Incremental costs of prostate cancer trials: Are clinical trials really a burden on a public payer system?

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Abstract

Introduction: Clinical trials are a critical component of improving cancer prevention and treatment strategies. However, the perception that patients enrolled in trials consume more resources than those receiving the standard-of-care (SOC) has contributed to an increasingly research-averse environment. Current economic data pertaining to the per-patient costs of prostate cancer trials relative to SOC treatment are limited.

Methods: A retrospective observational cohort study was conducted to compare costs incurred by 59 prostate cancer patients participating in a mix of industry and non-industry sponsored clinical trials with costs incurred by an equal number of eligible non-participants who received SOC over a year. Resource utilization was tracked and quantified to standardized price templates.

Results: No difference in overall resource utilization was seen between trial and SOC patients (two-tailed t-test, n = 118, $p = 0.99$). Variability in the types of resources used by each group indicated that, while trial patients may take up significantly more clinic time ($p = 0.001$) and undergo more tests and procedures ($p = 0.001$), SOC patients are more likely to receive other costly interventions, such as radiation therapy ($p < 0.001$). Other variables (e.g., pathology, diagnostic imaging, prescribed therapies) were statistically indistinguishable between groups.

Conclusion: This study revealed differences in the cost distribution of patients enrolled in clinical trials versus those receiving SOC, which could be used to improve resource allocation. The lack of evidence for a difference in overall cost provides an argument for payers to more fully support clinical research without fear of adverse financial consequences. Further analysis is required.

Introduction

Clinical trials are essential in the evaluation of the safety and efficacy of novel therapies.[1,2] However, per patient costs of these trials are generally not well-defined, and estimates are highly variable.[3] Bringing a new drug to market takes 12 to 15 years and costs about $1 billion,[4] but the cost breakdown is ambiguous and has led to speculation of where the burden weighs most heavily.

This year, more than 24 000 Canadians will be diagnosed with prostate cancer and 4300 will die.[5] Although prostate cancer is currently the leading cause of cancer in Canadian men, future advancements may facilitate the anticipation and prevention of the disease.[6] To attain this, financial support of clinical trials is fundamental; however, current economic data pertaining to the costs of treating prostate cancer are limited.[3,7-9] The perceived costs of conducting trials are therefore based on assumptions, and cancer clinical trials are facing a national funding crisis due to the perception that patients enrolled in clinical trials consume significantly more resources than patients receiving standard of care (SOC).[10,11] This perception is especially relevant in Canada, where a single payer health care system is severely burdened, and clinical research is being increasingly viewed as a luxury.

Studies conducted in the United States and United Kingdom suggest that differences in direct costs between patients enrolled in a clinical trial and those receiving SOC are minimal.[12,13] However, these results are difficult to generalize to Canada because of the inherent differences in the health care systems.[14] While Health Canada requires that budgets be included in clinical trial agreements (CTAs), the necessary level of detail is not specified, and CTAs or any financial agreements are not considered part of their inspection process.[15] The lack of standardization has resulted in a poor understanding of trial budget requirements. It is therefore important that Canadian studies be conducted to determine if there is empirical support for the belief that cancer clinical trial patients consume more resources and, if so, which areas incur the highest costs.

A thorough understanding of any added costs or demands of having a patient enrolled in a trial,[3] or conversely, cost savings as a result of patients participating in research, would be beneficial for researchers and administrators. Quantifying the initial costs of treating cancer patients in clinical tri-

als (including tests and procedures, nursing and physician time, diagnostic imaging, pathology, radiation therapy and pharmaceuticals) could inform decisions about their cost-effectiveness and could be used to (1) advocate the advantages of clinical trials; (2) encourage centres to take on more research; or (3) argue the need for increased funding from sponsors or others. Therefore, a retrospective cohort study was conducted at the Tom Baker Cancer Centre (TBCC) to quantify the costs incurred by prostate cancer patients enrolled in a clinical trial compared with the costs incurred by eligible non-participants who received SOC.

Methods

We examined 13 Phase II or III prostate cancer clinical trials open at the TBCC between May 2004 and May 2010. Six of these trials were industry sponsored, 6 were sponsored by cooperative groups and 1 was investigator-initiated. From these trials, the TBCC database was used to identify 59 patients. The SOC group consisted of patients who were offered participation in the chosen trials and declared eligible by a physician, but had refused trial participation. These patients were identified from pre-screening logs maintained by clinical trial coordinators and, in the absence of logs, a manual records search was conducted. For each of the 59 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.

