the Veterans Affairs Medical Center in Minneapolis or the University of Minnesota Hospital, because the utilization database does not include these institutions. Also excluded were the costs of experimental agents provided free of charge by trial sponsors or third parties such as drug companies. These items did not enter the billing systems of the institutions participating in the Rochester Epidemiology Project.

The utilization database contains detailed billing records for every medical encounter and service rendered by the participating providers. We used a costing system developed by researchers at the Mayo Clinic to assign a unit cost to each service. That system assigns a standardized inflation-adjusted unit cost to each service or procedure in 1995 U.S. dollars. Although the services provided represent the practice choices of Olmsted County providers, the value of each unit of service has been adjusted to national cost norms by use of widely accepted valuation techniques *(5)*.[2]

The use of standardized unit costs is desirable because of the well-known discrepancies between billed charges, which are directly available in the utilization database, and "opportunity" costs in health care *(5–8)*.[3] These differences vary by type of service, among providers, and over time, so billed charges can give a distorted picture of cost differences between groups of patients treated with different services over various times. The unit costing system assigns 1995 Medicare fee-schedule rates to all physician and outpatient ancillary services provided from 1987 through 1995. Hospital charges are converted to costs by applying department-level cost-to-charge ratios reported by all hospitals to Medicare. Each unit cost is normalized to a national 1995 value by use of regional hospital market-basket indexes reported annually by the Prospective Payment Assessment Commission *(9)*.

Lifetime (or 5-year) cost is most appropriately measured as the net present value of the stream of costs incurred over time from the trial entry date to the date of death or the end of the 5-year measurement period. The net present value of cumulative cost is the sum of costs incurred at each time point, weighted by a discount factor that reflects the decay in the value of money from trial entry to the time at which the cost is incurred. A commonly used annual discount rate for health care spending is 3% after adjustment for inflation *(10)*. We estimated

cumulative 5-year costs by using discount rates of 0% (i.e., no discounting) and 3%.

Although cost data are available at the level of the individual service and can be reported at any level of aggregation and by any unit of time, the small sample size precluded analysis of specific cost components (e.g., inpatient hospital, physician, and laboratory) or periods shorter than each 30-day interval after the trial entry or trial entry-equivalent date. Preliminary analysis of costs at a more disaggregated level showed no discernible patterns contradicting the findings for total medical costs.

### Statistical Analysis

The primary analysis of cost differences was conducted on the total sample of 122 observations, containing 61 matched pairs of case and control patients. Paired comparison formed the primary basis of analysis involving intrapair differences in costs before adjustment for censored observations. Two-sample comparisons were also conducted of the Kaplan–Meier sample average cost, an estimate of mean cumulative (5-year) cost across a population in the presence of censored observations *(11,12)*. The Kaplan–Meier sample average cost estimator has been shown to be an unbiased estimate of cumulative cost under conditions of independent censoring of observations, whereas cost analysis that is not adjusted for censored observations may be biased *(12,13)*.

All comparison-wise type I error rates were set at 5%, and all testing procedures were two-sided. Paired *t* tests based on matched samples of 61 observations provide 80% power to detect differences of 0.37 standard deviation from zero, a moderate effect size according to Cohen's classification *(14)*. The observed standard deviation of the differences in total cost was $74 354, so the 61 observations provided 80% power to declare an intrapair average difference of $27 510. Paired *t* tests on log-transformed costs led to no differences in inference and, therefore, are not reported. Power for the nonparametric procedures was of a comparable nature, given the assumptions of nonnormality. All *P* values are two-sided.

## Results

### Characteristics of Case and Control Patients

Table 1 shows the characteristics of case patients and control patients who survived each step of the matching process. The 133 case patients successfully matched in the first stage were similar to the original sample, except that those case patients for whom matches were found had poorer performance scores on average ($P<.001$).

The first-stage matching process found 617 unique control patients eligible for chart review. Patients with breast cancer and early stage cancers were heavily overrepresented in the pool of potential control patients, whereas patients with gastrointestinal cancers were underrepresented. The disproportionately small number of potential control patients with gastrointestinal cancers may have resulted from the stringent diagnosis date criteria used to match colorectal cancer patients.

Many potential control patients identified in the first stage of matching were rejected in the second stage of matching. Of the 133 case patients surviving the first stage, only 61 were successfully matched in medical record review. These 61 case patients were enrolled in 36 different clinical protocols. The majority (54%) of excluded control patients were not eligible for the trial or were not clinically equivalent to the case patient (Table 2). In 36% of the excluded records, however, discrepancies were found between the medical record and other data sources, particularly the tumor registry.

Comparison of case and control patients showed no statistically significant differences in the proportion of case patients who were censored, in the median number of months of follow-up, or in survival. By the end of the cost measurement period (December 1995), 45 (74%) case patients and 41 (67%) control patients had died. In 34 (56%) of the 61 matched pairs, both case and control patients died; in nine (15%) of the 61 matched pairs, both were still alive at the end of the cost measurement period. Roughly 10 subjects per year had index dates during the period from 1988 through 1991, and roughly five matched pairs per year had index years during the period from 1992 through 1994.

Table 1. Selected characteristics of case patients and control patients*

| | | First-degree matches | | | Final matches | | |
|---|---|---|---|---|---|---|---|
| | Original case patients | Case patients | Control patients | Two-sided $P$† | Case patients | Control patients | Two-sided $P$† |
| No. | 176 | 133 | 617 | | 61 | 61 | |
| Male, % | 44.3 | 46.6 | 29.5 | .001 | 50.8 | 50.8 | 1.0 |
| Censored, % | NA | 18.1 | 62.6 | <.001 | 24.6 | 32.8 | .32 |
| By site of cancer, % of total patients‡ | | | | .001 | | | 1.0 |
| Unknown | 2.3 | 3.0 | 0.8 | | 0.0 | 0.0 | |
| Gastrointestinal | 38.6 | 39.1 | 17.7 | | 32.8 | 32.8 | |
| Genitourinary | 13.6 | 12.0 | 5.8 | | 14.8 | 14.8 | |
| Breast | 11.9 | 15.8 | 44.1 | | 18.0 | 18.0 | |
| Lung | 9.7 | 12.8 | 18.0 | | 18.0 | 18.0 | |
| Central nervous system | 8.0 | 5.3 | 2.1 | | 3.3 | 3.3 | |
| Blood | 4.0 | 6.8 | 9.1 | | 9.8 | 9.8 | |
| Head/lymphatic | 1.8 | 5.3 | 2.4 | | 3.3 | 3.3 | |
| Other | 9.1 | 0 | 0 | | 0 | 0 | |
| By stage group, % of total patients‡ | | | | .001 | | | 1.0 |
| 1 | 11.9 | 14.3 | 38.1 | | 9.8 | 9.8 | |
| 2 | 14.8 | 12.0 | 14.6 | | 8.2 | 8.2 | |
| 3 | 34.1 | 32.3 | 23.8 | | 37.7 | 37.7 | |
| 4 | 34.1 | 34.6 | 14.4 | | 34.4 | 34.4 | |
| Unknown | 5.1 | 6.8 | 9.1 | | 9.8 | 9.8 | |
| ECOG score 0–1, % of total patients | 90.3 | 62.6 | 18.5 | <.001 | 93.4 | 91.8 | .5 |

*NA = not available; ECOG = Eastern Cooperative Oncology Group.

†Paired *t* test.

‡Not all columns add up to 100 as a result of rounding.

Table 2. Reasons for exclusion of potential control patients through records review

| Reason for exclusion | No. of patients excluded | %* |
|---|---|---|
| Protocol eligibility violated | | |
| Nonmetastatic disease for metastatic protocol | 137 | 31.2 |
| Site of metastatic disease not appropriate to protocol | 8 | 1.8 |
| Age outside protocol eligibility requirement | 1 | 0.2 |
| Other eligibility criteria not met | 30 | 6.8 |
| Patient otherwise nonequivalent | | |
| Too ill or poor performance status | 43 | 9.8 |
| Metastasis outside trial entry time frame | 19 | 4.3 |
| Data errors | | |
| Misclassified in Mayo Clinic Tumor Registry | 109 | 24.8 |
| Not an Olmsted County resident | 4 | 0.9 |
| Treated at Federal Medical Center | 24 | 5.5 |
| Enrolled on study protocol | 22 | 5.0 |
| Control patient matched to another case patient | 22 | 5.0 |
| Patient eligible for standard treatment | 2 | 0.5 |
| Other miscellaneous | 18 | 4.1 |

*Numbers in this column do not add up to 100 as a result of rounding.

The index date differed between the case patient and the matched control patient by 38 days (average, mean, and median; paired $t$ test $P = .55$; Wilcoxon signed rank $P = .54$). The maximum difference in index dates observed was just over 1000 days. Control patients were followed on average 3.7 months longer than case patients (median = 0; $t$ test $P = .3$; Wilcoxon $P = .53$).

Thirty-six subjects (30% of the 122 observations in the study) were censored at termination of cost measurement (December 1995). Of the 36 censored observations, the medical records of 35 subjects were active after the termination date. Thus, one study subject (a case patient) was potentially lost to follow-up before the cost measurement termination date.

About one half of the patients in the 61 matched pairs were drawn from the population of patients with gastrointestinal or genitourinary cancers (Table 1), and 18% of the patients had breast cancer. All but 17% of the patients had late stage tumors. The sexes were represented about equally. All but four of the case patients as well as five of the control patients had an Eastern Cooperative Oncology Group performance status of either 0 or 1.

## Cost Comparisons

Summary statistics for total costs before adjustment for censored observations are given in Table 3. The mean 5-year cost per patient was slightly more than $40 000 for both case and control patients, but costs for case patients were approximately 5% higher than those for control patients, who did not participate in trials. These results were not statistically significant, however, and variability among the pairs was marked. Some case patients incurred costs that were more than $200 000 greater than the costs incurred by their matched control patients, whereas some control patients incurred costs that were more than $200 000 greater than the costs incurred by their matched case patients (Fig. 1).

Discounting health care costs to their present value made little difference to the cost estimates or to the estimated differences between case and control patients, largely because a high proportion of patients lived for less than 1 year and the selected annual discount rate was low. For example, the mean intrapair difference in 5-year discounted costs was $1998 compared with an undiscounted difference of $2120. Because cost levels and differences were generally insensitive to discounting, we report only undiscounted costs.

In the first 30 days, patients enrolled in trials cost an average of $569 more than the control patients. Costs incurred during the first 90 days were almost identical between the two groups. By the end of the first year, however, the mean difference between case and control patients had risen to about $900, or about 4% of the mean cost for a patient not enrolled in a cancer trial. The difference in median cost at the end of the first year was statistically significant ($P = .03$), but the difference in means was not. Differences beyond the second year became more difficult to interpret because of the small number of patients surviving at that point. Overall, the average cost associated with being enrolled in a clinical trial was consistently 5%–11% higher than

Table 3. Mean (median) costs for various times from index date (1995 U.S. dollars)

| | Total cost from index date* | | | | |
|---|---|---|---|---|---|
| Period | Case patients (n = 61) | Control patients (n = 61) | Difference† (case − control) | % difference | Two-sided $P$‡ |
| First month | $5718 ($1842) | $5149 ($1941) | $569 (−$453) | 11.1 | .78 (.43) |
| First 3 months | $11 955 ($6172) | $11 937 ($5347) | $18 ($752) | 0.2 | 1.0 (.69) |
| First 6 months | $18 492 ($9052) | $17 427 ($6138) | $1065 ($3830) | 6.1 | .84 (.01) |
| First year | $24 660 ($14 213) | $23 763 ($11 881) | $898 ($6771) | 3.8 | .88 (.03) |
| First 5 years | $43 495 ($29 639) | $41 375 ($19 185) | $2120 ($7284) | 5.1 | .22 (.13) |

*All costs are undiscounted and for censored observations.

†The transitive property of subtraction applies only to the means (e.g., the mean of the differences is the difference of the means). The other statistics are calculated on the basis of intrapair differences.

‡Paired $t$ test.

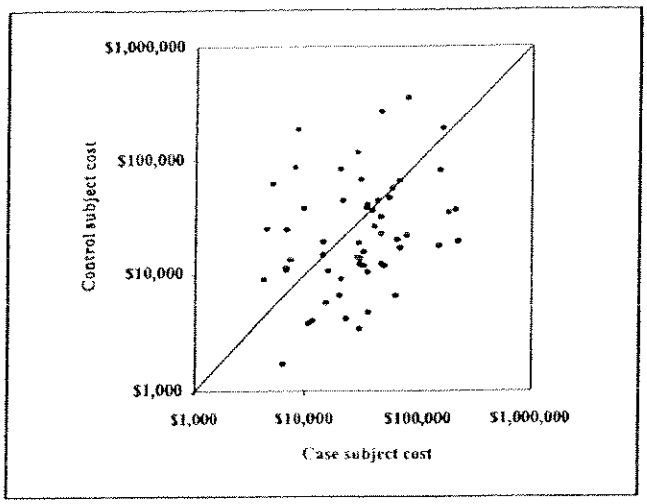


**Fig. 1.** Five-year cost comparison (log scales) for various case and control pairs presented in U.S. dollars adjusted to 1995 levels.

the average costs associated with not being enrolled in clinical trials.

For every 30-day month that a patient was alive and available to follow-up, the mean difference between case and control patients was $247, and the median difference was $366 (Table 4). Although neither of these measures was statistically significant, the median difference did have a $P$ value of .06. Thirty-nine (64%) of the pairs involved case patients who incurred more expenses than the matched control patient. Table 4 also presents the maximum monthly cost incurred for each patient. This analysis tests whether patients who enter trials experience bolus amounts of treatment upon initial entry or cause the system to incur greater catastrophic costs as a result of closer monitoring. Case patients had slightly higher costs on average ($177 and $1342 difference in the mean and median, respectively). However, in a substantial minority (25 pairs or 41%) of the 61 pairs, the maximum cost for the control patient was higher than that for the case patient.

We analyzed costs in the months preceding death for the 34 matched pairs in which both subjects died during the study period (Table 5). Costs in the last few months of life were higher for case patients than for control patients. In roughly 65% of the 34 pairs, case patients incurred greater costs consistently over the last year of life. Total 5-year costs in this subgroup averaged $49 400 per control patient, so costs incurred in the last 3 months of life amounted to about 15% of the total for control patients but were almost 29% for case patients. Patients in trials had monthly costs during the last 3 months that were twice as high as during the previous 9 months, whereas the monthly costs for control patients did not rise appreciably as death approached.

### Kaplan–Meier Analyses

Kaplan–Meier survival analysis did not reveal a statistically significant difference in survival (logrank $P = .06$), but control patients in the sample survived longer than did case patients (median survival time = 724 days and 493 days, respectively). After 1 year, the adjusted survival rate in case patients was 63 survivors per 100 subjects, compared with 68 survivors per 100 subjects in control patients.

The cumulative 5-year Kaplan–Meier sample average costs for case and control patients without discounting are shown in Fig. 2. The average cumulative 60-month cost after adjustment for censoring was $46 424 for the case patients and $44 133 for the control patients, a difference of 5.2%. This difference was not statistically significant ($P = .833$) based on an estimate of variance obtained by the bootstrap method involving 10 000 simulated samples *(15)*. At the end of the first 12 months, the Kaplan–Meier sample average cumulative cost was $24 645 for case patients versus $ 23 964 for control patients, a difference of 2.8%. In 61% of the bootstrapped samples, case patients had higher 5-year Kaplan–Meier sample average costs than control patients. Discounting at a rate of 3% per year had minimal effect on the results. Thus, the estimated costs for each group and cost differences between the two groups were essentially the same when adjustments were made for censored observations as when they were not.

