The perilous state of independent randomized clinical trials and related applied research in Canada

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Over the last 60 years, advances in the prevention and treatment of common conditions such as cardiovascular, tobacco-related and infectious diseases have led to substantial improvements in life expectancy. New prevention strategies and treatments have arisen from basic biomedical studies, large epidemiological studies and randomized clinical trials (RCTs) that often involve several thousands of patients. Some simple and very effective treatments (e.g., acetylsalicylic acid [ASA] to prevent cardiovascular events,[1] folate supplementation in pregnant women to prevent fetal neural tube defects)[2] had been overlooked until their value was established in large trials. However, other treatments were in wide use until large trials showed them to be useless or even harmful (e.g., antiarrhythmic drugs for ventricular arrhythmias,[3] or hormone replacement therapy postmenopause)[4].

Large randomized trials are critical for the evaluation of most therapies, diagnostic tests, devices, surgical procedures and health care implementation strategies. Some studies, particularly those investigating new drugs or devices, are funded by the companies who stand to gain commercially from the sales of the products in question. However, many important areas of research will not have a commercial sponsor, despite their implications for improving clinical care or public health. The necessary studies can only be done if they are supported by governments or charitable organizations; however, compared with other western countries, Canada provides relatively little support for clinical trials.

In this article, we will:

- Outline the rationale for better support of clinical trials by the Canadian government
- Consider how Canada's health research funding should be allocated among different forms of research
- Describe the current allocation of funding to clinical trials by Canada's main granting agency for health research (within the broader context of funding basic biomedical sciences v. all applied health sciences), how it compares to such allocations in the United States and the United Kingdom and how it has changed since the transition from the Medical Research Council of Canada to the Canadian Institutes of Health Research (CIHR)
- Describe additional barriers to conducting clinical trials in Canada.

In addition, we summarize potential solutions and steps to facilitate the performance of independent clinical trials in Canada (Box 1) and explain the rationale for our suggestions (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.110598/-/DC1).

Rationale for better support for clinical trials

Health research contributed substantially to the 50% increase in life-expectancy seen during the 20th century. However, all interventions require evaluation in clinical studies. Since the early clinical trials that showed the benefits of streptomycin to cure pulmonary tuberculosis,[5] or the polio vaccine to prevent poliomyelitis,[6] large RCTs have led to reliable evidence of treatments that save millions of lives worldwide, and their results routinely guide clinical practice in Canada and abroad.

But why would the Canadian government fund any clinical trial or any form of clinical research when one could "borrow" the fruits of research done in other countries? If laboratory experiments can be done in Japan, or chemistry or physics research done in Europe, why would Canada develop the capacity to do the same?

Key points

- Randomized controlled trials (RCTs) are funded at a disproportionately low level compared with other forms of health research.
- The Canadian Institutes of Health Research (CIHR), preferably with the creation of a new agency or vice-presidential position for human applied research, should increase funding for RCTs from 3.3% to 10% within 5 years, with dedicated and sustained funding for a national infrastructure in clinical trials to support large and high-impact studies.
- The CIHR, provincial governments, health charities and industry should partner together to develop collaborative programs for clinical research.
- Strategies are needed to overcome the many regulatory and institutional barriers to performing clinical trials efficiently.

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First, in the field of human health, the earliest impacts of clinical trials have been felt in the countries where the studies were done. For example, 30 years ago, Canadians with a history of transient ischemic attack who participated in an RCT were the first patients in the world to reliably benefit from reduced stroke and death with low-cost ASA therapy.[7] Ten years later, residents of Ontario and Quebec who had stable angina and took part in two Canadian RCTs of ASA therapy were among the first to have reliable reductions of myocardial infarction and death with this simple regimen.[8,9] More recently, Canadian women with post-term pregnancies who participated in a Canadian multicentre RCT of induction (v. monitoring) were the first to reliably avoid cesarean delivery for this condition.[10] Canadian newborns with severe respiratory distress enrolled in a multicentre Canadian RCT of nitric oxide were the first to reduce their risk of extracorporeal membrane oxygenation with this inexpensive regimen.[11] In a study involving more than 120 hospitals from Newfoundland to British Columbia, Canadians with vascular disease were among the first to benefit from the widespread use of an angiotensin-converting enzyme inhibitor.[12] Other landmark Canadian trials have shown us how to prevent gastrointestinal bleeding in patients requiring mechanical ventilation,[13] and that a less expensive, conservative transfusion policy was as good as or better than a more expensive liberal policy in saving the lives of patients with critical illnesses.[14] Furthermore, Canadians have benefitted from the early implementation of highly active antiretroviral therapy for the prevention of infection with HIV.[15]

