Clinical trials: the balance between protecting participants and promoting drug and product development

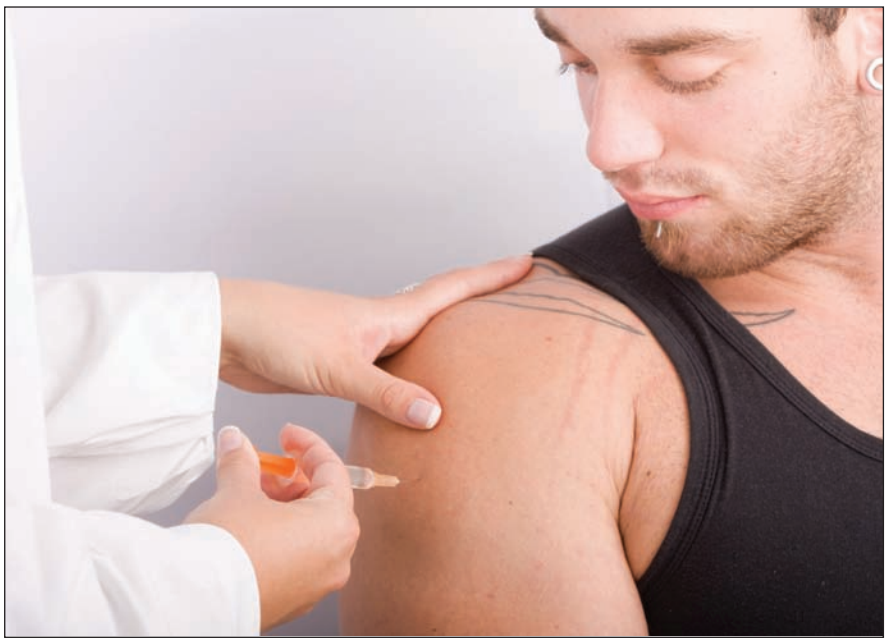
They have been called bureaucratic, cumbersome, a liability to the drug and research industries, and even harmful to patients. In fact, so maligned have research ethics boards been in Canada that they have spurred demands for the introduction of national accreditation centralized review for clinical drug trials involving multiple sites.

The purpose is straightforward — to protect human research subjects (as defined by granting council guidelines). Research ethics boards are groups of volunteers — doctors, lawyers, scientists, community members — that review clinical trial protocols to determine whether the risks of a study are "reasonable" and whether there's "undue" pressure on individuals to participate.

Because of the growth of clinical trials in Canada, research ethics boards seem to be proliferating across the nation. Busy teaching hospitals have created multiple boards to streamline and professionalize the process, as well as teams of research staff to support their work. Smaller hospitals, however, typically cannot afford such efficiencies.

Of late, though, research ethics boards have increasingly come under fire for delaying the process by which new drugs are tested for human use. Critics even say the system of boards and committees that now protects individuals who volunteer for scientific research actually harms more patients than it helps — by delaying novel projects that could lead to life-saving discoveries, and by clogging the system by approving studies that have already been done.

As Sir Iain Chalmers, a United Kingdom clinical trials expert, wrote in 2007, research ethics boards contribute to "the avoidable suffering and deaths of millions."



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Research ethics boards exist to protect patients in clinical trials, but some researchers claim they actually harm more patients than they help by delaying novel projects that could lead to life-saving discoveries.

Frustrated Canadian scientists often deride research ethics boards for their lack of scientific expertise and complain of waiting up to 2 years to win approvals for multisite clinical trials. Meanwhile, the pharmaceutical industry takes trials to other countries, in part to avoid delays in ethics review.

Review delays

There's little question that delays have become altogether common.

Dr. Laurie Morrison, a University of Toronto, Ontario, professor who runs resuscitation trials funded by the US National Institutes of Health and the Canadian Institutes of Health Research (CIHR), has become accustomed to waiting more than 18 months for sign-off from research ethics boards at the 40 or more hospitals involved in her trials.

"One of my studies never got off the ground because a European country could move faster," Morrison says. Another time she abandoned a trial after waiting nearly 2 years for approval from several hospitals, while watching from afar as a European group nearly completed its study. "That was just so painful."

To cut through the red tape, a Health Canada-sponsored group, the Experts Committee for Human Research Participant Protection in Canada, recently asked the federal government to create a new council to accredit research ethics boards that meet a set standard of performance.

Alberta, Quebec and Newfoundland and Labrador have gone further, mandating centralized ethics reviews for all human research. A recent draft of a revised version of the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* includes a new section recognizing the role of specialized or multi-institutional boards for collaborative research.

But researchers in most provinces still must approach each hospital separately for approval of a multisite project, respond separately to each research ethics board's questions, and provide each with ongoing reports about changes to a study and annual reports on its progress.

