RESEARCH PAPER

# Metrics Survey of Industry-Sponsored Clinical Trials in Canada and Comparator Jurisdictions between 2005 and 2010

# Sondage paramétrique des essais cliniques commandités par l'industrie au Canada et dans des pays de comparaison, entre 2005 et 2010


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## Abstract

Industry-sponsored clinical trials play a key role in the development of therapies. This survey suggests that between 2005 and 2010, research-based pharmaceutical firms worldwide initiated fewer trials and recruited fewer subjects annually. In contrast, at the country level, the

clinical trial activity of such firms increased in emerging countries and in Japan. Canada's trend in the number of new trials followed that of the global industry, but the trend in new sites and newly recruited subjects fell below the global rate. Informal comparisons point to potential issues for Canada in such areas as site capacity, cost per subject and time to first subject-in. When compared to certain Western European countries and the United States, Canada remained well positioned on a number of metrics. Nonetheless, Canada faces mounting challenges from both traditional locations and emerging countries and may require coordinated efforts to remain a place of choice to conduct trials.

## Résumé

Les essais cliniques commandités par l'industrie jouent un rôle clé dans la mise au point de thérapies. Ce sondage fait voir qu'entre 2005 et 2010, dans le monde, les sociétés pharmaceutiques axées sur la recherche ont initié moins d'essais et ont recruté moins de sujets annuellement. À l'opposé, il y a eu, au niveau du pays, une augmentation de l'activité des essais cliniques des sociétés pharmaceutiques dans les pays émergents et au Japon. Au Canada, la tendance dans le nombre de nouveaux essais suit celle de l'industrie mondiale, mais la tendance pour les nouveaux établissements et pour le recrutement de nouveaux sujets est moindre que celle indiquée par les taux mondiaux. Les comparaisons informelles font voir l'existence d'enjeux potentiels pour le Canada dans des domaines tels que la capacité des établissements, le coût par sujet et le temps d'arrivée du premier sujet. Comparé à certains pays d'Europe occidentale et aux États-Unis, le Canada se positionne assez bien pour certains paramètres. Cependant, le Canada fait face à de nombreux défis propres tant aux établissements traditionnels qu'au pays émergents et pourrait nécessiter des efforts coordonnés pour demeurer un endroit de choix pour mener à bien des essais.

Clinical trials provide pivotal evidence for the approval of new therapies, and they generate the primary research findings that underlie recommendations of evidence-based medicine. More generally, the value of clinical trials can be assessed in human, social and economic terms (ACAHO 2011). In 2007, Canada ranked among the top-tier countries as a location for industry-sponsored trials (Thiers et al. 2008; Glickman et al. 2009). However, Canada showed a marked decline in its relative growth rate for industry-sponsored clinical trials between 2002 and 2006 (Thiers et al. 2008). More recently, Health Canada (2011) reports progressively lower numbers of clinical trial applications in Canada between 2006 and 2010 (excluding bioequivalence studies). The Patented Medicine Prices Review Board annual reports (2006–2010) also point to a negative trend in industry expenditures on clinical trials in Canada. These trials nonetheless represent an important contribution to health research in Canada, as pharmaceutical companies sponsored over two-thirds of phase I to IV trials at Canadian sites in 2010 (US National Institute of Health 2011).

The present survey in part extends reported results on the ranking of countries as a function of location for industry-sponsored trials to a more recent timeframe. This study was conducted to estimate changes in the participation of members of Canada's Research-Based Pharmaceutical Companies (Rx&D) in clinical trials funded from global corporate operations, in relation to other jurisdictions between 2005 and 2010. The survey considered new trials, newly opened sites and newly recruited subjects. Moreover, we aimed to describe performance metrics (site capacity, recruitment to target, per-subject cost and time to first subject-in) related to the conduct of such trials in Canada and other countries. The time to first subject-in is further examined in Canada in terms of days to ethics approval and contract approval. This information is relevant to the cost-efficient delivery of trials and could serve as part of a strategy whereby Canada can remain competitive for the conduct of clinical trials. A partial analysis of the survey was presented at the Canadian Clinical Trials Summit (Laberge 2011).

## Method

### *Survey population*

Rx&D invited its member companies that conduct clinical trials in Canada to participate in the survey during the spring of 2011. Prior to the survey, a confidentiality agreement was executed between each participating company and the third party mandated to manage the survey data and ensure anonymous treatment of the information. The third party, Integrated Research Inc., is a contract research organization located in Canada that works with pharmaceutical and biotechnology companies worldwide.

A total of 14 companies submitted data out of 27 members contacted that we understood conducted clinical trials in Canada (taking into account mergers and acquisitions). Subsequent verification indicates that with a changing membership, we overlooked four companies with trial sites in Canada that joined Rx&D in 2009–2010. Companies that gained membership in 2011 are not included. Of the members that provided data, 11 are subsidiaries of major international companies, two are subsidiaries of medium-sized firms and one is a small firm. The parent companies of the 11 major Canadian subsidiaries are among the top 15 pharmaceutical firms, accounting for 73% of worldwide pharmaceutical research and development spent in 2009 by the 112 pharmaceutical companies listed in the leagues table (Department for Business Innovation and Skills 2010). Among the members contacted that did not provide data, three are large firms, five are medium-sized firms and five are small firms. Reasons provided for not participating in the survey included not being in a position to devote the necessary resources to complete the survey in a reasonable timeframe, or not being comfortable with disclosing the detailed information requested.

