The Costs of Industry-Sponsored Drug Trials in Canada

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Abstract

Objective The objective of this study was to estimate the provincial and nationwide costs of industry-sponsored drug clinical trials (CTs) in Canada.

Methods We used the Aggregate Analysis of ClinicalTrials.gov (AACT) database, and included all industry-sponsored drug CTs that were conducted in Canada and completed in 2016. We estimated the costs of the study drugs using the market price. Estimates of the costs of management and patient services were based on industry contracts.

Results The sample included 394 CTs that were conducted in 2039 facilities in Canada and provided services for 20,126 Canadian enrollees. Two-thirds of the CTs (277 of 394) were in the non-cancer category. On average, the drug costs per patient were 89,680 Canadian dollars ($\text{Can}$) during the lifespan of the CTs, and were higher in cancer CTs than in non-cancer CTs ($\text{Can}$216,876 vs. $\text{Can}$65,274). The total costs of industry-sponsored drug CTs completed in 2016 was $\text{Can}$2093.7 million. Drug costs accounted for the majority of this total ($\text{Can}$1804.9 million). Ontario ($\text{Can}$781.2 million) and Quebec ($\text{Can}$757.5 million) had the highest costs.

Conclusion The costs of industry-sponsored drug CTs completed in 2016 when measured in terms of market prices in Canada were valued at $\text{Can}$2.1 billion.

1 Introduction

Clinical trials (CTs) are critical components in the public assessment of new technologies. Industry-sponsored CTs can also play a role in relieving the healthcare cost burden through the trial-based care received by trial participants.

In industry-sponsored drug CTs, the sponsor usually pays for the drug, patient consultation and procedure costs, as well as the fees for ethics reviews and initial setups (e.g. laboratory, pharmacy). Current estimates of the costs of CTs in Canada come from an annual survey of industry conducted by the Patented Medicine Price Review Board (PMPRB); respondents to this survey report CT costs according to the cost of manufacturing, as defined in the Canada Income Tax Act [1]. The manufacturer’s cost is not the same as the price that would be paid for by the funders of healthcare (i.e. the insurer’s or consumer’s retail price). Nevertheless, there is a cost attributable to all healthcare services received by CT participants [2].

Currently, little is known about the costs of industry-sponsored drug CTs in large and diverse health systems. Accordingly, we estimated the provincial and nationwide costs of industry-sponsored drug CTs in Canada.
2 Methods

2.1 Study Design and Data Sources

We conducted an analysis using the Aggregate Analysis of ClinicalTrials.gov (AACT) database [3], which provides rich data elements on each CT, such as the number of enrollees, start and completion dates, treatment regimen, location(s) and funding. The AACT database has been used previously in research [2].

All industry-sponsored drug CTs that were conducted in Canada (either in Canada only or in Canada and other countries) and completed in 2016 (regardless of start date) were included. CTs with zero enrolment were excluded.

2.2 Variables of Interest

The main variable that we wished to estimate was the sum of the drug, management and patient services costs of industry-sponsored drug CTs completed in 2016 in Canada. For convenience, we refer to this variable as ‘total costs’ for the remainder of this paper. Other variables of interest included the distribution of the costs by trial arms, type of CT (cancer or non-cancer) and province.

2.3 Number of Enrollee Estimates

The AACT database provides only the total number of enrollees for each CT, and therefore we had to estimate the number of enrollees in Canadian facilities in the multinational CTs. To obtain the number of enrollees in each Canadian facility within a CT, we assumed that patient enrolment would be equal for each facility in a multinational or multisite CT. We then calculated the number of enrollees in each province within a CT by multiplying the total number of enrollees in the CT by the number of facilities in that province, and then divided by the total number of participating facilities in the CT.

2.4 Drug Costs

We used a previously reported algorithm to estimate the costs of the study drugs [2, 4]. Briefly, we first searched for each drug’s market price in the Alberta Drug Benefit List (ADBL) [5]. If a price was not found there, we searched the US Department of Veterans Affairs Pharmaceutical Prices (VAPP) database [6]. If there was no price in either the ADBL or the VAPP database, we used the Medscape website to find an alternative drug that was equivalent in indication, and used the relevant alternative drug for pricing. If an alternative drug could not be identified, we used the price of the drug used for patients in the control arm. As the last resort, we used the listed price of the relevant chemical compound on the MedChemExpress and Selleckchem.com websites [7, 8]. As the US drug price could be 3.4 times higher than that of the Canadian price, we adjusted for this price difference and converted the US price to the Canadian price using the Bank of Canada exchange rate ($US1 ≈ 1.298 Canadian dollars [$Can] on 7 August 2018) [9, 10].

