

# Incremental Treatment Costs in National Cancer Institute–Sponsored Clinical Trials

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**T**HE COST OF CONDUCTING cancer clinical trials has traditionally been supported by a combination of research sponsors, institutions, and third-party payers. However, private health insurance plans are frequently reluctant to reimburse for direct patient care provided as part of a clinical trial.<sup>1</sup> This reluctance, driven in part by a perception that patients enrolled in trials incur substantial additional costs,<sup>2,3</sup> impedes efforts to enroll patients in trials.<sup>4</sup> Yet there is a lack of generalizable evidence regarding the costs of treating patients in clinical trials. Given the importance of clinical research in identifying better treatments,<sup>5-9</sup> there is a need for precise estimates of the additional treatment costs associated with trial participation.

Although some private insurance companies reimburse routine costs—ie, care that would have been received in the absence of trial participation—the policy is far from universal and often is not made explicit.<sup>4</sup> Medicare is a notable exception, having agreed to cover treatment for trial participants in the year 2000. For those private insurance companies that do reimburse routine costs, the ambiguity of what is

**Context** Concern about additional costs for direct patient care impedes efforts to enroll patients in clinical trials. But generalizable evidence substantiating these concerns is lacking.

**Objective** To assess the additional cost of treating cancer patients in the National Cancer Institute (NCI)–sponsored clinical trials in the United States across a range of trial phases, treatment modalities, and patient care settings.

**Design** Retrospective cost study using a multistage, stratified, random sample of patients enrolled in 1 of 35 active phase 3 trials or phase 1 or any phase 2 trials between October 1, 1998, and December 31, 1999. Unadjusted and adjusted costs were compared and related to trial phase, institution type, and vital status.

**Setting and Participants** A representative sample of 932 cancer patients enrolled in nonpediatric, NCI-sponsored clinical trials and 696 nonparticipants with a similar stage of disease not enrolled in a research protocol from 83 cancer clinical research institutions across the United States.

**Main Outcome Measures** Direct treatment costs as measured using a combination of medical records, telephone survey, and Medicare claims data. Administrative and other research costs were excluded.

**Results** The incremental costs of direct care in trials were modest. Over approximately a 2.5-year period, adjusted costs were 6.5% higher for trial participants than nonparticipants (\$35 418 vs \$33 248;  $P = .11$ ). Cost differences for phase 3 studies were 3.5% ( $P = .22$ ), lower than for phase 1 or 2 trials (12.8%;  $P = .20$ ). Trial participants who died had higher costs than nonparticipants who died (17.9%; \$39 420 vs \$33 432, respectively;  $P = .15$ ).

**Conclusions** Treatment costs for nonpediatric clinical trial participants are on average 6.5% higher than what they would be if patients did not enroll. This implies total incremental treatment costs for NCI–sponsored trials of \$16 million in 1999. Incremental costs were higher for patients who died and who were in early phase studies although these findings deserve further scrutiny. Overall, the additional treatment costs of an open reimbursement policy for government-sponsored cancer clinical trials appear minimal.

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covered invites conflict, and this uncertainty must be disclosed during the informed consent process.<sup>10</sup> The result is to discourage enrollment by patients and participation by health care professionals. Better information about the incremental costs of trial partici-

pation over standard care could lead to more universal and consistent coverage policies for clinical research.

Several studies have investigated the costs of care within cancer clinical trials and generally have found cost differences of between 0% and 10% for pa-

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tients in National Cancer Institute (NCI)–sponsored trials compared with matched controls (W. Barlow, written communication, August 1999).<sup>11-15</sup> Part of the problem is that these findings reflect different treatment patterns, for each of these studies was conducted at major research institutions or specialized health maintenance organizations, which may have engaged in a nonrepresentative set of clinical trials. The additional costs of trial enrollment may also be different in community settings where most patients receive care. More generalizable data are needed to convince insurers and policymakers, and this has led to calls for additional estimates.<sup>16</sup> The Cost of Cancer Treatment Study (CCTS) was designed to address this need by providing a point estimate for the additional costs of trial enrollment across a range of trial phases, treatment modalities, and patient care settings.