Canadian investigators have also had leading roles in trials showing the futility or even harm of previously accepted therapies. For example, extensive and expensive laboratory research had appeared to show a reduction in atherosclerosis-related oxidative stress with vitamin E therapy; however, a large Canadian RCT clearly showed that the treatment was useless, allowing hundreds of millions of dollars to be saved.[16] Another Canadian trial has shown that the monoclonal antibodies that perform so well in the laboratory do not benefit critically ill patients with septic shock.[17]

Second, some questions can only be evaluated in a relevant Canadian setting. Certain interventions or strategies (e.g., behavioural or sociologic interventions, vaccination strategies) may have varying effects depending on such factors as the structure of health care and its delivery, the skills of health professionals, the availability of facilities, the community's social structure, values and culture, or the underlying disease prevalence or immunity in a population. For example, the first RCT to show the effectiveness and safety of nurse practitioners as providers of primary care was done in Canada,[18] as was the first RCT that showed how patient-directed, behaviourally oriented strategies could improve patient compliance with antihypertensive drugs and, as a result, the control of high blood pressure.[19] A community-based RCT showed that a cardiovascular health awareness program could reduce cardiovascular-related admissions to hospital in midsized communities in Ontario.[20]

Third, RCTs provide substantial economic benefits in the form of direct expenditures in the multimillions of dollars for their management and performance. For example, local Canadian innovative industries have developed from studies of photophrin (Visudyne, QLT), montelukast (Singulair, Merck Frosst) and various vaccines (Connaught Laboratories).

Fourth, wealthier countries have social and moral obligations to invest in research that bene-

Box 1: Approaches for facilitating large and efficient independent (i.e., noncommercial) randomized clinical trials (RCTs) and related research in Canada

Increase funding (operational, infrastructure, investigators):

- Facilitate cultural change within the Canadian Institutes of Health Research (CIHR) and health charities
  - Acknowledge the value of large RCTs and related well-designed studies
  - Create separate CIHR portfolios for basic and applied health research; alternatively, create separate national agencies
- Increase the proportion of allocations to applied health research
  - Reallocate existing CIHR budget (make similar allocations to basic biomedical and applied health research)
  - Increase CIHR funding for clinical trials
  - Develop additional mechanisms for funding large, multicentre studies
  - Reallocate the budgets of major national health charities to align with the CIHR for main initiatives
- Secure new funding for health research
  - Develop public and political support
  - Engage provincial health ministries
  - Promote partnerships with the Canadian Foundation for Innovation (clinical trials infrastructure), health charities (grants and investigators) and international health research agencies
  - Modify and expand CIHR's university–industry program

Facilitate the performance of clinical trials:

- Overcome administrative barriers (ethics review, contracts, informed consent, adverse events reporting, site monitoring)
- Improve and customize peer review processes to the different aspects of clinical research
- Develop and sustain clinical research infrastructure (data management/methods centres, disease-specific/thematic networks)
- Incorporate research into clinical practice
- Create linkages and increase access to administrative databases
- Promote innovative, simplified and efficient trial designs

fits humanity. As a wealthy country, Canada has a humanitarian responsibility to perform its fair share of societally beneficial research. Canadian-led RCTs are saving lives, not only in Canada, but worldwide.

Fifth, the Canadian scientists who conduct RCTs, though small in number, are world-class. Previous reports have documented the impact (in terms of quality, not quantity) of studies done in various categories by researchers in several countries.[21,22] In a report published in *Nature*, under the heading of "clinical medicine," which includes RCTs, Canada was second only to the US — ahead of England, France, Germany, Australia and Japan.[21] Canadian clinical scientists have much to contribute to the health not only of Canadians, but of people everywhere.

How should Canada's health research funding be allocated?