Using the treatment regimen from the CT protocols, we multiplied the average dosage by the treatment length and drug price to calculate the drug costs per patient during the lifespan of a CT. The total drug costs for each trial in each province were then derived by multiplying the per patient drug costs during the lifespan of that trial by the number of enrollees in that province. The methods for calculating the costs are shown in Box 1, where we provide a step-by-step example of the cost calculation for the trial NCT01133743, which is one of the trials included in the analysis [11]. Finally, we summed the drug costs of all trials in all provinces to calculate the total, Canada-wide CT drug costs.

2.5 Management and Patient Service Billings

The AACT database does not provide cost data. We estimated management and patient service billings for each CT based on a previous report on the economic contribution of industry-sponsored drug CTs in Alberta [2]. The management billings (e.g. start-up costs, document archival, advertisement) were estimated at $Can7180 and $Can18,721 for each cancer and non-cancer CT, respectively, in each province where it was conducted; the ethics fee specifically was estimated at $Can2500 for each CT, in each province. Patient service billings (e.g. screening, procedures, consultations, treatments of adverse events, laboratory tests, imaging procedures) were estimated at $Can11,909 and $Can17,350 per patient for cancer and non-cancer CTs, respectively. We adjusted these patient service billing estimates for each province according to the province’s hourly wage rate for health professions relative to those of Alberta in 2016 [12]. Similar to our methods for estimating drug costs, we then calculated the total patient service billings in each province by multiplying the per-patient service billings by the number of enrollees in that province. Management and patient service billings in all provinces were then summed to calculate the total, Canada-wide CT non-drug costs.

2.6 Statistical Analysis

We calculated per-enrollee drug costs during the lifespans of the CTs, and reported the means of these values (95% confidence interval [CI]), by trial arms (experiment or control) and type of CT (cancer or non-cancer). We reported the total economic values in determined values for Canada.
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2.7 Sensitivity Analyses

In the main analysis, we had adjusted for the US and Canada drug price differences at market exchange rates (ratio = 3.4), which is similar to the price differences at purchasing power parity (ratio = 3.3) [10]. We therefore conducted an analysis where we recalculated the drug costs using the unadjusted US price, to examine the impact on total drug costs. In addition, in the main analysis, we had assumed that the number of enrollees would be equal across facilities in a multinational CT. We therefore conducted another analysis where the number of enrollees in Canadian facilities was 25% lower and 25% higher than the average number of enrollees per facility in the CTs that were multinational.

All analyses were performed using STATA® version 14 (Stata Corp., College Station, TX, USA) and Microsoft Excel® version 2016 (Microsoft Corp., Redmond, WA, USA). The study did not require ethics approval.

3 Results

A total of 400 industry-sponsored drug CTs were completed in 2016 in Canada. After excluding six CTs that had zero enrolment, the final sample included 394 CTs conducted in 2039 facilities across the ten provinces. Of these, 60 CTs...
were conducted in Canada only and 334 CTs were conducted in both Canada and other countries. Two-thirds of the CTs (277 of 394) were in the non-cancer category and provided services for approximately 17,000 patients, while the rest (117 of 394) were in the cancer category and provided services for more than 3000 patients (see Table 1).

The mean lengths of the CTs were 41.2 (95% CI 37–45.4) and 31.3 (95% CI 28.6–34) months for cancer and non-cancer CTs, respectively.

3.1 Drug Costs

A total of 375 drugs were used in the CTs (the list of drugs is presented in the Electronic Supplementary Material Appendix). The ADBL, VAPP database and website (MedChemExpress and Selleckchem.com) prices were used for 135 (36%), 174 (46.4%) and 66 (17.6%) drugs, respectively. Approximately 28% (111 of 394) of the CTs involved biologic/biosimilar products, which accounted for 17% (64 of 375) of the drugs.

On average, the drug costs per patient were $Can89,680 during the lifespans of the CTs, and were higher in cancer CTs than in non-cancer CTs ($Can216,876 vs. $Can65,274; p < 0.001) and in the experimental arm than in the control arm ($Can132,537 vs. $Can3375; p < 0.001) (see Table 1).

3.2 Total Trial Costs

Overall, the total costs of industry-sponsored drug CTs in 2016 was $Can2093.7 million. Drug costs accounted for the majority of this total ($Can1804.9 million); cancer and non-cancer CTs contributed $Can737.4 million and $Can1356.3 million, respectively. Ontario ($Can781.2 million) and Quebec ($Can757.5 million) had the highest CT costs because of the large number of CTs conducted as well as the large number of enrollees in those provinces (see Table 2). Newfoundland and Labrador had the highest value per capita ($Can116), followed by Quebec ($Can91) and New Brunswick ($Can65) (see Fig. 1).