## METHODS

### Sampling

As described elsewhere,<sup>17</sup> the CCTS is a retrospective cohort study of a representative sample of clinical trial participants and matched nonparticipants. The sample sizes were chosen to detect a 10% difference in costs with a .80 power at a .05 significance level. This choice was made after private consultation with executives at 4 major private insurance companies who noted that estimates below this amount would be helpful in making informed decisions about whether to provide greater access to trial enrollment.

Using data on all nonpediatric phase 3 treatment trials supplied by the Cancer Therapy and Evaluation Program at the NCI, we randomly sampled 35 of 92 active clinical trials with probability of selection proportional to actual patient accrual from October 1, 1998, to March 31, 1999. The selected trials represented 66% of phase 3 accrual. The clinical investigation of experimental drugs is normally conducted in 3 phases. Phase 1 trials (to determine safety) and phase 2 studies (to determine efficacy) involve at most a few hundred patients and

**Table 1.** Data Sources and Sample Sizes\*

Data Source	All Participants (n = 1628)†	Trial Participants (n = 932)		Nonparticipants (n = 696)	
		Alive (n = 781)	Deceased (n = 151)	Alive (n = 595)	Deceased (n = 101)
Telephone surveys	1376	781	...	595	...
Medical records‡	1377	651	151	474	101
Medicare administration data	437	202	42	153	40

\*Patients can have multiple data sources.

†For inclusion in the Cost of Cancer Treatment Study, living participants must have completed a telephone survey. Deceased participants must have had at least 1 medical record submitted by their treating institution.

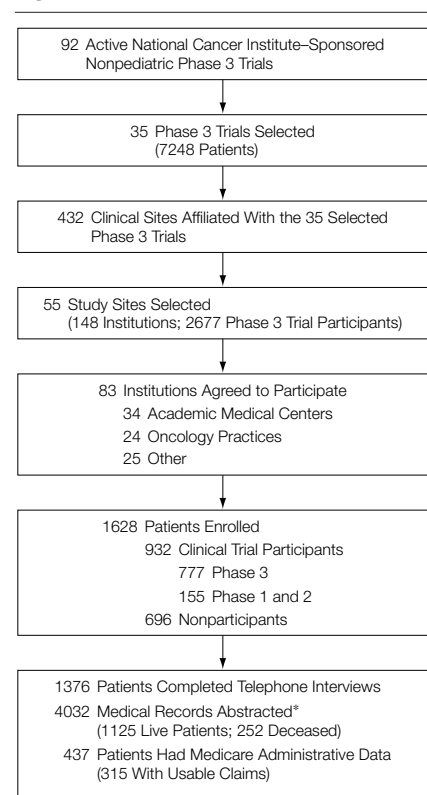
‡Patients with at least 1 record from a health care practitioner.

are short in duration. In contrast, phase 3 studies test the overall benefit and risk profile of an experimental drug, involve several hundred to several thousand patients, and typically last several years. We then compiled a list of all clinical sites (n=432) affiliated with these phase 3 trials and randomly sampled 55 study sites, again with probability proportional to accrual.<sup>18</sup> Each study site consisted of a multicenter program with a core institution and affiliates. Of the 148 institutions we approached, 83 agreed to participate. Participating sites accounted for 63% of overall trial accrual from all sites selected for our sample.

**Trial Participants.** At each institution, patients were eligible for our study if they enrolled in 1 of our 35 sampled phase 3 trials or any phase 1 or phase 2 trial between October 1, 1998, and December 31, 1999. Phase 1 and 2 trials were not restricted to a random sample because there were fewer of them, accrual was much lower than what it was for the phase 3 trials, and in some cases, accrual data were unavailable. At each institution, we identified a site captain (often a clinical trials coordinating nurse) who located eligible patients and obtained contact information. Of the trial participants contacted by the site captains, 61% enrolled in the CCTS (n=777). TABLE 1 provides a summary of sample sizes and the FIGURE provides a study flow chart.