What proportion of a country's health research budget should be allocated to different forms of research — basic biomedical, experimental animal, translational, clinical or implementation research? There is no right or wrong answer, but it is likely that most people can agree on three principles.

First, there must be a reasonable promise for the advancement of knowledge that will benefit human health, either directly or indirectly. Second, any national research strategy should span discovery, human evaluation and implementation. Third, it is important to invest more in research that will lead to prevention or better outcomes for people with common or serious conditions that represent a large part of the burden of disease.

Discoveries can come from clinical cases, formal observational studies, studies on social and policy determinants, mechanistic clinical and nonhuman studies and, sometimes, the incidental findings of trials. This entire range of discovery research (i.e., not what is considered "basic biomedical science") is critical.

Once potential and promising interventions are identified, they must be evaluated in different types of clinical trials: proof of concept and dose-finding studies (for drugs), safety evaluations or evaluations of processes (for health system changes) and large clinical trials. Until the whole range of studies has been done, one cannot be sure as to the human relevance of a finding from the discovery sciences (e.g., the importance of modifying a putative risk factor, blocking a receptor or enzymatic pathway or the association between various social factors and specific health outcomes). RCTs are essential to provide the ultimate validation or repudiation of concepts, mechanisms, putative risk factors or pathways.

To reliably detect or exclude plausible and clinically important differences, RCTs have to be large. Once we determine that certain drugs or interventions (surgical, behavioural or policy) are effective or ineffective, efforts at efficiently implementing or abandoning them must follow. It is therefore reasonable that a national strategy for research would have an appropriate balance of investments among discovery, evaluation and implementation. This would require similar levels of funding for each of these three main categories of health research.

Current funding allocations

The overall funding provided by the CIHR for research was about Can$1 billion in 2010/11 (i.e., Can$29 per capita or 0.07% of our overall gross domestic product).[23] In contrast, the overall funding of the National Institutes of Health in the US was Can$31 billion in 2010/11 (i.e., US$100 per capita or 0.2% of America's gross domestic product) (Figure 1).[24,25] In both countries, research receives additional funds from regional governments and health charities. In the UK, the two principal health funding agencies are the Medical Research Council and the National Institute for Health Research (which only funds England), with a combined budget of about £2.0 billion (Can$3.2 billion).[26,27] This represents 0.12% of the UK's gross domestic product and a per capita expenditure of £28.1 (Can$45), which is about 70% higher than in Canada. (These figures are underestimates, as there is additional funding from the governments of Wales and Scotland.)

The current allocation of funding among the different areas of research in Canada from the major government agencies that fund health research (such as the CIHR) seems to have

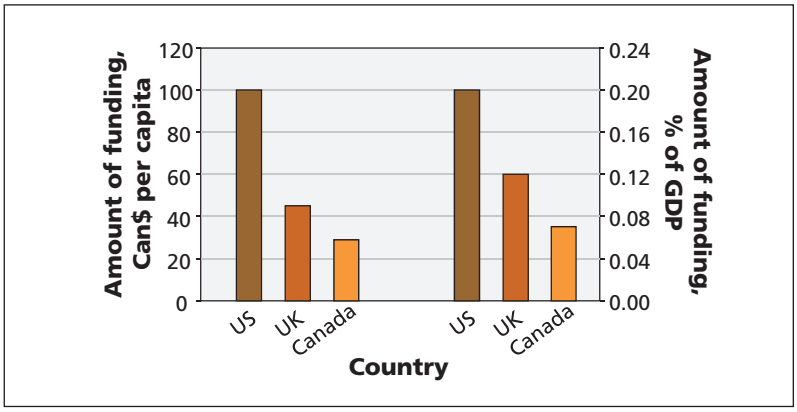

Figure 1: Federal funding for health research in 2010/11, by country. GDP = gross domestic product, UK = United Kingdom, US = United States.

arisen from historical precedent, rather than the result of an explicit discussion about the right balance based on disease burden, scientific opportunity or impact on human health or the economy. The narrow biomedical focus of Canadian health research was recognized about 10 years ago, when the CIHR was created with its four pillars of health research and a broader mandate than its predecessor, the Medical Research Council of Canada.[28] However, there have been only modest shifts in the patterns of research funding; the allocation to basic biomedical research is still substantially greater than that for the other three pillars combined (Figure 2).[29] During this same period, there remains relatively modest (and in our opinion inadequate) funding of clinical trials so that many proposals by Canadian researchers to evaluate potentially promising interventions have not been funded.

