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Clinical Trials Appear Not to Drive Up Cost of Cancer Treatment

Posted: 01/17/2003

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

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

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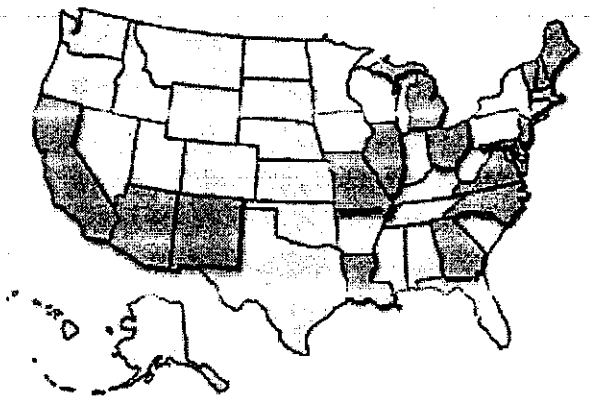
States That Require Health Plans to Cover Patient Care Costs in Clinical Trials

Updated [illegible]

A growing number of states have passed legislation or instituted special agreements requiring health plans to pay the cost of routine medical care you receive as a participant in a clinical trial.



Use this map to link to an overview of each state's law or agreement and its key provisions.

"Routine patient care costs" are the usual costs of medical care, such as doctor visits, hospital stays, clinical laboratory tests, x-rays, etc., that you would receive whether or not you were participating in a clinical trial. Some health plans don't cover these costs once you join a trial, even though studies have shown that they are not appreciably higher than costs for patients who are not enrolled in trials. (See Digest Page: Cost of Clinical Trials [1].)

Lack of such coverage is a significant barrier to many patients who might otherwise enroll in a trial. Lack of coverage also makes it harder for researchers to successfully conduct trials that could improve prevention and treatment options.

These laws and agreements do not cover the research costs associated with the conduct of the trial, such as tests purely performed for research purposes. In most cases, such costs would be paid for by the group sponsoring the trial, such as the National Cancer Institute or a pharmaceutical company.

For more of an overview, see Clinical Trials and Insurance Coverage: A Resource Guide. [2]

To find specific trials in PDQ -- the National Cancer Institute's database of ongoing cancer clinical trials -- go to the PDQ search page. [3]

To understand the basics of clinical trials, please see the variety of articles listed in the Understanding Clinical Trials [4] section of this Web site. Of particular interest might be What is a Clinical Trial? [5]

Another resource is NCI's State Cancer Legislative Database Program [6].

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Evidence Mounts That Clinical Trials Are Not Costly

Posted: 05/20/2000

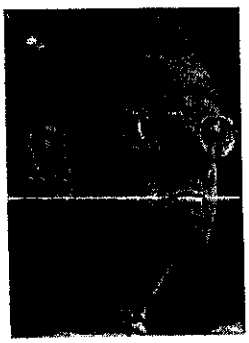
Related Pages:

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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Cancer Clinical Trials: Can We Afford Them?

Knowing What Insurance Providers Will Cover Is Key

Article date: 2002/01/15

Some insurance providers cite increased costs as a reason to limit patient access to clinical trials. Studies conducted examining this issue are few, but they are needed to look at the differences in expenses between clinical trials and standard forms of care.

In a report in the *Journal of Clinical Oncology* (Vol. 19, No. 23: 4330-4339), Charles M. Bennett, MD, PhD, and colleagues found clinical trials resulted in only moderately increased costs at most when compared to standard treatments.

Researchers studied this issue by looking at 377 patients in five previous cost-effectiveness studies. Overall costs for patients in clinical trials ranged from 10% less to 23% more than those being treated outside of the trials.

Insurance coverage of clinical trials varies a great deal between providers — and even between states — at the present time, but this may change in the near future. In the meantime, people considering entering a clinical trial should check with their insurers before agreeing to participate.

Cost a Barrier to What Could Be Life-Saving Treatment

Clinical trials are studies designed to test the safety and effectiveness of a new form of therapy in people. These types of studies are done after lab tests show a therapy holds promise.

