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AB 502

What are clinical trials?

- Medical research studies comparing new treatments to existing therapy
- Fundamental building blocks of good medical care
- Means to find new treatments, improve care, and contain costs
  - Yield data essential to coverage decisions by health plans' medical directors

Who benefits from clinical trials?

- Patients
  - Access to innovative, state-of-the-art treatments, and disease prevention strategies
- Physicians
  - Wide range of treatment options for seriously ill patients
- Health plans
  - Knowledge essential to make appropriate coverage decisions, enhance quality of care

ASSEMBLY COMMERCE & LABOR 1 of 22
DATE: 4/09/03 ROOM: 4100 EXHIBIT Z
SUBMITTED BY: John Ellerton

Myths and misconceptions about clinical trials

- They cost too much
- They are only for patients close to death
- Funding clinical trials is someone else's responsibility
- Clinical trials are just experiments that don't add much to patient care

Problems in access to clinical trials

- Widely variable, unpredictable decision making by health plans
  - Significant disincentive to patient enrollment
- Retrospective and prospective denials
  - Many payers do not even know when patients are enrolled

Funding for clinical trials

- Routine care costs
  - Physician visits
  - Hospitalizations
  - Tests, procedures
  - Typically paid by...
    - Health plans
    - Patients (cost sharing)
- Trial infrastructure
  - Investigational drugs
  - Trial-specific services
  - Data collection & analysis
  - Trial management
  - Typically paid by...
    - Government
    - Industry
    - Foundations

Cost of care in clinical trials

- NCI-sponsored studies
  - Group Health Cooperative of Puget Sound
  - Mayo Clinic
  - Kaiser Permanente
  - The RAND Corp. (study in progress)
- Key findings:
  - little cost difference between care in and out of trials

Group Health Cooperative

- 51 breast cancer cases (with controls) and 28 colorectal cases (with controls)
- Endpoint: costs at two years post diagnosis
- Key conclusions
  - breast:
    - care in clinical trial $1,140 less expensive
  - colorectal:
    - care in clinical trial $598 more expensive

The Mayo Clinic

- 61 cases and 61 controls
- Endpoint: lifetime medical costs of cancer patients
- Key conclusions
  - Average costs higher in clinical trials...not statistically significant
  - Adjusted lifetime costs similar across groups
  - No identifiable pattern to cost distribution

Kaiser Permanente of Northern California

- 135 matched pairs of breast cancer patients
- Endpoint: cumulative costs 1 year after diagnosis
- Key conclusions
  - care in trials costs 10 percent more
  - most stable cost differences due to chemotherapy during first six months
  - much excess costs attributable to patients who received autologous bone marrow transplant

Additional cost studies

- Stinson, Bennett, et.al.
  - Clinical trials 10 percent less expensive
- Quirk, et.al.
  - Clinical trials 17 percent less expensive
- Sherman, et.al.
  - Care in Phase I clinical trials no more costly than standard therapy

Clinical trial quality criteria

- Rigorous peer-reviewed trials only
  - National Institutes of Health (NIH)
    - NIH Center or Cooperative Group
  - Food & Drug Administration
  - Departments of Defense or Veterans Affairs
  - Selected Institutional Review Boards
    - Major hospitals/research groups only

Good quality criteria...

- Raise the bar for hospitals/physicians
  - Participate only in good trials or do not expect coverage and payment
- Reduce likelihood of patient participation in junk science
- Prevent plans from paying for commercial ventures masquerading as science

Clinical trials' economic impact

- Clinical trials care is cost-substitutive, not cost-additive
- Coverage affects small patient volume
  - Few patients meet rigorous trial criteria for entry
    - only 2 to 3 percent of all cancer patients are treated in clinical trials
- Data impact is large
  - Health plans and physicians make better decisions and design better care programs

Clinical trials' information impact

- Essential clinical data
  - Crucial to medical director decision making
    - Trials are scientific gold standard
    - Coverage decisions are less arbitrary
  - Necessary to build a value-driven health care system
    - Key means to judge what works, what doesn't, and at what cost

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Managed care experts on clinical trials

- Major managed care organizations support covering care in high quality clinical trials
  - AAHP
  - ECOG agreement with three leading mid-western plans
  - United HealthCare, Aetna US Healthcare
  - NJ voluntary agreement
- David Eddy, managed care expert, believes care in good trials should be covered*

In summary, an agreement...

