Estimation of drug cost avoidance and pathology cost avoidance through participation in NCIC Clinical Trials Group phase III clinical trials in Canada

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ABSTRACT

Background  Cost avoidance occurs when, because of provision of a drug therapy [drug cost avoidance (dca)] or a pathology test [pathology cost avoidance (pca)] during trial participation, health care payers need not pay for standard treatments or testing. The aim of our study was to estimate the total dca and pca for Canadian patients enrolled in relevant phase iii trials conducted by the NCIC Clinical Trials Group.

Methods  Phase iii trials that had completed accrual and resulted in dca or pca were identified. The pca was calculated based on the number of patients screened and the test cost. The dca was estimated based on patients randomized, the protocol dosing regimen, drug cost, median dose intensity, and median duration of therapy. Costs are presented in Canadian dollars. No adjustment was made for inflation.

Results  From 1999 to 2011, 4 trials (1479 patients) resulted in pca and 17 trials (3195 patients) resulted in dca. The total pca was estimated at $4,194,849, which included testing for KRAS ($141,058), microsatellite instability ($18,600), and 21-gene recurrence score ($4,035,191). The total dca was estimated at $27,952,512, of which targeted therapy constituted 43% (five trials). The combined pca and dca was $32,147,361.

Conclusions  Over the study period, trials conducted by the NCIC Clinical Trials Group resulted in total cost avoidance (pca and dca) of approximately $7,518 per patient. Although not all trials lead to cost avoidance, such savings should be taken account when the financial impact of conducting clinical research is being considered.

Key Words  Cost avoidance, phase iii trials

INTRODUCTION

Clinical trials play a pivotal role in improving the care of patients with cancer. They evaluate novel diagnostic, therapeutic, and palliative interventions. Cooperative group trials are created in collaboration with academic oncologists in the absence of commercial bias1. Cooperative group trials focus on scholarly questions, with an emphasis on patient-centred outcomes and public health. The conduct of clinical trials has become increasingly complex, leading inevitably to increasing costs.

Per-patient funding is often lower for cooperative group and investigator-initiated trials than for industry-sponsored trials. Because of such differences in per-patient funding, many academic institutions underwrite or limit accrual to cooperative group trials2. Institutional cost recovery for “non-standard-of-care” activities has increased, including but not limited to fees for protocol review by pharmacies, research ethics boards, and laboratories. At the same time, institutional funding for staffing clinical trials units has declined.

In cancer clinical trials, health care payers benefit not only from the academic rewards of disseminating trial...
results in peer-reviewed journals, but also in terms of cost avoidance, which occurs when trial participation leads to provision of a drug therapy [drug cost avoidance (dca)] or a pathology test [pathology cost avoidance (pca)]. Thus, payment for a standard treatment or test is not required. To date, studies evaluating dca have focused on either small geographic areas or short time intervals

The aim of the present study was therefore to estimate the total dca and pca for Canadian patients enrolled in ncic Clinical Trials Group (ncic ctg) phase iii trials over a 13-year period.

**METHODS**

Phase iii trials that involved systemic therapy and completed accrual during the period of interest (1999–2011) were identified using the ncic ctg Web site (https://www.ctg.queensu.ca/public/Clinical_Trials/clinical_trials.html). Trials were either led or sponsored by the ncic ctg. Eligible trials were defined as those that resulted in dca through the provision of a ncic ctg-supplied drug or pca through ncic ctg funding of a pathology test. Trials that led to registration of novel agents and that randomized patients to placebo or best supportive care were excluded.

To estimate dca, details about drug dosing, schedule, and protocol-specified duration of therapy were extracted from trial protocols (Tables i and ii). If actual drug administration data were not available, those data were estimated based on a body surface area of 1.8 m², a body weight of 70 kg, the published dose intensity, and the median number of cycles (for palliative trials) or the protocol-specified duration. Historical Canadian drug costs were obtained from the Ontario Drug Benefit Formulary for the period during which the trial was conducted. If those costs were unavailable, prices from the Alberta cancer formulary were used. For trials that supplied drugs to the experimental arm, patients randomized to the experimental arm were considered to have avoided the cost of the standard-of-care therapy identified from the protocol. The dca was calculated using the number of Canadian patients randomized to the experimental arm, the median drug administered per patient in the standard arm, and the cost of the standard-of-care therapy. For trials that supplied drugs to the experimental and standard arms, both arms of the trial were considered to have dca. The total dca for the trial was calculated using the number of Canadian patients accrued to the experimental and standard arms, the median drug administered per patient, and the cost of standard-of-care therapy. The mean drug administered was not reported for those trials, hence the use of medians.