**Nontrial Participants.** Nonparticipants for the CCTS were adult patients who met the eligibility criteria for 1 of our trials but who did not receive therapy as part of any clinical trial

**Figure.** Study Flow Chart



\*Patients may have more than 1 medical record.

(TABLE 2). For each CCTS trial participant, site captains attempted to enroll a matched nonparticipant at the same institution. Site captains identified eligible patients through tumor registries or other administrative data followed by a brief medical record screen, which is an efficient method for identifying cancer patients meeting an abbreviated set of trial entry criteria.<sup>19</sup> When nonparticipants were unavailable, we sought a nonparticipant with

similar clinical characteristics at a different member institution. Enrollment rates were slightly lower for non-

participants (56%) than for trial participants (61%). All trial participants and nonparticipants enrolled in

the CCTS through contact with site captains were alive. Enrollment of deceased trial participants and nonparticipants is discussed below.

**Table 2.** Comparison of Characteristics of Trial Participants and Nonparticipants\*

Characteristic	No. (%)			P Value†
	All Patients (n = 1628)	Participants (n = 932)	Nonparticipants (n = 696)	
Study phase				
1	37 (2)	19 (2)	18 (3)	<.01
2	221 (14)	136 (15)	85 (12)	
3	1370 (84)	777 (83)	593 (85)	
Deceased	252 (15)	151 (16)	101 (15)	.31
Cancer type				
Breast	678 (42)	366 (39)	312 (45)	<.01
Colorectal	265 (16)	145 (16)	120 (17)	
Gynecologic	201 (12)	116 (12)	85 (12)	
Hematologic	105 (6)	78 (8)	27 (4)	
Lung	69 (4)	42 (5)	27 (4)	
Melanoma	47 (3)	33 (4)	14 (2)	
Other	140 (9)	94 (10)	46 (7)	
Prostate	123 (8)	58 (6)	65 (9)	
Bone marrow transplant	54 (3)	33 (4)	21 (3)	.56
Women	1147 (70)	644 (69)	503 (72)	.13
Education				
<High school	137 (10)	79 (10)	58 (10)	.41
High school graduate or GED	379 (28)	213 (27)	166 (28)	
Some college	292 (21)	173 (22)	119 (20)	
Associate's degree	116 (8)	67 (9)	49 (8)	
College graduate	277 (20)	162 (21)	115 (19)	
Graduate or professional degree	174 (13)	86 (11)	88 (15)	
Nonwhite	128 (9)	86 (11)	42 (7)	.01
Insurance, not mutually exclusive				
Medicare	524 (35)	279 (33)	245 (38)	.03
Private insurance	960 (64)	555 (65)	405 (63)	.48
Medicaid	85 (6)	53 (6)	32 (5)	.33
Other conditions (not mutually exclusive)				
Arthritis	531 (33)	293 (31)	238 (34)	.24
Hypertension	495 (30)	278 (30)	217 (31)	.56
Weight loss	218 (13)	136 (15)	82 (12)	.10
Diabetes	175 (11)	110 (12)	65 (9)	.11
Other cancer	152 (9)	70 (8)	82 (12)	<.01
Gastric ulcers	118 (7)	70 (8)	48 (7)	.64
Emphysema	70 (4)	39 (4)	31 (4)	.79
Stroke	72 (4)	44 (5)	28 (4)	.50
Deep vein thrombosis	75 (5)	48 (5)	27 (4)	.23
Myocardial infarction	63 (4)	34 (4)	29 (4)	.59
Congestive heart failure	33 (2)	20 (2)	13 (2)	.69
Health locus of control‡				
Strongly agree with statement 1	639 (46)	359 (46)	280 (47)	.82
Strongly agree with statement 2	233 (17)	126 (16)	107 (18)	.47
Changed provider to enroll in trial	...	52 (7)	...	...
Age, mean (SD), y	57 (12.7)	56 (12.5)	59 (13.0)	<.01

Abbreviation: GED, general educational development test.