### *Data collection*

A data collection workbook was developed to meet the objectives of the survey, with input from representatives of the clinical research group within five member companies as part of a pilot exercise. In terms of trial performance, the pilot team recommended the metrics listed

above (site capacity, recruitment to target, first subject-in and per-subject cost) as an approach to assessing the efficient conduct of clinical trials. A *low site capacity* would lead to increased cost, with more sites opened in parallel. *Poor recruitment to target* can add delays as other sites attempt to compensate; in some cases, there would be added costs for opening subsequent sites. A *prolonged interval* between approval of the final protocol by the company and recruitment of the first subject reduces the potential of achieving the recruitment target within the agreed timeframe. Finally, *per-subject cost* (as defined in the study) is an indicator of how expensive it is to run the clinical trial as planned.

Although specific performance indicators used by companies can vary, it was felt that the data requested would be available internally without expecting members to perform additional analyses for the purpose of the survey. Following the pilot exercise, the workbook was distributed to all survey participants. Once completed, the workbooks were returned directly to the third party mandated to manage the survey data.

### *Scope of data*

The data collected covered interventional trials – in which an investigational product is used – funded by the global operations of member companies. These trials could include drugs or devices; however, no device company participated in the survey. Respondents were instructed not to include studies based on patient registries. Information on whether the trials were posted in a public registry or database was not requested, nor was information on whether commercially oriented networks, site management organizations or academic investigators conducted the trials. Data for the completed trials at sites in Canada specified that these trials were performed in institutions or private clinics. The latter can be managed by commercially oriented networks, but this factor was not determined.

Yearly data for the period 2005 to 2010 on newly launched trials, newly opened sites and newly recruited subjects were collected for Canada and 15 other countries selected during the pilot exercise to provide broad geographic coverage. The term "new" refers to a trial activity initiated in a given year. Similar global data – i.e., data on all interventional trials worldwide (not limited to the 16 countries) funded from the global operations of a company – were requested.

Data were also collected on global trials *completed* between 2005 and 2010 with sites in Canada. Companies were asked to include the data available for five countries (France, Germany, United Kingdom, United States and Spain) as well as globally in the above set of completed trials. The five comparator countries, selected during the pilot phase for this section of the survey, were perceived as having a socio-economic context similar to Canada's. Each company was asked to provide information on up to 20 such trials. The data pertained to the number of subjects, trial budget, days to first subject-in, days to ethics approval, days to contract approval, trial phase and therapeutic area. If a company had more completed trials involving sites in Canada, it was requested to choose a sample of 20 trials that reflected the variety of its clinical trial program in terms of therapeutic areas, trial phases and size. The members participating in the pilot phase of the survey advised that requesting detailed infor-

mation on more than 20 completed international trials involving Canadian sites per company would adversely affect the feasibility of participation in the study.

*Data analysis*

The data on new trials, newly opened sites and newly recruited subjects were used to describe trends in the participation of companies surveyed in clinical trials funded from global corporate operations in Canada and other jurisdictions. The annual sum for each variable was divided by the corresponding number of reporting companies, which varied by country and year. In the context of a varying number of reporting companies and data obtained without a closely controlled process, the non-parametric approach of Theil (1950) and Sen (1968) appeared to be more robust to gauge trends over time (it makes no assumptions about the distribution of the data and is resistant to data errors and outliers).

Subsequent analysis of the data at each time step indicates that in a number of cases their distribution is highly skewed based on the third-moment coefficient of skewness. We proceeded without using an estimate of the central tendency of the data at each time point and calculated instead the Theil–Sen trend directly from the individual data. In this case, the trend is the median of the slopes calculated from all possible pairs of individual observations, excluding the slopes between pairs of observations at the same time step. For purposes of comparison among jurisdictions, the rate of change per year for each variable was scaled as a percentage of change based on its median over the period 2005 to 2010. This approach indicates a relative trend with respect to the median of the time series. The trend over time for the global data on the same three variables was calculated in a similar manner. Rank-based summary statistics were used to characterize other metrics. When a median was calculated for an array of data such as across countries and years, the inter-quartile range was used to indicate dispersion. Graphic (box-plot) representation of summary statistics includes the median, inter-quartile range (IQR) and min–max values or the upper–lower adjacent values relative to the IQR to accommodate data with large variation.

The share of new trials was calculated by year, using the ratio of the number of new trials reported by country and year to the number of new trials by the same reporting companies pursued globally, by year. For each country, the median of the annual share is used as a representative value over the period 2005 to 2010. An estimate of site capacity was obtained from the ratio of newly recruited subjects to the number of newly opened sites in a country by year. The median of the yearly ratios was used for comparison purposes among jurisdictions. If either the number of subjects or sites was not available, the data were excluded from the capacity analysis.