The pca was estimated using the cost of the test and the number of patients tested for the trial. The cost of the 21-gene recurrence score for the years of accrual to the mac.12/tailorx trial (2007–2010) was obtained from genomic health (wong n. personal communication). The cost was converted to Canadian dollars using bank of Canada exchange rates for the respective years. The average cost of the assay over the study period was calculated in Canadian dollars, and the pca was obtained by multiplying the average cost of the assay by the number of registered patients. The cost of kras mutation testing for codons 12 and 13 at the university health network molecular diagnostics laboratory and at calgary laboratory services was compared, and the lower cost was used. The cost of microsatellite instability testing by immunohistochemistry was obtained from calgary laboratory services.

The overall dca and pca for Canadian patients on ncic ctg trials was calculated. Some trials provided both dca and pca, and thus total cost avoidance per patient was determined by dividing the sum of the dca and pca by the number of unique patients. All costs are reported in Canadian dollars with no adjustment for inflation.

**RESULTS**

Cost avoidance occurred in 19 of 117 phase iii clinical trials coordinated by the ncic ctg from 1999 to 2011 (Figure 1). Four trials resulted in pca (three in colorectal cancer and one in breast cancer). Total pca was $4,194,849 for 1479 tests (Table iii). The 21-gene recurrence score from the tailorx trial (nct00310180) accounted for 96% of the pca.

Seventeen trials resulted in dca, with the most common tumour types being breast (n = 6), colorectal (n = 4), and ovarian (n = 2). In eight trials, dca occurred because of sponsor drug provision for the standard arm as well as the experimental arm or arms. Total dca was estimated at $27,952,512 for 3195 patients across seventeen trials ($8,749 per patient, Tables iv and v). Per-patient dca for trials involving non-targeted therapies ranged from $90 to $13,665 (Table iv, figure 2). In comparison, per-patient dca for non-hormonal targeted therapies ranged from $4,290 to $22,588 (Table v, figure 2). Nonhormonal targeted therapy from five trials constituted 43% of the total dca ($11,900,775, Table v).

The combined pca and dca was $32,147,361, for a total cost avoidance per patient of $7,518.

**CONCLUSIONS**

The ultimate goal of clinical trials is to establish new therapies that improve patient outcomes and quality of life. Although not all trials lead to improvements in patient outcomes, some trials lead to cost avoidance or savings for health care payers. The cumulative cost savings because of provision of drug or pathology tests by the ncic ctg on account of participation in ncic ctg phase iii trials over the study period was $32,147,361. If the participating patients had not been treated on trial, most of those costs would have been borne by the Canadian health care system.

In Canada, decisions about drug funding approval and time to placement of a drug on the provincial formulary show considerable interprovincial variability(19). Payment for drugs not funded by the provincial health care system comes from patients, industry-sponsored drug access programs, and sometimes third-party health insurance payers. For example, the co.20 trial (open to accrual between February 2008 and 2011) provided cetuximab for patients with metastatic colorectal cancer in both the standard and the experimental arms. Provincial approval for, and access to, cetuximab funding ranged from August 2009 in british columbia to April 2011 in newfoundland and labrador. Clearly, the lag in funding approval for the standard of care was bridged in part by participation in clinical trials that supplied the drug. In such cases, dca actually benefits
patients by accelerating access to new therapies and alleviates the burden on the health care system.

The dca from both industry and cooperative oncology trials has previously been described\(^3,6,7\). In an evaluation of 101 trials conducted in Alberta during 1992–1997, median dca per patient ranged from $1,377 to $23,751\(^3\). Across eighty-eight trials conducted in eleven German hospitals, dca was US$2 million during 2002–2005\(^7\). In 2008, a single centre in Taiwan estimated dca to be $3,900 per participant-year, representing a total dca of US$11.2 million\(^6\).