For 52 weeks following the designated start date, patient costs were entered into a database. The seven cost variables examined were: (1) physician time; (2) nursing time; (3) tests and procedures; (4) diagnostics and imaging; (5) pathology; (6) radiation therapy; and (7) pharmaceuticals. These variables were chosen based on a literature review[3,7,11-13,16] and interviews with staff oncologists and nurses. Data pertaining to patient utilization of services were obtained from local health records. Cost information was obtained using the 2009 Clinical Trials Price-list for the TBCC. Drugs provided by a sponsor for specific trials at no cost to the institution were recorded as $0.00. For each patient in the trial and SOC groups, the total cost over the 52-week period for each of the seven individual variables was calculated, as well as the sum total of the seven variables. 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 across time. The study received approval from the local institutional review board.

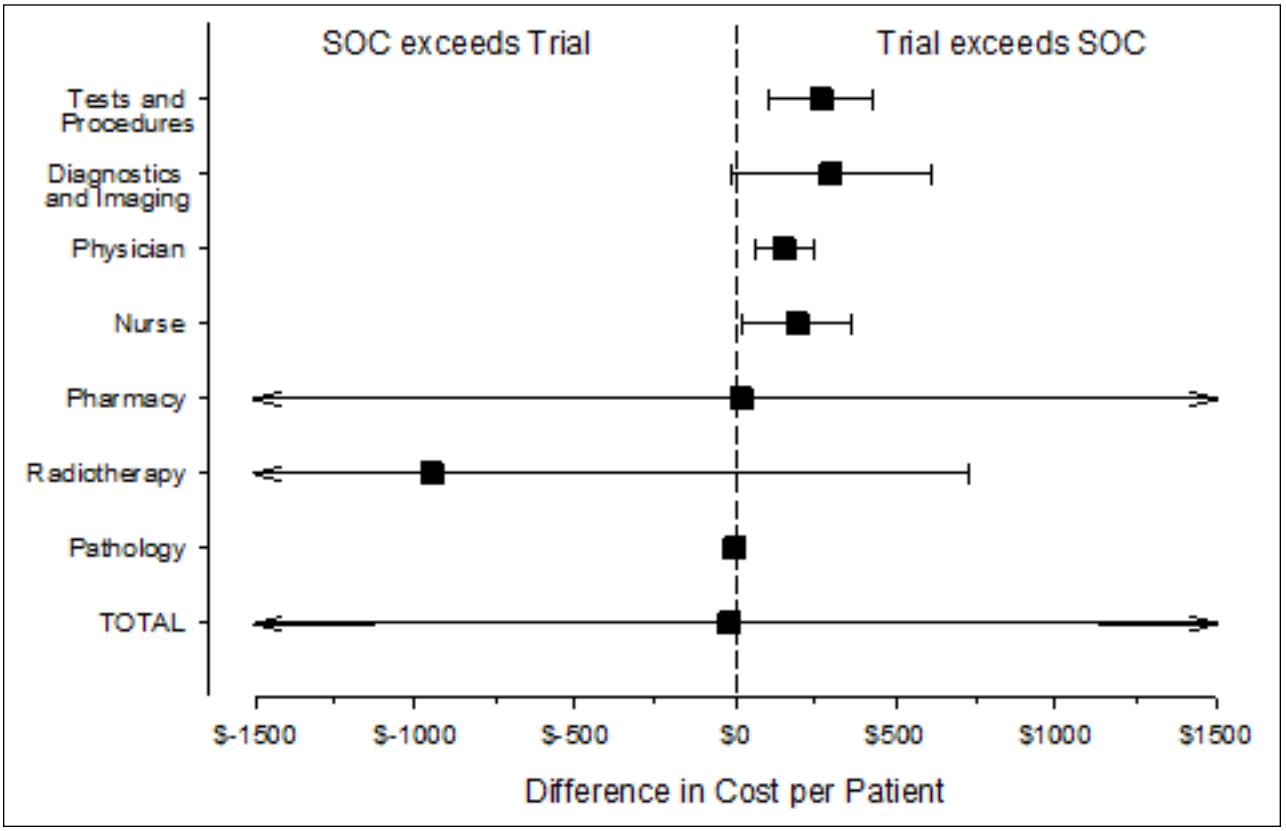

Fig. 1. Mean difference in per patient costs (with 95% confidence interval) between Clinical Trial enrollees and standard of care (SOC) patients ($Trial – $SOC).

