

# Trials and tribulations

As a declining share of global clinical trials threatens the future of health research in Canada, a national collaborative effort is underway to reverse the slide

By Joe McAllister



Canada's health researchers are acknowledged to be among the best in the world. Yet Canada is losing the global race for investments in clinical trials. The implications could not be more serious for the future of health research in this country.

"It doesn't matter how much science we do and how beautiful that science is. If we don't have an operating research machine that can make it work efficiently, cost-effectively and with high quality, then the beautiful science will never happen. Our operating machine is broken and there need to be more resources to make that machine well-oiled," says Karen Arts.

Arts is director of business development, clinical trials, for the Ontario Institute for Cancer Research (OICR), and was one of about 125 concerned representatives of academia, healthcare, government and industry who attended the Clinical Trials Summit in Ottawa in the fall of 2011.

The meeting was organized by the Association of Canadian Academic Healthcare Organizations (ACAHO), which represents the country's research hospitals, academic regional health authorities and their research institutes, where a large proportion of clinical trials are conducted; the Canadian Institute of Health Research (CIHR), the federal government's funding agency; and Canada's Research-Based Pharmaceutical Companies (Rx&D), the industry association for brand-name pharmaceutical firms operating in this country.

Worried that Canada is losing clinical trials at an alarming rate to other countries that are promoting their strengths more effectively, the three organizations sponsored the summit with a view to developing a national approach to reverse the trend.

The outcome of the meeting was an extensive document, *To Your Health & Prosperity ... An Action Plan to Help Attract More Clinical Trials to Canada*, which recommended nine steps that should be taken to make this country more attractive internationally as a location for clinical trials (see sidebar, page 16). A report on progress towards implementing the action plan is expected to be published by the time this article appears in print.

## Why are clinical trials important?

The loss of clinical trials matters, for reasons that were outlined by Dr. David Hill, integrated vice-president of research at London Health Sciences Centre and St. Joseph's Health Care in London, Ont., when he appeared on behalf of ACAHO before the Senate Standing Committee on Social Affairs, Science and Technology in May 2012.

"Clinical trials are a practical example of how academic healthcare organizations help to achieve human, social and economic benefits," said Dr. Hill. "Clinical trials enable us to provide leading-edge care to patients and families, and in so doing attract leading clinicians who want to explore the full possibility of their professions. Studies have shown that organizations that participate in clinical trials also have better patient care outcomes. At the same time, they also allow us to generate

products, services, jobs and revenues." ACAHO estimates that in 2008-'09, new clinical trial contracts with its member organizations had a potential value of \$340 million, he added.

Given all that, the news presented at the summit wasn't good.

Pharmaceutical trials account for the largest and most valuable share of all clinical trials, and Normand LaBerge, then vice-president of regulatory and scientific affairs for Rx&D and now executive director of the Quebec Medical Association (QMA), told the meeting that Canada's share of pharma-sponsored trial sites had dropped from 5% of the global total in 2005 to 4% in 2010.

As well, the number of Canadian sites participating in clinical trials had declined by 16%, researchers had enrolled fewer Canadians in those trials, and the cost of recruiting patients was among the highest in the world at over \$17,000 per patient.

Worse, the Patent Medicine Prices Review Board (PMPRB) report for 2011, released in June 2012, showed pharmaceutical research and development spending had fallen by 15.8% from the previous year, to \$991.7 million. That was on sales of \$17.8 billion by drug patent holders, an increase of 4.7% from 2010.

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Rx&D members, representing 75% of total patented drug sales, did slightly better on the research front, with a 9.9% decline in R&D expenditures.

A federal agency, the PMPRB tracks R&D spending by drug patentees. It was established as part of a 1986 act of Parliament that lengthened patent protection on pharmaceuticals. In return, the pharma industry, most notably Rx&D members, promised to spend at least 10% of sales on R&D in Canada. But while that target was met for a few years in the mid-'90s, there has been a steady erosion since then. In 2011, all patentees spent 5.6% of sales in 2011, while Rx&D members spent 6.7%.

