

A Comparison of Incremental Costs of Breast Cancer Clinical Trials to Standard of Care

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Abstract

Objective: Clinical trials are an essential element in the improvement of cancer prevention and treatment strategies. A widely held perception is that costs of care for clinical trial (CT) patients are higher than standard of care (SOC). There is a paucity of data supporting this assertion. The objective of this study was to determine the costs of breast cancer patients enrolled on a clinical trial compared to eligible patients who did not participate in a trial.

Methods: A retrospective cohort study was conducted to compare costs incurred by 97 breast cancer patients participating in a mix of industry and non-industry sponsored clinical trials with those costs incurred by 97 eligible nonparticipants who received SOC. Resource utilization was tracked for one year and quantified to standardized price templates. Seven cost variables were examined: physician time, nursing time, tests and procedures, diagnostic imaging, pathology, radiation therapy, and pharmaceuticals.

Results: Mean costs were marginally higher for the CT patients than the SOC patients for all seven cost variables, as were the mean total costs (\$16,418 versus 10,002, p-value=0.046). Pharmacy costs constituted the largest difference between the trial and SOC patients (mean difference=\$5,157, p=0.08). After excluding all drugs that were provided by the study sponsors at no charge, the remaining average pharmacy costs were more equal between groups (mean difference=\$990, p=0.45). As a result, the mean difference between the total costs of the two groups was reduced by two-thirds, from \$6,396 to \$2,227 and statistical significance was lost (p=0.14).

Conclusions: This study revealed only minor differences in the cost distribution of patients enrolled in CT versus those receiving SOC. This is similar to results previously seen for prostate cancer patients.

Keywords: Incremental costs; Breast cancer; Clinical trials; Health economics.

Introduction

Breast cancer continues to be the most common cancer diagnosis in Canadian women, with more than 2,000 new cases and 5,000 cancer deaths recorded annually [1]. Research has already drastically reduced the mortality associated with this disease and continued advancements are expected to facilitate more effective, targeted treatments [2]. Because evaluating novel therapeutics through clinical trials (CT) is the gold standard for establishing safety and efficacy [3], financial support of clinical trials is a fundamental necessity [4,5]. However, per patient costs of clinical trials are generally not well understood and estimates are highly variable [4,6]. A widely held perception that costs of care for trial patients are higher than standard of care continues to be a barrier to research in many cancer centres [7,8]. Several previous studies have suggested the costs incurred by patients enrolled in clinical trials and patients receiving the standard of care are, in fact, not significantly different [6,8]. For example, in a recent study examining the incremental costs of prostate cancer clinical trials,

differences in categorical resource allocation were noted but the study failed to show a significant difference in overall costs [9].

Data comparing the costs of treating breast cancer using standard of care methods to clinical trials [10], and the perceived costs of conducting trials are currently based largely on convention. Although budget justifications are required by Health Canada in all clinical trial agreements, the level of detail is not prescribed and financial agreements are not considered part of their inspection process [11]. There remains a poor understanding of clinical trial costs. Currently, the conduct of cancer clinical trials is hampered at least in part by a commonly held view that patients enrolled in clinical trials consume significantly more health-care resources than patients receiving standard of care [4,8]. This perception is especially relevant in Canada, where a single payer health care system operates under constant pressure to eliminate “non-essential” activities [12,13]. Clinical research is therefore sometimes viewed as a luxury by health-care administration. A thorough understanding of any added costs or demands of having a patient enrolled in a trial, or conversely, cost savings as a result of patients participating in research, would be beneficial for researchers and administrators to inform decision

making and budget negotiations in a setting of limited resources [14,15]. Therefore, a retrospective cohort study was conducted at the Tom Baker Cancer Centre in Calgary, Alberta (TBCC) to quantify the costs incurred by breast cancer patients enrolled into a clinical trial compared with the costs incurred by eligible non-participants who received standard of care (SOC).

Methods

Eight Phase III breast cancer clinical trials that were open at the TBCC between February 2006 and October 2009 were examined (Table 1). From among these studies, the TBCC clinical trials database

was used to identify 97 patients. During the same period of time, another 120 patients were deemed eligible by an initial physician assessment and were offered participation in the same trials, but had refused trial participation. The latter patients were identified from prescreening logs maintained by clinical trial coordinators, and in the absence of logs, a manual records search was conducted. For each of the 97 trial patients, a SOC patient was selected so that their date of refusal was closest to the trial patient's date of consent. The start date for data collection for the trial patients was their date of randomization and for the SOC patients the date they would have been randomized had they consented.