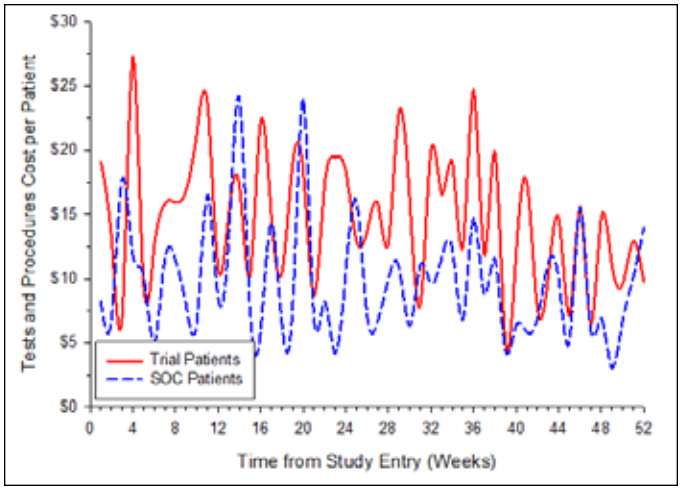

Fig. 2. Mean per patient costs of radiotherapy for clinical trial enrollees versus standard of care patients over 52 weeks. *P*-values: group = 0.008; time <0.001; group x time <0.001.

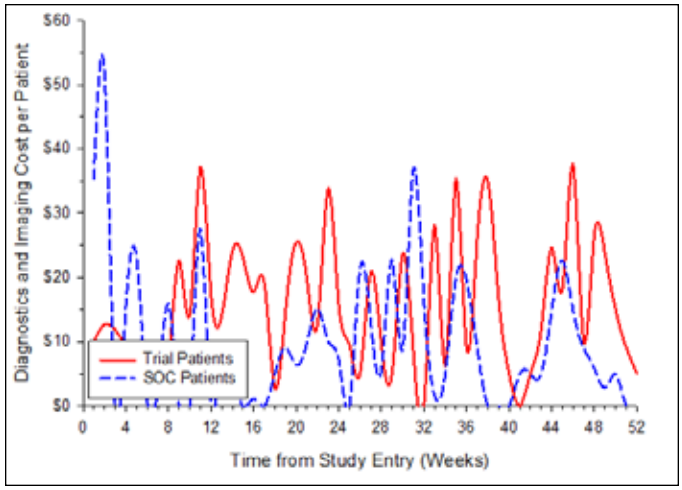

Fig. 3. Mean pharmacy costs per patient for clinical trial enrollees versus standard of care patients over 52 weeks. *P*-values: group = 0.97; time = 0.003; group x time = 0.25.

Results

The mean difference in sum total costs between trial and SOC patients was a negligible $20 (95% confidence interval: –$2480 to $2440, $p = 0.99$) (Table 1, Fig. 1). A subgroup analysis suggested that mean total costs were higher for trial patients if they were industry sponsored and were lower for non-industry sponsored (Table 1, bottom), but the differential effect was not statistically significant ($p = 0.41$). There was, however, some variability among the types of resources used by each patient group. The costs of nursing time ($p = 0.031$), physician time ($p = 0.001$) and tests and procedures ($p = 0.001$) were significantly higher for trial patients. SOC patients were not significantly more likely to receive costly radiation therapy ($p = 0.27$), however, there was a significant shift in cost distribution over time ($p < 0.001$) (Fig. 2) indicating a more sustained use of this treatment modality. Other variables, such as pathology ($p = 0.23$), diagnostic imaging ($p = 0.06$) and prescribed therapeutics ($p = 0.98$) (Fig. 3) were not significantly different between groups.

The mean sum total costs increased over the first 12 weeks of study entry and then decreased over the next 40 weeks for both trial and SOC patients (Fig. 4). The decline in costs was steeper for SOC patients. This trend is most clearly reflected in clinic and treatment costs.