- Preserves patient access, with health plan support, to innovative care in clinical trials
- Protects health plan interests by limiting financial liability
  - to only high quality clinical trials, offering treatment at least as good as standard care
  - to only routine patient care costs they fund anyway
- Supports the clinical trial system, while delineating everyone's rights, responsibilities

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Reimbursement for Patient Care Costs in Clinical Trials (approved June 16, 1994)

POSTED 07.01.2002

ASCO Policy Statement

For people with serious or life-threatening diseases, completely satisfactory or curative treatment often is not available. Those patients are nevertheless able to receive state-of-the-art therapy through high-quality clinical trials, offering not only an important treatment option but the opportunity to advance medical knowledge. Many third-party payors -- including the Medicare program -- specifically exclude coverage of "experimental" or "investigational" treatments. This coverage limitation is intended to protect the patient from treatment that may be harmful or of no therapeutic value. Increasingly, however, this policy has been used to deny coverage for high quality therapy in clinical trials. Any health care reform system must recognize the appropriate role of clinical research for people with serious or life-threatening diseases and must provide coverage for the patient care costs incurred in clinical trials. The cost of medical care provided when a patient with serious or life-threatening disease is entered on a Phase I, II, III, or IV (post-marketing) clinical trial -- including hospital, physician, and other health care items and services as well as the cost of approved drugs for labeled or unlabeled uses which might be part of the regimen[1]-- should not be denied coverage and reimbursement when all of the following are demonstrated:

- Treatment is provided with a therapeutic intent[2];
- Treatment is being provided pursuant to a clinical trial approved by one of the National Institutes of Health (NIH), an NIH cooperative group, or an NIH center; the Food and Drug Administration (FDA) in the form of an investigational new drug (IND) or new device (IDE) exemption; the Department of Defense; the Department of Veterans Affairs; or a qualified nongovernmental research entity as identified in guidelines issued by individual NIH Institutes for center support grants;
- The proposed therapy has been reviewed and approved by a qualified institutional review board (IRB);
- The facility and personnel providing the treatment are capable of doing so by virtue of their experience or training;
- There is no noninvestigational therapy that is clearly superior to the protocol treatment; and
- The available clinical or preclinical data provide a reasonable expectation that the protocol treatment will be at least as efficacious as noninvestigational therapy.

References 1. Items and services required by the design of the trial should be covered, except those items or services normally paid for by other funding sources such as the cost of certain investigational drugs, the costs of any nonhealth services that might be required for a person to receive the treatment, and the costs of managing the research. 2. Treatment with a therapeutic intent may be aimed at improving patient outcome relative to either survival or quality of life.

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Clinical Trials Appear Not to Drive Up Cost of Cancer Treatment

Posted: 01/27/2003

Related Pages:

Digest Page: Cost of Clinical Trials [1]
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.

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

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Evidence Mounts That Clinical Trials Are Not Costly

Posted: 05/20/2000

Related Pages:

Highlights from ASCO 2000 [1]
A roundup of news highlights from the 2000 annual meeting of the American Society of Clinical Oncology.

Digest Page: Cost of Clinical Trials [2]
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.

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 [3], 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

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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."

Table of Links

1 http://cancer.gov/asco2000/highlights

2 http://cancer.gov/clinicaltrials/digestpage/cost

3 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10920127&dopt=Abstract

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Clinical Trials Not Costly

Posted: 02/09/2000

Related Pages:

Digest Page: Cost of Clinical Trials [1]
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.

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 [2] 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.

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 [3] which also found that costs for clinical trials participants are almost identical to those incurred by non-participants.

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PATIENT CARE COSTS AND HIGH QUALITY CLINICAL TRIALS

Second in the *Summit Series on Clinical Trials*

February 25-26, 1999, Tyson's Corner, VA

Sponsored by:
Cancer Leadership Council
Cancer Research Foundation of America
Coalition of National Cancer Cooperative Groups
Oncology Nursing Society

Summit II on Clinical Trials: Patient Care Costs and High Quality Clinical Trials convened on February 25, 1999, to sustain momentum and generate further discussions of issues presented at the first Summit on Clinical Trials held in July 1998 as a corollary to THE MARCH: Coming Together to Conquer Cancer.