That's "a truly massive burden," says Dr. Merrick Zwarenstein, who runs international clinical trials at the Sunnybrook Health Sciences Centre in Toronto.

And it's expensive. For Morrison, the $125 000 per year she spends on staff to prepare applications to research ethics boards is the single biggest item in her research budget.

Balancing that is the need to properly protect research subjects — the raison d'être of ethics boards.

Dr. Julie Spence, an emergency physician who chairs the research ethics board at St. Michael's Hospital in Toronto, is accustomed to hearing scientists grumble about ethics reviews. The added costs associated with ethics review should be viewed as simply part of the cost of doing business as a researcher, especially when multiple hospitals are involved, she says, adding that doing science ethically requires an investment.

Dr. Greg Koski, a Boston-based clinical trials expert who led a US federal program for protecting human subjects in the 1990s, concurs.

Researchers could avoid delays if they did a better job designing, writing and documenting research proposals, Koski says, though he admits many doctors involved in research don't have the skills for that. "Clinical trials are not something you're trained to do in medical school — there's a whole realm of knowledge that needs to be mastered about what your responsibilities are."

Koski recommends that clinicians who do research receive extra training, which would eventually lead to better research ethics applications. But he acknowledges that ethics boards also need to become more efficient, more professional and less focused on "compliance for the sake of compliance per se."

Penny Brasher, a biostatistician at the University of British Columbia, is surprised by the number of studies that are "ill-conceived, poorly designed, poorly executed or analyzed suboptimally, or the analysis is simply wrong."

Such studies waste the time of their participants because the results aren't meaningful, she says.

But Brasher also notes that research ethics boards often approve mediocre proposals. She believes there are people who serve on research ethics boards who lack sufficient training and qualifications, charges supported by a US study (*Control Clin Trials* 2003;24:245-55).

The study, led by Dr. William Burman of the University of Colorado and the Tuberculosis Trials Consortium, found that the directives from local ethics boards (known as institutional review boards in the US) typically made the consent forms that volunteers must sign longer and less readable. Worse, the boards often asked researchers to make changes that introduced errors into consent forms.

> "REBs don't want to trust other REBs." — Raphael Saginur, chair of research ethics board, Ottawa Civic Hospital

An unpublished 2006 survey at the University of Toronto shows that Canadian scientists are also concerned about local ethics board processes. Investigators at the university's 13 affiliated hospitals who responded to a web-based survey led by Dr. Paula Rochon of Women's College Hospital and Dr. Valerie Sales of the University Health Network selected the need to reduce the turn-around time of approval of research protocols as the leading barrier to ethical best practice in research. In a section of the survey that asked for comments, the scientists wrote of "conflicting recommendations from different REBs at different hospitals" and "nit-picky details for consent forms that change from site to site."

The boards weigh down the process for informing and "consenting" research volunteers, according to several scientists and research coordinators who responded.

"Consent forms are now incomprehensible — simple studies of questionnaires or interviews that might be served with a 1-page simple consent are made long and inappropriate for patients," one researcher wrote. Another scientist noted that consent forms are "so long that patients are intimidated to read them."

Yet the research ethics board members, chairs and administrators who completed the survey had very different views, ranking the need to reduce the turn-around time as last in a long list of obstacles.

For the ethics board respondents, the barrier that topped the list was the need "to develop processes to inform investigators of new regulatory requirements."

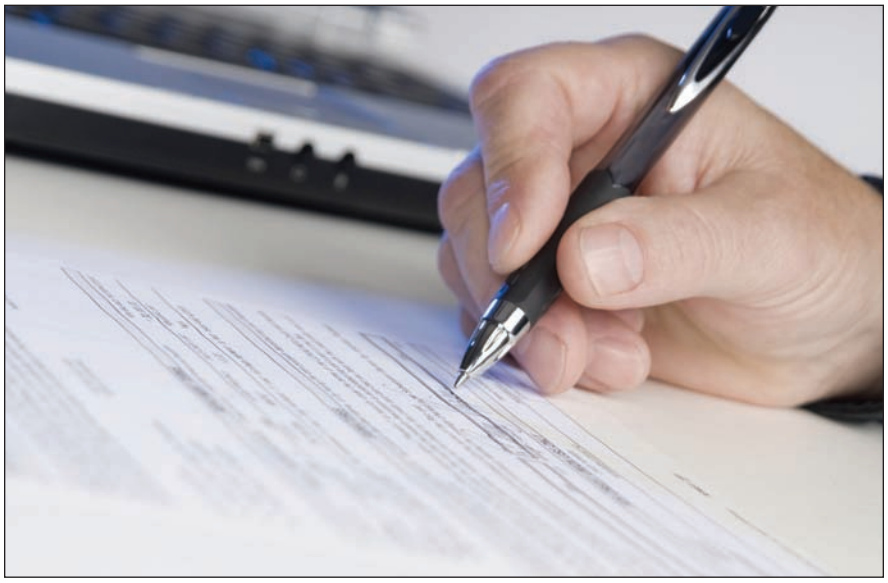
The different responses reflect an environment at teaching hospitals that's typified by scientists and board members sniping behind one another's backs.