## Discussion

This population-based study of the incremental patient care costs associated with participation in cancer trials showed that trial enrollment was associated with a modest (5%–10%) increase in costs over various follow-up periods. These results were robust across a variety of statistical procedures and distributional or logistic assumptions. The bulk of additional costs attributable to trial participation occurred in the first few months after trial enrollment. The observed cost differences decreased as time progressed. However, of those pairs whose members were

**Table 4.** Monthly cost estimates (1995 U.S. dollars)

| | Case patients (n = 61) | Control patients (n = 61) | Intrapair difference* (case − control) | Two-sided $P$† |
|---|---|---|---|---|
| Cost per month of follow-up | | | | |
| Mean (95% CI‡ for mean) | $2536 ($1894 to $3178) | $2290 ($1360 to $3220) | $247 (−$728 to $1222) | .61 |
| Median | $2052 | $1100 | $366 | .06 |
| Minimum | $89 | $63 | −$17 077 | |
| Maximum | $15 319 | $22 751 | $12 838 | |
| Maximum monthly cost | | | | |
| Mean (95% CI‡ for mean) | $10 709 ($7510 to $13 908) | $10 531 ($6328 to $14 734) | $177 (−$5094 to $5548) | .95 |
| Median | $6379 | $5545 | $1342 | .36 |
| Minimum | $278 | $268 | −$73 560 | |
| Maximum | $72 178 | $82 095 | $68 003 | |

*The transitive property of subtraction applies only to the means (e.g., the mean of the differences is the difference of the means). The other statistics are calculated on the basis of intrapair differences.

†Paired $t$ test.

‡CI = confidence interval.

Table 5. Mean (median) costs incurred (in U.S. dollars) within various times from death

| Period | Case patients (n = 34) | Control patients (n = 34) | Intrapair difference* (case − control) | Two-sided $P$† |
|---|---|---|---|---|
| Last months | $4038 | $3009 | $1029 | .44 |
| | ($1313) | ($223) | ($307) | (.18) |
| Last 3 months | $11 487 | $7311 | $4176 | .05 |
| | ($8844) | ($5189) | ($3769) | (.04) |
| Last 6 months | $18 304 | $10 789 | $7514 | .01 |
| | ($14 600) | ($10 142) | ($6417) | (.01) |
| Last year | $27 068 | $27 566 | −$498 | .95 |
| | ($23 174) | ($14 284) | ($9235) | (.07) |

*The transitive property of subtraction applies only to the means (e.g., the mean of the differences is the difference of the means). The other statistics are calculated on the basis of intrapair differences.

†Paired $t$ test.

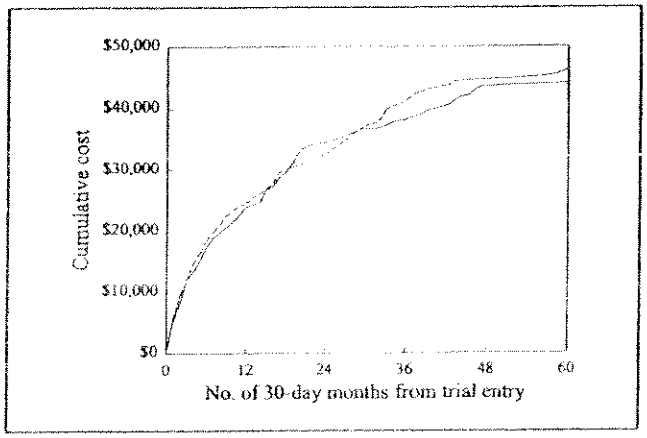


Fig. 2. Mean cumulative cost derived by the Kaplan–Meier sample average estimate. Data for the cost are expressed in U.S. dollars adjusted to 1995 levels. **Dashed line** = case patients. **Solid line** = control patients. The 95% confidence interval (CI) at 12 months after trial entry was $17 893–$31 397 for case patients and $13 244–$34 664 for control patients. At 60 months after trial entry, the 95% CI was $33 312–$59 536 for case patients and $27 610–$60 675 for control patients. These 95% CIs were based on estimates of variance obtained by the bootstrap method involving 10 000 simulated samples.

both followed until death, case patients incurred a substantially higher cost in the last 3 months of life than did control patients. Control patients in this sample lived longer than did trial participants, which may explain in part the decline in cumulative cost differences averaged across all subjects over the follow-up period.

Although several important categories of medical care costs went unmeasured, these were largely services that would be unlikely to differ systematically with trial enrollment. The most notable exception is outpatient prescription drugs. Experimental chemotherapeutic drugs are typically donated by the trial sponsor and would, therefore, not be part of the cost burden to patients or to insurers. However, other drugs, such as those for palliation of side effects or cancer symptoms, would add to patient care costs. If these outpatient prescription drug costs are higher under investigational protocols, their exclusion underestimates the incremental cost of clinical trials to patients and insurers. Also, to the extent that treatment trials compare an experimental drug donated by its sponsor with standard chemotherapy administered to hospital inpatients (whose costs were included in this study), the exclusion of experimental treatment costs underestimates the cost of cancer trials to society but not to insurers.

The longer survival of control patients in this sample affected the estimate of the per-month incremental costs of enrolling in a cancer trial. When total costs are divided by the number of months during which patients were available to follow-up, they were $247 per month higher for case patients than for control patients. However, over the full 5-year follow-up period, the Kaplan–Meier sample average monthly cost across the entire sample of case patients was only $38 higher than that for the control patients.

The high variation in 5-year costs within matched pairs underscores a major limitation of the study: its small sample size and the consequent limited statistical power to estimate true differences with much accuracy. High, unexplained variation in medical care expenditures is the rule rather than the exception throughout medical care. For example, in a study of non-elderly health maintenance organization enrollees in Minnesota, demographic and clinical predictors explained only 5%–10% of the variation in annual medical care costs *(16)*. Our data do suggest that health plans may find it difficult to manage the costs of cancer patients in general unless they can spread the risks across a large population.

This study demonstrated the difficulty that can be encountered in trying to match case patients with eligible control patients by the use of multiple criteria. Our two-stage matching process demonstrated that reliance on data elements typically available in institutional tumor registries is inadequate to ensure equivalence between patient groups. Not only are the data items collected in registries insufficient to describe the clinical and prognostic attributes of patients, but also sometimes they may disagree with the medical record on which they are based. Ironically, the pool of eligible control patients also may have been limited by the strong commitment to clinical research on the part of both cancer clinicians and patients in Olmsted County.

Even with intensive efforts to find equivalent patients through detailed medical records review, the case–control methodology cannot fully rule out the possibility of unobserved selection biases in trial enrollment. Those who choose not to enroll may be predisposed to use medical care more or less intensively than those who do enroll in such studies. Clinicians might also encourage patients with more aggressive disease to enroll in clinical trials. Some control patients might have been improperly declared eligible because clinical findings bearing on eligibility were not recorded in the medical record. We know of no studies

to suggest how such selection biases, if they exist, might be expected to affect treatment costs. Neither medical records nor clinical trial data systems routinely contain information on individuals who were judged eligible but refused enrollment. Systematic collection of such information as part of clinical trial designs would greatly facilitate the matching process in future research of this type.

That this study was conducted on cancer patients who were diagnosed at one institution and who resided in a single county with a population of approximately 110000 raises questions about the generalizability of the findings across a broader spectrum of health care environments. Most importantly, patients who did not enroll in trials typically were served by the same clinicians and health care providers as those who enrolled. Thus, they were not subjected to different practice styles apart from the circumstances of the trial. In other communities, the probability of trial enrollment might be contingent on the practice styles and referral pathways of the primary care and cancer providers. Larger differences (of unpredictable direction) in medical costs might result.

All of the clinical trials investigated in this study evaluated chemotherapeutic agents. None compared a highly expensive new technology, such as bone marrow transplantation for late stage breast cancer, with much less expensive conventional management, yet managed care organizations clearly focus on such "outlier" trials when they express misgivings about funding clinical research *(17)*. This study offers some reassurance that chemotherapeutic trials may not in and of themselves imply budget-breaking costs. Cancer itself is a high-cost illness. This study suggests that chemotherapy protocols may add relatively little to that cost. Replication of these results in other carefully designed studies across different care settings is needed before conclusive statements about relative costs can be made.

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## Notes

[1]The Rochester Epidemiology Project is an ongoing grant project funded since 1966 by Public Health Service grant AM30582-32 from the National Institute of General Medical Sciences, National Institutes of Health, Department of Health and Human Services, to link medical records from virtually all sources of medical care available to and used by the local population of Olmsted County, including the Mayo Clinic and its affiliated hospitals, the Olmsted Medical Center and its affiliated hospital, the University of Minnesota Hospitals, and the Veterans Affairs Medical Center in Minneapolis. The Rochester Epidemiology Project maintains the capability to electronically match patients' names and addresses with medical registration information for purposes of undertaking approved medical research projects.

[2]Detailed documentation of the unit costing methodology is available from the authors upon request.

[3]The logic behind the concept of opportunity cost is described by Kahn *(8)* as follows: "The basic economic problem, in short, is the problem of choice. A decision to produce one good or service is a decision to produce less of all other goods and services taken as a bunch. It follows that the cost to society of producing anything consists, really, in the other things that must be sacrificed in order to produce it." (page 66).

The views expressed in this article are those of the author and do not necessarily represent the views of the Congressional Budget Office.


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RAPID PUBLICATION

# 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

By Charles L. Bennett, Tammy J. Stinson, Victor Vogel, Lyn Robertson, Donald Leedy, Patrick O'Brien, Jane Hobbs, Tamara Sutton, John C. Ruckdeschel, Thomas N. Chirikos, Roy S. Weiner, Marguerite M. Ramsey, and Max S. Wicha

***Purpose:*** **Medical care for clinical trials is often not reimbursed by insurers, primarily because of concern that medical care as part of clinical trials is expensive and not part of standard medical practice. In June 2000, President Clinton ordered Medicare to reimburse for medical care expenses incurred as part of cancer clinical trials, although many private insurers are concerned about the expense of this effort. To inform this policy debate, the costs and charges of care for patients on clinical trials are being evaluated. In this Association of American Cancer Institutes (AACI) Clinical Trials Costs and Charges pilot study, we describe the results and operational considerations of one of the first completed multisite economic analyses of clinical trials.**

***Methods:*** **Our pilot effort included assessment of total direct medical charges for 6 months of care for 35 case patients who received care on phase II clinical trials and for 35 matched controls (based on age, sex, disease, stage, and treatment period) at five AACI member cancer centers. Charge data were obtained for hospital and ancillary services from automated claims files at individual study institutions. The analyses were based on the perspective of a third-party payer.**

***Results:*** **The mean age of the phase II clinical trial patients was 58.3 years versus 57.3 years for control patients. The study population included persons with cancer of the breast (n = 24), lung (n = 18), colon (n = 16), prostate (n = 4), and lymphoma (n = 8). The ratio of male-to-female patients was 3:4, with greater than 75% of patients having stage III to IV disease. Total mean charges for treatment from the time of study enrollment through 6 months were similar: $57,542 for clinical trial patients and $63,721 for control patients (1998 US$; *P* = .4).**

***Conclusion:*** **Multisite economic analyses of oncology clinical trials are in progress. Strategies that are not likely to overburden data managers and clinicians are possible to devise. However, these studies require careful planning and coordination among cancer center directors, finance department personnel, economists, and health services researchers.**

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MUCH CONCERN HAS been raised about the expense of clinical trials in oncology, despite the fact that only 3% of adult cancer patients actually participate in clinical trials. A major barrier to clinical trial accrual is related to financial considerations.[1-3] Many private insurers often do not reimburse providers for care associated with clinical trials and often deny payment for any medical care delivered to patients who are enrolled onto these trials. In June 2000, President Clinton ordered Medicare to reimburse for medical care that occurs in the context of clinical trials. Moreover, two large private insurers, the Mayo Health Plan and United Health Care, established policies in the late 1990s that reimburse for patient care costs incurred alongside National Cancer Institute (NCI)–associated clinical trials. However, fewer than 50 patients have actually been enrolled onto clinical trials as a result of these new policies.[4,5]

Policy makers focused on the financial aspects of cancer clinical trials as they considered enacting legislation or policies for clinical trials.[6] The Medicare Cancer Clinical Trial Act of 1997 sought to authorize a $750 million demonstration project that would have required reimbursement for routine patient care alongside an approved clinical trial, with a report to Congress due by January 1, 2002. The clinical trials that would have been covered were those that were conducted by a program that was approved by the

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National Institutes of Health (NIH), the national cooperative clinical trial groups, the United States Food and Drug Administration, the Department of Veterans Administration, the Department of Defense, or an NIH-sponsored cancer center. However, this legislation was not passed as a result of concerns over the actual economic impact of the policy, as well as the expense of the demonstration project. President Clinton's June 2000 policy order supporting clinical trial costs for Medicare recipients obviates the need for the Medicare demonstration project.

The President and Congress have been influenced in their efforts by estimates of the costs of clinical trials. Original estimates from the Congressional Budget Office were that costs of care alongside clinical trials were 25% greater than those associated with routine clinical practice, accounting for some of the hesitation in approving the Medicare Cancer Clinical Trial Act.[5] A high but declining portion of trial-related patient care costs was estimated by the Congressional Budget Office to be paid by private health insurance plans, because NIH covers only research costs and occasionally provides free pharmaceuticals when they are associated with an investigational agent. Until recently, empirical data on both the costs and charges of clinical trials have been lacking. The Mayo Clinic estimated that during the years 1988 through 1994, the costs of care for 61 clinical trial patients were found to be 3% to 13% greater in comparison with a matched control sample.[7] These data led the Congressional Budget Office to revise its estimates of incremental clinical trial costs to 10%.

The Association of American Cancer Institutes (AACI), a consortium of cancer institutes, has initiated a project to help inform policy makers on the costs and charges of NCI-sponsored phase I, II, and III clinical trials at cancer centers. After review of a pilot report on the feasibility, expense, and timeliness of data collection efforts, AACI member institutions will provide detailed cost and charge information on phase I, II, and III clinical trial patients and a matched cohort of patients not on clinical trials. In this report, we describe the overall goals and study methods and present the first set of pilot data for phase II clinical trials from the AACI/Northwestern University Cancer Clinical Trial Costs and Charges Project.

## METHODS

The AACI is a voluntary organization made up of representatives of cancer centers in the United States. For this study, centers were selected from regions with congressional members who were involved with federal legislative efforts related to reimbursement of clinical trials. These regions included Alabama, California, the District of Columbia, Florida, Louisiana, Massachusetts, Texas, New York, Illinois, Michigan, Ohio, Vermont, and Pennsylvania. The selected cancer centers included the University of Alabama at Birmingham Cancer Center, the Jonsson Comprehensive Cancer Center of the University of California at Los Angeles, the Lombardi Cancer Center of Georgetown University, the H. Lee Moffitt Cancer Center of the University of South Florida, the Tulane Cancer Center, the Dana-Farber Cancer Institute, the University of Michigan Cancer Center, the Memorial Sloan-Kettering Cancer Center, the Arthur James Cancer Center of Ohio State University, the Fox Chase Cancer Center, the University of Pittsburgh Cancer Institute, the M.D. Anderson Cancer Center, the Robert H. Lurie Comprehensive Cancer Center of Northwestern University, and the University of Vermont Cancer Center. A physician principal investigator and a financial investigator were appointed from each of the selected AACI cancer centers. The coinvestigators attended an introductory meeting that described the goals of the study, heard presentations from investigators at the Mayo Clinic, Memorial Sloan-Kettering, and the NCI who were involved in similar studies, and assisted with designing the project. Frequent conference calls followed to optimize the methodology. Because the timing of completion of the pilot study was targeted to provide background information for congressional members and staff who were proposing Patient Bill of Rights legislation for the 1999 congressional session, investigators devised a simple pilot study protocol that could be completed in a short time period with minimal resources. The economic analyses were based on the perspective of a third-party payer.