Trial Name	Description	Phase	Sponsor Type	Number of Patients
BETH NCT00625898	A Multicenter Phase III Randomized Trial of Adjuvant Therapy for Patients With HER2-Positive Node-Positive or High Risk Node-Negative Breast Cancer Comparing Chemotherapy Plus Trastuzumab With Chemotherapy Plus Trastuzumab Plus Bevacizumab	III	NSABP	7
MAC 4 SOFT NCT0066690	Suppression of Ovarian Function Plus Either Tamoxifen or Exemestane Compared With Tamoxifen Alone in Treating Premenopausal Women With Hormone-Responsive Breast Cancer (SOFT)	III	International Breast Cancer Study Group	3
MAC 9 NCT00127205	S0307 Zoledronate, Clodronate, or Ibendronate in Treating Women Who Have Undergone Surgery for Stage I, Stage II, or Stage III Breast Cancer	III	SWOG	37
NSABP B.37 NCT00074152	A Randomized Clinical Trial Of Adjuvant Chemotherapy For Radically Resected Loco-Regional Relapse Of Breast Cancer	III	International Breast Cancer Study Group	6
NSABP B.38 NCT00093795	A Phase III, Adjuvant Trial Comparing Three Chemotherapy Regimens in Women With Node-Positive Breast Cancer: Docetaxel/Doxorubicin/Cyclophosphamide (TAC); Dose-Dense (DD) Doxorubicin/Cyclophosphamide Followed By DD Paclitaxel (DD AC→P); DD AC Followed By DD Paclitaxel Plus Gemcitabine (DD AC→PG)	III	NSABP	1
RAPID NCT00282035	A Multi-centre Randomized Trial to Determine if Accelerated Partial Breast Irradiation, Utilizing 3D CRT, is as Effective as Whole Breast Irradiation Following Breast Conserving Surgery in Women With Ductal Carcinoma in Situ or Invasive Breast Cancer With Negative Axillary Lymph Nodes	III	Ontario Clinical Oncology Group	13
TAILORX NCT00310180	Hormone Therapy With or Without Combination Chemotherapy in Treating Women Who Have Undergone Surgery for Node-Negative Breast Cancer (The TAILORx Trial)	III	NCI	29
TRIO 012 NCT00703326	A Multicenter, Multinational, Randomized, Double-Blind, Phase III Study of IMC-1121B Plus Docetaxel Versus Placebo Plus Docetaxel in Previously Untreated Patients With HER2-Negative, Unresectable, Locally-Recurrent or Metastatic Breast Cancer	III	Eli Lilly	1

Table 1: Trials by type and number of patients recruited.

Following the designated start date, patient costs incurred over the next 52 weeks were entered into a database. The cost variables measured from provider perspective were physician time, nursing time, tests and procedures, diagnostic imaging, pathology, radiation therapy, and pharmaceuticals. These variables were chosen based on a literature review [4,6,8,13,16,17] and interviews with staff oncologists and nurses. Data pertaining to patient utilization of services were obtained from the ARIA Oncology Information System utilized at the TBCC. Physician time was recorded based on scheduled visit times and salary data was used to calculate costs. Nursing time was recorded

based on scheduled visit times as well as infusion times and costs were calculated using salary data. Cost information for tests and procedures and diagnostic imaging was obtained using the 2009 Clinical Trials Price-list for the TBCC. Pharmaceutical data was taken from the Holy Cross Pharmacy database.

For each patient in the trial and SOC groups, the weekly costs recorded for each of the seven individual variables were summed over the 52-week period, yielding variable-specific costs. These variable-specific costs were then summed together to yield a total cost over the 52-week period. The mean cost differences between trial and SOC

patients were compared using a two-sample t-test. A two-way analysis of variance was also performed to assess the mean weekly cost per patient over time. The study received approval from the local institutional review board.