An even more startling statistic is how the funding is distributed across different kinds of research in Canada and the extremely low levels of funding for clinical trials. For example, the CIHR allocated only 3.3% of its overall budget to clinical trials in 2009/10,[23] whereas the US National Institutes of Health spent 11% of its overall budgets on RCTs.[24,25] This means that the US spends nine times as much money per capita on publicly funded trials than does Canada. Several years ago, the UK recognized the relative paucity of funding for clinical research, particularly clinical trials. This realization led to the creation of the National Institute for Health Research, with an annual budget of about £1 billion for 2010/11. About 20%–25% of this budget is devoted to supporting and conducting RCTs, and supporting related centres and health professionals (Jonathan Bickley [Section Head, Research and Development Briefing and Parliamentary Business, Department of Health, London, UK]: personal communication, 2011).

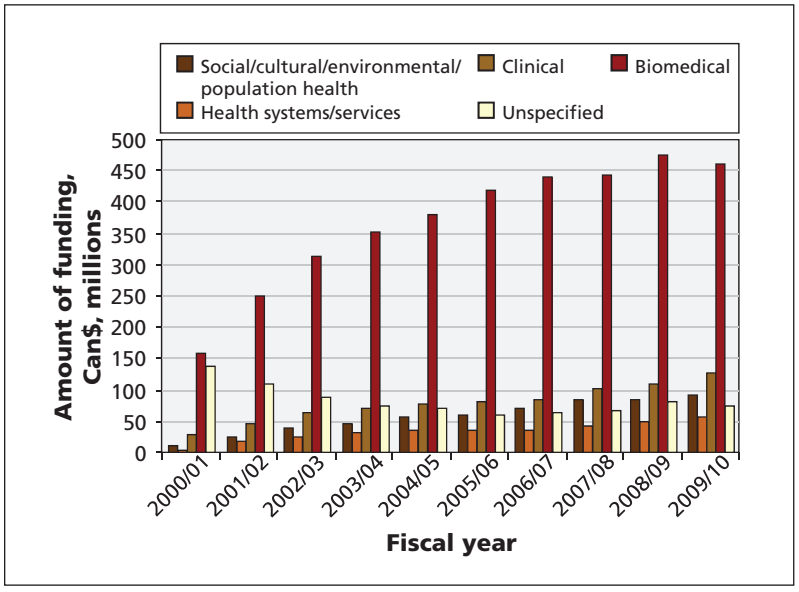

Figure 2: Types of research funded by the Canadian Institutes of Health Research, 2000/01 to 2009/10.[29]

Two problems are obvious in terms of the funding of independent clinical research in Canada. First, the overall levels of funding for health research are substantially lower in Canada than in the US and the UK. Second, the proportion of funding allocated to clinical trials is also substantially lower in Canada than in the US and the UK. This latter problem arises because all forms of applied research (including clinical trials) are undervalued in Canada and in the traditional thinking of many research organizations and committees awarding prizes. This issue was discussed in a report of the Cooksey committee[30] for the UK government, which lead to a substantial realignment of funding in the UK. By 2011, about one half of government funding for health research was allocated to basic biomedical sciences and one half to the applied sciences. (In the US, in 2005/06, 55% of funding from the National Institutes of Health was targeted at basic biomedical research, and 45% at applied research.)

The Cooksey report also emphasized that hypotheses that lead to improvements in health have come from a range of sources (basic biomedical studies, clinical observations from cases, large epidemiological studies and previous clinical trials). In fact, a prospective study of 100 major findings that were considered to be promising for human health and published in leading journals such as *Cell*, *Science* and *Nature* (and therefore deemed rigorous and important) translated to human use only five times (5%), with only one (1%) leading to an important health impact.[31]

The aforementioned points provide a key perspective on the evolution of the CIHR since its creation in the year 2000. The transformed, inclusive and broadened vision and mandate replaced the predominant focus on basic biomedical research held by the Medical Research Council of Canada. The new vision recognized the importance of the substantial enhancement of support for applied and implementation sciences as a more direct path to improving the health of Canadians and having a favourable impact on the economy. Sadly, 10 years after the creation of the CIHR, the relative proportion of funds allocated to basic biomedical research remains much greater than that of the other three pillars combined (Figure 2).[29] This contrasts sharply with the transformation in the allocation of research funding that has happened during the same period in the US and the UK.