\*Education, nonwhite, and locus of nonparticipant exclude deceased patients.

†P values are from t tests of equivalence between trial participants and nonparticipants, except phase, cancer type, and education, which used  $\chi^2$  tests.

‡Health locus of control statements are (1) "I can overcome most illnesses without help from medically trained professionals" and (2) "If I get sick, it is my own behavior which determines how soon I get well again."

**Data Sources**

**Telephone Survey.** Recognizing that some patients might receive care from multiple practitioners, we used a telephone survey to obtain the names of all of the physicians whom patients had seen since their cancer diagnosis or since January 1, 1998, if the diagnosis date was earlier. The survey also elicited information on demographics, attitudes toward care, insurance coverage, health status, and comorbidities. Survey respondents also were asked to enumerate physician office visits, home care visits, inpatient stays, and lengths of stay for each practitioner over the preceding 6 months.

**Medical Records.** Medical records were requested from all inpatient and outpatient practitioners identified in the survey and abstracted to obtain information on utilization. We defined an observation window as the period over which we observed all utilization and costs, starting from the date of diagnosis. We used date of diagnosis for trial participants rather than the date of trial enrollment for 3 reasons: (1) the 2 correspond very closely; (2) the date of diagnosis provides an analogous index date for the nonparticipant patients not enrolled in clinical trials; and (3) some services received prior to trial enrollment could be associated with the trial (eg, clinical examinations and laboratory tests to determine protocol eligibility). For some patients, diagnosis was later or practitioners submitted medical records earlier in the study, making the observation period shorter. This period averaged 2.5 years (SD, 7.5 months) but varied across patients. The mean period of observation for living patients was 28.7 months for trial participants and 29.9 months for nonparticipants. Corresponding periods for deceased patients were 34.1 and 33.1 months, respectively.

Trained nurse abstractors abstracted 4032 medical records using computer-

ized forms developed for this study. Initially, all records were reabstracted by a quality control supervisor; this rate was reduced to 10% and then 5% over time as interrater reliability remained in excess of 95%. Abstracted data included number of physician visits, lengths of stay for inpatient care, and counts of specified tests and procedures. (A technical appendix with more detail is available at [http://www.rand.org/health/goldman\\_app.pdf](http://www.rand.org/health/goldman_app.pdf).) We include all drugs administered in a physician's office, hospital outpatient department, or chemotherapy setting (technically, any drug reimbursed by Medicare). Like other studies, we did not include outpatient drugs.<sup>11</sup>

**Deceased.** We requested medical record data for 454 trial participants and nonparticipants who were eligible for the study but who died before they could be contacted. In some instances, the institutions provided records, and in others, they obtained consent to provide records from an executor or family member. We received medical records for 252 deceased patients.

**Medicare Administrative Data.** For 437 patients who were Medicare eligible, we also obtained enrollment and claims data for 1998-2000 from the Centers for Medicare and Medicaid Services as an additional validation of our results. We excluded 122 patients who were enrolled in a Medicare health maintenance organization because claims were missing or who entered Medicare subsequent to diagnosis. For the remaining 315 patients, we computed total expenses by both Medicare and the patient from the date of diagnosis.

**SEER-Medicare.** For our cost imputations, we used Medicare data from 60995 patients from the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, which links Medicare billing records to tumor registry information for cancer patients registered in the NCI's SEER program database.<sup>20</sup>

### Cost Measurement

Costs refer to total payments to providers for direct medical care, which in-

**Table 3.** Unadjusted Treatment Costs Using Alternative Data Sources

Variables	Participant		Nonparticipant		% Difference	P Value*
	No.	Cost, \$	No.	Cost, \$		
CCTS costs†	932	33 325	696	32 364	3	.74
Alternate samples and measures of costs						
Medicare claims‡	182	29 208	133	30 405	-4	.71
Medical records§						
Partial	802	34 746	575	33 291	4	.66
Complete¶	512	29 085	327	29 397	-1	.90

\*P values correspond to a test of equal costs for trial participants and nonparticipants.