### TABLE I Assumptions made in estimating drug cost avoidance for cytotoxic therapies by trial

| Trial | Arms\(^a\) | Drug | Dose intensity | Duration of therapy |
|-------|------------|------|----------------|---------------------|
| MA.27\(^8\) | Anastrozole | X | Anastrozole | 62% completed 5 years, remaining 38% assumed to have stayed on treatment for 2.5 years (median time on treatment) |
|     | Exemestane | X | | |
| MAC.1\(^9\) | CMF×6 or AC×4 | X | CMF (n=5) or AC (n=8) (same ratio as full trial population) | 100% | Completed all cycles |
|     | Capecitabine | | | |
| MAC.4\(^10\) | Tamoxifen | X | Tamoxifen | Of patients randomized to tamoxifen, 21.7% discontinued early | If patients stopped early, they were assumed to have stopped halfway through (2.5 years); the rest of the patients were assumed to have completed 5 years |
|     | Tamoxifen–OFS | | | |
|     | Exemestane–OFS | X | | |
| MAC.5\(^10\) | Tamoxifen–OFS | X | Tamoxifen | Of patients randomized to tamoxifen, 21.7% discontinued early | If patients stopped early, they were assumed to have stopped halfway through (2.5 years); the rest of the patients were assumed to have completed 5 years |
|     | Exemestane–OFS | X | | |
| MAC.7 | Anastrozole | X | Anastrozole | Assumed 100% | Duration of therapy on control arm was used even though duration of therapy was slightly longer on experimental arm |
|     | Anastrozole–fulvestrant | X | | |
| HN.6\(^b\) | Cisplatin plus RT | X | Cisplatin | 100% | 70% received all 3 doses of cisplatin, 23% received 2 doses, and 7% were assumed to have received 1 dose |
|     | Panitumumarb plus RT | X | | |
| CO.13\(^12\) | IFL | X | Irinotecan | Median of 4 cycles in IFL arm (Goldberg RM. Personal communication) |
|     | FOLFOX | X | | |
|     | IROX | X | | |
| CRC.2\(^13\) | FOLFOX | X | Oxaliplatin | Median dose intensity: to cycle 6, 99.4%; to cycle 12: 76.4% | Finished 12 cycles: 79% |
|     | FOLFOX–ceutiximab | X | | |
| PA.2\(^14\) | FUFA | X | FUFA | 79% | 4 Cycles |
|     | Gemcitabine | X | | |
| OV.16 | Carboplatin–paclitaxel×8 | X | Paclitaxel | 99.4% (from NCIC CTG) | 4 Cycles |
|     | Cisplatin–topotecan×4 and carboplatin–paclitaxel×4 | X | | |
| OV.17\(^15\) | Carboplatin–paclitaxel×6 | X | Paclitaxel | 99% | 6 Cycles |
|     | Carboplatin–PLD×6 | X | | |
| LY.12 | Rituximab–DHAP×2 | X | Cytarabine | 100% (from NCIC) | 2 Cycles |
|     | Rituximab–GDP×2 | X | | |
| BRC.3\(^16\) | Cisplatin–etoposide×4 | X | Etoposide | 78% | 67% completed 4 cycles; rest assumed to have completed 2 cycles |
|     | Cisplatin–irinotecan×4 | X | | |

\(^a\) Drugs in boldface type were provided by the trial. Control arm of each trial is listed first.

\(^b\) Extrapolated from Forastiere et al., 2003\(^11\).