Overall CIHR funding has grown 2.5-fold since its inception, whereas funding for RCTs has

grown only 1.3-fold. During this period, the number of grants funded in the open grants competition increased 1.6-fold overall. The increases in the categories of basic biomedical research (2.9-fold), clinical research (4.6-fold), health systems research (9.8-fold) and population health research (11.1-fold) (the latter three categories starting from very low baseline levels of funding) were substantially higher than the number of grants for RCTs, which increased by only 1.3-fold.

In the final five years of the Medical Research Council's existence, 40% of grants ranked in the top 25th percentile of the overall open grants competition were funded; 21.3% of grants ranked in the top 25th percentile of the clinical trials competition were funded. Since the inception of the CIHR, the rates of funding of grants in the top 25th percentile in the overall grants competition has fallen to 28.5%, compared with 23.9% for RCTs. This gap has narrowed over the last few years because the overall funding rates in the open grants competition has declined, while the funding rates of the clinical trials committee have been steady (but lower). Recently, the CIHR has allowed grants for clinical trials with smaller budgets to be reviewed through other panels.

In 2009/10, about 33% of the CIHR's budget was allocated to strategic initiatives (~100–150 requests for applications [RFAs]); none of them, as far as we are aware, specifically targeted clinical trials.[27] In fact, a very large proportion of RFAs explicitly disallowed applications from clinical trials, even when RCTs would have been an appropriate method to address some of the questions considered. For example, the 2007 RFA for the Clinical Research Initiative explicitly excluded proposing specific RCTs, although specific projects could be proposed by applicants in other areas.

There is substantial underfunding of personal awards for scientists in clinical research, and particularly clinical trials. Between 2004/05 to 2009/10, there was an increase of 245 awards for scientists with doctorates (PhDs), which were overwhelmingly directed toward basic biomedical scientists, whereas there was an increase of only 8 awards for health professionals.[23] Although the clinical earnings of colleagues may subsidize the research activities of some clinician–researchers through department or faculty practice plans, a high proportion of clinician–researchers receive little or no base salary support. When they receive an operating grant from the CIHR to compensate for the unpaid time devoted to research, they must generate clinical "billings" on weekends or during the evening, which is suboptimal for pursuing an academic career. Consequently, many bright young people involved in clinical research may consider options such as leaving Canada, shifting their focus to industry-funded trials or, worse, abandoning clinical research entirely.

Additional barriers to independent clinical trials in Canada

Even after a study has been funded, there are numerous administrative requirements before a large multicentre RCT can begin.[32] These include: obtaining separate approvals from research ethics boards at each participating institution for the same study; completing a detailed contract with each institution; obtaining regulatory approvals in each country; arranging for study materials and drugs to be imported; and arranging for each site and participating investigator to be indemnified and insured. We estimate that once funding has been received for a multicentre trial involving 100 sites in 10 countries, a few thousand hours of effort on the part of the principal investigators and several times this effort from other team members are required over a period of 18–24 months to successfully navigate more than 500 administrative steps.[33] This complexity and restrictive regulatory requirements, coupled with the difficulties in obtaining funds for independent studies, dissuade many clinicians from embarking on a career involving RCTs.

It should be noted that this increase in the number of bureaucratic hurdles is a recent worldwide phenomenon, but Canada (unlike some other countries) has not yet taken steps to reduce the bureaucracy. In the UK, the National Institute of Health Research dedicates efforts and a specific portion of its budget to "bureaucracy busting."[34] Although many bureaucratic challenges are also faced by industry, it usually has sufficient resources and expert manpower directed at overcoming these barriers;[35] this is simply not the case in academic studies.

In Appendix 1, we describe potential solutions and steps to facilitate the performance of independent clinical trials in Canada (Box 1). These steps are aimed at increasing funding at three levels and introducing a wide range of initiatives to facilitate the performance of these trials. Developing, enhancing and sustaining Canada's capacity to conduct world-class clinical studies will enable Canada to make important contributions that will improve health.

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