†Cost of Cancer Treatment Study (CCTS) costs combine data from medical records, Medicare claims, and (in some cases) self-reported utilization to compute costs, as described in more detail in the text.

‡The term *Medicare claims* refers to the sample with usable Medicare administrative data; these sample sizes differ from those reported in Table 1 because we excluded patients who joined Medicare after the date of diagnosis or who were enrolled in a Medicare health maintenance organization during the observation window. The alternative estimate of treatment costs for this group come directly from the Medicare claims.

§The term *medical records* refers to cost estimates using utilization from the medical record and prices from the Surveillance, Epidemiology, and End Results—Medicare program.

||The term *partial records* refers to samples for whom we received at least 1 medical record.

¶The term *complete records* include live patients for whom we received medical records from all providers identified through telephone survey and deceased patients.

cluded third-party payments and any expenses that would be the responsibility of patients. Our primary measure was derived by applying prices (actually cost weights) developed from the SEER-Medicare database to abstracted medical record utilization data. To develop the prices, we first adjusted payments in the SEER-Medicare database to 1998 constant dollars using Medicare time and geographical adjustment factors for part A and part B.<sup>21</sup> We then identified in the Medicare-SEER data 79 outpatient utilization measures and 67 inpatient measures that we also abstracted from medical records. For each hospital admission, we then regressed total cost (in 1998 dollars) on inpatient utilization measures. Separate regression analyses were performed for admissions that occurred within 6 months of diagnosis and admissions that occurred thereafter. For outpatient services, we regressed total outpatient costs for services after diagnosis on outpatient utilization measures and binary variables defining the period of treatment after diagnosis. The cost weights derived from these regression models were then applied to utilization from the CCTS medical records. More detail, including regression results, are provided in the technical appendix.

Some living patients had incomplete or no medical record data. For those with incomplete data, we in-

flated their costs by simple adjustment for the number of practitioners. More complicated methods that used the survey data to adjust for self-reported utilization for each practitioner yielded similar imputed values. There were also 251 living patients for whom we obtained no medical records. To impute costs for these patients, we first estimated a multivariate regression analysis using 1125 living patients with at least some medical records data. The regression predicted costs as a function of age, sex, race, educational status, census region of residence, type of cancer, self-reported comorbidities, and costs from Medicare claims, when available. We then imputed costs for the 251 missing patients using predictions from this regression. The results of the study were insensitive to the inclusion of these patients and the method of imputation (TABLE 3).

### Cost Analysis

We used multivariate regression analyses to compare the costs of trial participants and nonparticipants. This joint approach—matching combined with regression adjustment—is preferable to matching alone.<sup>18</sup> Medical costs (logarithmically transformed) were regressed on demographic characteristics, comorbid conditions, prior therapy, stage, histology, insurance status, and

**Table 4.** Adjusted Treatment Costs for Different Patient Groups

Patient Group	Treatment Costs, \$		Additional Cost, %*	P Value†
	Participants	Nonparticipants		
All	35 418	33 248	6.5	.11
Phase 3	32 686	31 569	3.5	.22
1 and 2	40 898	36 679	12.8	.20
Institution type				
AHC	38 449	35 693	7.7	.10
Non-AHC	32 766	31 108	5.3	.15
Vital status				
Alive	34 369	33 199	3.5	.25
Deceased	39 420	33 432	17.9	.15

Abbreviation: AHC, academic health center.

\*Additional cost is the percentage cost increase for treating a trial participant vs a nonparticipant.