Discussion

The results of the present study demonstrated that participation in a mix of industry and non-industry sponsored clinical trials exacted virtually identical mean total costs summed over the seven variables of interest, and thus, exhibited no greater demand for financial resources than SOC. However, trial patients can be differentiated in terms of follow-up intensity, as evidenced by more frequent clinic visits (Fig. 5) and use of more treatment time (Fig. 6) after the first six months. More frequent clinic visits translate into a higher number of tests and procedures (Fig. 7). The higher costs of tests and procedures for trial patients are likely due to protocol requirements to ensure patient safety and to closely

Table 1. Breakdown of costs incurred over 52 weeks by patient type ($CDN)

Item	Trial patients mean (SD)	SOC patients mean (SD)	Difference mean (95%CI)	*p* value
Tests and procedures	747 (443)	480 (445)	267 (105 , 429)	0.001
Diagnostics and imaging	808 (954)	509 (742)	299 (–13 , 611)	0.06
Physician	362 (284)	210 (215)	152 (60 , 244)	0.001
Nurse	419 (593)	227 (323)	192 (18 , 366)	0.031
Pharmacy	4783 (6961)	4763 (5410)	20 (–2253 , 2294)	0.98
Radiation therapy	3472 (4387)	4421 (4829)	–949 (–2631 , 733)	0.27
Pathology	1 (6)	2 (6)	–1 (–4 , 1)	0.23
TOTAL	10593 (7618)	10613 (5743)	–20 (–2480 , 2440)	0.99
TOTAL Industry (n = 21)	13810 (9946)	12496 (7384)	1314 (–4149 , 6778)	0.63
TOTAL Non-industry (n = 38)	8815 (5327)	9572 (4370)	–757 (–2984 , 1471)	0.50

SD: standard deviation; CI: confidence interval.

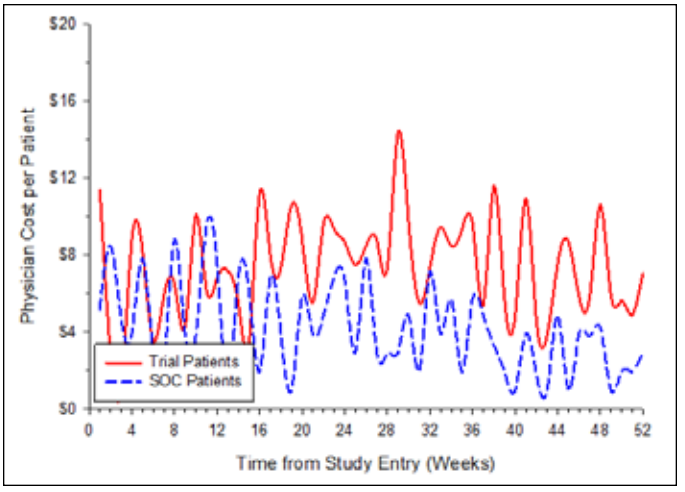

Fig. 4. Mean sum total costs per patient incurred by clinical trial enrollees and standard of care patients over a 52 week examination window. *P*-values: group = 0.98; time <0.001; group x time = 0.25.

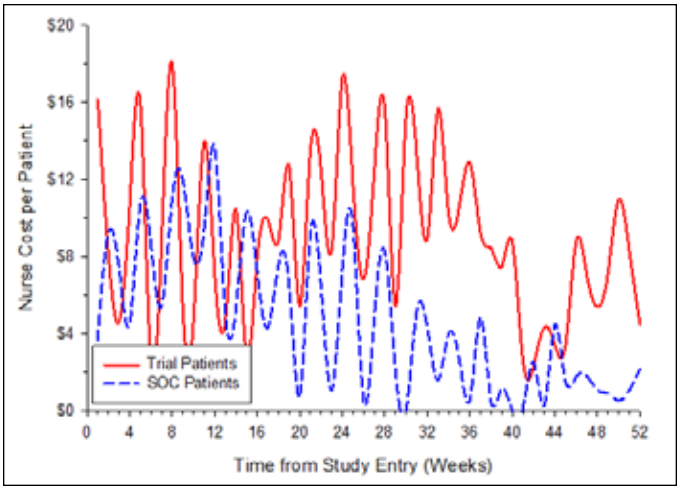

Fig. 5. Mean per patient costs incurred for physician visits for clinical trial enrollees versus standard of care patients over 52 weeks. *P*-values: group <0.001; time = 0.02; group x time = 0.06.

monitor disease response.[17] Diagnostic imaging cost trends are similar, likely on account of the closer monitoring of disease progression seen in trial patients (Fig. 8). Pathology costs were low in both subsets (Fig. 9). As pathology is most often employed in patient diagnosis,[18] it largely fell outside the study window.