Data from completed trials funded from global corporate operations are used to assess "recruitment to target" and "first subject-in" for Canada compared to global data and data for the countries initially selected for this part of the survey. The data in the first three years were based on a smaller number of trials (and companies), in particular for the European comparator countries and the United States. The data for the European countries were pooled in an "EU-4" group to obtain larger, and presumably more reliable, annual samples. Recruitment to

target consists of the median ratio of recruited subjects to the number of planned subjects per trial by year. The time to first subject-in is defined as the median number of days to recruit a first subject – as determined by the signature on the informed consent – following final protocol approval from the company, by year. For data on sites within Canada, additional metrics were used: number of days from first package shipment to ethics approval at the site, duration (in days) for the site's contract approval and days from first package shipment to first subject who signed the informed consent form at the site.

Data from completed trials also served to assess per-subject cost for Canada and the five comparator countries. The per-subject cost consists of the median ratio of the total committed budget (converted to Canadian dollars at market exchange rates) to the planned number of subjects per trial. Bilateral comparisons between Canada and each of the five comparator countries were based on common sets of trials over the survey period.

## Survey Results

Overall characteristics of the survey data set are shown in Table 1. The data set includes a total of 8,474 "new" interventional trials funded from the global operations of companies. Each trial likely included more than one country. The wide range in the number of subjects per country and year arises at least in part from differences in country size. Of the number of completed trials with detailed information requested per company (up to 20 trials), a total of 246 were provided. However, 15 did not contain usable information.

**TABLE 1.** Data set characteristics, 2005–2010

| Data Set | Total | Median | (Inter-quartile Range) | (Min – Max) |
|---|---|---|---|---|
| **New Trials** | | | | |
| No. of specific countries<br>No. reporting companies | 16<br>14 | | | |
| per country and year | | 9 | (8–10) | (6–12) |
| global per year | | 11.5 | (11–12) | (11–12) |
| No. of global trials* reported | 8,474 | | | |
| per country and year | | 121 | (74–186) | (34–704) |
| global per year | | 1,438 | (1,362–1,487) | (1,204–1,555) |
| No. of subjects (for global) | 1,443,682 | | | |
| per country and year | | 5,244 | (3,016–9,113) | (649–67,132) |
| global per year | | 239,258 | (221,920–262,765) | (166,991–311,435) |
| **Completed Trials Data Set (up to 20 requested per company)** | | | | |
| No. of specific countries<br>No. reporting companies | 6<br>14 | | | |

**TABLE 1.** Continued

| Data Set | Total | Median | (Inter-quartile Range) | (Min – Max) |
|---|---|---|---|---|
| per country and year | | 5 | (2–7) | (1–13) |
| global per year | | 9 | (6–12) | (3–14) |
| No. of global trials reported | 231** | | | |
| per country and year | | 11 | (4–17) | (2–66) |
| global per year | | 34 | (15–61) | (13–69) |
| No. of subjects (for global) | 221,686 | | | |
| per country and year | | 797 | (352–2,297) | (66–11,234) |
| global per year | | 28,683 | (17,252–59,387) | (8,611–72,646) |

* Global trial defined as an interventional trial funded from the global operations of a company

** Total of 246 *completed* trials were reported; however, 15 did not have usable information and were not entered

### *International ranking*

Canada's participation in global trials initiated annually and that of 15 other countries are shown in Table 2. For each country, the median of the annual share is provided as a representative value over the period 2005 to 2010. With participation in 13.7% of new trials funded from global company operations, Canada essentially shared the fourth rank with France among 16 countries, behind the United States, Germany and the United Kingdom.

### *Trends over time*

The relative rate of change per year in the number of new trials, newly opened sites and newly recruited subjects reported by companies nationally and globally between 2005 and 2010 are summarized in Table 3. Of the 16 countries listed, 12 were associated with a negative trend in the number of new trials initiated annually. The trend for Canada (–2.6% per year) was similar to that seen globally (–2.7% per year). For newly opened sites, seven countries showed positive trends, led by Japan, China, the

**TABLE 2.** Participation in new trials funded from global corporate operations,* ranked by country

| | Median (min–max) 2005–2010 |
|---|---|
| United States | 47.0% (45.6%–47.9%) |
| Germany | 16.5% (15.6%–17.9%) |
| United Kingdom | 14.6% (14.0%–15.8%) |
| France | 13.8% (12.2%–14.8%) |
| Canada | 13.7% (13.0%–14.7%) |
| Spain | 11.8% (10.9%–13.4%) |
| Sweden | 9.4% (7.5%–10.1%) |
| Poland | 8.9% (7.5%–10.9%) |
| Japan | 8.7% (4.7%–12.3%) |
| Australia | 8.2% (7.9%–9.8%) |
| Russian Federation | 7.6% (5.3%–8.9%) |
| India | 5.5% (4.9%–6.1%) |
| Argentina | 5.5% (4.4%–5.9%) |
| Brazil | 4.9% (3.6%–5.2%) |
| South Africa | 4.6% (3.5%–4.9%) |
| China | 3.5% (2.3%–4.6%) |

* Annual ratio of the number of new trials reported in a country to all new trials by the same reporting companies pursued globally (shown as percentage)

Russian Federation and India. Canada exhibited a decrease of 5.9% per year in the number of sites opened yearly, while the trend was flat for global data. In terms of subject recruitment, India led with a rate of increase of 29.1% per year, followed by China (13.9% per year) and Japan (11.7% per year). The other countries demonstrated either a flat trend or negative rates of change. Canada's trend corresponded to a declining rate of 14.2% per year versus a rate of –6.8% for the global trend.