Any way you cut it, the pharmaceutical industry isn't spending as it used to on research in Canada. And now, as part of free-trade talks with Europe, the federal government is considering an extension of patent protection for pharmaceuticals, a move that's vigorously opposed by generic drug companies.

"No proven link exists between increased intellectual property protection and increased Canadian R&D investments by brand-name pharmaceutical companies," said Jim Keon, president of the Canadian Generic Pharmaceutical Association, following the release of the PMPRB report for 2011. "In Canada, market monopolies for brand-name drug companies have increased eight times since 1987, yet investments continue to

decline, with R&D spending in Canada by brand-name drug companies at its lowest level since 1988.”

## Why is this happening?

Dr. Shurjeel Choudhri is a respected microbiologist with extensive global experience and a former member of the Canadian HIV Clinical Trials Network. In 1999 he joined Bayer Canada, where he’s now senior vice-president and head of medical and scientific affairs.

“We want to do research in Canada,” says Dr. Choudhri. “It’s in our interest, but the challenge is we have competition in other parts of the world for those clinical trials.”

He says about 40 to 50 clinical trials, or arms of global clinical trials, are sponsored by Bayer each year in Canada. His job, and others at Bayer, depend on his ability to persuade the company’s global headquarters in Germany to continue bringing trials to Canada, rather than the many other countries where they’re conducted, often at a much lower cost.

Both Dr. Choudhri and Arts believe that Canada can compete in the global research market with better organization and the quality of our scientists, even if we can’t match the low cost of developing countries.

One factor that discourages investments in Canada is the complexity of the business and regulatory environment. Each province is responsible for healthcare, and in some cases there are distinct differences in ethical requirements and privacy laws.

## ACTION PLAN FOR CLINICAL TRIALS

The Clinical Trials Summit of 2011 concluded that by improving cost, quality, speed and relationships with companies and institutions performing global clinical trials, Canada could garner more investments. A follow-up report expected to be released in December 2012 will review progress made towards meeting the nine-point action plan that came out of the summit:

1. Establish a national implementation office and resources. Ideally, this would be aligned with the CIHR Strategy for Patient-Oriented Research. Summit participants felt that without national co-ordination, any other initiatives would fail.
2. Establish a set of metrics to measure, monitor, manage and market clinical trial performance.
3. Integrate health system and research infrastructure.
4. Improve efficiencies of ethics reviews and advance strategic issues.
5. Develop a database of patient registries and consider a national recruitment strategy.
6. Adopt common standard operating procedures, training and certification.
7. Improve and use the common clinical trials contract.
8. Optimize intellectual property protection policy and scientific research and experimental development tax credits.
9. Go out and promote Canada’s research expertise. This recommendation suggests a “concierge (storefront) service for investors.”

Further details are available at [www.acao.org](http://www.acao.org)



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“Unless we make an effort to co-ordinate across multiple jurisdictions, domains and provinces, what we may look like to pharmaceutical, device and vaccine companies is multiple smaller markets,” says Tina Saryeddine, assistant vice-president, research and policy, at ACAHO. For global companies and researchers, she says, “We have multiple forms, multiple processes to, for example, get an ethics approval completed, a contract signed, understand diverse procedures, or find eligible and interested patients.”

Jonathan Fairest, president and CEO of Sanofi Canada, agrees: “The complexity of the bureaucracy lets Canada down.”

Fairest speaks as a newcomer to Canada with 20 years’ experience in the pharmaceutical industry in Europe. He’s impressed by what he has seen since his arrival earlier this year. “The level of expertise and professionalism in Canadian health research institutes is quite phenomenal. There’s some groundbreaking work going on here at a world-class level.”

But Canada needs to do a better job of marketing these strengths, he says, adding that bringing drug patent protection into parity with Europe “would make R&D companies look at Canada differently, as a less hostile environment.”

Dr. Anne-Véronique Juneau is clinical research director in Canada for global clinical trial operations for Merck. She attended the 2011 summit and agrees Canadians need to be more attuned to the needs of multinational trials. Her company has an international program that consults with researchers early in the process of designing clinical trials, before protocols are determined. She has used this program to get feedback from Canadian researchers so that when global trials are being determined, a Canadian perspective is taken into account.