Costs for radiation therapy were higher for SOC patients than for clinical trials patients, and, although this difference was not statistically significant, these costs were largely responsible for balancing overall costs between the two patient groups. Radiation therapy may have been the most reasonable option for SOC patients once trial options were rejected. In that case, clinical trials could have delayed or abrogated the need for this expensive resource, but such a hypothesis would require further study. The persistent uptake of radiation therapy in non-trial patients is also worthy of further study as the difference over time between the two groups did reach statistical significance (Fig. 7). Although the observed lack of cost difference between the groups was in large part due to the radiation therapy costs in the SOC group, even when this is excluded, the relative cost of clinical trials would amount to <$1000 more per patient. This is arguably easily offset by direct cost recovery for industry trials and improved survival on a macro level.[19]

While some patients are resistant to trial participation because of perceived higher cost,[20] this factor is less important in Canadian trials because of universal health care coverage. A study by Castel and colleagues showed that patients themselves are rarely a critical impediment to trial recruitment, finding instead that physicians play the vital role in

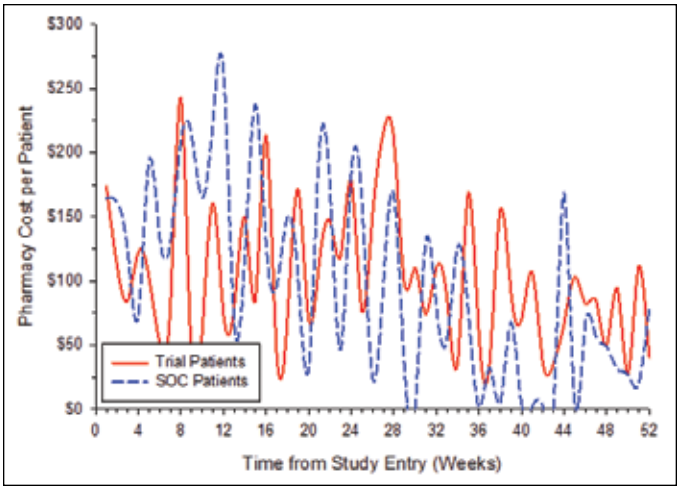

Fig. 6. Mean per patient costs associated with nursing time for clinical trial enrollees versus standard of care patients over 52 weeks. *P*-values: group <0.001; time = 0.01; group x time = 0.55.

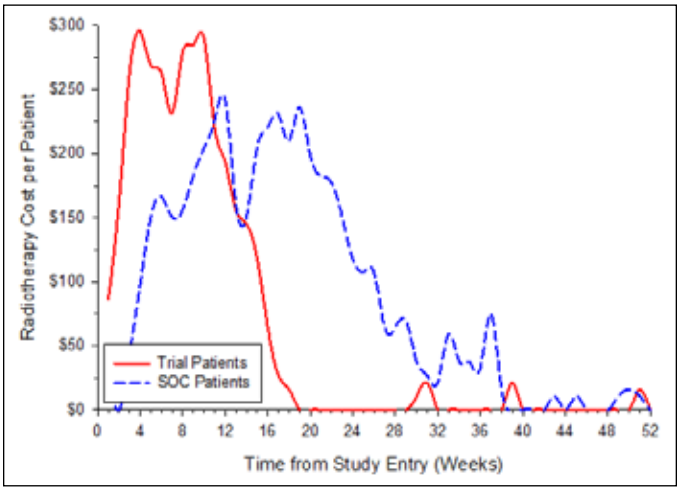

Fig. 7. Mean per patient costs of tests and procedures performed for clinical trial enrollees versus standard of care patients over 52 weeks. *P*-values: group <0.001; time = 0.02; group x time = 0.87.