**TABLE 3.** Clinical trial activity relative trends ranked by jurisdiction, 2005–2010*

| New Trials | | Newly Opened Sites | | Newly Recruited Subjects | |
|---|---|---|---|---|---|
| Japan | 7.1% | Japan | 13.5% | India | 29.1% |
| China | 2.0% | China | 11.1% | China | 13.9% |
| Brazil | 0% | Russian Federation | 10.2% | Japan | 11.7% |
| United States | 0% | India | 9.2% | Russian Federation | –0.1% |
| Sweden | –1.8% | Brazil | 5.3% | United States | –3.6% |
| Canada | –2.6% | Poland | 4.5% | Brazil | –6.4% |
| **Global** | **–2.7%** | Australia | 2.4% | **Global** | **–6.8%** |
| Russian Federation | –2.8% | **Global** | **0%** | South Africa | –7.5% |
| Poland | –3.6% | South Africa | 0% | Germany | –10.7% |
| France | –3.7% | United States | –1.4% | Spain | –10.8% |
| Germany | –4.3% | Germany | –1.6% | Australia | –12.3% |
| United Kingdom | –4.8% | United Kingdom | –3.0% | France | –13.0% |
| Australia | –5.0% | Argentina | –3.6% | Sweden | –13.1% |
| Spain | –7.1% | Sweden | –3.6% | Canada | –14.2% |
| South Africa | –8.3% | France | –5.0% | Argentina | –14.6% |
| Argentina | –8.8% | Spain | –5.1% | United Kingdom | –15.0% |
| India | –11.1% | Canada | –5.9% | Poland | –16.4% |

* Rate of change in the individual number of new trials, newly opened sites or newly recruited subjects reported by companies annually by jurisdiction. The trend (slope) for each variable is expressed as a percentage change based on the median of the individual observations by jurisdiction over the period 2005 to 2010.
Applies to interventional trials funded from global operations of companies initiated annually.

### *Participation in new clinical trials by trial phase*

Canada's extent of participation in global new trials by phase and corresponding trends per year in the number of trials are shown in Table 4. The more detailed information specifying the trial phase was requested only for Canada and globally. New phase I trials in Canada funded from global operations represent a relatively small proportion of these trials funded worldwide. New phase II trials appeared to have a positive trend in Canada, contrasting with

a decreasing rate for global trials. On the other hand, the rate of change of phase III trials appeared to be decreasing both for Canada and globally. Phase IV trials showed no change in rate in both cases. Note that locally funded phase IV trials were not captured in the survey.

**TABLE 4.** Participation in new trials and relative trends by phase, Canada vs. globally, 2005–2010

| Phase | Share Over Survey Period* Median (min–max) | Rate of Change** (per year in no. trials) | |
|---|---|---|---|
| | | **Canada** | **Global** |
| Phase I | 3.4% (2.5%–5.2%) | 0% | 2.4% |
| Phase II | 19.2% (14.1%–23.9%) | 5.0% | –6.1% |
| Phase III | 27% (20.9%–30.1%) | –7.1% | –6.5% |
| Phase IV | 16.1% (11.8%–17.5%) | 0% | 0% |

* Ratio of number of new trials by phase reported for Canada to all new trials by phase by the same reporting companies pursued globally (shown as percentage)
** Rate of change in the individual number of new trials reported by phase. The trend in this variable is expressed as a percentage change based on its median over the period 2005 to 2010.
Median number of reported new trials across years:
Canada: Phase I = 20, Phase II = 61, Phase III = 90, Phase IV = 13
Global: Phase I = 598, Phase II = 337, Phase III = 343, Phase IV = 83
Number of reporting companies across phases: median (min–max), 11 (10–12)

### *Site capacity estimate*

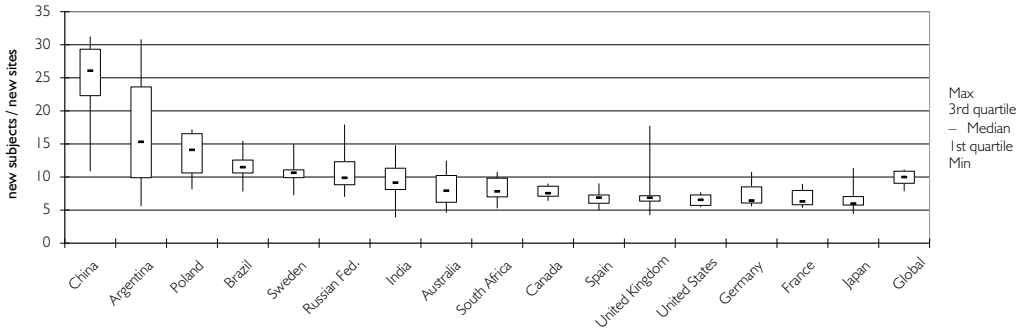
Figure 1 shows the median site capacity estimate for each country and globally over the period surveyed. China exhibited the largest median site capacity estimate (26.1). With an estimate of 7.6, Canada ranked tenth among the 16 countries represented. Compared to the global data (i.e., worldwide, not limited to the 16 countries listed), Canada was one of 11 countries with a site capacity estimate below that of the global median. The value for China was unusually large compared to the other jurisdictions. Were the data for China to be subtracted from the global data, the median global ratio would change from 10.1 to 9.9, and Canada would be one of 10 countries with a site capacity estimate below the median for global figures.