The goal of Summit II was to open a dialogue and help bridge the gap between the cancer care community and third-party payers. Participants had the opportunity to express their respective positions on cancer clinical trials and reimbursement and help refute misconceptions, allowing a greater understanding of practices and a consensus on how to improve the system for the benefit of everyone. Attendees included representatives from government and industry, academic and community oncologists, patient advocates, oncology nurses, legislative agencies and representatives of third-party payers and managed care organizations.

The first day included an overview of the Summit I and insight into current programs already addressing coverage of patient care costs. The agenda was then set for discussion groups to approach on day two, which would hopefully culminate in strategic direction for next steps.

Summit I focused on defining a quality clinical trial, clinical trial availability and protocol design, and patient and physician participation. Several principal tenets agreed upon at the close of Summit I were:

- Clinical trials are critical components of high-quality patient care.
- A high-quality clinical trial addresses important scientific questions.
- Trials need to be not only good science but they must ultimately benefit standard patient care.

QUANTITATIVE SURVEY

A QUANTITATIVE SURVEY OF PUBLIC ATTITUDES TOWARDS CANCER CLINICAL TRIALS.

Robert L Comis, MD [1]; Carolyn R Aldigé [2]; Ellen L Stovall [3]; Linda U Krebs, PhD, RN [4]; Peter J Risher [5]; and Humphrey J Taylor [5]

1) Coalition of National Cancer Cooperative Groups, Philadelphia, PA; 2) Cancer Research Foundation of America, Alexandria, VA; 3) Cancer Leadership Council, Washington, DC; 4) Oncology Nursing Society, Pittsburgh, PA; and 5) Harris Interactive Inc., New York, NY

Introduction

Background. In 1998 the Coalition of National Cancer Cooperative Groups, the Cancer Research Foundation of America, the Cancer Leadership Council, and the Oncology Nursing Society came together to initiate the *Summit Series on Clinical Trials*. Participants at the Summits include representatives of all of the stakeholders in the cancer research enterprise: patients and patient advocacy organizations; physicians, nurses, and other health care professionals; managed care organizations and third party payers; public and private funding agencies and the pharmaceutical industry.

The purpose of the *Summit Series on Clinical Trials* is to provide a platform for all stakeholders in the clinical cancer research enterprise to come together to express what each sees as positive and negative aspects in the existing system and to suggest ways in which it can be made better. The hope is that by building a more responsive and efficient system, trial enrollment will increase which will permit faster development of advances in cancer treatment, prevention, control and symptom management.

Fewer than 5 percent of adult cancer patients in the United States are enrolled in clinical trials. The reasons for such dismal participation has been examined in a number of studies which have raised a variety of real or perceived barriers from the perspective of physicians, patients and others. Participants in Summit Conferences I-III recommended that a quantitative survey of public attitudes toward clinical research be undertaken as a first step in the development of a national strategic plan on cancer research. Such a project was initiated in mid-1999 in collaboration with Harris Interactive. In all six surveys will be completed targeting (1) the public, (2) the news media, (3) cancer patients (those who have as well as those who haven't participated in a trial), (4) family members of cancer patients, (5) primary care physicians, and (6) oncology nurses and physicians. *[Slide 1]*

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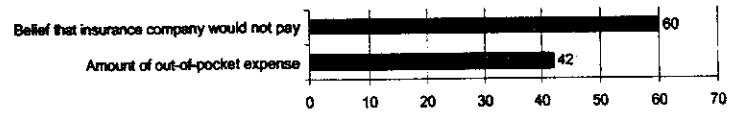
Insurance Coverage Barriers
Perceptions vs. Reality

Trial Non-Participants

Two important reasons for non-participation:



Trial Participants

Conclusions

The potential for increased participation in clinical trials exists. Greater participation is achievable if information about the benefits of trials is more widely disseminated, misconceptions about drawbacks are dispelled, treatment costs are reimbursed, and a more active role is played by physicians in getting patients to consider trials. The fact that patients who participate have positive experiences, the public is receptive to the idea of participation, and physicians would like to see more patients participate, can only help in efforts to make greater participation a reality. *[Slide 15]*