Meanwhile, on both sides of the border, the upshot of the studies is a rather muddled picture about the quality of operations at research ethics boards.

National accreditation

As a consequence of complaints from scientists about research ethics boards, the Sponsors' Table for Human Research Participant Protection in Canada (a group consisting of 15 of the nation's leading research sponsors including CIHR and Canada's Research-Based Pharmaceutical Companies [Rx&D]) organized an expert committee to study the topic. Nearly 2 years later, in June 2008, the committee's report — *Moving Ahead* — was released. It proposed that a national accreditation panel be established, complete with teams doing on-site visits of boards and a rating system deeming whether a board was utilizing acceptable processes and procedures.

Simultaneously, the federal Canadian General Standards Board has been



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Some research scientists say that patient consent forms have become too long and confusing, intimidating patients.

working with Health Canada to spell out accreditation standards for research ethics board reviews of clinical trials. Draft standards are scheduled for public release this spring.

Meanwhile, the federal secretariat on research ethics has held consultations on revisions to the Tri-Council Policy Statement.

"There's no reason we couldn't accredit to a Canadian standard, and there's no reason we couldn't accredit to the Tri-Council Policy Statement," said Susan Zimmerman, executive director of the Interagency Secretariat on Research Ethics, at a January consultation session in Toronto.

Pharmaceutical companies are pushing for national process standards, believing they would be more productive than the current system of separate provincial initiatives, explains Russell Williams, president of Rx&D. Enforcing the national standards would probably fall to accreditation teams, yet it's not at all clear that the move toward national accreditation will survive.

A Government Consulting Services cost estimate of the experts committee proposal for an accrediting agency found it would require an outlay of $9 million to $10 million annually.

But the organizations that could theoretically fund it — a group called The Sponsors' Table, consisting of 15 of the nation's leading research sponsors, including Health Canada, CIHR and Rx&D — didn't support it, so a new agency is not in the works.

To Dr. Raphael Saginur, an infectious disease specialist who chairs the research ethics board at the Ottawa Civic Hospital in Ottawa, Ontario, a Canadian system for accrediting research ethics boards is nothing less than the Holy Grail.

Scientists need it "for international competitiveness," he says, "but we are not there yet."

At present, the only accreditation available to research ethics boards in Canada comes from a Washington, DC-based organization called the Association for the Accreditation of Human Research Protection Programs.

It has accredited only 1 Canadian board: the one run by ethica Clinical Research Inc., a Montréal, Quebec-based contract research organization. President Janice Parente believes the accreditation has made her company's ethics board more accountable and raised its profile among companies that sponsor trials.

But the American process is costly. At a major research centre with a research ethics board overseeing several thousand studies, the fee just to start the process with the US association can be more than US$70 000, followed by annual fees to maintain accreditation.

Centralized review

An easier and more effective route may be the sort of centralized system of ethics review now available in nearly every European country, including the United Kingdom, as a result of requirements imposed by the European Union Clinical Trials Directive.

For example, the European team that completed its study of prehospital care before Toronto's Morrison could get hers approved benefited from centralized review by designated central committees adhering to national standards.

The basic model is a single board making the major decisions about a study, with local boards considering local issues specific to their institution, with both levels responding quickly. In the UK, where centralized review began in 1997, local hospitals are prohibited from changing a research protocol once the central approval body, the National Research Ethics Service, gives the green light.

Similarly, in France, scientists submit their protocols to the "competent" regional ethics committee, which then has 35 days to give an answer that is valid for all sites in the country. In Italy and Switzerland, the investigator coordinating a multisite trial submits the protocol to his or her institution; other sites may accept or reject the central decision but cannot request changes apart from minor local issues. For example, a Catholic hospital may need to tweak a trial designed for a secular institution.

Although most researchers in Canada can't take a central route, Alberta's centralized review process has been *de rigueur* since 1998 for doctors doing research in community hospitals. These researchers are obliged to use a central board set up for them by the province's College of Physicians and Surgeons. University-affiliated hospitals use their university research ethics boards.

Last April, Quebec rolled out a new centralized process for all multihospital projects. Quebec's process, which applies only to projects with 5 or more sites, is similar to the European model in that once the central board — the so-called "board of record" — gives a study

the nod, boards at other sites are obliged to focus solely on local considerations.