The physician principal investigators from each site were asked to recruit physicians from their cancer centers who treated the following common cancers: breast, colorectal, lung, prostate, ovarian, and lymphoma. Each investigator was asked to identify three to five patients treated for cancer in their specialty area on a phase II clinical trial and match these to patients treated using a standard regimen on the basis of age, sex, disease, stage, and treatment period. Information was also provided on the dates and type of treatment received for each patient. Patients selected were to be those who received all or most of their treatment at the cancer institute from 1996 through 1998. The financial coinvestigator was asked to obtain complete inpatient and outpatient billing data files for each patient, from the time of study enrollment (or the corresponding phase in treatment for standard-regimen patients) through 6 months.

Financial data (automated hospital billing files) and clinical data (abstracted by investigators) were de-identified and sent to economic analysts at Northwestern University. A tear sheet at the bottom of each case report form was the only identification of whether patients were treated on clinical trials or by standard methods. Data entry was blinded as to whether patients were on phase II clinical trials. Billing information was cross-checked for completeness using treatment dates and therapy descriptions provided on the case report forms. Descriptive statistics were summarized for the clinical characteristics of the study population, including age, sex, disease, and stage. Pearson $\chi^2$ tests were used to analyze differences in proportions. Mean total charges (inflation adjusted to 1998 US$) were compared using paired $t$ tests. Mann-Whitney U tests were used to compare median values. All type I error rates were set at 5%, and testing procedures were two-sided. The observed SD of the difference in total charges was $44,610, so the 35 paired samples provided 80% power to detect a difference of $29,882.

## RESULTS

Thirty-five matched pairs of patients from five cancer institutes were evaluated in this pilot effort. The majority of the patients were treated for breast cancer (n = 12 pairs), lung cancer (n = 9 pairs), and colon cancer (n = 8 pairs), but the data set also included prostate cancer (n = 2 pairs)

**Table 1. Study Group Characteristics: Clinical Trial Versus Standard Therapy Patients**

| | Trial Patients | | Control Patients | | |
|---|---|---|---|---|---|
| | No. of Patients | % | No. of Patients | % | *P* |
| Total no. of patients | 35 | | 35 | | — |
| Mean age, years | 58.3 | | 57.3 | | .73 |
| Sex | | | | | .99 |
| Male | 43 | | 43 | | |
| Female | 57 | | 57 | | |
| Disease | | | | | .99 |
| Breast cancer | 12 | 34.3 | 12 | 34.3 | |
| Colon cancer | 8 | 22.9 | 8 | 22.9 | |
| Lung cancer | 9 | 25.7 | 9 | 25.7 | |
| Lymphoma | 4 | 11.4 | 4 | 11.4 | |
| Prostate cancer | 2 | 5.7 | 2 | 5.7 | |
| Stage | | | | | .74 |
| I | 2 | 5.7 | 4 | 11.4 | |
| II | 5 | 14.3 | 3 | 8.6 | |
| III | 10 | 28.6 | 9 | 25.7 | |
| IV | 18 | 51.4 | 19 | 54.3 | |

and lymphoma (n = 4 pairs). Approximately 56% of the patients were treated by chemotherapy regimens alone, 19% with high-dose therapy with stem-cell rescue, and 19% with chemotherapy plus radiation. The study groups were evenly matched on the basis of clinical factors (Table 1). The mean age was 57 to 58 years and 43% were male. Approximately one quarter of the patients had stage III disease at the time of treatment, and more than 50% had stage IV disease. Both study groups had a similar proportion of survivors during the 6-month study period (33 of 35 for the clinical trial group and 34 of 35 for the control group). The nonsurviving patients in the clinical trial group were on study for 5.5 months, and the control patients for 4 months.

The total mean charges of treatment (in 1998 US$) from the time of study enrollment through 6 months were $57,542 (SD = $38,356) for clinical trial patients and $63,721 (SD = $48,393) for control patients (Table 2). The mean difference, $6,180, was not statistically significant ($P$ = .42). Median 6-month charges were also similar between clinical trial patients (median, $47,375; range, $8,584 to $148,305) and control patients (median, $50,827; range, $5,549 to $220,468; $P$ = .69). The mean charges for stem-cell transplantation patients were $107,377 for clinical trial patients and $123,255 for control patients ($P$ = .57). When 6-month charges for clinical trial and control patients were compared by type of cancer, mean charges were similar

**Table 2. Total Charges From Enrollment Through 6 Months of Treatment: Clinical Trial Versus Standard Therapy Patients (1998 US$)**

| | Trial Patients ($) | Control Patients ($) | Difference (trial − control) ($) | Difference (%) | *P* |
|---|---|---|---|---|---|
| Total charges | | | | | |
| Mean | 57,542 | 63,721 | −6,180 | −10.7 | .42 |
| SD | 38,356 | 48,393 | | | |
| Total charges | | | | | |
| Median | 47,375 | 50,827 | −3,452 | −7.3 | .69 |
| Range | 8,584-148,305 | 5,549-220,468 | | | |
| Charges excluding stem-cell transplantation patients | | | | | |
| Mean | 45,083 | 48,838 | −3,755 | −8.3 | .60 |
| SD | 30,408 | 33,098 | | | |
| Charges for stem-cell transplantation patients | | | | | |
| Mean | 107,377 | 123,255 | −15,879 | −14.8 | .57 |
| SD | 23,535 | 56,323 | | | |

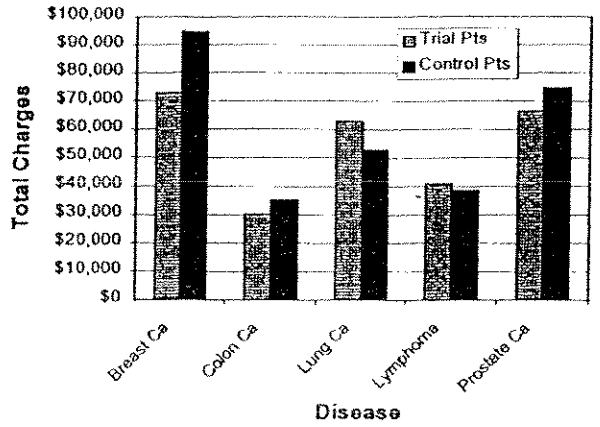


**Fig 1. Mean 6-month total charges (1998 US$) by disease: clinical trial versus control patients. Differences in charges for clinical trial patients were not significant from those for control patients. Abbreviations: Pts, patients; Ca, cancer.**

for each diagnosis (Fig 1). Mean 6-month charges for breast cancer patients were larger than for the other diagnoses due to the large number of patients who underwent stem-cell transplantation. The variability among the sample pairs was high but seems to be evenly distributed (Fig 2).

## DISCUSSION

Medicare and third-party payer coverage of clinical trial cancer treatment has been controversial. The AACI has undertaken a broad effort to help inform this debate. This article is the first report from the AACI/Northwestern University Cancer Clinical Trials Costs and Charges Project, an evaluation of financial information for clinical trial participants associated with phase II clinical trials conducted at NCI-designated comprehensive cancer centers. Proposed future analyses will include the costs and charges of phase I clinical trial patients (which will include individuals with all types of cancer diagnoses) and phase III clinical trial patients (which will include only patients with lymphoma or breast, lung, colorectal, prostate, and ovarian cancer). For each clinical trial patient, a control patient will be identified with the same approximate age, disease, stage, and time frame of treatment. For both the clinical trial patient and control patients, detailed financial information will be collected for a retrospective 6-month time period for phase I and phase II trials, and for a 2-year period for phase III trials. Medicare as well as privately insured patients will be included in the study.

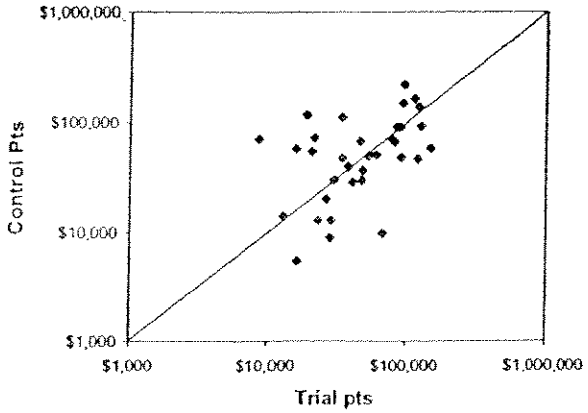


**Fig 2. Charge comparison (log scale) for case-matched trial and control patients (1998 US$).**

This study illustrates that our proposed strategy for obtaining financial information for clinical trial participants and a comparison group of patients can be readily carried out at several collaborating cancer centers. First, we were able to complete these analyses in a 5-month period by building on methods for financial data collection and analysis that have been developed by us and others, coordinating the economic study analysis with cancer center leadership at each participating center and working with a multidisciplinary project team that has been evaluating costs of cancer care for a decade.[8-14] Second, we addressed operational considerations, such as identifying control patients, by working closely with clinicians at individual institutions who had large clinical practices for each of the selected tumor types. Third, our economic analyses were based on detailed financial information obtained from each study site, where good communication channels had been developed with cancer center directors, physicians, and personnel in the finance departments. Data were available primarily in electronic form, allowing for affordable data entry as well as an evaluation of data quality. Fourth, good communication channels with the central office of the AACI were maintained throughout the project by frequent email and phone conversations. These operational issues are important to decision makers at cancer centers who must decide how to use resources that are scarce.

This project represents the first multisite attempt at evaluating the financial impact of clinical trials conducted by the AACI. In addition to receiving the results of our analyses, cancer center directors involved in the AACI have received feedback of the type and amount of work performed by clinicians, health services researchers, finance departments, and policy researchers; the costs of the study; and the levels of oversight that accompanied the data analysis to prevent bias in the evaluation. To make important policy decisions related to support for clinical trials, policy makers require detailed economic information but

must be able to obtain these data without disrupting the conduct of clinical efforts.

Our pilot study results from 70 cancer patients enrolled on phase II clinical trials found that, in 1996, charges for participants on cancer-related clinical trials were no greater than charges for participants incurred outside of the clinical trial setting. These estimates can be compared with those reported from other recent single-site studies. The Mayo Clinic reported that costs (not charges) of care for 122 matched cancer patients treated during an earlier time period, from 1988 to 1994, were similar for patients on a clinical trial and were not statistically different ($12,200 *v* $10,073).[7] Similarly, 6-month cost (not charge) estimates for 135 clinical trial and 135 matched control patients at Kaiser health maintenance organizations during 1994 to 1997 were similar to those reported from the Mayo Clinic ($12,242 *v* $9,930).[15] Two studies found that the financial impact of clinical trial participation was less than that associated with standard medical care. Preliminary findings from a study of 152 matched Medicare cancer patients from Memorial Sloan-Kettering Cancer Center, an AACI member institution, found mean 6-month charges similar to those found in our study and a 17% savings associated with participation in clinical trials in 1995.[16] Six-month costs (not charges) for advanced lung cancer patients treated at the Karmanos Cancer Center in Detroit were $1,400 less on average for clinical trial participants.[17] Taken together, the findings seem to have influenced policy makers in individual states. Comprehensive clinical trial legislation has been enacted in Rhode Island (July 1997), Maryland (May 1998), Georgia (July 1998), Virginia (April 1999), Louisiana (June 1999), Illinois (August 1999), and New Jersey (December 1999).[18] In June 2000, immediately after the presentations of the data from the AACI and Memorial Sloan-Kettering at the May 2000 American Society of Clinical Oncology Annual Meeting, President Clinton ordered the federal Medicare program to reimburse for medical care costs alongside clinical trials.

This project was designed with several objectives in mind. First, our pilot data were presented at briefings to policy makers who were considering congressional and presidential initiatives for clinical trial reimbursement, as outlined in various Patient Bill of Rights proposals introduced by congressional members in 1999, and more recently in the text of President Clinton's order to Medicare.[17] The first meeting of the AACI investigators occurred in February 1999, data were received from the first three centers within 2 months, and the pilot data analyses were completed within 5 months. Although a recently initiated RAND (Santo Monica, CA)/NCI study is designed to be comprehensive in scope, complete results may not be available until 2002. Second, the study methods must be valid. At our initial meeting, representatives from each of the AACI programs reviewed methodologic approaches associated with studies from the Memorial Sloan-Kettering Cancer Center, the Mayo Clinic, the Kaiser Permanente Health System, the Group Health system, and the NCI. Senior investigators from the NCI clinical trials and economics programs attended this initial meeting. Subsequent decisions about patient eligibility, data sources, and time frame were made by both physician and health services researchers. The final study protocol was reviewed by a senior investigator from the NCI Cancer Clinical Trial Cost Study and revisions were made on the basis of these comments. The overall methods were based on those reported previously as developed by health economists at Northwestern University and the NCI/American Society of Clinical Oncology Working Group on Cancer Costs and used in cost-effectiveness studies carried out in conjunction with the Eastern Cooperative Oncology Group, the Pediatric Oncology Group, and the Southwest Oncology Group, three of the largest NCI-sponsored cooperative clinical trial groups.[8-13] The expense of data collection efforts was borne entirely by the individual study institutions, without the benefit of external grant support. The study team for the project included a physician and a representative of hospital finance from each institution, who helped facilitate these efforts. Finally, the project has been designed to occur in stages. The initial efforts for the project were targeted to a small number of AACI centers to identify operational, institutional, financial, and intellectual concerns that would impact the subsequent roll-out of the project to the remaining AACI centers. Subsequent reports are proposed to include data from all 14 centers and incorporate economic information from phase I, II, and III clinical trials.

The limitations of our study design should be identified. First, the sample size of 70 patients is small but similar to that included in other recently reported estimates of clinical trial costs. However, our pilot results allow us to estimate that we will have adequate power to detect meaningful differences in costs and charges between clinical trial and control patients in our study of 2,100 patients enrolled on phase I, II, or III studies. Second, there is the potential for bias in the manner that the patients were selected. Investigators were asked to select three trial patients for a specific cancer, but instructions were not provided on how to do this in a random manner or by any bias-limiting selection process. In contrast, the Mayo Clinic and Kaiser studies of cancer trial costs matched on patient eligibility for specific clinical trials. As such, our study could have included patients with much more heterogenous conditions relative to the clinical trial patients. Third, data were collected from

five study institutions, which limits the generalizability of our findings. Fourth, our data were based on charges, not costs. Charges are always greater than costs, as evidenced by the mean charge for stem-cell transplantation patients of $120,000 in this study, in comparison with previously reported estimates of costs that are approximately one third to one quarter as great and mean 6-month charge estimates in the range of $60,000 in our study versus 6-month cost estimates from the Mayo Clinic and Kaiser health maintenance organizations that are only one fifth as great.[7,15,19,20] Although hospital-specific and resource-specific cost-to-charge ratios are available from the finance departments at each of our study institutions, these ratios vary markedly for individual resources and among the various cancer centers. Future analyses will report comparisons of both costs and charges for clinical trial and control patients. Finally, the selected time frame chosen for the study can influence the study results. Costs and charges of care in the first 6 months of treatment are likely to be less than those that are observed shortly before death, and the differences in costs and charges between clinical trial and control patients might be less. However, only three deaths were noted among our 70 study patients during the 6-month study period. The impact of clinical trial participation on terminal care costs will undoubtedly require a longer time period for evaluation.