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Conclusions

- 85% of cancer patients are unaware that clinical trials are a treatment option in which they have a right participate;
- Patients who received treatment while on a clinical trial cite it as a very positive experience;
- The role of the oncologist is essential to securing patient participation in clinical trials;
- Even the perception that insurance coverage may be denied acts as a barrier to participation; and
- Public and patients are willing to consider trials if properly informed

Clinical Trials Cooperative Group Program

(Original available; currently being reviewed and revised)

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Introduction

The Clinical Trials Cooperative Group Program was conceived in 1955 when Dr. Sidney Farber, Mary Lasker, and others approached Congress with a proposal that it increase support for studies of chemotherapy for cancer. Congress responded by appropriating $5 million to the National Cancer Institute to establish the Chemotherapy National Service Center. By 1958, seventeen Groups were organized which operated under research grants from NCI; their main thrust was the testing of new anticancer agents from the NCI drug development program. Over the intervening years the Program has evolved into one which places major emphasis on definitive studies of combined modality approaches to the treatment of cancer. The scope of this program includes:

- Approximately 20,000 new patients are accrued onto Group treatment studies each year.
- 12,000 new patients are evaluated annually on ancillary laboratory correlative studies, and many times the combined number are in follow-up.
- Thousands of individual investigators participate in Cooperative Group protocols.

The Cooperative Groups are heterogeneous in their research objectives and their structures. These Groups presently are four major types:

1. Groups that are specifically disease oriented (e.g., gynecologic oncology)
2. Groups that are designed to deal primarily with high technology, single modality studies (e.g., radiation therapy)
3. Groups in which the investigators have a particular expertise (e.g., pediatricians)
4. Multimodal National Groups

The common thread, however, is the development and conduct of large-scale trials in a multi-institutional setting.

Purpose of the Cooperative Group Program

The essential feature of the Clinical Trials Cooperative Group Program is the support of organizations which continually generate and conduct new clinical trials consistent with national priorities for cancer treatment

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research. Emphasis is placed on definitive, randomized Phase III studies and the developmental efforts preliminary to them. While a wide variety of investigational efforts are therefore appropriate, this Program specifically does not overlap with or replace funding mechanisms for more narrowly focused, Research Project Grant activities (e.g., RO1, PO1 grants and U01, U19 cooperative agreements).

One of the primary objectives underlying the formation of the Groups is the conduct of large multicenter trials for the investigational agents sponsored by CTEP. This allows the rapid accrual of patients while reducing the possible bias of studies carried out at a single or a few institutions.

Goals of Cooperative Group Research

1. IMPROVE THERAPY

Therapeutic research aimed at improving the survival and quality of life for persons with cancer is of highest priority to CTEP.

2. ADJUNCT STUDIES

The database of patient information accumulated in the course of treatment research, and the possibilities for large-scale collection of biologic samples with subsequent correlation of specific features with patient outcome, provide the Groups with unique opportunities to address scientific questions about molecular genetics, epidemiology, pathology and other cancer-related topics. Such ancillary investigations can add considerable strength to a Group's total scientific program, and are encouraged. While certain studies may be eligible for inclusion in a Group application for financial support, particularly when the laboratory efforts are integral to the clinical trials proposed, a variety of other funding mechanisms - including investigator-initiated grants (R01s, P01s) and cooperative agreements for discrete projects (U01s, U19s) - may also be appropriate.

3. CLINICAL TRIALS METHODOLOGY

The Groups provide a unique framework for research in clinical trials methodology. While CTEP encourages development of and experimentation with new study designs within the Group framework, purely statistical research is appropriately funded through other mechanisms.

CTEP and the Cooperative Group Program

The NCI's Clinical Trials Cooperative Groups (the Cooperative Groups) consist of researchers at institutions affiliated with the Cooperative Groups, who jointly develop and conduct cancer treatment clinical trials in multi-institutional settings. Administered by CTEP staff, they are a major component of the extramural research effort of the DCTD, NCI. Each Cooperative Group is supported to continually generate new trials compatible with its particular areas of interest and expertise, as well as with national priorities for cancer treatment research. Unlike most other major NIH cooperative clinical trials efforts, the Cooperative Group structure and funding are not usually linked to any specific clinical trial(s).