All new therapies must go through several clinical trials before the US Food and Drug Administration (FDA) will approve them for use.

These studies are especially critical in diseases such as cancer, where current forms of therapy can be toxic and do not always cure. Clinical trials may help the patients who participate in them, and may also aid patients in the future.

Although there is an urgent need to find new and better ways to treat cancer, fewer than 5% of adult cancer patients now participate in clinical trials. Many patients decide not to take part in a research study, worried that their insurance company may not cover the costs.

Concerns of patients are understandable considering recent rises in health care costs. Bills for many forms of cancer treatment can easily run into the tens of thousands of dollars.

Coverage of Clinical Trials Varies Widely

Insurers who do cover the cost of clinical trials generally pay for those aspects of treatment considered to be "standard care" — expenses that would be accrued even if a patient were not taking part in a study. These might include doctor visits, routine lab tests, and imaging tests.

The clinical trial sponsor usually covers the cost of other expenses specific to the trial, such as new medications and any lab or imaging tests that would not normally be part of standard treatment.

As the article's authors point out, the amount of coverage provided varies widely among insurance providers. Many actually cover study expenses even though they have policies to the contrary.

New laws introduced in the past few years have made it easier for some people to get treatment in research studies. As of 2000, Medicare is authorized to cover many of the costs related to certain clinical trials.

While no federal laws have yet been passed, 14 states have laws mandating insurance providers cover certain clinical trial costs. Some large private insurers, meanwhile, have acted on their own, agreeing to reimburse for medical care that occurs with clinical trials.

The authors of the report acknowledge that it would be difficult to try to set nationwide coverage policies based on the limited data available so far. Two new studies examining the cost differences are now underway. They should help clarify these issues and provide insurers with better guidance in the future.

In the meantime, cancer patients should take heart in the fact that more and more providers are now routinely covering clinical trials costs.

At the same time, patients need to be aware that not all insurers do so. Cancer patients considering a clinical trial, should find out up front what insurance will — and will not — pay for. If needed, patients can ask their health care team to check with the trial sponsor as well. Some may be willing to foot the bill even if the insurance company does not.

Measuring the Incremental Cost of Clinical Cancer Research

By Dana P. Goldman, Michael L. Schoenbaum, Arnold L. Potosky, Jane C. Weeks, Sandra H. Berry, Jose J. Escarce, Beverly A. Weidmer, Meredith L. Kilgore, Nikhil Wagle, John L. Adams, Robert A. Figlin, Joy H. Lewis, Joel Cohen, Richard Kaplan, and Mary McCabe

Purpose: To summarize evidence on the costs of treating patients in clinical trials and to describe the Cost of Cancer Treatment Study, an ongoing effort to produce generalizable estimates of the incremental costs of government-sponsored cancer trials.

Methods: A retrospective study of costs will be conducted with 1,500 cancer patients recruited from a randomly selected sample of institutions in the United States. Patients accrued to either phase II or phase III National Cancer Institute–sponsored clinical trials during a 15-month period will be asked to participate in a study of their health care utilization (n = 750). Costs will be measured approximately 1 year after their trial enrollment from a combination of billing records, medical records, and an in-person survey questionnaire. Similar data will be collected for a comparable group of cancer patients not in trials (n = 750) to provide an estimate of the incremental cost.

Results: Evidence suggests insurers limit access to trials because of cost concerns. Public and private efforts are underway to change these policies, but their permanent status is unclear. Previous studies found that treatment costs in clinical trials are similar to costs of standard therapy. However, it is difficult to generalize from these studies because of the unique practice settings, insufficient sample sizes, and the exclusion of potentially important costs.

Conclusion: Denials of coverage for treatment in a clinical trial limit patient access to trials and could impede clinical research. Preliminary estimates suggest changes to these policies would not be expensive, but these results are not generalizable. The Cost of Cancer Treatment Study is an ongoing effort to provide generalizable estimates of the incremental treatment cost of phase II and phase III cancer trials. The results should be of great interest to insurers and the research community as they consider permanent ways to finance cancer trials.

J Clin Oncol 19:105-110. © 2001 by American Society of Clinical Oncology.