In conclusion, the AACI/Northwestern University Cancer Clinical Trial Costs and Charges Project is likely to be an important source of information for policy makers faced with legislation about funding of cancer clinical trials. Pilot data on the charges associated with phase II clinical trials were completed in 5 months' time, followed methods outlined by investigators involved in similar studies in other settings, and were obtained without the need for external funds. These feasibility concerns are especially relevant today as cancer center directors consider participation in the larger AACI/Northwestern University Cancer Clinical Trials Costs and Charges Project, which will include 2,100 patients at 14 cancer centers who participated in phase I, II, and III clinical trials.

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# Cost of Care for Patients in Cancer Clinical Trials

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***Background:*** **Information on the costs of medical care for patients enrolled in clinical trials is needed by policymakers evaluating ways to facilitate clinical research in a managed care environment. We examined the direct costs of medical care for patients enrolled in cancer clinical trials at a large health maintenance organization (HMO).** ***Methods:*** **Costs for 135 patients who entered 22 cancer clinical trials (including 12 breast cancer trials) at Kaiser Permanente in Northern California, from 1994 through 1996 were compared with costs for 135 matched control subjects who were not enrolled in such trials. Cancer registry data and medical charts were used in matching the control subjects to the trial enrollees with respect to cancer site, stage, date of diagnosis, age, sex, and trial eligibility. The direct costs of medical care were compared between trial enrollees and the control subjects for a 1-year period, with data on costs and utilization of services obtained from Kaiser Permanente databases and medical charts.** ***Results:*** **Mean 1-year costs for the enrollees in trials were 10% higher than those for the control subjects ($17 003 per enrollee compared with $15 516 per control subject; two-sided $P = .011$). The primary component of this difference was a $1376 difference in chemotherapy costs ($4815 per trial enrollee versus $3439 per control subject; two-sided $P<.001$). Costs for the 11 enrollees in trials that had a bone marrow transplant (BMT) arm were approximately double the costs for their matched control subjects (borderline significance: two-sided $P = .054$). The $15 041 mean cost for the enrollees in trials without BMT was similar to the $15 186 mean cost for their matched control subjects.** ***Conclusions:*** **Participation in cancer clinical trials at a large HMO did not result in substantial increases in the direct costs of medical care. [J Natl Cancer Inst 2000;92:136–42]**

It is widely agreed that clinical trials are crucial to the evaluation of an ever-increasing number of new treatments, but there is growing concern that the availability of patients for clinical trials is constrained by managed care organizations reluctant to pay for costly "experimental" care *(1,2)*. As yet, little has been published about the medical care costs of patients enrolled in clinical trials. A recent National Cancer Institute (NCI) review of its clinical trials program, the largest in the world, suggested that " . . . if the clinical trials system is to survive in the managed care environment, greater effort must be made to determine the actual costs of trials with the ultimate goal of finding ways to cut costs without hindering quality" *(3)*. A full assessment of the overall cost of clinical trials should consider the costs of research infrastructure, data collection, and various indirect costs as well as the direct costs of medical care. Here we examine the latter.

We examined the cost of medical care received by cancer patients who entered clinical trials from 1994 through 1996 at Kaiser Permanente in Northern California, a large nonprofit health maintenance organization (HMO). We compared 135 patients enrolled in NCI-sponsored clinical trials with 135 matched control subjects, assessing the direct 1-year costs of medical care. Although trials open to Kaiser Permanente patients may not be representative of all trials and Kaiser Permanente patients in trials may not be representative of all patients in the same trials, analysis of the costs of care in trials at Kaiser Permanente may be useful beyond this HMO in evaluating ways to facilitate the conduct and financial support of cancer clinical trials in a managed care environment.

## Subjects and Methods

### Setting

Kaiser Permanente is a 50-year-old nonprofit HMO integrated with a multispecialty group practice that provided comprehensive health care to approximately 2.4 million people at 17 hospitals and 31 clinics in Northern California during the 1994 through 1997 study period. The Kaiser Permanente population is diverse with respect to race/ethnicity and socioeconomic status, although the poor, the unemployed, the rich, and the aged are somewhat underrepresented *(4)*. Approximately 100 patients per year enrolled in oncology clinical trials at Kaiser Permanente, trials sponsored mainly by the NCI (through the National Surgical Adjuvant Breast and Bowel Project [NSABP] and the Southwest Oncology Group [SWOG]) but increasingly by pharmaceutical/biotech companies. Kaiser Permanente oncologists ($n = 50$, of whom five constitute a steering committee that coordinates trials) open available trials to enrollment according to their perceptions of patients' needs and interests, their own scientific interest in the research, the burdens of the research on physicians and the health-care delivery system, and the adequacy of the resources provided. Enrollment in randomized bone marrow transplantation (BMT) trials for breast cancer patients has been robust (higher than most research centers). While it was assumed that medical care in BMT trials is costly, it was decided that open access to well-designed BMT trials was the best approach to dealing with the complex issues of BMT coverage in unforeseen situations.

For the study period, the Regional Cancer Registry at Kaiser Permanente records approximately 12 000 incident cases per year, including about 2000 incident cases per year of breast cancer, the cancer site of more than half of the Kaiser Permanente patients in clinical trials. The percentage of adult cancer patients eligible for a trial who enroll in a trial is modest (<10%) at Kaiser Permanente, as it is nationwide (perhaps 2%–3%).

Permission to conduct this research was obtained from the Institutional Review Board of the Kaiser Foundation Research Institute.

### Study Subjects and Follow-up Time

There were 237 patients who enrolled in NCI-sponsored trials at Kaiser Permanente from 1994, when automated cost data were first available, through 1996, the last year of enrollment, permitting a full year of follow-up. We sought matched control subjects (comparison subjects) with cancer for all 203 enrollees (86%) who were Kaiser Permanente members and who were included in the NCI's Surveillance, Epidemiology and End Results (SEER)[1] registry. For each enrollee, we identified as potential control subjects everyone in the SEER registry who met the following criteria: Kaiser Permanente membership with match-

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*See* "Notes" following "References."

ing cancer site and stage at diagnosis, sex, year of birth (within 5 years), and date of diagnosis (within 1 year).

For each trial enrollee, the medical charts of potential control subjects were reviewed in random order until a control subject was identified who met the eligibility criteria for the enrollee's clinical trial (but never enrolled in a cancer trial). For example, eligibility for NSABP B-28 required completely resected breast cancer confined to one breast and ipsilateral lymph nodes. Patients had to have had a total mastectomy or lumpectomy and axillary lymph node dissection and histologic confirmation of invasive adenocarcinoma with at least one involved axillary lymph node. In the presence of bone pain, they must have had a bone scan and/or an x-ray negative for metastases. They could not have had contralateral breast cancer, ulceration, erythema, infiltration of skin or underlying chest wall, or peau d'orange. The potential participants must have been female between the ages of 18 and 78 years, with a life expectancy of at least 10 years. At the time of randomization, they had to have a white blood cell count of at least 4000/mm$^3$ and a platelet count of at least 100 000/mm$^3$. They had to have normal bilirubin and aspartate aminotransferase or alanine aminotransferase levels. Their creatinine level must have been normal. Potential participants with a lumpectomy were ineligible if the primary tumor was greater than 5 cm on physical examination or if they had any of the following: an invasive tumor or ductal carcinoma *in situ* in resection margins, diffuse tumors on mammogram (unless surgically amenable to lumpectomy), ipsilateral mass following lumpectomy (unless histologically benign), or breast irradiation before randomization. The estrogen and progesterone receptor status was required before randomization. Patients could not have had any prior therapy for breast cancer other than surgery. They could not have any contraindication to doxorubicin or paclitaxel therapy, including myocardial infarction, angina pectoris requiring medication, and history of documented congestive heart failure. They could not have any nonmalignant systemic disease that precluded treatment or follow-up, including any psychiatric or addictive disorder that precluded consent.

Matched control subjects were found for 135 (67%) of the 203 trial enrollees (291 patients in the SEER registry identified as potential control subjects were rejected after chart review because they did not fully meet the matching criteria). A "start date" was identified for each enrollee and each matched control subject, marking the beginning of the 12-month follow-up period for which costs were ascertained and compared. For enrollees, the start date is the date of enrollment in the trial. For control subjects, we sought dates in the course of their clinical care that were likely to be similar clinically to the enrollees' dates of enrollment. Thus, if the enrollee received chemotherapy in the trial and the control subject also received chemotherapy (while eligible for that trial), then we began follow-up for the control subject on a date before chemotherapy (that was matched to the enrollee for the number of days before the start of chemotherapy). If either the enrollee or the matched control subject did not receive chemotherapy, our algorithm for identifying the beginning of the control subject's follow-up then depended on whether or not the referent enrollee had metastatic disease when enrolled in the trial. If so, we counted the days from the enrollee's diagnosis of metastatic disease until enrollment, we then added this number of days to the date on which the control subject was diagnosed with metastatic disease to obtain the control subject's start date. Finally, if the enrollee did not have diagnosed metastatic disease on the date of enrollment, we counted the days from the enrollee's last hospital discharge date prior to enrollment (or cancer diagnosis date if this was later) until enrollment; we then obtained the control subject's start date by adding this number of days to the last hospital discharge date (or cancer diagnosis date) of the control subject prior to eligibility for the trial.

In four matched pairs, follow-up of either enrollee or control subject was shorter than 1 year because of dropout from the health plan. In these instances, follow-up of the other member of the pair was shortened so that the enrollee and the matched control were followed for the same number of days. However, if follow-up was shortened because of death, follow-up was continued for a full year from the start date for the other member of the pair. Death was ascertained from the SEER registry through 1997, mortality files of the State of California through 1997, and health plan clinical and administrative databases through 1998.

## Ascertainment of Costs

We ascertained the direct costs of medical care that was provided (or paid for) by Kaiser Permanente over the 1-year follow-up period. Detailed data on each course of chemotherapy, including each drug name, dose, intravenous or oral administration, and outpatient or inpatient setting, were ascertained by chart review. All other data on the use and cost of medical care were obtained from linked automated clinical and administrative databases at Kaiser Permanente *(5)*. The Kaiser Permanente Cost Management Information System (CMIS) was used to ascertain the costs of hospital services and outpatient clinic services that were provided by Kaiser Permanente, including pharmacy, laboratory, imaging, and home health services. CMIS integrates utilization data with the Kaiser Permanente general ledger. All costs in the ledger (with the exception of costs for insurance-related functions, such as marketing and membership accounting) are fully allocated to health care services. CMIS uses standard cost-accounting methods to allocate all building and administrative overhead. Similar cost-accounting methods were used to estimate costs for chemotherapy characterized by chart review. From the economist's perspective, we are examining "average" or "long-run" costs (rather than marginal costs), appropriate for evaluating the average or long-run medical costs of a program or policy that facilitates participation in clinical trials. For each unit of services, we used unit costs that reflect average annual costs throughout Kaiser Permanente in Northern California (rather than unit costs that are specific to the month and clinic of the utilization event), unadjusted for inflation and not discounted. Such adjustments would be of little consequence because there was little inflation at Kaiser Permanente from 1994 through 1997, follow-up lasted only 1 year, and cost differences between trial enrollees and matched control subjects would be inflated and discounted at the same rates.

For services that were provided by non-Kaiser Permanente providers, but paid for by Kaiser Permanente, we used the charges of the non-Kaiser Permanente providers as the costs to Kaiser Permanente of these "outside" services. The costs of donated drugs were omitted from our primary analyses but were included in additional analyses to assess the sensitivity of results to these costs.

Cost analysis is primarily from the HMO perspective. We report the direct costs of services covered by Kaiser Permanente. Out-of-pocket costs by patients to Kaiser Permanente (i.e., co-payments) are included, but costs for care obtained elsewhere and not covered by Kaiser Permanente, such as some alternative care or long-term care, are omitted. Building and administrative overhead supporting medical care are included. Research costs (recruiting patients, collecting and managing data, and development of research infrastructure) are omitted but will be examined in a separate analysis.

## Statistical Analysis

The cost distributions of the trial enrollees and their matched control subjects, as well as the paired differences in cost, were examined. Means, standard deviations, and selected percentiles are reported for total medical care costs and for costs in selected categories, including chemotherapy and other outpatient and inpatient services.

The primary focus is a matched analysis of the paired cost differences between enrollees and control subjects. While the subjects' cost distributions are very skewed, the distributions of paired cost differences are more symmetric. The distributions of paired differences are flatter than the bell-shaped normal curve, and there are influential outliers, but log transformation would yield less interpretable results and would be especially problematic in cost categories, such as inpatient services, where some patients have no costs. Therefore, nonparametric Wilcoxon signed rank tests and corresponding confidence intervals (CIs) *(6)* were used for the primary assessment of the null hypothesis that clinical trials do not increase or decrease the cost of medical care. To permit consideration of the robustness of our findings, we also evaluated results obtained from paired *t* tests (and corresponding parametric estimates of CIs) using costs and also the log of costs.

Given the matched design, we relied mainly on close matching, rather than on regression models, to adjust for potential confounders. We supplemented the primary univariate analysis (of paired differences) with an ordinary least-squares regression model to adjust for differences in the Charlson Comorbidity Index *(7,8)* on the basis of hospital diagnoses (in addition to cancer) during the 5 years prior to the year under study. To evaluate differences among cancer clinical trials in their impact on costs, we added to this one-covariate regression model a set of trial-specific indicator variables for all enrollees in larger trials (more than two trial enrollees in our sample), with the enrollees in smaller trials (fewer than three enrollees) as the reference group. In this supplementary model, we focused on cost ratios rather than on cost differences, specifying the dependent variable as the paired difference in the log of costs (in part because this internal comparison examined only total costs rather than costs in categories of services that were not used by all patients).

We also expanded the univariate matched analyses of costs in selected service

categories (e.g., BMT, other chemotherapy, other pharmacy, laboratory, and imaging) with univariate unmatched two-part analyses (akin to "two-equation models"), reporting 1) the proportion of enrollees and control subjects who had any costs in the service category and 2) the mean costs and enrollee/control cost ratios among patients with nonzero costs.

The variation in enrollees' costs was compared with the variation in control subjects' costs by use of the $F$ test. Cox regression was used to compare mortality among trial enrollees with that among control subjects. All statistical tests are two-sided, with a .05 significance level.

## RESULTS

The 135 trial enrollees were enrolled in 22 clinical trials, including 12 trials for treatments of breast cancer and trials for melanoma, lymphoma, and cancers of the colon, lung, kidney, ovary, stomach, and brain. The mean age of the enrollees and the control subjects was 52 years. In 89% of the matched pairs, the age difference between the trial enrollee and the matched control subject was 3 years or less. Ninety percent of the matched pairs were female, including 44% of pairs with enrollees in trials for cancers other than breast cancer. Among the trial enrollees, 121 (90%) were white compared with 120 (89%) of the control subjects.