Except for Prince Edward Island, which had only one cancer CT, New Brunswick had the highest proportion of costs from cancer CTs (89.6%); Ontario, which had the highest overall costs from industry-sponsored drug CTs, had the same proportion of costs from cancer CTs as the national average (35%) (see Fig. 2).

3.3 Sensitivity Analyses

Using the unadjusted US VAPP database drug prices led to an additional $Can696.7 million in drug costs for all industry-sponsored drug CTs completed in 2016 in Canada. Varying patient enrolment in the Canadian sites within the 334 multinational CTs, from 25% less than the average to 25% higher than the average, resulted in a range of Canadian enrollees between 16,043 and 24,182. Accordingly, the total costs of industry-sponsored drugs CTs in 2016 in Canada ranged from $Can1612.8 million to $Can2593.9 million (Table 3).

4 Discussion

Our study identified 394 industry-sponsored drug CTs that were completed in 2016. These CTs provided care to more than 20,000 enrollees in Canada. We estimated that the Canadian healthcare systems would have had to spend an additional $Can2.1 billion if these industry-sponsored CTs had not taken place and had not provided healthcare services to the trial participants and the experimental drugs had been approved. Ontario and Quebec had the highest absolute trial

| Table 1 Summary of drug costs in all clinical trials (2016) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Variable        | Clinical trials (n) | Total enrollees (n)a | Canadian enrollees (n)b | Value per enrollee ($Can)b [mean (95% CI)] |
| All trials      | 394              | 315,014          | 20,126          | 89,680 (85,147–94,213) |
| Experimental arm| 203,282          | 13,448           | 132,537 (123,482–141,592) |
| Control arm     | 111,732          | 6678             | 3375 (2864–3887) |
| Non-cancer drug trials | 277 | 268,099          | 16,886          | 65,274 (61,078–69,471) |
| Experimental arm| 171,361          | 11,039           | 98,451 (89,672–107,231) |
| Control arm     | 96,738           | 5847             | 2637 (2090–3183) |
| Cancer drug trials | 117          | 46,915           | 3240            | 216,876 (199,795–233,957) |
| Experimental arm| 31,921           | 2409             | 288,732 (258,892–318,571) |
| Control arm     | 14,994           | 831              | 8573 (7168–9978) |

CI: confidence interval, $Can: Canadian dollars

a The total number of enrollees was from the Access to Aggregate Content of ClinicalTrials.gov (AACT) database

b Number of Canadian enrollees and drug costs per enrollee were estimated

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Using unadjusted US drug prices led to an increase of $Can0.7 billion in drug costs, while varying patient enrolment by 25% around the point average corresponded to a range of total costs between $Can1.6 billion and $Can2.6 billion. Our timelines cover all trials that were completed in 2016. Each year, new trials start and ongoing ones reach completion. We therefore assume that our results could be a rough approximation for 1 year’s worth of economic activity.

We found that the cost contribution from industry was heavily concentrated in Ontario and Quebec, which has also been reported by the PMPRB. However, the PMPRB reported a lower research and development (R&D) expenditure of $Can918 million from drug companies in Canada in 2016, equalling the reported percentage of R&D-to-sales of 4.4% [14]. The PMPRB uses a valuation method set by Canada’s taxation agency, Revenue Canada, that reports costs of raw materials and labour costs of production and depreciation. This valuation method is appropriate when comparing the use of resources between industries, and is

Table 2 Summary of industry-sponsored drug clinical trial costs in Canada (2016)