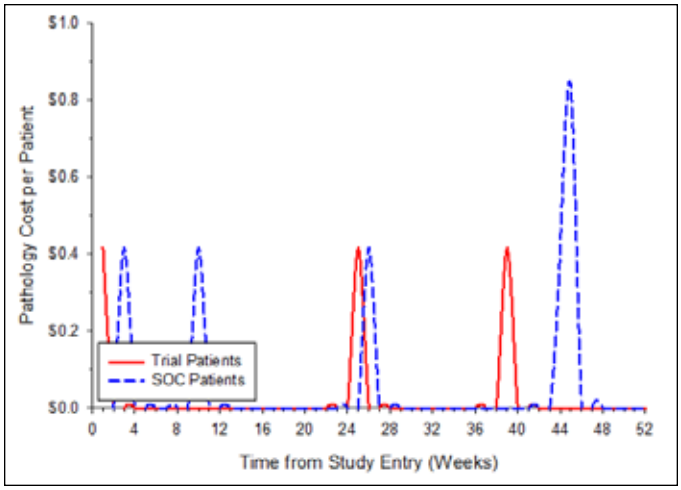

Fig. 8. Mean per patient costs of diagnostic imaging for clinical trial enrollees versus standard of care patients over 52 weeks. *P*-values: group = 0.002; time = 0.06; group x time = 0.14.

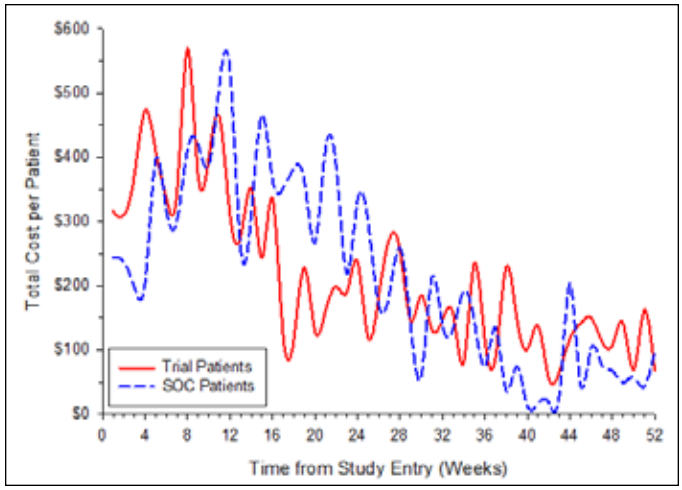

Fig. 9. Mean per patient costs of pathology for clinical trial enrollees versus standard of care patients over 52 weeks. *P*-values: group = 0.21; time = 0.12; group x time = 0.49.

accrual.[21] Many patients view clinical trials as a desirable form of treatment as they feel they will be monitored more closely and will therefore have a better prognosis. Clinical trials are also viewed as a means by which the most up-to-date breakthrough treatments can be accessed.

A few study limitations are worth noting. Although it was shown 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 have significantly more frequent clinic visits than 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.

Conclusion

The importance of clinical trials in furthering improvements in patient outcomes cannot be overstated.[22,23] It is imperative that new treatments be tested in large clinical trials to impartially assess safety and efficacy and to inform physician decisions about treatment options.[10,12] Clinical trials are being conducted in an increasingly complex and integrated environment,[10] yet many peer-reviewed funding agencies often allocate less than 5% of their budget to clinical trials.[24] While certain trials are inarguably more expensive than SOC, future benefits may offset these short-term costs.[25] Even though the results of the present study are limited to a single-tumour group, it represents a first step towards dispelling a commonly held belief that clinical trials are a burden on a public-payer health-care system and a larger, multi-tumour group analysis is currently underway. The authors would like to encourage the research community to engage in similar analyses to allow for comparisons between different institutional practices across the country.

Competing interests: None declared.

This paper has been peer-reviewed.

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References

1. Canadian Cancer Statistics. www.cancer.ca. Accessed May 17, 2011.
2. Prostate Cancer Statistics. http://www.prostatecancer.ca/Prostate-Cancer/Prostate-Cancer/Statistics.aspx. Accessed May 26, 2010.
3. Fireman BH, Fehrenbacher L, Gruskin EP, et al. Cost of care for patients in cancer clinical trials. *J Nat Cancer Inst* 2000;92:136-42. http://dx.doi.org/10.1093/jnci/92.2.136
4. Wright JR, Roche K, Smuck B, et al. Estimating per patient funding for cancer clinical trials: An Ontario based survey. *Contemp Clin Trials* 2005;26:421-9. http://dx.doi.org/10.1016/j.cct.2005.03.003
5. A national cancer clinical trials system for the 21st century: reinvigorating the NC I cooperative group program. *IOM Nat Academies: Report Brief* 2010;1-4.
6. Goldman DP, Berry SH, McCabe MS, et al. Incremental treatment costs in National Cancer Institute-sponsored clinical trials. *JAMA* 2003;289:2970- 7. http://dx.doi.org/10.1001/jama.289.22.2970
7. Fireman B, Fehrenbacher L, Gruskin EP, et al. Cost of care for patients in cancer clinical trials. *Natl Cancer Inst* 2000;92:136-42. http://dx.doi.org/10.1093/jnci/92.2.136
8. Fourcade RO, Benedict A, Black LK, et al. Treatment costs of prostate cancer in the first year after diagnosis: a short-term cost of illness study for France, Germany, Italy, Spain and the UK. *BJU Int* 2009;105:49-56. http://dx.doi.org/10.1111/j.1464-410X.2009.08716.x