“We need to engage clinical investigators into the design of the protocol. I think that’s crucial so that when the protocols are signed, they meet the Canadian reality,” Juneau says.

The paramount factor in attracting clinical trials is the speed with which they can be set up, run and accurately reported, and that depends mainly on how many patients can be recruited, and how quickly.

“In our business, time is money,” says Dr. Choudhri. “Every month you shave off completing a trial saves money, often exceeding the cost of recruiting.”

Finding enough patients who fit trial criteria can be difficult in Canada, he notes.

Recruiting is a problem Karen Arts knows well as she manages clinical trials for the OICR. “Con-

sidering that between 2% and 5% of patients go on trial, I think there’s room to grow there. I think that has something to do with public and patient awareness of clinical trials.”

Patients sometimes fear they’ll be treated like guinea pigs in a clinical trial, when in fact they’ll often have their health monitored more closely than regular patients. And ethical, privacy and patient rights laws make sure they get the best possible care during the course of a trial.

“We need to do a better job of educating the public that clinical trials are an option that’s open to them,” Arts says.

## A Team Canada approach

Normand LaBerge at the QMA was instrumental in having the association’s delegates put forward a resolution at the Canadian Medical Association meeting in Yellowknife this past summer, expressing concern about the state of clinical trials in Canada and their importance to delivering good healthcare. He says there was almost unanimous approval of the resolution.

But LaBerge worries that the usual federal-provincial rivalries, plus inter-institutional friction, will continue. “It should be all about Canada. It’s not about academia or government. We need a Team Canada. That step is the most difficult one, and one I don’t see.”

The Team Canada idea was also used by Robert McMaster, executive director of the Vancouver Coastal Research Institute, and Heather Harris-Harper, director of operations for the British Columbia Clinical Research Infrastructure Network, in a recent article that referred to the Olympic Own the Podium program: “If this is a winning formula for international business, we share a belief that Canada can use a similar approach for reclaiming its global position as one of the most attractive environments in the world for clinical trial research.”

When she arrived a decade ago at OICR, Arts quickly realized that researchers doing clinical trials — whether academic, knowledge-based research or drug trials — faced similar organizational problems across all medical specialties. She was involved in the development of what eventually became the Network of Networks, which has grown from eight to 54 organizations

## MAJOR RECOMMENDATIONS OF THE OGILVIE REPORT

On Nov. 1, 2012, the Senate Standing Committee on Social Affairs, Science and Technology, chaired by Senator Kelvin Ogilvie, published its report, *Canada’s Clinical Trial Infrastructure: A prescription for Improved Access to New Medicines*. Echoing much of the action plan from the Clinical Trials Summit, the recommendations include:

- **That the federal government assume a leadership role in facilitating and co-ordinating clinical trial infrastructure by:**
  - Establishing a national framework for co-ordinating clinical trials to provide a point of contact between industry and networks.
  - Convening a federal/provincial/territorial conference of health ministers to discuss initiatives to sharing best practices and reducing duplication of efforts.
  - Encouraging the inclusion of all relevant stakeholders in discussions and consultations.
- **That the federal minister of health:**
  - Require clinical trial registration to the greatest degree permitted.
  - Require that all foreign clinical trials that are used to support applications for market authorizations in Canada have met equivalent registration standards.
  - Ensure transparency of the clinical trial process and of the processes at Health Canada.
  - Establish an orphan drug status for specified rare conditions and assist in researching and approving orphan drugs.
- **That Health Canada:**
  - Immediately develop an accreditation program for research ethics boards and a national standard for research ethics boards.
  - Review intellectual property and tax incentives to “improve Canada’s global competitiveness in drug development.”
  - Improve transparency in reporting of clinical trials, increase monitoring and enforcement of clinical trials, with 2% of trials to be audited each year by the federal government and development of an electronic adverse drug reaction reporting system.

The full report can be found at [www.parl.gc.ca](http://www.parl.gc.ca)

spanning the health research community from universities, hospitals and governments to industry.

The Networks of Networks’ greatest accomplishment is in education and standardization of operating procedures. Too often, when a clinical trial is started in Canada, the lead researcher must train staff on procedures and ensure lab, clinical and administrative standards are met. Standardizing education and operating procedures across the country makes it easier to conduct research — a bonus both for multinational companies and for Canadian academic researchers doing preclinical research.