### *Recruitment to target*

Table 5 shows the recruitment to target for Canada and comparator jurisdictions from global trials that included Canadian sites and were completed between 2005 and 2010. Differences between the number of trials conducted in Canada and globally are due to the exclusion of trials for which either the number of planned or recruited subjects was missing. The comparator jurisdictions are the ones initially selected for the part of the survey on completed trials, with the four European countries pooled in the EU-4 group. In the first three years, the data for the United States were obtained from only a few trials. The median of the ratios of recruited to planned subjects at the trial level is near unity in the later half of the time period for all jurisdictions. The use of sample means, not as descriptive of the bulk of the data for skewed

samples, gave Canada the highest (but inflated) ratios initially, followed by a decrease and stabilization near unity (data not shown).

**FIGURE 1.** Site capacity estimate* by jurisdiction, 2005–2010




* Site capacity estimate: ratio of newly recruited subjects to the number of newly opened sites in a jurisdiction by year
Number of data points with information on both the number of sites and subjects: median (inter-quartile range):
across countries and years: country data = 503 (324 – 836); across years: global data = 24,261 (21,895 – 25,293)

**TABLE 5.** Recruitment to target§ for completed trials by jurisdiction

| | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 |
|---|---|---|---|---|---|---|
| Canada (n)* | 1.03 (14) | 1.23 (9) | 1 (13) | 1 (45) | 0.89 (63) | 0.98 (66) |
| EU-4** (n) | 1 (12) | 1 (7) | 0.99 (4) | 0.91 (18) | 0.98 (26) | 0.98 (26) |
| United States (n) | 1.19 (4) | 0.84 (2) | 0.60 (4) | 1.07 (23) | 0.88 (33) | 1 (29) |
| Global (n) | 1.06 (14) | 1 (13) | 1 (17) | 1.01 (50) | 1.01 (65) | 1.02 (69) |

§ Recruitment to target consists of the median ratio of recruited to planned subjects at the trial level for trials completed in the year
* n = number of completed trials
** EU-4 group: France, Germany, Spain and United Kingdom

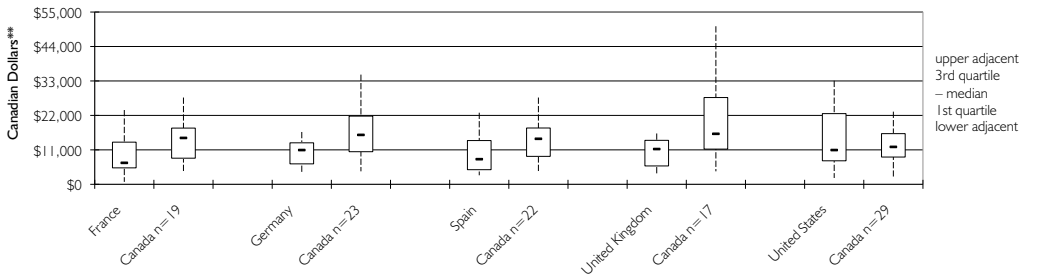
The supplemental material provided in the Appendix (online only) shows the recruitment to target by trial phase (Table S1) and by therapeutic area (Figure S1) for completed trials over the combined years from 2005 to 2010.

### *Per-subject cost*

Per-subject costs are compared in Figure 2 using completed trials that are common between Canada and a comparator country pooled over 2006 to 2010 (no matching trials were reported for 2005). The comparator jurisdictions are those initially selected, and represent traditional countries where Canada might be in a position to compete on cost. The bilateral com-

parisons are based on 17 to 29 trials each, but the matching data came from a limited number of large international companies (Canada–United Kingdom, 4; Canada–United States, 4; Canada–France, Germany or Spain, 3 each). The median per-subject cost for Canada is consistently above that of the European countries and is essentially at parity with the United States. However, there is marked overlap in the range of data.

**FIGURE 2.** Per-subject cost* for same completed trials compared bilaterally to Canada, 2006–2010




* Per-subject cost consists of the median ratio of total committed budget to the planned number of subjects per trial

** At market exchange rates

Upper adjacent value: largest observation ≤ [3rd quartile + (inter-quartile range x 1.5)]

Lower adjacent value: smallest observation ≥ [1st quartile – (inter-quartile range x 1.5)]

Values outside these ranges are not shown but are included in the calculation of the median and quartiles.

Number of companies reporting information on same completed trials bilaterally = 3 to 4 large international firms.