TRADITIONALLY, THE cost of conducting cancer clinical trials has been supported by a combination of research sponsors, institutions, and third-party payers. However, health insurers and other payers are increasingly reluctant to reimburse for direct patient care provided as part of a clinical trial.[1] These policies—driven in part by a perception that patients enrolled onto trials incur substantial additional costs—impede efforts to enroll patients onto clinical trials.[2] Yet there is a lack of generalizable evidence regarding the costs of treating patients in clinical trials.

Given the importance of clinical trials in extending longevity and improving quality of life,[3-7] there is an urgent need for unbiased information on the possible effects on patient care costs of participation in government-sponsored clinical trials. Such data would make any cost-sharing burden explicit and could lead to better mechanisms for financing clinical trials. This article summarizes current knowledge on the incremental costs of treating cancer patients in clinical trials and the methodologic challenges in generating precise and generalizable estimates of costs. We also introduce the Cost of Cancer Treatment Study (CCTS), an ongoing effort to obtain national estimates of the direct care costs of patients who participate in National Cancer Institute (NCI)–sponsored clinical cancer trials.

POLICY CONTEXT

The issue of coverage for patient care costs in clinical trials is complex and involves at least two important policy questions. The first is, do insurance barriers impede patient recruitment onto clinical trials. Most insurers or plans have policies that exclude coverage for services provided as part of a clinical trial and define them as experimental.[2,8-10]

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However, since most payers do not track who is enrolled onto clinical trials, these policies are not always enforced.[11] Exclusions tend to be invoked only for expensive experimental procedures—eg, stem-cell transplantation—which, even when given outside a research protocol, typically require preauthorization for coverage. Thus, the question is really an empirical one.

Unfortunately, there are few, if any, careful studies quantifying this problem, but a recent study by the General Accounting Office (GAO) does provide some qualitative evidence. After interviewing health insurers, clinical researchers, government officials, and medical directors at health plans, the GAO concluded that there are not widespread limitations on patient access but cautioned that "neither the insurers nor the cancer centers were statistically representative groups, and thus the findings from our interviews cannot be generalized."[2] In addition, the mere existence of these exclusions probably discourages enrollment.[2] Other studies also suggest that physicians may automatically exclude patients with certain types of insurance from trials because of reimbursement concerns[11]—a practice that may explain why participation rates are lower in some managed-care settings.[12]

The second question is, do insurers erect these barriers because of cost concerns? Here the answer is clearer. In the GAO report, medical directors indicated that decisions about trial participation are made on a case-by-case basis, with costs tantamount to scientific merit as the two most important factors in the decision.

As a consequence, public and private efforts are underway to remove insurance barriers to trial enrollment. Public agreements allow less discretion in the choice of trials. For example, NCI has entered into agreements with the United States Department of Defense and the Department of Veterans Affairs to provide their beneficiaries coverage when participating in any NCI-sponsored clinical trial; and Virginia, Illinois, Maryland, and Rhode Island have enacted laws mandating at least partial coverage for participants in federally approved clinical trials. Most importantly, President Clinton signed an executive order in June 2000 mandating that Medicare cover routine costs associated with all clinical trials, with the purpose of encouraging elderly patients, who comprise 65% of all new cases, to enroll onto cancer clinical trials.[13]

Several private initiatives are also underway, although these provide insurers with more discretion. One exception is the agreement signed by the Governor of New Jersey with a coalition of insurance companies to provide an estimated 25,000 cancer patients in that state access to federally approved clinical trials.

Even with these policy changes, however, there is still a need for generalizable estimates of the cost of trial participation. First, many of these arrangements are being conducted as demonstrations (*Journal of the National Cancer Institute* news articles[14]), and cost information must be developed before coverage will become a permanent benefit. Second, and most importantly, no clear consensus has emerged regarding the definition of standard care costs. The Institute of Medicine recently recommended that Medicare reimburse routine care for patients in clinical trials in the same way it reimburses routine care for patients not in clinical trials.[11] The Institute of Medicine also recommended that the Health Care Financing Administration pay more than routine costs, at least for selected trials.[11] Obtaining valid and precise estimates of costs would help insurers develop simpler and more consistent financing strategies for clinical trials.