| Variable                                      | Canada | AB   | BC   | MB   | NB   | NL   | NS   | ON   | PE   | QB   | SK   |
|-----------------------------------------------|--------|------|------|------|------|------|------|------|------|------|------|
| Number of trials*a                           | 394    | 133  | 146  | 52   | 28   | 29   | 58   | 316  | 1    | 239  | 23   |
| Number of facilities                         | 2039   | 174  | 223  | 56   | 34   | 46   | 61   | 875  | 1    | 544  | 25   |
| Number of enrollees                          | 20.126 | 1317 | 2069 | 385  | 290  | 651  | 485  | 9434 | 10   | 5142 | 343  |
| Drug costs                                   | 1804.9 | 117.5| 153.5| 45.3 | 44.9 | 51.5 | 37.7 | 650.8| 0.1  | 687.9| 15.7 |
| Experiment arm                                | 1782.4 | 115.8| 151  | 44.8 | 44.6 | 50.6 | 37.3 | 641.2| 0.1  | 681.6| 15.4 |
| Control arm                                   | 22.5   | 1.7  | 2.5  | 0.5  | 0.3  | 1    | 0.4  | 9.6  | 0    | 6.3  | 0.3  |
| Management and patient service billingsb     | 288.7  | 23.6 | 31.4 | 6.2  | 4.3  | 10   | 7.4  | 130.4| 0.1  | 69.6 | 5.7  |
| Ethics review                                 | 2.6    | 0.3  | 0.4  | 0.1  | 0.1  | 0.1  | 0.1  | 0.8  | 0    | 0.6  | 0.1  |
| Management billings                          | 15.7   | 2.0  | 2.3  | 0.8  | 0.4  | 0.5  | 0.9  | 4.8  | 0    | 3.7  | 0.3  |
| Patient service billings                      | 270.5  | 21.2 | 28.8 | 5.3  | 3.8  | 9.4  | 6.3  | 129.4| 0.1  | 65.3 | 5.4  |
| Total costs ($Can, million)                   | 2093.7 | 141.1| 184.9| 51.5 | 49.2 | 61.5 | 45.1 | 781.2| 0.2  | 757.5| 21.5 |

AB Alberta, BC British Columbia, MB Manitoba, NB New Brunswick, NL Newfoundland and Labrador, NS Nova Scotia, ON Ontario, PE Prince Edward Island, QB Quebec, SK Saskatchewan

Total number of trials in all provinces is greater than the number of trials in Canada because a particular trial could take place in more than one province

Management and patient service billings were estimated from a previous report (Tran et al. [2])

Fig. 1 Summary of total costs (in Canadian dollars [$Can]) for industry-sponsored drug clinical trials in Canada, by province (2016). AB Alberta, BC British Columbia, MB Manitoba, NB New Brunswick, NL Newfoundland and Labrador, NS Nova Scotia, ON Ontario, PE Prince Edward Island, QB Quebec, SK Saskatchewan

Fig. 2 Distribution of total costs for cancer versus non-cancer clinical trials in Canada, by province (2016). AB Alberta, BC British Columbia, CTs clinical trials, MB Manitoba, NB New Brunswick, NL Newfoundland and Labrador, NS Nova Scotia, ON Ontario, PE Prince Edward Island, QB Quebec, SK Saskatchewan

△ Adis
Table 3  Sensitivity analysis results

| Variable                        | Unadjusted US drug price | Patient enrolment at Canadian facilities |
|--------------------------------|--------------------------|------------------------------------------|
|                                |                          | 25% less than average | 25% higher than average |
| Canadian enrollees (n)         | 20,126                   | 16,043         | 24,182         |
| Drug costs ($Can, million)     | 2501.6                   | 1371           | 2238.9         |
| Experiment arm                 | 2456.2                   | 1353.4         | 2211.4         |
| Control arm                    | 45.4                     | 17.6           | 27.5           |
| Management and patient services billings ($Can, million) | 288.7                  | 241.8         | 355.1         |
| Total costsa ($Can, million)   | 2790.3                   | 1612.8        | 2593.9        |

$Can Canadian dollars

aTotal costs may not be exactly the same as sum of drug costs and management and patient services billings because of rounding.

5 Conclusions

When valued using a market price method, the costs of industry-sponsored drug CTs are substantial. In addition to the creation of knowledge, these trials play an important role in alleviating the healthcare cost burden in Canada. Appropriate policy should be in place to foster industry investments in clinical research to advance both scientific and economic merits.

Author Contributions PJ and DTT conceptualized the study. DTT and IA searched the Access to Aggregate Content of ClinicalTrials.gov (AACT) database for trial details and carried out the costing analyses. DTT drafted the manuscript. All authors contributed to the writing of the manuscript and critically reviewed the manuscript for intellectual content.

Compliance with Ethical Standards

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Conflict of Interest Dat T. Tran, Ilke Akpinar and Philip Jacobs have no conflict of interest to declare.

Data Availability Statement The datasets analysed during the current study are available in the public domain: (1) the Access to Aggregate Content of ClinicalTrials.gov (AACT) dataset was downloaded on 15 July 2018 and is available at https://aact.ctti-clinicaltrials.org/; (2) the Alberta Interactive Drug Benefit List was downloaded on 7 August 2018 and is available at https://www.ab.bluecross.ca/dbl/publications.html; and (3) the US Department of Veterans Affairs Pharmaceutical Prices file was downloaded on 7 August 2018 and is available at https://www.va.gov/opal/nac/lss/pharmPrices.asp.

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