### *Time to first subject-in*

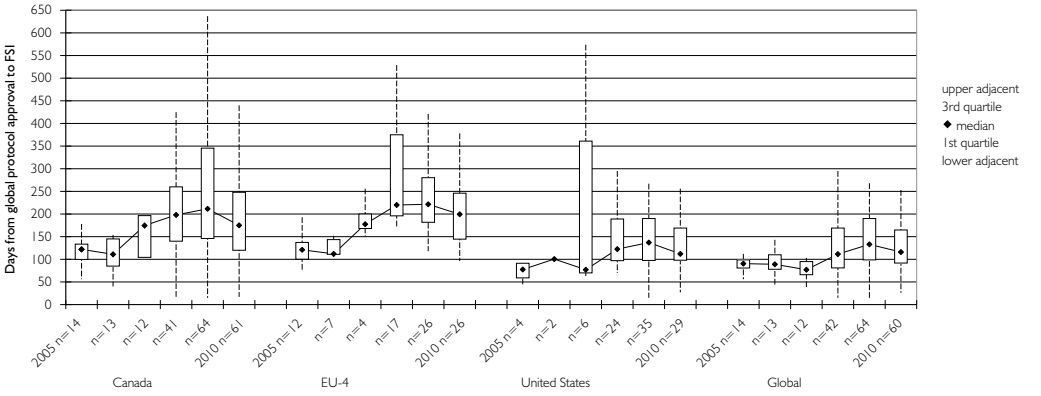
The annual medians and other rank-based summary statistics for the time to first subject-in for Canada and comparator jurisdictions from completed global trials that included Canadian sites are plotted against time in Figure 3. The small difference between the number of trials in Canada and globally is due to incomplete information provided. The graphical comparison suggests that the median number of days to enrol the first subject for Canada is similar to the EU-4 group, while the United States has a similar performance to that seen globally. In the later half of the time series (2008–2010), which consisted of larger samples, the US and all global locations combined appear to require a shorter median time to enrol the first subject than the former two jurisdictions. There is nonetheless overlap in the range of data. In pooling the European data, the shortest time to enrol the first subject in a trial was used by definition. The information requested in the survey did not cover specific country processes and approval requirements.

### *Canadian sites*

Data collected about sites in Canada for completed trials permitted an estimate of time to ethics approval, research contract approval and first subject-in. The information on a site basis was not collected for other countries. The median number of days is plotted by year in Figure 4. The graphical comparison suggests that the time to ethics approval for institu-

tional research ethics boards (REBs) is longer than for private REBs in Canada. Similarly, the time to contract approval and first subject-in is correspondingly longer for institutional sites. However, the data consist of heterogeneous trials, and the mix may be different for the two groups. Within institutional sites, the time to ethics and contract approval appears to be generally comparable, although there is some yearly fluctuation. A similar pattern was seen for private sites. If contract negotiations and ethics review are carried out sequentially, the interval between obtaining both approvals and enrolment of the first subject seems relatively short. On the other hand, if the former two processes are pursued in parallel, the time to first subject-in appears to substantially exceed the time to obtain the above approvals.

**FIGURE 3.** First subject-in (FSI)* for completed trials, by jurisdiction and year



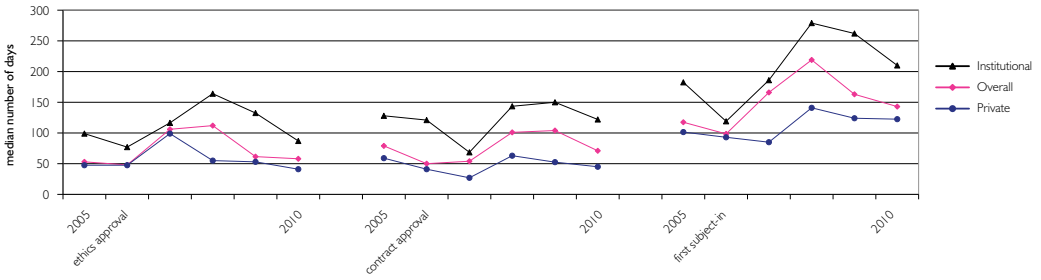

* Time to first subject-in is defined as the median number of days required to enrol the first subject following global protocol approval by year

Upper adjacent value: largest observation ≤ [3rd quartile + (inter-quartile range x 1.5)]

Lower adjacent value: smallest observation ≥ [1st quartile – (inter-quartile range x 1.5)]

Values outside these ranges are not shown but are included in the calculation of the median and quartiles.

**FIGURE 4.** Time to ethics and contract approval and first subject-in, by year, Canada*




* Sites in Canada involved in completed trials that were globally funded. Definition of metrics:

Ethics approval: duration from first package shipment to ethics approval at the site;

Contract approval: duration for the site's contract approval; and

First subject-in: duration from first package shipment to first subject who signed the informed consent form at the site

Number of sites: median (inter-quartile range) across years and the three metrics: overall sites 226 (98 – 252); private sites 132 (81 – 173); institutional sites 80 (36 – 120)

## Discussion

Consistent with the findings of Thiers and colleagues (2008), our results indicate that Canada ranked in the top five countries over the period from 2005 to 2010 in terms of its participation in trials funded by the global operations of major pharmaceutical companies, but the basis for ranking is different (share of sites versus share of trials, in our case). The data presented by Glickman and colleagues (2009) is not amenable to direct comparison because it groups some key countries by region. Although not identical, the rankings based on the number of sites or trials they report have a fair degree of overlap.

Both of those studies used data retrieved from the registry of the US National Institute of Health (2011). This registry is likely more comprehensive after 2008 given that late in 2007, the *Food and Drug Administration Amendments Act* expanded the types of trials that must be registered when they have at least one site in the United States, although it provides an exemption for phase I trials (US Public Law 2007). As well, a number of metrics we used to characterize the conduct of clinical trials, such as newly recruited subjects annually, per-subject costs, days to first subject-in, days to REB approval and days to contract approval, are not within the scope of the registry. We relied on our workbook/questionnaire as a single data collection tool designed to capture information meeting the objectives of the present survey, albeit participation was on a voluntary basis.