ESTIMATES OF THE COST OF TRIAL PARTICIPATION

Three recent studies have investigated the costs of care among cancer patients in single institutions or health plans and provide some useful evidence. Wagner et al[15] found that 61 cancer patients in phase II and phase III cancer trials at the Mayo Clinic had at most 10% higher costs than a set of matched controls not enrolled onto trials over a 5-year period, although the difference was not statistically significant. Fireman et al[16] estimated that 135 patients in NCI-sponsored cancer trials at a large group model health maintenance organization (HMO) (Kaiser Permanente, Northern California) had approximately 10% higher costs over 1 year than 135 matched controls, with most of the difference attributable to chemotherapy administration costs. Finally, Barlow et al (manuscript in preparation) estimated treatment costs over a 2-year period among 77 patients in NCI-sponsored breast and colorectal cancer trials at another large HMO (Group Health Cooperative–Puget Sound). Compared with a general sample of nontrial patients with the same age range, time of diagnosis, and initial cancer stage, trial patients incurred slightly lower treatment costs, although the difference was not statistically significant; however, using data from 26 patients in breast cancer trials and matched controls, trial patients incurred 26% higher costs over a 2-year period. (Barlow et al, manuscript in preparation).

Several unpublished studies presented at the Thirty-Sixth Annual Meeting of the American Society of Clinical Oncology (May 20-23, 2000) reached similar conclusions. Quirk et al[17] found that 77 patients in phase II and phase III cancer trials at Memorial Sloan-Kettering Cancer Center had lower mean treatment costs (hospital costs plus physician charges) than 75 matched controls not enrolled onto a

clinical trial, although the difference was not statistically significant. Stinson et al[18] found that 35 patients in phase II clinical trials at five cancer centers belonging to the American Association of Cancer Institutes had lower mean treatment costs than 35 matched controls, although the difference was not statistically significant.

These studies provide important evidence about the costs of care associated with trials. Nevertheless, as Brown[19] has argued previously, more study is warranted. There are a number of technical reasons for this conclusion. First, existing studies have had sample sizes that were insufficient to detect cost differences that may be important for policy purposes, mainly because of the limited number of available trial patients at any single institution or health plan. Second, cases and controls matched at a single institution may differ in unobserved but important ways that affect treatment costs due to self-selection into trials. Third, these studies excluded some potentially important dimensions of treatment. For instance, each published study excluded treatment provided by clinicians outside the delivery system in which the respective study was conducted[15,16] (Barlow et al, manuscript in preparation), and one study excluded the costs of medications.[15]

More important, however, is that treatment patterns differ across institutions, and—with the exception of the study by Stinson et al[18]—each of these studies was conducted within a single institution or health system. In all the previous studies, trial patients and matched controls in each study received care at major research institutions or specialized HMOs, where the costs of treatment may be different from costs in the community settings where many patients receive care. This makes the results difficult to generalize.

THE CCTS

Precise and generalizable estimates of the effects of trial participation on patient care costs could help policy makers refine mechanisms for financing clinical trials, with the goal of facilitating timely clinical research. Given the inherent limitations of previous studies, the most likely way to obtain such estimates is via a large, nationally representative sample of institutions involved in cancer trial research.

The CCTS is a 3-year study designed to provide such estimates. Approximately 1,500 cancer patients will be recruited from a broad cross-section of trials and institutions nationwide. Ultimately, the CCTS will yield a precise answer to the question "How much more expensive is it to treat a patient on an NCI-sponsored clinical trial?" This answer will allow policy makers, insurers, and others to estimate the additional treatment cost, if any, of providing blanket access to these trials.

The CCTS will use a retrospective cohort design. Patients accrued to NCI-sponsored clinical trials in 1998 will be asked to participate in a study of their health care utilization approximately 1 year after their trial enrollment. Costs will be measured for all services used by this sample. Similar data will be collected for a comparable group of cancer patients not receiving care in a research study who will serve as the controls for the CCTS. Efforts will be made to estimate the cost of care for a wide spectrum of services from all of a patient's providers using a combination of billing records, medical records, and an in-person survey questionnaire. Further details about the CCTS, and how it is designed to address previous limitations, are presented below.