Results

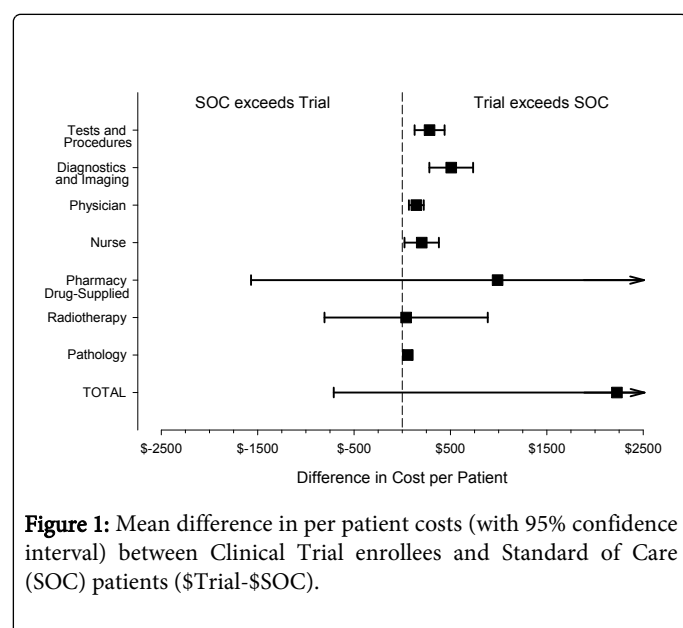
On average, the costs were higher among CT patients than among SOC patients for all seven items, with a mean total cost difference of \$6,396 (95% confidence interval: \$131 to \$12,661, $p=0.046$, Table 2). Pharmaceutical costs constituted the largest mean difference between

CT and SOC patients with a difference of \$5,157 (95% confidence interval: -\$657 to \$10,974, $p=0.08$, Table 2), and overshadowed all other cost categories. After excluding drugs that were provided by the study sponsor at no charge to the institution, the remaining mean pharmacy costs became more comparable between groups (mean difference = \$990, 95% confidence interval: -\$1,469 to \$3,549, $p=0.45$, bottom of Table 2). By excluding in-kind pharmaceuticals from the analyses, the mean cost differential between CT and SOC patients was reduced to \$2,227 (95% CI: -\$711 - \$5,166, $p=0.14$, bottom of Table 2 and Figure 1).

Item	Trial Patients Mean (SD)	SOC Patients Mean (SD)	Difference Mean (95% CI)	P-value
Tests and Procedures	470 (640)	187 (439)	283 (128, 439)	<0.001
Diagnostic Imaging	948 (945)	440 (626)	508 (28, 735)	<0.001
Physician	338 (303)	192 (238)	146 (69, 224)	<0.001
Nurse	434 (738)	232 (503)	202 (2, 380)	0.03
Pharmacy	10345 (25415)	5188 (14047)	5157(-657,10974)	0.08
Radiotherapy	3764 (2939)	3724 (3043)	40 (-807, 887)	0.93
Pathology	117 (168)	60 (132)	57 (15, 100)	0.009
TOTAL	16418 (27186)	10022 (15480)	6396(1, 12661)	0.046
Pharmacy-Drug-Supplied	3846 (8417)	2855 (9611)	990(-1569, 3549)	0.45
TOTAL-Drug-Supplied	9917 (10262)	7690 (10491)	2227(-11, 5166)	0.14

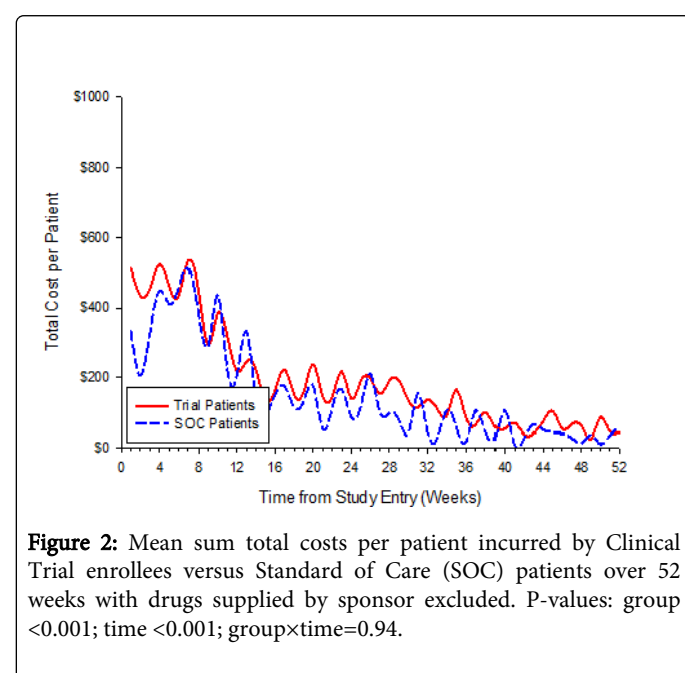
SOC: Standard of Care; SD: Standard Deviation; CI: Confidence Interval

Table 2: Yearly costs incurred by trial patients and standard of care (SOC) patients separated by variable (CDN Dollars).