Our results point to a slightly negative rate of change in new trials funded from the global operations of major international companies worldwide between 2005 and 2010. The rate of change in new sites was flat globally, but this rate appeared to be positive in Japan, the BRIC countries, Poland and, to a lesser extent, Australia. Only three countries (India, China and Japan) showed a positive rate of change for newly recruited subjects.

India's negative rate of change for new trials initiated annually contrasted with its positive rate of change for opening new sites and recruiting new subjects. Japan's high rank with respect to the above three metrics may indicate the country's effort to address regulatory obstacles to participation in global clinical trials (Tamura 2010). The rate of change for new trials in Canada was similar to the global trend, but the rate for new sites and newly recruited subjects was below that of global data.

The metrics related to performance suggest that Canada had a site capacity estimate above that of the United States and Western European comparator countries. For recruitment to target, Canada had a median ratio of recruited to planned subjects near unity in the later half of the survey period, as did the other jurisdictions. As well, Canada's per-subject cost was similar to that of the United States, and its time to first subject-in was similar to the EU-4 comparator group. A moderate increase in the timelines from protocol release to first subject-in between 2003 and 2007 has been reported for clinical trials sponsored by large companies in the European Union following the implementation of new legislation (Klingman 2009).

On the other hand, we found that relative to the BRIC countries and other emerging countries, Canada's site capacity was lower. As well, bilateral comparisons with the Western

European countries point to a higher per-subject cost for Canada among these countries, while Canada's time to first subject-in appeared to be longer than that for all global locations combined and that of the United States, based on the later half of the survey period.

The data on institutional and private sites within Canada illustrate the influence that longer ethics reviews and research contract negotiations can have on the time to first subject-in. In either situation, consideration could be given to reducing the time taken to enrol the first subject after having obtained contract and ethics approvals, depending on the extent to which the latter two processes are actually pursued in parallel. Although protocols for most clinical trials also require approval from the regulator (Health Canada), we did not collect data on the time to complete this process.

*Limitations of the survey*

The survey data come largely from 11 major pharmaceutical companies. These are among the top 15 in the industry, accounting for a high proportion of pharmaceutical research and development expenditures. Our results are expected to reflect the situation in this segment of the industry. However, among members contacted that did not provide data, the number of small and medium firms exceeded the number of large firms. A broader response from members would have provided data more representative of the mix of companies that carry out clinical trials in Canada.

The data collected through the survey have a large variability, which may have reflected inherently different levels of clinical trials activity within companies at different times and locations, as well as difficulties in capturing the requested data. Not all respondents provided full data sets, particularly for trials *completed* between 2005 and 2007 for the five selected comparator countries and, to a lesser extent, Canada and globally. Data availability can be affected, for instance, by differences in corporate structure, incompatibility of internal tracking processes with the survey needs and merger activities over the period surveyed. For the completed trials, companies were instructed to select a mix of trials representative of their clinical development program if there were more than 20 trials to choose from. Confidential treatment of the data would encourage companies to provide this information. Nonetheless, choices may have been influenced by the relative ease of accessing all the requested data on individual trials. The observation that markedly more trials completed in the second half of the survey period were included would seem to support this presumption.

Another source of variability may be differences in interpretation of definitions such as "total committed budget" for a trial and in tracking "days between final protocol and first subject-in." Also, with respect to the latter metric, a jurisdiction that subsequently joined a trial under special circumstances (e.g., to shore up lagging recruitment) would be ascribed an unusually long interval.

Pooling the data on completed trials for the four European comparator countries yielded larger and presumably more reliable annual samples for the analysis of recruitment to target

and time to first subject-in. However, for the United States, the sample size in the first three years remained based on a smaller number of trials, and may be less reliable. For per-subject costs, a potential source of bias is the fact that although common sets of trials in comparable numbers were obtained, the information came from the same three to four large international companies for the bilateral comparisons. However, the type of company in this group is not unlike the majority of respondents in the overall sample.

For all estimated trends and comparisons made, it should be kept in mind that they are informal and that any issue arising from multiple comparisons was not addressed.

## Conclusion

Our results suggested a slightly downward trend in the number of clinical trials initiated annually and funded by the global operations of major pharmaceutical companies internationally between 2005 and 2010. Although the global trend in newly opened sites was flat, seven of the 16 specific countries in the survey showed a positive rate of change – yet a positive trend in subject recruitment is seen in only three of these countries. This situation suggests the need to improve efficiency in the delivery of clinical trials.

In this context, informal trends and comparisons point to challenges for Canada in maintaining its share of trial activity. Canadian efforts are ongoing to address delays in ethics reviews for multi-centre clinical trials (Saginur et al. 2008; Shuchman 2009) and in protracted agreement negotiations for trials (CIHR 2011; Vogel 2011). A further coordinated effort from all stakeholders in Canada is likely required to devise and implement policies aimed at improving site capacity, maintaining recruitment to target and better managing per-subject cost to enhance the cost-efficient delivery of clinical trials while ensuring a high level of protection for participating subjects.