The mean of total medical care costs during the year after enrollment in a clinical trial was $17 003, 10% more than the $15 516 mean cost for matched control subjects during the comparable year ($P$ = .011) (Table 1). Among the trial enrollees, chemotherapy, including the costs of clinic visits for administering the drugs as well as the cost of the drugs, accounted for 28% of all medical care costs. The chemotherapy costs of trial enrollees were 40% higher than the chemotherapy costs of the matched control subjects. Most of this difference is attributable to a higher number of chemotherapy visits, although drug cost differences were attenuated because many trial enrollees received donated drugs. The $1376 difference in chemotherapy costs between trial enrollees and control subjects amounts to 93% of the $1487 difference in total costs. The mean differences between trial enrollees and control subjects in the costs of hospital and clinic services other than chemotherapy were smaller and unstable.

The total costs for control subjects were more variable and skewed than those for enrollees in trials (Table 1). The standard deviation of total 1-year costs was 23% higher for control subjects than for enrollees in trials ($F$ test; $P$ = .017). Among pairs of trial enrollees and nontrial control subjects, the difference in total costs was more highly correlated with control subjects' costs ($r$ = .75) than with enrollees' costs ($r$ = .58). The ratio of enrollees' costs to control subjects' costs was 1.45 comparing the 25th percentiles of the cost distributions, 1.34 at the medians, 1.07 at the 75th percentiles, and 0.94 at the maxima (Table 1).

The possibility that chance alone accounts for the paired cost differences is evaluated in Table 2. The null hypothesis "that clinical trials do not increase or decrease the cost of care" is

Table 1. One-year costs of care for 135 patients enrolled in trials and 135 matched control subjects (Kaiser Permanente in Northern California, from 1994 through 1997)

| Source of cost | Mean $ cost (SD*) | Percentiles of $ cost | | | |
|---|---|---|---|---|---|
| | | 25th | 50th | 75th | 100th |
| Chemotherapy | | | | | |
| Trial enrollees | $4815 ($3810) | $2585 | $4384 | $6338 | $22 289 |
| Control subjects | 3439 (4346) | 0 | 2760 | 5168 | 24 465 |
| Other outpatient | | | | | |
| Trial enrollees | 8165 (7126) | 4511 | 6628 | 9648 | 57 114 |
| Control subjects | 6931 (6342) | 3472 | 5788 | 8328 | 44 018 |
| Inpatient | | | | | |
| Trial enrollees | 4025 (11 455) | 0 | 0 | 2818 | 94 224 |
| Control subjects | 5146 (15 487) | 0 | 0 | 3766 | 100 607 |
| Total | | | | | |
| Trial enrollees | 17 003 (16 339) | 8298 | 12 912 | 18 973 | 116 126 |
| Control subjects | 15 516 (20 111) | 5728 | 9653 | 17 671 | 123 559 |
| Ratio: trial enrollees/control subjects | 1.10 | 1.45 | 1.34 | 1.07 | 0.94 |

*SD = standard deviation.

Table 2. Differences in cost of care between patients in trials and matched control subjects, matched analysis of 1-year costs (135 pairs of patients at Kaiser Permanente in Northern California from 1994 through 1997)

| | Mean cost difference, $, enrollee − control subject | Median cost difference, $ (95% confidence interval) | $P$* | % of pairs in which | | |
|---|---|---|---|---|---|---|
| | | | | Enrollee cost > control cost | Enrollee cost < control cost | Enrollee cost = control cost |
| Chemotherapy | $1376 | $999 ($776–$2209) | < .001 | 60 | 27 | 13 |
| Other outpatient services | 1232 | 803 (5–1921) | .049 | 56 | 44 | |
| Inpatient services | 1121 | 0 (−474–0) | .713 | 26 | 32 | 42 |
| Total | 1487 | 2081 (564–4563) | .011 | 61 | 39 | |

*Two-sided Wilcoxon test of the null hypothesis of no difference in costs.

rejected with respect to chemotherapy costs ($P<.001$), other outpatient costs ($P = .049$), and total costs ($P = .011$) but not with respect to inpatient costs ($P = .71$). The 95% CI for the impact of trials on chemotherapy costs extends from $776 to $2209. The 95% CI for the impact of trials on total costs is wider: It extends from $564 to $4563. This upper bound for trials' impact on total 1-year costs amounts to about 29% of the $15 516 mean for control subjects.

There were 83 matched pairs (61%) in which the total costs of care for the trial enrollee exceeded the costs for the matched control subject compared with 52 pairs (39%) in which the control subject's costs were higher (a statistically significant difference by use of a binomial sign test).

Most chemotherapy costs were incurred during the initial 6 months of the study period: 94% of the chemotherapy costs for patients in trials and 83% for the matched control subjects. The percent of other clinic costs incurred during the initial 6 months was 70% for trial enrollees and 62% for control subjects. In both groups, hospital costs were similar during the first and second halves of the 1-year study period. During each half year, control subjects' hospital costs were higher than those of the trial enrollees, but these differences were not statistically significant. The higher total costs for trial enrollees shown in Tables 1 and 2 are apparent only in the initial 6 months of follow-up and appear to derive primarily from chemotherapy.

BMT was received by four enrollees in trials (including one with BMT several months after a non-BMT trial) and four control subjects (Table 3). These eight patients with BMT include the four with the highest total 1-year costs among all 270 patients in the study population. While 11 of the trial enrollees were in trials with a BMT arm, only three received BMT. Another enrollee was randomly assigned to the BMT arm but never received the treatment; the remaining seven were randomly assigned to receive other treatments. Nevertheless, 1-year costs among these 11 patients were higher than 1-year costs among their matched control subjects (Wilcoxon test: $P = .054$); roughly twice as high, exceeding the costs of control subjects by about $20 000. All four of the control subjects who received BMT were matched to enrollees in trials without any BMT arm. Patients in BMT trials received relatively costly chemotherapy, even when they did not receive BMT. If we put aside the 11 matched pairs in BMT trials to focus on the remaining 124 matched pairs, the $15 041 mean cost of enrollees in trials were very similar to the $15 186 mean cost of their matched control subjects. Among the 95 enrollees in non-BMT adjuvant breast cancer trials, mean 1-year costs were $13 921, less than the $14 607 for their matched control subjects.

In the entire sample of 135 matched pairs, 61% of the excess chemotherapy costs of patients in trials is associated with the increased likelihood of having any chemotherapy, while the remaining 39% is associated with more costly chemotherapy. Pharmacy, laboratory, and clinic visit costs other than for chemotherapy also were higher among patients in trials (Table 3). The patients in trials had a mean of 5.0 more clinic visits than their matched control subjects during the follow-up year (28.8 versus 23.8 visits; paired $t$ test; $P = .001$).

Fewer than 10% of the patients in trials and control subjects used Kaiser Permanente home health services, but these services were costly among those who used them, especially among control subjects. Hospitalization was a little more common among control subjects, and hospital costs, given hospitalization, were higher among the control subjects (Table 3). The somewhat higher hospital costs and home health costs of the control subjects could be due to chance alone ($P = .779$ for hospital costs and $P = .525$ for home health costs).

Table 4 compares costs by clinical trial for the 10 clinical trials for which we have costs for three or more patients. The differences among trials in mean cost are substantial. The $40 633 mean 1-year cost for patients in SWOG 9061, a BMT trial, are sevenfold higher than the $5608 mean cost in SWOG 9035, a melanoma vaccine trial. Heterogeneity in the ratio of costs for trial enrollees to costs for control subjects is much less substantial: These ratios range from 0.84 to 2.16. While it is suggestive that the highest of these ratios is for a BMT trial, the numbers of patients per trial is modest, and we cannot reject the global null hypothesis of no differences among these trials.

## Discussion

The 1-year costs of medical care for the 135 enrollees in trials at Kaiser Permanente exceeded those for their matched control subjects by an average of $1487 per person, or about 10%. The primary component of this difference in total costs is the $1376 higher cost for chemotherapy among enrollees (median, $999; 95% CI = $776–$2209). Patterns of use and cost among the 110 breast cancer control subjects in this study were similar to those reported from a much larger Kaiser Permanente study of 8152 breast cancer patients (whose mean costs were approximately $17 000 during the year after diagnosis compared with $2500 for control subjects without cancer) *(9)*. The cost of treating patients

**Table 3.** Mean 1-year costs among patients with any use, by type of service (135 trial enrollees versus 135 matched control subjects at Kaiser Permanente in Northern California from 1994 through 1997)

| Type of service | No. (%) of patients with any use of services | | Mean $ cost of patients with any use | | | |
|---|---|---|---|---|---|---|
| | Enrollees | Control subjects | Enrollees | Control subjects | Ratio: enrollees/ control subjects | $P^*$ |
| Bone marrow transplant | 4 (3) | 4 (3) | 54 396 | 80 657 | 0.67 | .207 |
| Chemotherapy | 112 (83) | 90 (67) | 5804 | 5159 | 1.13 | .030 |
| Other pharmacy | 134 (99) | 128 (95) | 2092 | 1096 | 1.91 | .004 |
| Radiotherapy | 51 (38) | 60 (44) | 3727 | 4114 | 0.91 | .923 |
| Laboratory, imaging | 135 (100) | 135 (100) | 1009 | 785 | 1.29 | .001 |
| Home health | 11 (8) | 12 (9) | 2905 | 4738 | 0.61 | .525 |
| Hospital | 44 (33) | 52 (39) | 12 350 | 13 361 | 0.92 | .779 |
| Other visits, ancillaries | 135 (100) | 135 (100) | 2851 | 2428 | 1.17 | .012 |

*$P$ value (two-sided) based on the $t$ test of the null hypothesis of no difference in mean log costs.

**Table 4.** Costs by trial* (mean 1-year costs of care for trial enrollees compared with control subjects, NCI-sponsored trials at Kaiser Permanente in Northern California from 1994 through 1997)

| Cooperative trial | Brief description | No. of pairs | Cost in enrollees, mean, $ | Cost in control subjects, mean, $ | Ratio: enrollee/control subjects |
|---|---|---|---|---|---|
| NSABP B-28, breast | T1–3, N1, M0, at least one positive lymph node<br>Arm I: AC<br>Arm II: AC then paclitaxel | 42 | 12183 | 14584 | 0.84 |
| SWOG 9410, breast | T1–3, N1, M0, at least one positive lymph node<br>Arm Ia: standard dose Adria in AC then TAX then TAM<br>Arm Ib: standard dose Adria in AC then TAM<br>Arm IIa: intermediate dose Adria in AC then TAX then TAM<br>Arm IIb: intermediate dose Adria in AC then TAM<br>Arm IIIa: high-dose Adria in AC (with G-CSF) then TAX then TAM<br>Arm IIIb: high-dose Adria in AC (with G-CSF) then TAM | 20 | 17342 | 20294 | 0.85 |
| SWOG 9035, melanoma | T3, N0, M0, no positive lymph nodes<br>Arm I: biological response modifier therapy, allogeneic melanoma cell vaccine containing detoxified endotoxin<br>Arm II: observation only | 11 | 5608 | 4415 | 1.27 |
| NSABP B-24, breast | DCIS or LCIS, no positive lymph nodes<br>Arm I: radiotherapy + antiestrogen therapy<br>Arm II: radiotherapy + placebo | 9 | 6818 | 5020 | 1.36 |
| SWOG 9313, breast | T1–3, N0–1, M0, three or fewer positive lymph nodes<br>Arm I: AC simultaneously (with G-CSF)<br>Arm II: A then C (with G-CSF) | 9 | 18835 | 13514 | 1.39 |
| SWOG 9061, breast | Stage 2–3, at least 10 positive lymph nodes<br>Arm I: CAF<br>Arm II: CAF then bone marrow transplant | 8 | 40633 | 18823 | 2.16 |
| NSABP B-25, breast | Stage 2, at least one positive lymph node<br>AC with G-CSF, three levels of intensity | 6 | 19464 | 16738 | 1.16 |
| NSABP B-23, breast | Stage 1, no positive lymph nodes<br>Arm I: CMF then tamoxifen for 5 y<br>Arm II: CMF then placebo for 5 y<br>Arm III: AC then tamoxifen for 5 y<br>Arm IV: AC then placebo for 5 y | 5 | 10225 | 8706 | 1.17 |
| NSABP B-26, breast | Stage 3b–4, metastatic<br>Arm I: paclitaxel (3-h infusion)<br>Arm II: paclitaxel and G-CSF (24-h infusion) | 4 | 39927 | 21323 | 1.87 |
| SWOG 9326, ovarian | Stage 3, single agent consolidative chemotherapy, hexamethyl melamine | 3 | 17742 | 17751 | 1.00 |
| Other trials | Colon, cervix, brain, lymphoma, kidney, and lung | 18 | 24357 | 23969 | 1.02 |
| All trials | | 135 | 17003 | 15516 | 1.10 |

*NCI = National Cancer Institute; NSABP = National Surgical Adjuvant Breast and Bowel Project; SWOG = Southwest Oncology Group; AC = Adriamycin and cyclophosphamide; Adria = Adriamycin; TAX = paclitaxel (Taxol); TAM = tamoxifen; G-CSF = granulocyte colony-stimulating factor; DCIS = ductal carcinoma *in situ*; LCIS = lobular carcinoma *in situ*; CAF = cyclophosphamide, Adriamycin (doxorubicin) and 5-fluorouracil; CMF = cyclophosphamide, methotrexate, and 5-fluorouracil; and TNM = tumor–node–metastasis, the staging system of the American Joint Committee on Cancer classifying tumors by their anatomic site and histology *(14)*.

in cancer trials at Kaiser Permanente is high but not much higher than for cancer patients outside trials.

Overall, similar results were obtained by use of parametric statistical methods that are more influenced by "outliers"—patients with unusually high costs. For example, paired *t* tests done on log-transformed cost data yielded results similar to those obtained by use of the Wilcoxon test.

Two other recent studies have examined the direct medical care costs of patients in cancer clinical trials. Wagner et al. *(10)* compared the costs for 61 patients in cancer trials at the Mayo Clinic with those of matched control subjects, reporting mean 1-year costs of $24 645 in trial enrollees compared with $23 964 in control subjects *(10)*. With data available on some patients for as long as 5 years, they found that trial enrollees cost as much as 10% more than control subjects over some follow-up periods.

At Group Health Cooperative (GHC), a nonprofit HMO in the Seattle area, Barlow and colleagues examined the costs for 40 patients in breast cancer trials and 28 patients in colon cancer trials (Barlow W, Taplin S, Beckord J, Ichikawa L: unpublished data), with adjusted comparisons to unmatched control subjects as well as matched analyses of the trial enrollees for whom well-matched (chart-confirmed) control subjects could be found. The 40 enrollees in the breast cancer trials had mean costs no higher than the 1100 unmatched control subjects during the 2 years following diagnosis, but the costs for trial enrollees were 26% higher than those for control subjects in the 26 available matched pairs ($P = .04$; Wilcoxon test). Patients in colon cancer trials at GHC cost slightly more than unmatched control subjects, but the difference was not statistically significant. Thus, these recent studies at the Mayo Clinic and GHC, like our study, did not find that participation

in cancer trials is associated with large increases in the costs of medical care.

In the Kaiser Permanente setting, BMT trials have been the most costly, with trial participants (less than half of whom received BMT) about twice as costly as control subjects, who were themselves more costly than the control subjects for most other trials. Neither of the other published studies include patients from BMT trials. In any setting, the relative costs of participation in clinical trials may be influenced by the mix of the clinical trials that are offered and selected.