†P values correspond to a test of equal cost. The Cost of Cancer Treatment Study was designed to identify a 10% difference in costs across all patient groups at the .05 significance level.

trial status (whether the patient participated in a trial). Trial status was interacted with phase and whether the patient was deceased to allow for separate estimates by type of trial and vital status with phase 1 and phase 2 combined because of the small sample size. Costs were predicted using consistent retransformation methods that allow for heteroscedasticity based on quintiles of expected log costs.<sup>22</sup>

### Nonresponse

All cost analyses were weighted to adjust for the sample design, nonresponse, and possible selection bias between trial participants and nonparticipants. There were no nonresponding trials in our design, and our institution sample represented a broad cross-section of cancer practitioners participating in clinical trials: 34 were academic medical centers, 24 were oncology practices participating in the NCI's Community Clinical Oncology Programs, and 25 were other types of institutions, such as private hospitals or providers' offices. Site captains asked nonrespondents for permission to report patient background information, including age, sex, race or ethnicity, date and stage of diagnosis, and date of recent hospitalization. These data were used to construct nonresponse weights. We poststratified to match all bivariate distributions of phase, cancer type, and vital status using data from our nonresponse screeners and the Cancer

Therapy and Evaluation Program. The largest effect of these weights was to downweight breast cancer and phase 3 patients. In addition, we constructed propensity score weights to accommodate nonrandom assignment between trial participants and nonparticipants.<sup>23</sup>

### RESULTS

There were 1628 patients enrolled in the CCTS, which comprised 932 trial participants and 696 nonparticipants (Table 1). We completed 1376 telephone interviews with living patients to identify all their medical practitioners and were able to obtain at least 1 medical record for 1125: 651 records for trial participants and 474 for nonparticipants. A total of 4032 records were abstracted for an average of 3.6 records per patient and 71% of all records requested. We also obtained 1 medical record for each of 252 deceased patients. Medicare data were received for 355 living patients and 82 deceased patients.

Table 2 compares the sample characteristics. Patients in phase 3 trials are overrepresented because national data on accrual from the Cancer Therapy and Evaluation Program for 1999 suggest about 71% of patients enrolled in phase 3, 22% in phase 2, and 7% in phase 1. Our analysis allows for different treatment costs in phase 3 trials, and our overall estimates were adjusted to reflect the national data. The populations other-

wise look very similar, and there were no significant differences in comorbidities. Trial participants rarely changed practitioners to enroll in a trial and did not differ from nonparticipants in their attitudes toward medical care. Nonparticipants more often have breast cancer, are less likely to be nonwhite, are more likely to have Medicare coverage, and are older. They also were diagnosed more recently. Because our statistical approach does not rely on exact matching, such differences will not induce bias because we include these characteristics in the multivariate analysis.

Table 3 shows unadjusted cost differences using alternative samples and sources and measured in 1998 dollars. Our primary measure of costs combines information from the medical records, Medicare claims, and (occasionally) self-reported utilization as described above. Participants averaged \$33 325 in treatment costs compared with \$32 364 for nonparticipants over the period of observation—typically 30 months. The 3% difference between the 2 groups was not statistically significant. Cost differences varied substantially within trials, with incremental cost differences ranging from -30% to 49% among trials with at least 15 study participants and matched nonparticipants. As a check on these results, we compared costs from the Medicare claims files for the smaller sample for whom such data were available. Treatment costs for this sample were 4% less than nonparticipants. Using the sample of patients with at least some medical record data suggests trial participants are 4% more expensive. Finally, for those with complete medical records (ie, patients for whom there was no imputation) trial participants are 1% less expensive than nonparticipants.

TABLE 4 shows our main results using the entire sample and adjusting for possible confounding factors. (Full regression results are given in Table A4 of the technical appendix.) Overall, trial participation results in a cost increase of 6.5%. Although the CCTS was not powered to consider subgroup analyses, some interesting findings do emerge

when the data are analyzed this way. Phase 3 studies had lower cost differences (3.5%) than the earlier study phases (12.8%). There was not a large difference in incremental costs between academic health centers (AHCs) and other care settings. The largest difference was by vital status. Patients who died during trials incurred much higher costs (17.9%) than nonparticipants who died, whereas the additional cost of trial participation for patients who survived was small (3.5%).

TABLE 5 suggests why trial participants were more expensive to treat. Trial participants received more physician visits, more expensive tests (magnetic resonance imaging, computed tomography, and multiple gated acquisition scans, endoscopies, and nuclear medicine procedures), and more pathology reports. Much of the increased service use was for deceased participants, who used significantly more physician visits, expensive diagnostics, and pathology reports than did deceased nonparticipants. Overall, nonparticipants had more hospital days, but the difference was not significant.