A CIHR committee is currently working on ethics review harmonization opportunities, including the feasibility of common application and consent forms, as recommended in the clinical trials summit action plan.

Maybe the furthest along in planning is a model clinical trial template agreement proposed by members of ACAHO and Rx&D, with funding support from CIHR. It was recently pilot-

tested across the country and will be improved based on feedback from users. If broadly accepted by companies, universities, hospitals, research institutes and governments, the template agreement could go into use within a year or two.

But whether the global research community, particularly pharma, will accept the draft contract is another question.

Margaret Kerr isn't so sure they will. She's a Toronto lawyer who specializes in clinical trial contracts.

"We used to see more local affiliates of the pharmaceutical companies doing research in Canada. Now they've moved to a model where trials are global and the fastest-recruiting countries get into the trials," she says. Faced with a template legal agreement, these companies "are much more likely to say, 'Here's our agreement,' and they'll fight you to the death if you want to make changes to it," she adds.

### A call for federal leadership

"If they can't come up with a standardized ethics review board, then there's something wrong," says Senator Kelvin Ogilvie. "My personal opinion is there's no reason they can't come together for standardization."

Ogilvie is chair of the Senate Standing Committee on Social Affairs, Science and Technology, which in November released an eagerly awaited report (see sidebar, page 17), whose recommendations closely mirror the action plan that came out of the clinical trials summit. It calls on the federal health minister to take a lead role in standardizing ethical reviews, contracts and professional accreditation for research facilities across Canada.

Sitting as a Conservative senator appointed by Prime Minister Harper in 2009, Ogilvie says there's an "obvious" role for Health Canada and CIHR to play in standardizing Canada's research. He doesn't share the view of many scientists and commentators that the Harper government is averse to science and research. "My own dealing with government has convinced me they clearly understand the importance of research."

He believes it would be a "win-win for both researchers and government" if the government acted on the report's call for a national framework for co-ordinating clinical trials. He was encouraged when, before the report was actually tabled in the Senate but after public hearings were completed, Health Minister Leona Aglukkaq acted on two of the report's recommendations, announcing a comprehensive, national list of registered clinical trials and a new approach to researching orphan drugs.

"I felt both announcements were positive," says Ogilvie, "and the minister very clearly indicated this is the beginning of an effort, a start of continuous development in this area."

Although there are questions about funding a national co-ordinating framework, Ogilvie doesn't think money should be a problem, even at a time when governments are fiscally constrained. "We were very careful in our report to try and structure recommendations that would operate within existing bodies. We're not talking about huge amounts of capital needed to move this forward."



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Ogilvie thinks it might be wise for Canada to recognize the changes in the global pharmaceutical market and tie any further patent protection to a promise to support Canadian commercialization of our research findings.

Kerr, ever the lawyer, has a warning about promises: "If you don't have ironclad agreements with people, there's no reason for them to do things they said they'd do. If a client says to me, 'He promised he'd do it, but I don't have a contract,' I say, 'Well that's too bad, there's the door.'"

Ken Hughes, who has taken over LaBerge's job as vice-president of scientific and regulatory affairs at Rx&D, thinks the way forward is through collaboration. "We have to work together to make Canada most attractive to incoming dollars. The best situation to attract those dollars is to have synergies between government, academic and private-sector groups. That's certainly the way it is going forward."

Ogilvie has first-hand experience of the difficulty faced by researchers in commercializing their findings. In the 1980s, he discovered ganciclovir, a drug now used worldwide to fight infections that occur when the immune system is weakened.

But as a chemist, not a medical doctor, he was given short shrift when he went looking for money to prove his findings. "My idea was considered so radical the National Research Council wouldn't support it. It was, in fact, a Canadian entrepreneur" who helped set up a small company, which was later sold after research proved the significance of Ogilvie's discovery.

"Ultimately, great science is going to pull in the dollars," says Hughes. "What we have to do is create infrastructure around that to make sure the global companies see Canada as a fertile ground to invest." **HRI**

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