This mechanism thus has the potential for

- considerable flexibility in resource allocation
- the rapid testing of promising new cancer therapies in large patient populations

This is feasible through the Cooperative Groups as they provide the apparatus for conducting such trials where the apparatus is constantly in place.

The Cooperative Groups have been instrumental in the development of new standards of cancer patient management, and in the development of sophisticated clinical investigation techniques. See Clinical Trials Cooperative Group Accomplishments, 1986-2001 (MS Word .doc)

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CTEP funds over 150 U10 cooperative agreements encompassing the following Cooperative Groups:

1. Cancer and Acute Leukemia Group B (CALGB)
2. Children's Cancer Study Group (CCSG)
3. Eastern Cooperative Oncology Group (ECOG)
4. Gynecologic Oncology Group (GOG)
5. National Surgical Adjuvant Breast and Bowel Project (NSABP)
6. North Central Cancer Treatment Group (NCCTG)
7. Pediatric Oncology Group (POG)
8. Radiation Therapy Oncology Group (RTOG)
9. Southwest Oncology Group (SWOG)
10. Intergroup Rhabdomyosarcoma Study Group (IRSG)
11. National Wilms' Tumor Study Group (NWTSG)
12. American College of Surgeons Oncology Group (ACOSOG)

The annual funding amount for the Cooperative Groups is approximately $90 million. Clinical trials for investigational anticancer agents are conducted under more than 175 INDs sponsored by DCTD, NCI and are carried out in part by the Clinical Trials Cooperative Groups. This includes investigational agents provided to DCTD, NCI by over 50 Industry Collaborators.

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Cost of Care for Patients in Cancer Clinical Trials

Bruce H. Fireman, Louis Fehrenbacher, Elisabeth P. Gruskin, G. Thomas Ray

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 unproven 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."

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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 intertrial 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	8163 (7126)	4311	6824	9648	58 714
Control subjects	6931 (6342)	3372	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.

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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 Arm I: AC Arm II: AC then paclitaxel	42	12 183	14 584	0.84
SWOG 9410, breast	T1–3, N1, M0, at least one positive lymph node Arm Ia: standard dose Adria in AC then TAX then TAM Arm Ib: standard dose Adria in AC then TAM Arm IIa: intermediate dose Adria in AC then TAX then TAM Arm IIb: intermediate dose Adria in AC then TAM Arm IIIa: high-dose Adria in AC (with G-CSF) then TAX then TAM Arm IIIb: high-dose Adria in AC (with G-CSF) then TAM	20	17 342	20 294	0.85
SWOG 9035, melanoma	T3, N0, M0, no positive lymph nodes Arm I: biological response modifier therapy, allogeneic melanoma cell vaccine containing detoxified endotoxin Arm II: observation only	11	5608	4415	1.27
NSABP B-24, breast	DCIS or LCIS, no positive lymph nodes Arm I: radiotherapy + antiestrogen therapy Arm II: radiotherapy + placebo	9	6818	5020	1.36
SWOG 9313, breast	T1–3. N0–1, M0, three or fewer positive lymph nodes Arm I: AC simultaneously (with G-CSF) Arm II: A then C (with G-CSF)	9	18 835	13 514	1.39
SWOG 9061, breast	Stage 2–3, at least 10 positive lymph nodes Arm I: CAF Arm II: CAF then bone marrow transplant	8	40 633	18 823	2.16
NSABP B-25, breast	Stage 2, at least one positive lymph node AC with G-CSF, three levels of intensity	6	19 464	16 738	1.16
NSABP B-23, breast	Stage 1, no positive lymph nodes Arm I: CMF then tamoxifen for 5 y Arm II: CMF then placebo for 5 y Arm III: AC then tamoxifen for 5 y Arm IV: AC then placebo for 5 y	5	10 225	8706	1.17
NSABP B-26, breast	Stage 3b–4, metastatic Arm I: paclitaxel (3-h infusion) Arm II: paclitaxel and G-CSF (24-h infusion)	4	39 927	21 321	1.87
SWOG 9326, ovarian	Stage 3, single agent consolidative chemotherapy, hexamethyl melamine	3	17 742	17 751	1.00
Other trials	Colon, stomach, brain, lymphoma, kidney, and lung	18	24 357	23 769	1.02
All trials		135	17 003	15 516	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

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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

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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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