Although the mean costs varied over time, costs were generally higher in the first 12 weeks of study entry (Figure 2), especially for the

physician, nursing, and radiotherapy categories. Thereafter, the means costs over time reached an approximate steady state.



Discussion

This study demonstrated that while there are differences in the cost-of-care distribution of patients enrolled in breast cancer clinical trials versus SOC managed patients, the difference is relatively small and non-significant when corrected for the drug cost savings effect that is prevalent in these kind of studies. These findings are similar to those seen in a cohort of prostate cancer patients we previously examined [18], and so the aggregate of these findings further question the idea that clinical trials are a burden on a public-payer health-care system.

Pharmacy costs, though not significantly different between groups, were the largest contributing factor to the total difference in costs. The variation in pharmacy costs between groups represents the variety of breast cancer treatments available for different stages of disease. If the drugs supplied by the sponsor were excluded from the analysis, significance was lost and the groups became statistically indistinguishable (Figure 2). This drug-cost-savings effect has been noted in previous publications [19].

Both the mean physician and nursing costs were consistently higher across time, supporting the suggestion that trial patients are followed more closely [20], which may involve increased documentation on case report forms. This finding may be relevant for physicians concerned about the extra workload associated with trial patients [27]. As the clinical trial nursing time was included in the calculation of overall nursing time, it is important to note there are additional employees present to share the burden. The spikes in mean costs observed at specific time points in the tests and procedures, diagnostic imaging, and pathology reflect the additional documentation that may be required to fulfill the clinical trial protocol. These results may argue to reduce the amount of information being collected in cancer clinical trials that are not often analyzed [21]. It should be noted however that this study did not take into account individual trial budgets that have been negotiated for these studies, and it is assumed that (at least for industry sponsored trials), many of the extra costs identified in this study should have been recovered from the sponsor.

A few study limitations are worth noting, in particular being limited to a single tumor group at a small to medium sized single center. On average, the Centre has 7 breast cancer trials open to recruitment each year, opening on average 3 new studies each year. The total accrual for a year is approximately 50 patients. The number of patients reported in our study captures a representative sample of patients at the Centre and is reflective of ones where there was at least 52 weeks of data available within a reasonable timeframe. Although the study showed that clinical trial patients take up significantly more physician and nursing time than SOC patients, these times were determined based on scheduled appointments in patient charts, so the accuracy of visit lengths is, at best, an estimate. At the TBCC, visit times are constant for a specific type of visit (e.g. consult, follow-up) whether the patient is on trial or SOC. While the appointment time may not accurately reflect the visit length, it does accurately show visit frequency and so it can be concluded that trial patients had an equivalent number of visits as SOC patients. The window of the study may have also introduced a bias. When a patient consents to be enrolled into a trial, a large number of tests are conducted to determine their eligibility. It is difficult to determine if similar procedures would also be performed for SOC patients at a later date. A broader window may have uncovered different trends. Conversely, given that follow-up on many breast clinical trials can exceed the 1-year window of our study, the observed differences in cost of care could be amplified, or suppressed, through longer follow-up. This question merits further study.

Cancer is consuming an increasingly larger proportion of health care resources in developed nations due to aging populations, increasing complexity of treatment, decreased mortality and population expansion bredin [22-24]. The importance of clinical trials in furthering improvements in patient outcomes cannot be overstated [25]. It is imperative that new treatments be tested in large clinical trials to impartially assess both safety and efficacy and inform physician decisions about treatment options [7,16]. While certain trials are inarguably more expensive than SOC, future benefits may offset these short term costs [26,].

This study served to provide evidence for the breakdown of individual costs and highlighted the importance of proper budgeting to ensure proper remuneration. It also demonstrated the impact of pharmaceutical costs, a factor that may shift the cost balance in favor of conducting clinical trials to enable institutional cost-savings.

Conflict of Interest

The authors declare that they have no conflict of interest.

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