Some scientists are pleased. Dr. Louise Pilote, head of General Internal Medicine at McGill University in Montréal, found that in a trial with 8 sites, the centralized process cut the approval time to about 2 months, while under the old system "with the back and forth and the delays, it would have taken at least 6 months if not more."

It was "a quantum leap in the right direction," Pilote says.

In Ontario, however, the indications are that hospital leaders may be more comfortable with a system that has historically vested local boards with control.

As in Ontario, no US hospital is required to share authority with other boards. A survey of US boards, led by Burman and Dr. Carol Dukes Hamilton of the Duke University Clinical Research Institute, reveals why many are reluctant to relinquish control.

Among 63 review board chairs and administrators who responded, about a third "had used central review and were generally happy with that experience," says Burman.

Why not cooperate?

But many boards had specific policies against giving another institutional review board the right to rule on a study in their institution. The main reasons for not seeking central or cooperative review were: a hospital's potential legal liability if subjects were harmed, the possibility of low-quality review, and an external board's lack of knowledge about the local population. Local review, wrote one survey respondent, "provides better insight while promoting accountability."

Burman and Hamilton did the survey after encouraging their collaborators in the US–Canadian TB Trials Consortium to use a central review board based at the US Centers for Disease Control in Atlanta, Georgia.

As an investigator, Burman has found the central process decreases his team's workload by about 80%–90%, but after 6 years, the majority of the consortium sites have yet to sign on. Says Hamilton, "each IRB [institutional review board] feels like, 'Gosh, could we possibly let somebody else have this authority?'"

Boards in Ontario struggle with the same issues.

Saginur puts it bluntly: "We don't want to trust others."

However, Lorraine Ferris, associate vice-provost at the University of Toronto, believes distrust won't block the development of central boards in Canada.

Under the revised version of the Tri-Council Policy Statement, Ferris explains, it's not up to a hospital's ethics board to make the call about using a central board; it's up to the institution. In Ferris's view, that means hospital chief executive officers will have to get involved.

Cancer board

There is a central board in Ontario for reviewing cancer trials, modelled on the central board at the US National Cancer Institute that reviews trials for about 500 local boards. The Ontario Cancer Research Ethics Board was established 5 years ago by the Ontario Institute for Cancer Research and now reviews multicentre cancer trials for 17 Ontario hospitals.

It has been criticized by Trudo Lemmens and colleagues at the University of Toronto law school for promoting itself and advertising Ontario as a good place for drug research. It's also missing a few of Ontario's leading cancer centres, but represents the sort of limited cooperation that Ontario hospitals can live with, says Saginur, who was involved in its development.

Compounding the problem is that not everyone agrees that central ethics review is ideal. That's true even in the UK. Researchers from the University of Birmingham complained that the UK "has slipped from one of the most attractive to one of the least attractive places to do clinical trials" due to increasing bureaucracy and lack of harmony among several regulatory bodies including the Medicines and Health Care Products Regulatory Agency and the National Institute of Health Research (*BMJ* 2008;337:1085-7).

But the British system offers standardized forms, a central approval site and, since last year, online capability for submissions and reviews.

It's a model that's being emulated by the US Veterans Administration and National Institutes of Health, with both agencies now encouraging scientists to use available cooperative or central ethics review mechanisms.

Back in Toronto, Morrison's study team is initiating a clinical trial with 200 sites by travelling to individual hospitals across Ontario to ensure every research ethics board application is properly signed and delivered.

She calls the process "a total nightmare."

It's further evidence that, despite the many groups engaged in the debate around how to improve research ethics boards, it may be some time before research ethics in Canada enters the digital age.

"What's needed to resolve such problems and deficiencies, says Saginur, is leadership at a national level, someone who'll stand up and say, 'We're going to do things better.'" — Miriam Shuchman MD, Toronto, Ont.

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Dr. Shuchman chairs the research ethics board at Women's College Hospital, which is part of the system of University of Toronto teaching hospitals in Toronto, Ontario. *CMAJ* Editor-in-Chief Dr. Paul Hébert was recused from review of this article due to his involvement with the Canadian Institutes of Health Research initiative to revise ethics review board operations across the nation.

This article is part of a series on clinical trials that the *CMAJ* News section will run throughout 2009. Previous articles included an overview of the landscape of trials in Canada (*CMAJ* 2009;180[1]:20-2), a short history of trials (*CMAJ* 2009;180[1]:23-4) and articles on the rising costs of trials (*CMAJ* 2009;180[3]:277-8), drug development costs (*CMAJ* 2009;180[3]:279-80), recruiting patients (*CMAJ* 2009;180[4]:375-8) and recruiting doctors (*CMAJ* 2008;180[5]:500-2). Future articles will explore registration, patient safety, reporting and the push for reforms.