METHODOLOGIC CHALLENGES

A number of conceptual and methodologic issues must be resolved in order to produce cost estimates in a timely and cost-effective way. They include the sample size necessary to assess policy-relevant differences in treatment costs, the characteristics of the appropriate control patients, the appropriate follow-up period, and the types of medical care that should be included in cost estimates.

Sample Size and Design

After consulting with policy makers and insurance industry leaders, members of the CCTS group determined that to be useful to policy makers, a national cost study should have sufficient sample size to detect a 10% difference in costs. Power calculations then dictated that the study needed 750 patients on trials and 750 matched controls in order to have an 80% chance of detecting such a difference.[20] In addition, cross-institution samples would be necessary for the study to be generalizable, given the likelihood that practice patterns and treatment costs vary across institutions. However, it was clear at the outset that the CCTS would not be feasible if it were necessary to approach hundreds of different providers and institutional review boards and collect records and data from huge numbers of sites. Otherwise, the costs of obtaining permissions from a multitude of study investigators and institutional review boards, and the effort needed to collect and record data, would make the study prohibitively expensive.

The existence of timely national data on accrual from the cooperative groups—which are responsible for most of the clinical trial accrual on NCI-sponsored protocols—provided a convenient sampling frame for a clustered multistage design. (Details are provided elsewhere.[20]) However, using data supplied by NCI's Cancer Therapy Evaluation Program, we sampled 35 NCI-sponsored phase III treatment trials active in 1998. A list of all institutions affiliated with these 35 trials was then compiled, and a final list of 55 study

sites was then sampled randomly. The study sites include a heterogenous mix of providers in the cancer research community, ie, 14 NCI-designated cancer centers, 12 community clinical oncology programs, and 29 other institutions, such as academic medical centers. These institutions also affiliate with community clinics and hospitals that accrue patients under the auspices of the core institution (in some cases, the affiliates are owned or operated by the core institution, but not always). Patients in the sampled phase III trials, as well as an additional sample of phase II patients, will be selected from these institutions for recruitment into the CCTS.

Identifying Controls

One critical issue in assessing the incremental costs of trial participation is to identify an appropriate comparison population. Most fundamentally, to find controls for patients in a particular trial, CCTS will select patients who met the protocol eligibility criteria for that trial during the same time period during which the case enrolled but who did not receive cancer therapy as part of any treatment trial. Patients enrolled onto the control arm of a clinical trial are considered "cases" in the CCTS.

Ideally, the CCTS would identify controls through a systematic review of medical records to determine which patients met the relevant the protocol entry criteria.[14] However, such a strategy is prohibitively expensive given the number of patients and institutions involved. Instead, the CCTS will use a variety of sources at each institution. Patient logs will be consulted in some cases to identify people who were approached for trial enrollment but who did not enroll. The number of such patients will be limited, however, so the majority will be identified through tumor registries (or other administrative data) followed by a brief medical record screen. An expert panel of oncologists has been convened to identify the screener criteria for each sampled trial.

Selection Bias

Trial participation is voluntary, so patients who are eligible for a trial but do not enroll may be systematically different from those who do enroll. These differences may affect treatment costs if, for instance, patients with a preference for aggressive treatment proactively seek out trials or are more likely to enroll onto a trial if offered the opportunity. Within the CCTS, we will attempt to minimize this potential source of bias in several ways. First, we will use chart reviews to identify any differences in underlying disease severity. Any residual severity differences between cases and controls will then be controlled for using multivariate analysis. Second, the patient survey will assess characteristics that might affect the type of care patients might seek out or agree to if offered, such as patients' preferences for care, their access to trials (eg, whether they had ever sought out a trial, or whether a trial had ever been offered to them), and their health locus of control.