9. Crawford ED, Black L, Eaddy M, et al. A retrospective analysis illustrating the substantial clinical and economic burden of prostate cancer. *Prostate Cancer Prostatic Dis* 2010;13:162-7. http://dx.doi.org/10.1038/pcan.2009.63
10. Lara PN, de Vere White R. Accrual issues in genitourinary cancer clinical trials. *Urologic Onc* 2006;24:379-83. http://dx.doi.org/10.1016/j.urolonc.2005.11.037
11. Potworowski JA. Clinical trials in Canada: what should we do if we want more of them? *Biotechnology Focus* 2003.
12. Warren JL, Yabroff R, Meekings A, et al. Evaluation of trends in the cost of initial cancer treatment. *J Natl Cancer Inst* 2008;100:888-97.
13. Grover SA, Coupal L, Zowall H, et al. The economic burden of prostate cancer in Canada: forecasts from the Montreal Prostate Cancer Model. *CMAJ* 2000;162:987-92.
14. Castel P, Négier S, Boissel JP. Why don't cancer patients enter clinical trials? A review. *European J Cancer* 2006;42:1744-8. http://dx.doi.org/10.1016/j.ejca.2005.10.033
15. Chopra SS. Industry funding of clinical trials: benefit or bias? *JAMA* 2003;290:113-4. http://dx.doi.org/10.1001/jama.290.1.113
16. Mulay M. Understanding the finances. *Making the Decision: A cancer patient's guide to clinical trials.* Jones & Bartlett Publishing, Burlington, MA;2002;ch. 9.
17. Davison BJ, So A, Goldenberg SL, et al. Measurement of factors influencing the participation of patients with prostate cancer in clinical trials: a Canadian perspective. *BJU Int* 2007;101:982-7. http://dx.doi.org/10.1111/j.1464-410X.2007.07349.x
18. Ferris LE, Naylor CD. Physician remuneration in industry sponsored clinical trials: the case for standardized clinical trial budgets. *CMAJ* 2004;171:883-6. http://dx.doi.org/10.1503/cmaj.1040338
19. Harris TJR, McCormick F. 2010. The molecular pathology of cancer. *Nat Rev Clin Oncol* 2010;7:251-65. http://dx.doi.org/10.1038/nrclinonc.2010.41
20. Tuohy CH. Single payers, multiple systems: the scope and limits of subnational variation under a federal health policy framework. *J Health Polit Policy Law* 2009;34:453-95. http://dx.doi.org/10.1215/03616878-2009-011
21. Swanson GP, Carpenter WR, Thompson IM, et al. Urologists' attitudes regarding cancer clinical research. *Urology* 2007;70:19-24. http://dx.doi.org/10.1016/j.urology.2007.03.019
22. Snyder CF, Frick KD, Blackford AL, et al. How does initial treatment choice affect short-term and long-term costs for clinically localized prostate cancer? *Cancer* 2010;116:5391-9. http://10.1002/cncr.25517
23. DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. *J Health Econ* 2003;22:151-85. http://dx.doi.org/10.1016/S0167-6296(02)00126-1
24. Dubois A, Rochon J, Lamparter C, et al. Pattern of care and impact of participation in clinical studies on the outcome in ovarian cancer. *Intl J Gynecol Cancer* 2005;15:183-91. http://dx.doi.org/10.1111/j.1525-1438.2005.15202.x
25. Crook JM, O'Callaghan CJ, Ding K, et al. A phase III randomized trial of intermittent versus continuous androgen suppression for PSA progression after radical therapy (NCIC CTG PR.7/SWOG JPR.7/CTSU JPR.7/ UK Intercontinental Trial CRUKE/01/013). *J Clin Onc* 2011;29:2011 (suppl abstr 4514).

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