The relative costs of trials will also be influenced by the likelihood of receiving aggressive, intensive care outside clinical trials. At Kaiser Permanente, usual care outside trials appears to be quite variable in cost. The control subjects included the most expensive as well as the least expensive patients. However, the cost distributions shown in Table 1 suggest that trials decrease the likelihood of low costs more than they increase the likelihood of high costs. Trials typically focus attention on differences between an experimental treatment and a standardized version of usual care. In trials, care is typically delivered by protocol and thereby rendered unusually homogeneous within each treatment arm. Apparently, the variation in cost between arms of the trial is often less than the variation within "usual care" outside trials. Recently, there have been expanded efforts to measure costs within clinical trials, permitting comparison of treatment arms with respect to cost and cost-effectiveness *(11)*. It should be kept in mind that medical care outside clinical trials is likely to be more heterogeneous in cost (and effectiveness) than medical care in a trial's "control" arm.

Variation in "usual care" outside trials within Kaiser Permanente or any other setting renders problematic the selection of control subjects. If usual care varies according to physician and patient propensities that are difficult to measure, it is then a challenge to identify control subjects whose experience can inform us about what enrollees in trials would cost had they never been offered trials. How successfully did we meet this challenge and to what extent is problematic matching a source of bias in our results? No matched control subject was found for 68 of the enrollees (33%) in trials during the study period. The studies from the Mayo Clinic *(10)* and GHC (Barlow W, Taplin S, Beckord J, Ichikawa L: unpublished data) also report difficulty identifying closely matched control subjects (for whom there is evidence in the medical chart of eligibility for the clinical trial). We ascertained 1-year costs for 65 of the 68 unmatched trial enrollees by use of the same methods reported above. The mean of their 1-year costs was $25 957 compared with $17 003 for the 135 matched trial enrollees. A relatively high percentage of the unmatched enrollees had metastatic disease (25%) compared with the matched enrollees (18%), suggesting that they may have been relatively costly, regardless of enrollment in trials. Ten of the unmatched trial enrollees were in BMT trials. Mean 1-year costs were $49 008 for these 10, which was 25% higher than the mean costs for the 11 matched enrollees in BMT trials. (Three of the 10 unmatched trial enrollees received BMT compared with three of the 11 who were matched.) Another 31 of the unmatched trial enrollees had enrolled in other trials represented in our sample of 135 matched pairs. Mean 1-year costs were $15 822 among these 31 enrollees, only slightly above the $15 186 among their matched control subjects. Thus, the unmatched enrollees lend support to our findings that BMT trials are relatively costly, but matched enrollees in other trials at Kaiser Permanente have cost little more than they would have cost without trials.

Although the 135 control subjects were well matched by our criteria, they may differ from trial enrollees in unmeasured ways in the severity of their illness and in their propensity to use costly services. If our matched control subjects were more reluctant to undergo aggressive treatments, our results may then overstate the costs of trials. On the other hand, if our control subjects are sicker in unmeasured ways, they may be costlier than ideal control subjects, and our results may then understate the cost of trials. There were 22 trial enrollees (16%) with Charlson comorbidity scores unequal to those of their matched control subjects: eight enrollees with more comorbidity and 14 with less. Adjustment for comorbidity score would increase slightly from $1487 to $1531, our estimate of the additional cost of medical care associated with enrollment in clinical trials.

During the 1-year study period, there were 12 deaths among the control subjects compared with seven among the enrollees in trials. Extending follow-up through 1998, there were 33 deaths among control subjects compared with 23 among enrollees. Cox regression, stratified by trial, yielded an estimated relative risk of mortality of 0.60 for trial enrollees compared with control subjects (95% CI = 0.34–1.06; $P$ = .08). The possibility of relatively favorable survival among enrollees in trials raises the possibility that they were less ill than their control subjects on the start date in unmeasured ways and/or that they received more effective medical care. While the survival benefits of experimental treatments in cancer trials have usually been modest or undetectable compared with control groups within trials, it is possible that trials tend to improve care in all arms by offering care that is more protocol guided, attentive, and/or aggressive. "Selection bias" is also possible; perhaps the physicians and patients who participate in trials are those whose interaction would result in more effective care inside or outside trials. Given that most of our trial enrollees had breast cancer, it is worth noting that survival with breast cancer has been reported to be more favorable at Kaiser Permanente in Northern California than in the surrounding fee-for-service population in a study of Medicare enrollees *(12)*.

We focused on costs of care during the 1-year interval following enrollment in the trial. The modest differential in chemotherapy costs and total costs was entirely within the first 6 months. Among enrollees in trials, 94% of 1-year chemotherapy costs and 72% of 1-year total costs were incurred during the initial 6 months. Among control subjects, 83% of chemotherapy costs and 64% of 1-year total costs were in the initial 6 months. It seems likely that cost differentials during time periods beyond 1 year would be shaped primarily by recurrence and mortality. Any cost impact that is years downstream, and secondary to the impact of trials on disease progression and death, may be presumed remote from the cost concerns of managed care organizations facing policy decisions on patient access to clinical trials. If we do have evidence that clinical trials improve survival, then this would be the important finding. The downstream cost consequences of longer lives should not affect policy decisions on clinical trials.

The 1-year follow-up interval began at enrollment in the trial. Trials may incur costs before enrollment for tests done to ascertain eligibility, tests that otherwise might not be done. Costs for laboratory tests and imaging procedures during the 2 preceding weeks were $183 more per patient among enrollees than among

their matched control subjects. Addition of the costs of these tests during the preceding 2 weeks, to the total of all medical costs during our 1-year follow-up period, raises by one percentage point (from 9.6% to 10.6%) our estimate of the percentage increase in medical care costs attributable to trials.

Cost differences between enrollees and control subjects are also somewhat higher than the 10% differential reported in Tables 2 and 4, if we add an estimate of the costs of donated drugs, as might be appropriate were we assessing costs from the societal perspective rather than the HMO perspective *(13)*. The addition of imputed costs for donated drugs increased chemotherapy costs by $2629 per enrollee and increased total costs by $2672. Thus, if Kaiser Permanente had purchased these drugs, our estimate of the percentage increase in 1-year direct medical costs attributable to trials would increase from 10% to 27%. From the societal perspective, however, it may be more appropriate to use cost estimates for donated drugs that are much lower, based on what it costs the drug company to manufacture and donate the drugs rather than what it would cost Kaiser Permanente to buy them.

The enrollees in non-BMT trials in this study were treated by Kaiser Permanente physicians rather than referred to academic medical centers. How costs to an HMO may be associated with "losing control" of referred patients is beyond the scope of this report. A full accounting of the costs to Kaiser Permanente for participation in clinical trials would assess not only direct medical care costs but also the burden of recruiting patients, assuring that treatment protocols are followed, collecting and managing data, and supporting the infrastructure for research. Furthermore, trials may bring to the provider organization indirect benefits as well as costs. Participation in trials may enhance the appeal of an HMO to patients and physicians. Clinical trials are forces for technologic innovation in medicine. The clinical and scientific knowledge generated by trials is publicly available, regardless of participation in clinical trials. Nevertheless, participation in clinical trials by HMO physicians may position them to adopt new treatments sooner and otherwise influence how they deliver care outside clinical trials.

## Conclusion

Comparing 135 enrollees in trials with 135 control subjects, we found that the trial enrollees, on average, had higher 1-year medical care costs by $1487, about 10%. The costs of trial enrollees most exceeded control subjects' costs in BMT trials. The costs of enrollees in trials without BMT were no higher than control subjects' costs. Kaiser Permanente has been participating in cancer clinical trials without substantial increases in the direct costs of medical care.

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## Notes

[1]*Editor's note:* SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.


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# Clinical Trials: Are They a Good Buy?

By Charles L. Bennett, Jared R. Adams, Kirstin S. Knox, Andrew M. Kelahan, Samuel M. Silver, and Joseph S. Bailes

**Purpose:** Concern that clinical trials may be too costly has been used to justify traditionally restrictive insurer policies regarding clinical trials. Additionally, fear of insurer reimbursement denial can be a significant barrier to clinical trial participation. In this study, we reviewed the empirical data on costs of clinical trials versus standard care and summarized the current status of policy initiatives related to clinical trial insurance reimbursement.

**Methods:** Electronic and print data sources were searched for studies on the costs of oncology clinical trials. Information on policy initiatives for clinical trial reimbursement was obtained from the American Society of Clinical Oncology, the American Society of Hematology, and the Coalition of National Cancer Cooperative Groups and from searches of World Wide Web sites.

**Results:** Five pilot studies provided information for 377 patients on phase II/III clinical trials matched with controls on standard care. Cost estimates ranged from 10% lower to 23% higher costs/charges for clinical trials in comparison to standard medical care. Medicare, 14 states, and several private insurers now cover the costs of patient care in "qualifying" clinical trials.

**Conclusion:** Findings from small pilot studies suggest that phase II and III clinical trials result in at most modest increases in cost over standard treatment costs. Also, an increasing number of policy makers have decided to support clinical trial reimbursement initiatives. It is hoped that economic data from large observational studies will facilitate widespread and permanent decisions that support reimbursement for phase I, II, and III clinical trial participation.

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IT IS ESTIMATED THAT fewer than 5% of adult cancer patients participate in clinical trials.[1] In a recent Harris Interactive survey of 5,980 cancer patients, 60% of patients who were aware of clinical trials (14% of survey sample) and elected not to participate (71% of aware patients) cited concerns about insurance denial as a primary barrier to participation.[2] However, a United States General Accounting Office report found that many insurers already pay for many patients who participate in clinical trials, despite policies excluding payment for "experimental" therapies.[3] As policy makers have become aware that patient concerns over potential reimbursement denial may be a barrier to clinical trial accrual, legislators and insurers have begun to address clinical trial reimbursement policies. The Medicare Cancer Clinical Trial Coverage Act of 1997 sought to authorize a $750 million demonstration project which would reimburse routine patient care costs alongside approved clinical trials. The act also commissioned a report on the actual costs of the funded clinical trials. This legislation was not passed, primarily because of concerns over actual study costs. In 2000, the Institute of Medicine released its report, "Extending Medicare Reimbursement in Clinical Trials," which recommended that the Health Care Financing Administration (HCFA), the former administrator of the Medicare program, reimburse "routine care for patients in clinical trials in the same way it reimburses for routine care for patients not in clinical trials."[1] The report projected that the financial impact of clinical trial reimbursement would be small, based on the findings of pilot studies in 1998 and 1999 from the Group Health Cooperative of Puget Sound, the Mayo Clinic, and Kaiser Permanente.[4-6] Nonetheless, as health care costs rise, the questions related to reimbursement for clinical trials become increasingly relevant. After the favorable reports on the cost of clinical trials from pilot studies, federal policy makers, private insurers, and several state legislatures have introduced policies or laws that support reimbursement of routine medical care in clinical trials. In this article, we address the current status of reimbursement for clinical trials by reviewing the methodologies, results, and future plans for studies on the costs of clinical trials and reviewing the content of federal, state, and private sector clinical trial reimbursement initiatives.

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*The opinions expressed herein are solely those of the authors and are not meant to represent those of the committees and departments at the American Society of Clinical Oncology or the American Society of Hematology, where some of the background information was obtained.*

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Table 1. Comparison of Estimates of Incremental Costs/Charges of Clinical Trials From Five Studies

| | Memorial Sloan-Kettering | AACI/ Northwestern | Kaiser Permanente | CBO/Mayo Clinic | Group Health Cooperative |
|---|---|---|---|---|---|
| Reference no. | 8 | 7 | 5 | 4 | 6 |
| Clinical trial patients | 77 | 35 | 135 | 61 | 49 breast/20 colorectal |
| Study years | 1995 | 1996-1998 | 1994-1996 | 1988-1994 | 1990-1996 |
| Phase | II/III | II | III | II/III | II/III |
| Cost Data | | | | | |
| Units used to measure costs | Costs | Charges | Costs | Costs | Costs |
| At 6 months | | | | | |
| Control patients (C) | $30,775 | $63,721 | $9,930 | $10,073 | |
| Clinical trial patients (T) | $37,055 | $57,542 | $12,242 | $12,200 | |
| % Difference (T-C) | 17 | (−10) | 23 | 21 | |
| At 12 months | | | | | |
| Control patients (C) | | | $15,516 | $14,762 | |
| Clinical trial patients (T) | | | $17,003 | $16,819 | |
| % Difference | | | 10 | 14 | |
| At 24 months | | | | | |
| Control patients (C) | | | | | $25,000* |
| Clinical trial patients (T) | | | | | $30,000 |
| % Difference | | | | | 20 |
| At 60 months | | | | | |
| Control patients (C) | | | | $26,797 | |
| Clinical trial patients (T) | | | | $27,090 | |
| % Difference | | | | 1 | |

Abbreviation: AACI, American Association of Cancer Institutes; CBO, Congressional Budget Office.

*Twenty-six closely matched breast cancer patients only; other diseases did not show a remarkable cost difference.

## METHODS

MEDLINE, EMBASE, HEALTHSTAR, and abstracts from the *Proceedings of the American Society of Clinical Oncology* from the years 1995 to 2001 were searched for reports on costs of clinical trials. Key words included cancer costs, clinical trial costs, and clinical trial participation. Leaders at the Department of Public Policy of the American Society of Clinical Oncology, the Committee on Practice of the American Society of Hematology, the Coalition of National Cancer Cooperative Groups, the Department of Defense, and the National Cancer Institute were also queried about ongoing policy initiatives related to clinical trial reimbursement. Individual bills pertaining to mandated insurance reimbursement of clinical trials were found through searches of the legislative history on the Web site of the respective legislative bodies. Web sites of health care insurers and managed care organizations operating on a national basis were reviewed to identify programs that voluntarily reimbursed medical care costs incurred on clinical trials.

This article addresses routine care costs in clinical trials. For most of the research articles and legislative bills, routine care costs (often referred to as patient care costs in legislation) include conventional care, items or services that are typically provided absent a clinical trial; administrative items, items or services required solely for the provision of the investigational item or service (such as the administration of a noncovered chemotherapeutic agent) and for clinically appropriate monitoring related to complications and treatment effects; and reasonable and necessary care, items or services arising from the provision of an investigational item or service, including the diagnosis or treatment of complications. Routine patient care costs do not include items and services that are customarily provided by the research sponsors free of charge for individuals participating in the trial (such as investigational drugs or items); tests or measurements conducted primarily for the purpose of the clinical trial involved; or the administrative costs associated with collecting research data.

## RESULTS

### *Pilot Studies on Costs and Charges of Clinical Trials*

Three published studies[4,5,7] and two preliminary reports[6,8] conducted an economic evaluation of the routine medical care costs of clinical trials. These studies included information on patients enrolled onto phase II (one study), phase III (one study), and phase II and III clinical trials (three studies). (Table 1) A total of 377 patients on clinical trials were included in the five studies (range, 35 to 165 patients per study). Three studies included information on patients treated in the mid-1990s, one study covered the years 1988 to 1994, and one covered the years 1990 to 1996. Two studies were for patients who received care at managed care organizations (Kaiser Permanente and Group Health Cooperative), two were single-site studies from tertiary cancer centers (Memorial Sloan-Kettering Cancer Center and the Mayo Clinic Cancer Center), and one was from five tertiary cancer centers that belong to the Association of

Table 2. Comparison of Methodologies Among the Five Economic Assessment of Clinical Trials

| Study | No. of Cancer Centers | Payment System | No. of Cancer Types | Case Selection | BMT Cases | Control Selection Matching | Excluded Resources | Costs | Analysis |
|---|---|---|---|---|---|---|---|---|---|
| CBO and Mayo Clinic | 1 | Fee-for-service | 9 | All possible cases | No | Performance status | Outpatient prescription drugs | Costs, 5 years | Paired *t* test |
| Kaiser Permanente | 17 | Managed care | 9 | All possible cases | Yes | Eligibility for trial | None | Costs, 1 year | Univariate regression |
| Memorial Sloan-Kettering | 1 | Medicare | 7 | Patients treated primarily at the cancer center | No | Survival | Resources used outside of MSKCC | Costs, 6 months | Unpaired *t* test |
| AACI/Northwestern | 5 | Fee-for-service | 5 | Patients treated primarily at the cancer center | Yes | Eligibility for trial | Resources used outside of the AACI center | Charges, 6 months | Paired *t* test |
| Group Health Cooperative | NA | Managed care | 2 | GH members on SWOG studies | Not stated | Comorbidity, (eligibility for trial: 26 breast cancer patients) | Not stated | Costs, 2 years | Not stated |

Abbreviations: BMT, bone marrow transplantation; GH, Group Health; MSKCC, Memorial Sloan-Kettering Cancer Center; NA, not applicable; SWOG, Southwest Oncology Group.