A major step towards an action plan for Canada on this matter has been taken through a multi-stakeholder Clinical Trials Summit held in 2011 (ACAHO 2012). Strategic approaches are also being pursued elsewhere, including among Canada's closest competitors – the European Union and the United States (English et al. 2010; Menikoff 2010; Goldman 2011; European Commission 2011). How quickly such initiatives can begin to improve trends remains to be assessed. Without a renewed effort, the conduct of clinical trials in Canada and other traditional countries risks becoming increasingly uncompetitive with respect to the BRIC and other emerging countries. At the same time, Canada remains well positioned relative to Western European countries and the United States on a number of performance metrics. It should envisage measures to maintain its level of clinical trial activity by competing on a range of operational factors and cost against these traditional locations.

The performance metrics we surveyed constitute key attributes when deciding where to conduct clinical trials. However, as a prerequisite, sites must be able to comply with all applicable international and local ethical and scientific quality standards. The proceedings from the 2011 Clinical Trials Summit (ACAHO 2012) provide a discussion from a Canadian perspective of

a broader range of issues that affect clinical trial competitiveness. An additional difficulty in site selection is the conflict in commitments that can arise when sites recruit subjects to similar trials in the same therapeutic area. Continued monitoring of Canada's performance metrics should be considered to clarify their dynamics and gauge the impact of ongoing and new initiatives.

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RESEARCH PAPER

# Metrics Survey of Industry-Sponsored Clinical Trials in Canada and Comparator Jurisdictions between 2005 and 2010

## Sondage paramétrique des essais cliniques commandités par l'industrie au Canada et dans des pays de comparaison, entre 2005 et 2010

JEAN-MARIE LECLERC, NORMAND LABERGE AND JEAN MARION

## Appendix: Supplementary Information

### *Recruitment to target by phase for completed trials*

The recruitment to target by phase for completed trials over the combined years from 2005 to 2010 is shown for Canada and comparator jurisdictions in Table S1. Sample size varies by jurisdiction and phase, smaller samples being associated with the EU-4 group and the United States. The median ratio was generally at unity, but appeared to be below unity in some instances (Canada in phase II; EU-4 group and the United States in phase IV).

**TABLE S1.** Recruitment to target for completed trials by phase,* 2005–2010

| | Phase I | Phase II | Phase III | Phase IV |
|---|---|---|---|---|
| Canada | 1 | 0.89 | 1 | 1 |
| (n)** | (20) | (66) | (109) | (13) |
| EU-4 | — | 0.99 | 0.99 | 0.82 |
| (n) | (0) | (31) | (52) | (8) |
| United States | 1 | 0.95 | 0.98 | 0.73 |
| (n) | (3) | (36) | (48) | (7) |
| Global | 1 | 1.02 | 1.01 | 1.01 |
| (n) | (21) | (73) | (119) | (13) |

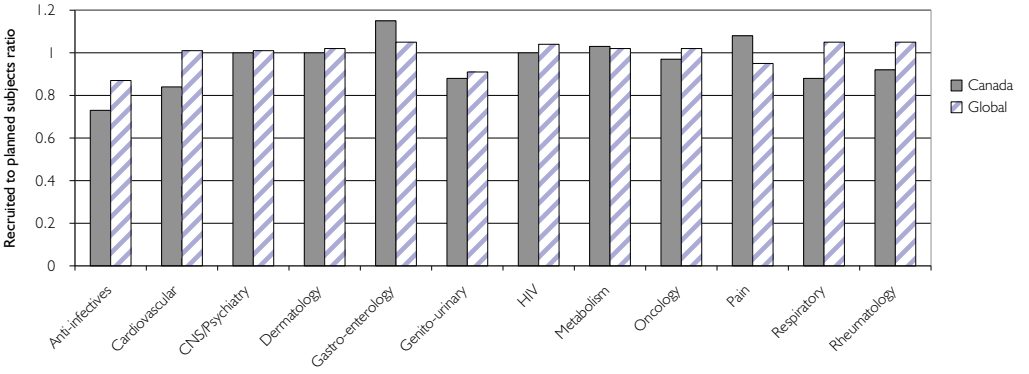
* Recruitment to target consists, in this case, of the median ratio of recruited to planned subjects at the trial level by phase for completed trials over the combined years from 2005 to 2010.

** (n) = number of completed trials

### *Recruitment to target by therapeutic area for completed trials*

The recruitment to target by therapeutic area for completed trials over the combined years from 2005 to 2010 is shown for Canada and the global data in Figure S1. Differences were not marked in most therapeutic areas. Canada's recruitment to target appeared to be above that for the global data in the gastroenterology and pain areas, but below that for the global data in the cardiovascular, respiratory and rheumatology areas. Both jurisdictions were below unity in the anti-infective and genito-urinary areas.

**FIGURE S1.** Recruitment to target for completed trials by therapeutic area,* 2005–2010




* Recruitment to target consists, in this case, of the median ratio of recruited to planned subjects at the trial level by therapeutic area for completed trials over the combined years from 2005 to 2010.

Number of reported trials: median (min-max) across therapeutic areas for all years combined:
Canada = 14.5 (5 – 38); Global = 15.5 (5 – 46)