CMF = cyclophosphamide–methotrexate–5-fluorouracil; AC = doxorubicin–cyclophosphamide; OFS = ovarian function suppression; RT = radiation therapy; IFL = irinotecan–5–fluorouracil–leucovorin; FOLFOX = oxaliplatin–5–fluorouracil–leucovorin; IROX = irinotecan–oxaliplatin; FUFA = 5–fluorouracil–leucovorin; CTG = Clinical Trials Group; PLD = pegylated liposomal doxorubicin; DHAP = dexamethasone–cytarabine–cisplatin; GDP = gemcitabine–dexamethasone–cisplatin.
Our analysis has several limitations. Cost estimates did not account for inflation, the potential for temporal changes in drug prices, and interregional variability in drug prices. Drug administration data was used when available; however, patient nonadherence was not factored into the estimate. The data were insufficient to provide a range for the actual dca per trial based on factors such as duration of therapy on trial, dose intensity, and (for certain drugs) body surface area. The present work was not a cost-effectiveness analysis, and thus the clinical benefits with respect to patient outcomes and the costs of managing adverse events were not included. Unfortunately, drugs provided through clinical trials can be wasted because of storage temperature excursions, drug expiry dates, and the NCIC CTG policy of prohibiting the sharing of intravenous drug vials between patients. (Standard practice permits sharing.)

Our study did not incorporate the incremental patient care costs associated with clinical trial participation such as extra clinic visits, drug administration, nursing time, and laboratory and radiologic investigations. The Cambridge University Hospitals NHS Foundation Trust evaluated the treatment cost difference for industry and non-industry trial therapies compared with standard-of-care therapy. An overall treatment cost saving of £388,719 in 2009 and £496,556 in 2010 was observed, largely attributable to dca. Access to clinical trials for Medicare patients in the United States has improved since the institution of the Patient Protection and Affordable Care Act. However, details about coverage for the costs associated with clinical trial participation are lacking. The potential for cost avoidance through trial participation should be considered for such patients.

In summary, the present analysis of cost avoidance as associated with NCIC CTG phase III clinical trials demonstrates a wide range of per-patient dca and pca. The estimates are conservative, given that we analyzed only phase III trials.

### TABLE II

| Trial | Assumptions made in estimating drug cost avoidance for nonhormonal targeted therapies by trial |
|-------|--------------------------------------------------------------------------------------------------|
| CO.20 | Cetuximab X Cetuximab–brivanib X Cetuximab 239 mg/m² weekly 15.1 Weeks |
| CRC.5 | Chemotherapy plus bevacizumab X Bevacizumab 83% 12 Cycles |
| MA.31 | Taxane plus trastuzumab X Trastuzumab 100% (data from NCIC) 36 Weeks |
| REC.1 | Interferon alfa X Interferon alfa Median dose intensity: 96% in interferon-only arm 4.2 Cycles in interferon-only arm |
| LY.12 | Rituximab–DHAP X Rituximab 100% (data from NCIC) 2 Cycles |
| LY.12 | Rituximab–GDP X Rituximab 100% (data from NCIC) 2 Cycles |

**Notes:**
- Drugs in boldface type were provided by the trial. Control arm of each trial is listed first.
- Chemotherapy was the investigator's choice and consisted of 5-fluorouracil, leucovorin, and either oxaliplatin or irinotecan (FOLFOX or FOLFIRI). Preliminary results from the study were presented in abstract form; no information about the duration of therapy was provided. Extrapolated from Saltz et al., 2008.
- Extrapolated from Escudier et al., 2007.
- DHAP = dexamethasone-cytarabine-cisplatin; GDP = gemcitabine-dexamethasone-cisplatin.

### FIGURE 1

Evaluation of trials for cost avoidance.

### TABLE III

| Pathology cost avoidance by trial |
|-----------------------------------|
| Trial | Pathology test | Tests performed (n) | Cost per test ($) | Cost avoidance ($) |
| CO.20 | KRAS mutation testing (codons 12 and 13) | 334 | 298 | 99,395 |
| CRC.3 | Microsatellite instability by immunohistochemistry | 62 | 300 | 18,600 |
| CRC.5 | KRAS mutation testing (codons 12 and 13) | 140 | 298 | 41,663 |
| MAC.12 | 21-Gene recurrence score | 943 | 4279 | 4,035,191 |
randomizing patients to a standard-of-care arm. Cost avoidance in NCIC CTG phase II studies was not included, nor was avoidance in phase III studies that established a new standard of care that would normally be observed\textsuperscript{23–25}.