American Cancer Institutes (AACI). Control groups included patients with the same diagnosis and tumor stage and similar comorbidity levels who received similar treatments in the setting of standard cancer care.

The studies found that the differences in costs (four studies) or charges (one study) ranged from a 10% savings to a 23% increment for clinical trial participation at 6 months of follow-up, a 10% to 14% increment at 12 months' follow-up, a 20% increment at 24 months, and a 1% increment at 60 months' follow-up (Table 1). There was a wide variation in costs/charges for individual patients and controls, with some clinical trial patients differing by more than $200,000 in costs/charges from matched controls. For breast cancer patients who underwent autologous stem-cell transplantation, mean costs were 120% greater than costs for controls who received standard chemotherapy, while charge estimates were 15% lower in comparison to charge estimates for controls who received autologous stem-cell transplantation outside of a clinical trial.

In evaluating the findings of these studies, several methodologic considerations related to selection of cases and controls, identification of resources, estimation of costs, and statistical analyses should be discussed (Table 2). These areas represent the most important features of economic analyses of cancer care.[9-11]

The studies included patients with between two and nine different types of cancer diagnoses, with breast cancer being the most common diagnosis. Two studies identified cases by reviewing logs from cancer registries at the managed care organization, two studies identified patients through searches of electronic and paper files, and one study included a random sample of a specified number of clinical trial participants at each of five tertiary cancer centers. In some cases, the same patient participated in more than one clinical trial during the study period. The AACI/Northwestern University and the Memorial Sloan-Kettering Cancer Center studies included only those patients who received the majority of their care at the participating cancer center because of the operational difficulties associated with cost identification for medical care provided in multiple settings.

Identification of appropriate controls was the most challenging aspect of study design. Controls were matched for diagnosis, stage, and age in all five studies. Matching was based on eligibility for the clinical trial in two studies, on survival in one study, and on performance status or comorbidity in two studies. However, the type of comparative treatment varied and in all cases differed from that used for case patients who participated in the clinical trials. For example, three studies included breast cancer patients who received an autologous stem-cell transplant, but two of these identified controls who received standard-dose chemotherapy and one included controls who underwent transplantation outside of the clinical trial setting. For the four published studies, control patients who had similar clinical and demographic characteristics but differed with respect to the specific treatment regimen could be identified for two thirds to three quarters of the clinical trial patients.

Measurement of the resources to be included in the economic analyses varied. These data were obtained from electronic claims files in all studies, which facilitated data collection efforts. In the Kaiser Permanente and Group Health Cooperative studies, almost all of the resources associated with cancer care were captured in the electronic data files. The Mayo Clinic study excluded outpatient prescription drugs, durable medical equipment, ambulance and other transportation services, outpatient services provided by allied health professionals, and nursing home care. The other two studies excluded resource use that occurred outside of the tertiary cancer center.

The methodology for deriving economic inputs was unique to each study. The Mayo Clinic study assigned a value for each unit of service that was adjusted to national cost norms using Medicare fee-schedule rates for physician and outpatient ancillary services. Hospital charges were converted to costs by applying department-level cost-to-charge ratios obtained from Medicare reports. Unit costs were normalized to national 1995 values by use of regional hospital market-basket indexes obtained from annual Prospective Payment Assessment Commission reports. The Kaiser Permanente study used a proprietary system that assigned a value to each unit of pharmacy, laboratory, imaging, and home health services, with additional allocation of building and administrative overhead rates that were specific to the Kaiser system. Unit costs reflected average annual costs throughout Kaiser Permanente in Northern California. For out-of-network services, provider charges were used as the estimate for costs. Copayments by patients, representing out-of-pocket costs to patients, were also included. Costs in the Memorial Sloan-Kettering Cancer Center study included hospital costs and physician charges, based on estimates derived from Medicare cost-to-charge ratios for the relevant resources. The Group Health Cooperative Study is currently revising its cost estimation effort. The AACI/Northwestern University pilot study used charges, not costs, in the analyses, primarily because the five-site study would have required a different cost estimation effort for data from each tertiary cancer center. In most cases, the preferred method for economic analyses is based on estimates of costs, not charges, because of marked discrepancies that exist between billed charges and opportunity costs in health care.[12] These differences vary by type of resource, among physicians, and over time, resulting in a distorted estimate of economic differences between groups of patients treated with a variety of medical resources.

Analytic approaches also differed. The Mayo Clinic reported costs over a 5-year time period, the Group Health Cooperative reported costs over a 2-year time period, the Kaiser Permanente study reported on costs over a 1-year time period, and the Memorial Sloan-Kettering Cancer Center and the AACI/Northwestern University studies reported costs over a 6-month time period. Censoring of patients with incomplete follow-up was done only in the Mayo Clinic study because of the long follow-up period. Statistical differences were determined using paired *t* tests based on matched samples in the studies from the Mayo Clinic and the AACI/Northwestern University, a one-covariate (Charlson comorbidity score) ordinary least squares regression model in the Kaiser Permanente study, and unpaired *t* tests in the Memorial Sloan-Kettering Cancer Center study.

There are two ongoing large-scale efforts designed to develop valid and reliable estimates of the incremental costs of clinical trials carried out in diverse academic and community settings. The RAND/National Cancer Institute (NCI) Costs of Clinical Trials Study is evaluating the costs of 750 individuals enrolled onto phase II/III clinical trials from multiple community and tertiary cancer centers and 750 matched controls.[10] The AACI/Northwestern University Clinical Trials Costs and Charges Project has proposed a complementary study that will evaluate and compare the costs of 100 patients enrolled onto phase I clinical trials conducted at tertiary cancer centers with those of an equal number of matched controls. These studies are warranted for several reasons. First, the five pilot studies had sample sizes that were insufficient to detect cost differences that may be important for policy purposes. Second, treatment patterns differ across institutions, and four of these studies were conducted within a single institution or health system, which makes it difficult to generalize. Third, cases and controls matched at a single institution may differ in unobserved but important ways that affect treatment costs, as a result of self-selection into trials. Fourth, the pilot studies excluded some potential important dimensions of treatment, such as clinicians outside the delivery system. Finally, single-institution studies may underestimate the financial impact of transferring care from a community setting in order to participate in some clinical trials.[10]

### *Federal, State, and Private Sector Policy Initiatives Related to Reimbursement of Clinical Trials*

*Federal efforts.* Federal policy initiatives related to clinical trial reimbursement began in 1994 when the Department of Defense (DOD) initiated a demonstration project that covered the costs of bone marrow transplantation in clinical trials (Table 3). In 1996, this demonstration project was expanded to include all phase II and III cancer treatment trials funded by the NCI. The DOD demonstration project was limited to NCI trials because the imprimatur of the NCI is only given to cancer trials that have demonstrated

Table 3. Federal Cancer Clinical Trial Legislative Efforts

| Cancer Clinical Trial Reimbursement Legislation | | | | |
|---|---|---|---|---|
| Federal Efforts | | | | |
| Federal Agency | Year | Trial Purpose | Phase | Qualified Trials |
| DOD/TRICARE | 1996,1999* | Prevention,* early detection,* screening,* treatment | II, III | DOD/NCI Cancer Clinical Trials Demonstration Project; NCI (NIH) trials only** |
| DVA | 1997 | Prevention, diagnosis, treatment | I, II, III, IV | NCI and DVA cost-sharing agreement; NCI (NIH) trials in DVA hospitals |
| Medicare/Medicaid | 2000 | Diagnosis, treatment | Any trial undertaken with therapeutic intent | All clinical trials, not just cancer, NIH, CDC, AHRQ, HCFA, DOD, DVA, FDA; other qualified trials |

Abbreviations: NIH, National Institutes of Health; DVA, Department of Veteran's Affairs; AHRQ, Agency for Healthcare Research and Quality; CDC, Centers for Disease Control; FDA, Food and Drug Administration.

*Expanded benefits added at the later date.

themselves to be addressing a critical public need with rigorous scientific methodology. In 1997, the Department of Veterans Affairs (VA) joined the federal demonstration project effort. In 1999, the DOD expanded their NCI cancer trials demonstration project to include coverage of prevention, early detection, and screening trials. Enrollment onto the program has increased three-fold since the beginning of the project in 1996. Of the approximately 11,700 patients diagnosed with cancer annually under the DOD (TRICARE) health coverage umbrella, 51 enrolled in 1996 (0.5%) and 131 enrolled in 2000 (1.5%). In 2001, an estimated 240 cancer patients (2.0%) are expected to enroll onto the DOD/NCI trial program.

Medicare policies were not supportive of clinical trials during the 1990s.[13] The HCFA excluded coverage of routine care costs associated with clinical trial participation for Medicare enrollees, on the basis that the treatment was experimental or investigational.[1] However, the United States General Accounting Office found that less than 4% of claims for clinical trial costs incurred by Medicare beneficiaries were denied.[2] Furthermore, they found that oncologists frequently submitted bills for components of complex treatments, without specifying the procedure itself. HCFA is estimated to have paid 50% to 90% of routine patient care costs in clinical trials, after taking into account both costs for which no reimbursement was sought and claims that were submitted and rejected. In 1993, the Office of the Inspector General of the Department of Health and Human Services found that Medicare was being billed millions of dollars for surgical procedures involving unapproved medical devices. Almost all of the 130 hospitals under investigation had billed for clinical trials. However, quickly passed legislation prevented HCFA from collecting from the hospitals.[1]

In addition, no federal clinical trials legislation has been passed. One 1993 bill, the Cancer Treatment Improvement Act, addressed the issue of clinical trial coverage but never made it past committee. In 1996, the Medicare Cancer Clinical Trial Coverage Act was introduced in the Senate and the Medicare Cancer Clinical Trial Demonstration Act in the House. The bill, which applied to the 44 million individuals whose coverage was regulated by Employee Retirement Security Act plans, would allocate $750 million to cover cancer clinical trials sponsored by the National Institutes of Health (NIH), DOD, and the DVA, would require development of federal regulations that would define routine patient care costs, and would study the impact of clinical trials reimbursement on group health insurance plans. The Medicare Cancer Clinical Trial Coverage Act was reintroduced in 1997, 1998, and 1999, without success. The Health Insurance Bill of Rights Act of 1997 introduced mandated coverage by all group health plans of federally funded clinical trials for "seriously ill patients with no standard treatment alternative." The language regarding clinical trials was folded verbatim in 1998 into the Patient Bill of Rights Act. The Sydney E. Salmon Access to Cancer Clinical Trials Act of 1999 was among the 90% of bills that never make it past committee. The Bipartisan Consensus Managed Care Improvement Act, introduced by Representatives Charlie Norwood (R-Georgia) and John Dingell (D-Michigan) in 1999, was passed by the House in 2000 but tabled by the Senate. The bill would have mandated group health plan coverage of all phases of federally funded prevention, early detection, and treatment trials for patients with serious or life-threatening illnesses.

In 2000, after years of lobbying of HCFA leadership by individuals, patient groups, health care workers, and organizations who were concerned about reimbursement denials of clinical trial costs and the low rates of accrual to clinical trials, former President Clinton issued a memorandum stating that HCFA was authorized to cover the costs of cancer clinical trials. This decision was supported by the

**Table 4. Pending Federal Legislative Initiatives for Cancer Clinical Trials**

| On the Horizon in Congress | | | | |
|---|---|---|---|---|
| Legislative Body | Year | Trial Purpose | Phase | Qualified Trials |
| House of Representatives by Pryce (R-Ohio), HR 967 | 2001 | Treatment | Not restricted | The Access to Cancer Clinical Trials Act of 2001 would mandate group health plans to cover all federally supported cancer trials (NIH, CDC, AHRQ, HCFA, DOD, DVA, DOE, NIH COOP groups, NIH-supported centers) and trials of IND-exempt drugs |
| Senate by Snowe (D-Washington), S 257 | 2001 | Treatment | Not restricted | The Improved Patient Access to Clinical Studies Act of 2001 would mandate all ERISA and group health plans to cover care received in all trials sponsored by HHS, NIH, FDA, VA, DOD, or NIH-qualified nongovernment research entity |
| Senate by McCain (R-Arizona), Edwards (D-North Carolina), Kennedy (D-Massachusetts), (S 1052) | 2001 | Not specified | Not restricted | The Bipartisan Patient Protection Act would mandate group health plans to cover trials approved and sponsored by NIH, NIH COOP group or center, FDA, DOD, or VA |
| House of Representatives by Ganske (R-Iowa), Dingell (D-Michigan), Norwood (R-Georgia), (HR 2563); Norwood (House Amendment 303) | 2001 | Not specified | Not restricted | The Bipartisan Patient Protection Act would mandate group health plans to cover trials approved and sponsored by NIH, NIH COOP group or center, FDA, DOD, VA, or NIH-qualified nongovernment entity |

Abbreviations: DOE, Department of Energy; COOP, cooperatives; ERISA, Employee Retirement Security Act; DHHS, Department of Health and Human Services.

empirical evidence on the cost of clinical trials from the Group Health, Kaiser, and Mayo Clinic studies, the Institute of Medicine's report recommending Medicare coverage of routine patient costs on clinical trials, and the growing body of state legislation and voluntary initiatives from private insurers. This benefit included a broad definition of "qualified" clinical trials. The Final National Coverage Determination issued by HCFA extended the definition of qualified clinical trials beyond those funded or conducted by government bodies to trials that satisfied qualifying criteria. Certain trials were deemed to be qualified and automatically covered: those funded by the NIH, the Centers for Disease Control and Prevention, the Agency for Health Research and Quality, HCFA, the DOD, and the DVA; trials supported by centers or cooperative groups that are funded by these organizations; and trials conducted under an investigational new drug (IND) application reviewed by the Food and Drug Administration. The Agency for Healthcare Research and Quality has, in conjunction with other federal agencies and input from interested specialty groups and other stakeholders, developed additional criteria to identify high-quality trials that would be qualified. These criteria await approval from the new administrator of the Center for Medicare and Medicaid Services (formerly the HCFA). Until these qualifying criteria are available, trials that are exempt from having an IND will be automatically considered to be qualified trials if the study evaluates an already defined Medicare benefit, is designed with a therapeutic intent (not to evaluate toxicity), and enrolls beneficiaries with a diagnosed disease if the study is for a therapeutic intervention (but it may enroll healthy beneficiaries if the trial is for a diagnostic intervention). Medicare will cover reasonable and necessary care required to diagnose and treat complications arising from participation in clinical trials, as well as items and services required for the provision of the investigational item. All clinical trials submitted for Medicare coverage will be entered onto a national registry. Medicare will cover all routine costs of automatically qualifying and investigator-certified trials. However, if the Center's chief clinical officer subsequently finds that a clinical trial was misrepresented, the provider may be held liable for the costs.