## COMMENT

Uncertainty about the incremental costs from trial enrollment has led to uneven policies by insurance companies. Medicare may be the most salient example. It covers "routine costs" associated with clinical trials. The Institute of Medicine recently recommended that Medicare should pay for more than routine costs, at least for selected trials.<sup>10</sup> Such language is standard but invites misinterpretation. The definition of routine costs can be unclear, and this language encourages clinical researchers to design research protocols in such a way that the treatment costs will not exceed standard care by too much. This may explain why the additional treatment costs from trial participation are so small, but it also may have adverse consequences for the clinical investigation.

We undertook the CCTS to provide precise and generalizable estimates of the incremental treatment costs associated

**Table 5.** Differences Between Trial Participants and Nonparticipants in Per-Patient Service Use

	Participant	Nonparticipant	P Value	Deceased Only		
				Participant	Nonparticipant	P Value
Hospital days	7.4	8.2	.27	17.9	17.4	.86
Intensive care unit days	0.61	0.66	.84	1.5	1.9	.80
Physician visits	22.0	17.9	<.001	13.1	7.0	<.01
Ancillary services						
Expensive diagnostics*	4.6	3.6	<.01	5.1	3.5	<.01
Pathology reports†	7.6	6.3	.02	6.8	4.2	.01
Laboratory tests‡	48.5	39.7	.10	66.7	54.5	.24

\*Expensive diagnostics include magnetic resonance imaging, computed tomographic, and multiple gated acquisition scans; endoscopies; and nuclear medicine procedures.

†Pathology reports include cytopathology, virology, and biopsies.

‡Laboratory tests include chemistry, hematology, and microassays.

with nonpediatric clinical trials for cancer treatment. We focused on direct costs for patient treatment since these are the costs that insurance companies might reasonably be asked to pay in the absence of a trial. Of course, government-sponsored clinical trials involve other administrative and research costs beyond direct care, including staff training, trial administration, analysis, and reporting. These costs, primarily underwritten by the study sponsors, clearly warrant further investigation.<sup>24</sup> Our study also excludes industry-sponsored trials, which have been estimated to enroll roughly the same number of cancer patients (20 000 to 25 000 annually).<sup>25</sup> However, unlike NCI-sponsored trials, there is no central data repository from which we could draw a sampling frame for industry-sponsored trials. Furthermore, there is evidence that industry-sponsored trials cover more of the costs of treatment, and in fact generate additional income for participating institutions.<sup>26,27</sup>

Our findings suggest that treatment costs for an adult patient enrolled in an NCI-sponsored trial are, on average, 6.5% higher over a period of 2.5 years than what they would be if the patient did not enroll in a trial. Much of the additional cost comes from higher use of physician visits and expensive diagnostic testing. Fireman et al<sup>12</sup> also found evidence that trial participants had higher rates of ancillary services.

We expected that the CCTS would yield larger differences in costs relative to others because our study included health care settings outside AHCs. In fact, we found little difference in incremental treatment costs between AHC and non-AHC providers, which explains why our results are close to what others have found in single-institution studies. It is possible that patients may change institutions to participate in a clinical trial although only 8% of our trial participants did so. In part, this may reflect the success of the NCI's Community Clinical Oncology Program, designed to make trials available in settings where patients already receive their care. Little published evidence about the nature and scope of such switching exists. Studies of patient characteristics associated with being offered enrollment in a cancer trial<sup>28,29</sup> have generally been conducted among patients at academic medical centers and have not examined whether patients had been referred to these institutions from other providers. Similarly, studies of clinician characteristics associated with referring cancer patients to clinical trials<sup>30-32</sup> have focused on clinicians involved in cancer research and/or at AHCs.