Our results echo other cost-avoidance studies evaluating oncology trials performed in Europe, North America, and Asia\textsuperscript{3–7}. The cumulative global impact is unmeasured and could be a focus for future research. Beyond raising the bar for cancer care, some clinical trials provide a financial savings opportunity for the health care system. Those opportunities are yet another reason for health care payers to continue and to improve their support of clinical research.

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CONFLICT OF INTEREST DISCLOSURES
We have read and understood Current Oncology’s policy on disclosing conflicts of interest, and we declare that we have none.

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**TABLE IV** Drug cost avoidance for non-targeted therapies by trial

| Trial | Arms\textsuperscript{a} | Pts (n)\textsuperscript{b} | Drug cost avoidance | Drug | Mean $ per patient | Total $ for trial |
|-------|-------------------------|---------------------------|---------------------|------|-------------------|------------------|
| MA.27 | Anastrozole             | 640                       | Anastrozole         | 7,317| 9,519,856         |
|       | Exemestane              | 661                       |                     |      |                   |                  |
| MAC.1 | CMF or AC               | 15                        | CMF or AC           | 535  | 6959              |
|       | Capecitabine            | 13                        |                     |      |                   |                  |
| MAC.4 | Tamoxifen               | 45                        | Tamoxifen           | 569  | 26,764            |
|       | Tamoxifen plus OFS      | 41                        |                     |      |                   |                  |
|       | Exemestane plus OFS     | 47                        |                     |      |                   |                  |
| MAC.5 | Tamoxifen plus OFS      | 85                        | Tamoxifen           | 569  | 50,111            |
|       | Exemestane plus OFS     | 88                        |                     |      |                   |                  |
| MAC.7 | Anastrozole             | 21                        | Anastrozole         | 2,005| 88,209            |
|       | Anastrozole plus fulvestrant | 23                   |                     |      |                   |                  |
| HN.6  | Cisplatin plus RT       | 160                       | Cisplatin           | 90   | 14,391            |
|       | Panitumumab plus RT     | 160                       |                     |      |                   |                  |
| CO.13 | IFL                     | 45                        | Irinotecan          | 10,565| 1,595,249         |
|       | FOLFOX                  | 67                        |                     |      |                   |                  |
|       | IROX                    | 39                        |                     |      |                   |                  |
| CRC.2 | FOLFOX                  | 142                       | Oxaliplatin         | 13,665| 3,689,425         |
|       | FOLFOX plus cetuximab   | 128                       |                     |      |                   |                  |
| PA.2  | FUFA                    | 45                        | FUFA                | 93   | 3,993             |
|       | Gemcitabine             | 43                        |                     |      |                   |                  |
| OV.16 | Carboplatin plus paclitaxel×8 | 235                  | Paclitaxel          | 3,011| 710,586           |
|       | Carboplatin–topotecan×4 and carboplatin–paclitaxel×4 | 236 |                     |      |                   |                  |
| OV.17 | Carboplatin plus paclitaxel×6 | 42                    | Paclitaxel          | 4,996| 169,858           |
|       | Carboplatin plus PLD×6  | 34                        |                     |      |                   |                  |
| LY.12 | Rituximab plus DHAP     | 158                       | Cytarabine          | 1,088| 171,914           |
|       | Rituximab plus GDP      | 158                       |                     |      |                   |                  |
| BRC.3 | Cisplatin plus etoposide| 3                         | Etoposide           | 1,106| 4,423             |
|       | Cisplatin plus irinotecan| 4                      |                     |      |                   |                  |

\textsuperscript{a} Drugs in boldface type were provided by the trial. Control arm of each trial is listed first.

\textsuperscript{b} Boldface type indicates arm with cost avoidance.

Pts = patients; CMF = cyclophosphamide–methotrexate–5-fluorouracil; AC = doxorubicin–cyclophosphamide; OFS = ovarian function suppression; RT = radiation therapy; IFL = irinotecan–5-fluorouracil–leucovorin; FOLFOX = oxaliplatin–5-fluorouracil–leucovorin; IROX = irinotecan–oxaliplatin; FUFA = 5-fluorouracil–leucovorin; PLD = pegylated liposomal doxorubicin; DHAP = dexamethasone–cytarabine–cisplatin; GDP = gemcitabine–dexamethasone–cisplatin.
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