Third, the CCTS will try to identify control patients who were prevented from enrolling onto the particular trial for external reasons. For instance, the CCTS will seek controls by examining logs of patients approached for each sampled trial at a particular institution but whose insurance refused to authorize trial participation. In addition, the CCTS will identify patients who were actually ineligible for a particular trial but whose clinical characteristics differed from the protocol entry criteria in ways that were likely to have a minor effect on the course of treatment. In the CCTS, a panel of oncologists is reviewing the protocol eligibility criteria of each sampled trial to identify criteria that may be unlikely to affect patients' course of treatment.

Fourth, the CCTS will seek some controls for particular trials at institutions where that trial was not taking place. Matching patients and controls within the same institution may be difficult, because such patients may be hard to find: most patients at an institution who are clinically eligible for an open trial at that institution may be enrolled. Indeed, Wagner et al[15] report having to drop more than half of their available trial patients because no matched control could be identified at the Mayo Clinic. Thus, the CCTS will draw some control patients from other institutions where the trial is or was not being conducted. These patients, who were never approached about entering a trial, will not be self-selected as cases.

Measuring Costs

Data on treatment costs could be collected prospectively or retrospectively. In principle, a prospective design could substantially improve data quality relative to retrospective data collection, which is why such a design is preferred by studies such as the Medical Expenditure Panel Study.[21] However, prospective cost studies are expensive to implement when patients are accruing slowly and enrollment is taking place at hundreds of institutions. (This also partly explains why administration of clinical trials is so expensive.) Because of this expense—as well as the delay in getting results—the CCTS chose to follow other studies and use a retrospective design to assess costs[15,16,21,22] (Barlow et al, manuscript in preparation).

Data on health care use and costs will come from a combination of patient report and administrative records. The design requires patients to report about past health care use and to identify health care providers from whom administrative records can be obtained (with patients' consent). Most of the literature on recall bias supports this design. The major problem with self-reported utilization

Table 1. Matrix for Measuring Costs for Subgroups

	Treated Primarily at Academic Medical Center	Treated Primarily by Community Provider
Patients in trials	A	B
Controls not in trials	C	D

data is the net omission of medical events,[23] a phenomenon experimental psychologists associate with the exponential decay of memory.[24-26] Fortunately, the omissions tend to be less salient—and costly—events, with the recall of inpatient episodes better than that of outpatient care.[27] Patients also sometimes include utilization outside of the recall window—a process known as telescoping.[28,29] Overall, the literature supports retrospective assessment of health care use over a 6-month period, at most; however, patients may be able to identify their medical providers over a longer period, and administrative records can be collected from these providers for periods covering more than the previous 6 months.

Estimating Costs in Multiple Settings

Patients reach clinical trials in a number of ways. In many cases, patients may seek out or be referred to a clinical trial being conducted at the institution where they are already receiving care. However, some patients may change providers in order to participate in a clinical trial, for instance, from a community provider to an academic medical center (or from a community provider that does not do clinical research to one that does). If practice patterns and/or health care costs differ across different types of institutions, as seems plausible, treatment costs for these patients will change. The CCTS will measure costs for the subgroups shown in the matrix in Table 1.

Comparing groups A and C gives the incremental cost (A − C) of trial participation at academic medical centers. This can be compared with at least two important alternatives: (1) B − D, the incremental cost of trial participation in community settings, and A − D, the incremental cost of trial participation assuming patients change providers from a community setting to an academic medical center to be on a trial.

As a consequence, the CCTS will be able to provide generalizable cost estimates in both tertiary and community settings, as well as for patients who leave community settings to enroll onto a clinical trial.

DISCUSSION

Evidence suggests that, at least in some circumstances, health plans are reluctant to pay for care delivered as part of a clinical trial. Such denials of coverage limit patient access to trials and could impede clinical research. Public and private efforts are underway to change these policies, but their permanent status is unclear given cost concerns.

Preliminary estimates of the cost differences are available, but these come from studies at selected institutions. The CCTS is an effort to measure the incremental treatment cost of cancer trials and to address limitations of previous studies.

Successful implementation is predicated on the participation and cooperation of the cancer community. If successful, the study will provide generalizable results that should be of great use to insurers, the cancer research community, and policy makers as they consider ways to finance clinical trial research.

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