We find that the incremental cost is associated with more services, especially physician visits, expensive tests, and pathology reports. In a phase 3 study, these services may accrue differentially for patients in the treat-

ment and control arms. Thus, it is an open question whether patients in the control arm of a trial actually receive more treatment than the nonparticipants in the same institution. This also raises the question of whether trial participants are getting any health benefits for these incremental services. In their review of the literature, Braunscholtz et al,<sup>33</sup> found limited evidence for such a “trial effect.”

The type of trial also matters. Patients enrolled in early phase studies have much higher additional treatment costs compared with those in phase 3. In part this is due to more aggressive treatment of trial participants in phase 1 or 2 studies relative to phase 3, but also the higher likelihood that these patients will die during the study period. Deceased trial participants in our study had costs that were about 18% more expensive than they would have incurred had they not enrolled in a study, and early phase trials include patients with the worst prognoses. This finding appears in other studies; Wagner et al<sup>11</sup> note that trial participants incurred “substantially higher cost” in the last 3 months of life in their 5-year study at Mayo Clinic, Rochester, Minn. Patients in trials may prefer more aggressive treatment despite incurable disease. However, we observed no differences between trial participants and nonparticipants in preferences for aggressive care, as measured in our survey.

Alternatively, physicians conducting trials may be more aggressive in trying to save trial participants. The higher costs for deceased trial participants also could be an artifact of our inability to identify all the clinicians who served each patient. Survey respondents saw approximately 4 different practitioners between interview and diagnosis, but we only obtained 1 record per deceased patient. Undercounting utilization will only bias our results if it is systematically different between deceased trial participants and nonparticipants. Based on our telephone survey, trial participants identified seeing only slightly fewer practitioners than non-

participants (4.18 vs 4.25, respectively). Thus, there is little evidence for a systematic bias among the living respondents.

There is little evidence that our trial participants differ in unobserved ways from our nonparticipants. As noted, we observed no differences between trial participants and nonparticipants in attitude toward care, and enrollment rates were similar across the 2 groups (61% for trial participants; 56% for nonparticipants). Also, some of our nonparticipants were drawn from institutions that did not participate in study trials, so our sample does not include only patients who chose not to participate in a clinical trial. Differential nonresponse by trial participants and nonparticipants was accounted for in our weighting scheme using data provided by institutions on nonrespondents.

Our 6.5% estimate can be interpreted as the incremental cost conditional on a representative set of trials and institutions from 1999. Changes in the mix of patients enrolling in trials, or the type of trials being conducted, would likely yield a different result. At the time this study was conducted, Medicare did not routinely pay for medical care incidental to clinical trials. This is no longer the case, and Medicare is also considering what level of inducements would be allowable to encourage trial participation by Medicare beneficiaries.<sup>34</sup> If these inducements were substantial, the fraction of trial enrollees coming from Medicare could rise. The question then arises whether the incremental treatment costs vary when the mix of enrollees changes substantially. Estimates from auxiliary models (not shown) did not find any significant interactions between payer status (Medicare) and additional treatment costs, but it is not clear whether this is due to a different mix of trials for this population or due to different treatment of Medicare beneficiaries within trials. This is an issue worthy of future research.

Of equal import, it may be that an open reimbursement policy could result in greater incremental costs by inducing a behavioral response in the trials

that are undertaken, especially in more aggressive trials. This cost increase presumes that uncertainties about reimbursement in the status quo limit which trials are initiated. Putting aside that eliminating this barrier is likely to accelerate improvements in cancer treatment, it also will result in higher incremental costs than we report herein. If one assumes that the early phase studies provide an upper bound—an extreme assumption about how the mix of trials would change—then the incremental costs would be at most 13% as shown in Table 4.

## Conclusion

In 1999, approximately 19 000 adult patients participated in NCI-sponsored US clinical trials which, incurred direct treatment costs of approximately \$268 million. These costs would have been \$252 million if these patients had not enrolled in trials, implying that the incremental treatment costs associated with NCI-sponsored trial enrollment were \$16 million. Given that trial participants represent only about 3% of all adults with cancer and given that the incremental costs are only 6.5%, the additional treatment costs of an open reimbursement policy for NCI-sponsored trial participation appear minimal.

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