Efforts to pass broad clinical trial legislation have moved forward in 2001 (Table 4). The recently approved Patient Protection Act legislation led by Senators McCain (R-Arizona), Edwards (D- North Carolina), and Kennedy (D-Massachusetts) in the Senate (S. 1052) and Congressman Ganske (R-Iowa), Dingell (D-Michigan), and Norwood (R-Georgia) in the House (H.R. 2563) includes a section mandating coverage of all phases of federally funded treatment trials for the seriously ill. However, after incorporation of an amendment related to financial and administrative considerations for lawsuits by Representative Norwood (House Amendment 303) that was negotiated with President Bush, the Senate and House bills differ markedly in their language regarding other aspects of managed care and will need to be reconciled in the conference process of the Congress. A bill dealing specifically with coverage of patient care costs of cancer clinical trials was introduced in the House by Representative Deborah Pryce (R-Ohio) as the Access to Cancer Clinical Trials Act of 2001 (H.R. 967). This bill is in line with the Medicare National Coverage Decision and mandates coverage of all phases of federally funded cancer prevention, diagnostic, and treatment trials,

trials approved and funded by "qualified nongovernmental research entity identified in the guidelines issued by the National Institutes of Health for center support grants," and IND-exempt investigator-initiated trials. During debate over the McCain-Kennedy-Edwards legislation, the Senate approved a nonbinding "Sense of the Senate" amendment on clinical trials by an 89 to 1 vote. The amendment, offered by Senator McCain, expresses the sense of the Senate that individuals with life-threatening diseases should have the opportunity to participate in federally approved or funded clinical trials. All versions of the proposed legislations state that qualified individuals have life-threatening or serious illnesses "for which no standard treatment is effective" and that participation in the trial offers "meaningful potential for significant clinical benefit." This language raises concern that patients might be excluded from clinical trials if the standard therapies are a reasonable option. Attempts to clarify this language are ongoing. President Bush has also voiced support for coverage of patient care costs for treatment in qualified clinical trials in a February 2001 statement sent to Congress related to "principles" for a patient's bill of rights. Thus, the prospects for passage of comprehensive federal legislation supporting clinical trial reimbursement are good, although the exact details remain uncertain.

*State legislative efforts.* As of August 2001, 14 states have passed laws mandating coverage of patient care costs associated with treatment provided on specified categories of cancer clinical trials (Table 5). The question put before state legislatures has been whether the insurance barrier to clinical research is best removed through the voluntary action of health insurers or if formal legislation is needed. Rhode Island was the first state to legislate insurance coverage for clinical trials in 1995. The bill originally supported coverage of phase III and IV cancer treatment trials but was amended in 1997 to cover phase II, prevention, screening, and phase III trials. Qualifying trials were those that were funded by the NIH, DVA, or DOD or conducted in an NCI-affiliated cancer center. Georgia mandated insurance for selected pediatric cancer trials in 1998. Maryland and Virginia expanded on the idea in 1999, mandating insurance for cancer trials conducted in in-state academic institutions. Also in 1999, Maine passed a law requiring coverage of NIH-sponsored trials in cooperative groups or NCI-designated cancer centers. The same year, Louisiana passed a law including these trials as well as trials sponsored by the Food and Drug Administration, DOD, DVA, and the Coalition of National Cancer Cooperative Groups. Several other states followed suit in 2000 and 2001. Illinois extended its guarantee of coverage to all "seriously ill patients for which no standard therapy is available." This ambiguous clause defined the qualified patient as necessarily lacking "standard care," phrasing echoed in the Patient Bill of Rights. Furthermore, it only required that insurers had to offer this as an option, not that employers had to buy the benefit as part of their employee health coverage package. Most of the state-level legislation does not define a qualified patient but instead defines qualified trials. Similar legislation is pending in a number of other states. Many of the current coverage initiatives exclude phase I trials partly because no data exist on costs, little data exist on the investigative treatment, and the treatments have little chance of being therapeutic. Other initiatives limit their scope to trials with a therapeutic intent. Most initiatives limit coverage to cancer clinical trials, in part because the national infrastructure surrounding cancer trials is the most established and comprehensive of all diseases and cancer clinical trials are subject to high levels of controls, monitoring, and oversight. State legislative efforts do not pertain to employees of self-insured corporations as defined under the Employee Retirement Security Act of 1974. Lastly, concern over variable scientific quality has led many state legislatures to limit reimbursement to trials funded by federal agencies. Although institutional review boards ensure that a trial is designed and conducted ethically, they do not assess scientific validity. However, this policy excludes a great many high-quality clinical trials that are funded by sources other than the federal government.

*Private insurer efforts.* Private insurers may be concerned that clinical trial costs are excessive, primarily as a result of extensive observation and testing periods. Uncertainty over reimbursement, rather than actual denial of reimbursement, may adversely affect participation in clinical trials. Furthermore, some clinical trials, such as trials of bone marrow transplantation for breast cancer, were undoubtedly expensive. In the early 1990s, private insurers who refused reimbursement for bone marrow transplants for breast cancer paid large jury awards and settlements to families of the affected individuals. Subsequently, many states and private insurers adopted policies to reimburse for the procedure. In 1999, findings of an absence of clinical benefit with bone marrow transplantation for breast cancer were reported. The reports had been delayed by several years because poor clinical trial accrual had led to an extended study period.

At the end of the prior decade, several large private health insurers agreed to reimburse for medical care that occurs with clinical trials. These insurers included the New Jersey Association of Health Plans, OhioMed, United Healthcare, and the Mayo Health Plan[14] (Table 6). The New Jersey Association of Health Plans agreement is unique in that it represents the first instance for which all private insurers in a single state have voluntarily agreed to provide cancer

**Table 5. State Legislative Efforts for Cancer Clinical Reimbursement**

| State Legislation | | | | Cancer Clinical Trial Reimbursement Legislation |
|---|---|---|---|---|
| State | Year | Trial Purpose | Phase | Qualified Trials and Pending Initiatives |
| Alabama | | | | None |
| Alaska | | | | None |
| Arizona | 2000 | Prevention, palliation, treatment | I, II, III, IV | NIH, NIH COOP group, DVA, FDA, entity meeting NIH grant criteria, academic institutions in Arizona |
| Arkansas | | | | None |
| California | 2001 | | I, II, III, IV | NIH, FDA, DOD, DVA, trials of IND-exempt drugs |
| Colorado | | | | None |
| Connecticut | 2001 | Prevention, treatment | III (prevention); I, II, III, IV (treatment) | NIH, COOP groups, FDA, DOD, DVA |
| Delaware | 2001 | Treatment | Not specified | NIH, COOP group, cancer center, CCOP, DOD, DVA; part of state patients' bill of rights |
| District of Columbia | | | | None |
| Florida | | | | Bill introduced in 2001; did not progress through committee |
| Georgia | 2000 | Treatment | II, III, IV | Bill introduced to amend current law to include adults in NIH, COOP group trials; did not progress through committee |
| | 1998 | Treatment | II, III | Pediatric trials only, NIH, FDA, meets COG standards |
| Hawaii | | | | None |
| Idaho | | | | None |
| Illinois | 2000 | Treatment | II, III, IV | Terminally ill patients with no standard treatment, NIH, DHHS, FDA*; benefit must be offered but employer not required to purchase |
| Indiana | 2001 | Detection, prevention, treatment | I, II, III, IV (detection, prevention); II, III, IV (treatment) | Bill introduced, referred to committee; NIH trials |
| Iowa | 1998 | | | Health Insurance Consumers' Bill of Rights introduced but did not come out of committee |
| Kansas | | | | None |
| Kentucky | | | | None |
| Louisiana | 2000 | Detection, prevention, treatment | II, III, IV | NIH, COOP group, cancer center, FDA, DOD, DVA, Coalition of National Cancer Cooperative Groups |
| Maine | 1999 | Treatment | Not specified | DHHS, NIH, COOP group, cancer center |
| Maryland | 1999 | Prevention, early detection, treatment | I, II, III, IV | NIH, NIH COOP group, DVA, FDA, academic center in Maryland, IRB-approved trials at institution with MPA from OHRP |
| Massachusetts | | | | Bills introduced in House and Senate, referred to committee |
| Michigan | | | | Voluntary agreement, pending final sign-off |
| Minnesota | | | | Voluntary agreement, pending final sign-off |
| Mississippi | | | | None |
| Missouri | | | | Bill introduced in 2001, referred to committee |
| Montana | | | | None |
| Nebraska | | | | None |
| Nevada | | | | None |
| New Hampshire | 2001 | Treatment | I-IV | NCI (COOP groups, centers, CCOPs), FDA, DOD, DVA, IRB-approved trials at institutions that have MPA from OHRP |
| New Jersey | 1999, 2000† | Prevention, early detection, treatment | I†, II†, III | Voluntary agreement covering NIH, FDA, DOD, DVA* |
| New Mexico | 2001 | Prevention, detection, treatment | I, II, III, IV | NIH, COOP group, cancer center, DOD, DVA, NIH-qualified nongovernment agency |
| New York | 2001 | | | Bill introduced for coverage of "experimental drugs" for breast cancer; referred to committee |
| North Carolina | 2001 | | | Two bills introduced, still in committee |
| North Dakota | | | | None |
| Ohio | | | | Coverage of trials on individual case basis |
| Oklahoma | 2001 | | | Bill introduced, but clinical trial clause removed in conference committee |
| Oregon | | | | None |
| Pennsylvania | 2001 | | | Bill reintroduced, still in committee |
| Rhode Island | 1995, 1997† | Treatment | II†, III, IV | NIH, NCI, COOPs, DVA, FDA, NIH-qualified institute following NCI guidelines |
| South Carolina | | | | None |
| South Dakota | | | | Possible coverage through off-label drug provision |
| Tennessee | | | | Possible coverage through off-label drug provision |
| Texas | | | | None |
| Utah | | | | None |
| Vermont | 2001 | Prevention, early detection, treatment | I, II, III, IV | Cancer trials at Norris Cotton Cancer Center and Vermont hospitals |
| Virginia | 1999 | Treatment | II, III, IV | NIH, VA, FDA, academic center in Virginia |
| Washington | | | | Two bills did not progress through committee in 1999 and 2000; not yet reintroduced |
| West Virginia | | | | None |
| Wisconsin | 1999 | | | Voluntary agreements by selected payers associated with UWCCC |
| Wyoming | | | | None |

Abbreviations: CCOP, Community Clinical Oncology Program; COG, Children's Oncology Group; IRB, institutional review board; MPA, Multiple Project Assurance; OHRP, Office of Human Research Protection; UWCCC, University of Wisconsin Comprehensive Cancer Center.

*These projects will include an analysis of the economic impact of clinical trial reimbursement.

†Expanded benefits added at the later date.

Table 6. Private Insurance Plan Agreements for Cancer Clinical Trial Reimbursement

| Private Insurance Plan Agreements | | | | |
|---|---|---|---|---|
| Organization | Year | Trial Purpose | Phase | Qualified Trials |
| New Jersey Association of Health Plans | 1999, 2000* | Prevention, early detection, treatment | I*, II*, III | NIH, FDA, DOD, DVA† |
| Ohio Med | 2000 | Treatment | II, III | NCI (NIH) trials only† |
| United Healthcare | 2000 | Prevention, diagnosis, treatment | I, II, III, IV | Trials of COOP groups participating in Coalition of National Cancer Cooperative Groups and trials of the Coalition† |
| Aetna-US Healthcare | 2000 | Not specified | Not specified | FDA, NCI, or similar national cooperative body |

*Expanded benefits added at the later date.

†These projects will include an analysis of the economic impact of clinical trial reimbursement.

clinical trial coverage. The agreement was the result of a collaborative effort of a working group consisting of insurers, consumers, and physicians. In the face of recent expansion in state legislation on health insurance, Michigan and Minnesota have recently followed the New Jersey example by encouraging collaborative task forces to work with private insurers to voluntarily pursue clinical trial coverage. Policy makers in Minnesota felt that a voluntary agreement among insurers avoided the antagonistic nature of mandated health coverage and would more likely lead to a broader definition of qualified clinical trials than piecemeal legislation. Voluntary initiatives might also foster cooperation. However, the task force from New Jersey also warned that oversight of the insurance agencies was still warranted.

## DISCUSSION

A paradox exists in reimbursement policies in which insurers may refuse to cover a promising new therapy because it is available only through clinical trials while covering what is considered standard treatment even though it may often be ineffective and sometimes more expensive. Pilot studies have found that the incremental costs and charges of clinical trial participants are similar or only slightly greater than those incurred by patients not enrolled onto clinical trials. It is expected that the large RAND/NCI Costs of Clinical Trials Study, which addresses phase II and phase III studies, the AACI/Northwestern University Clinical Trials Costs and Charges Project, which addresses phase I studies, and the economic projects built into several of the health policy initiatives will provide empirical data that allow for derivation of generalizable estimates of the costs of clinical trials. The small cost increment observed in pilot studies to date is justified by the additional benefits that clinical trials bring to all patients. If increased clinical trial enrollment could facilitate the completion of a trial that demonstrates an innovative therapy to be effective or a current therapy to be ineffective even a year earlier, thousands of lives could potentially be saved. Moreover, clinical trials remain our best source of information on drug safety. During phase I, II, and III clinical trials, reporting of adverse events is virtually complete, with comprehensive reports of these events as well as assessments of possible or definite causality. Identification of rare but potentially fatal side effects is facilitated in the clinical trial setting.

There are three strategic options for addressing clinical trial reimbursement: litigation, legislation, and voluntary cooperation. Litigation, as might be suggested by the bone marrow transplant studies in breast cancer, may be unlikely to lead to the most coherent, egalitarian, and entirely scientific reimbursement policy. Legislation and voluntary industry initiatives are the most probable paths to rational health policy decisions about clinical trial reimbursement. Initiatives such as the DOD/NCI cancer clinical trials demonstration project have started slowly, but the numbers of participants in the DOD demonstration in 2000 almost doubled from the year before and will most likely double again this year. Several states, several large private insurers, and Medicare have agreed to reimburse for medical care that occurs in the setting of certain clinical trials, although phase I clinical trials are frequently excluded. Medicare has made the largest leap in extending coverage to all clinical trials and drafting criteria to extend the range of qualified clinical trials beyond those sponsored by the NIH, DVA, or DOD. The New Jersey Working Group expects that their health insurance cooperative agreement, which covers 98% of insured patients in New Jersey, will increase the 3.3% rate of New Jersey cancer patients currently on clinical trials to 15% in 3 years.

Most major improvements in cancer treatment have been accomplished through controlled clinical trials. While a Harris Interactive survey found that both the general public as well as persons who participated in cancer trials had a favorable impression of clinical trials,[2] only 4% of cancer patients participate in these studies. If recruitment to clinical

trials continues to be poor, then the generalizability and timeliness of clinical trial findings will be jeopardized. Enrolling large numbers of patients onto clinical trials facilitates translational efforts to identify the most effective medical treatments, enhances comprehensive assessments of drug safety, and helps identify therapies that are likely to be ineffective. Finally, if empirical data continue to show that clinical trials result in only modest increases in costs, and if broad-based policy initiatives continue to occur, then there is no reason that clinical trial coverage should not ultimately be a permanent benefit that is supported by federal, state, and private sector policies.

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