

Clinical trials: chasing recruits

“Are you a healthy, nonsmoking MALE OR FEMALE 18–55 YEARS OF AGE. free of daily medications? If so, you may be eligible for our upcoming clinical research studies. ... Compensation may range from \$1000 to \$1500 depending on the length of the study.”—Metronews.ca (Toronto) Dec. 8, 2008.

In Canada’s largest cities, the back pages of free news tabloids carry advertisements designed to entice “healthy volunteers” to participate in phase 1 clinical trials, in which drugs are tested on humans for the first time. The appeal is straightforward: money. The ads are targeted at people who need it, rarely appearing in more “upscale” publications.

The tabloid advertisements for participants are the most visible public face of the increasingly commercial clinical trial business in this country. While financial payments are the norm for phase 1 trials, they aren’t made to participants in more advanced phase 2 and 3 trials, which are primarily conducted on people who have the disease or condition that the drug seeks to treat.

These patients have typically exhausted treatment options, so they’re generally motivated to participate in a trial either to gain access to a new medication or, ultimately, to help others who will be afflicted with the disease in the future. They’re generally compensated for such expenses as parking, meals or travel.

Phase 2 and 3 trials require more research participants and are highly sought by governments, researchers, doctors and some patient advocacy groups because they typically yield new investments and jobs, as well as access to new medications.

Canadian patients, obviously essential to these trials, are in demand. But there are persistent, major concerns about the interests and safety of Canadian research participants — concerns

exacerbated by Canadians’ lack of information about numbers, recruitment practices and problems involved in conducting clinical trials. The piecemeal nature of the way research participants are protected is an abiding issue for ethicists, policymakers and legislators.

Changing nature of research

The pharmaceutical industry finances about 80% of clinical trials in Canada (*Int J Health Serv* 2008;38[3]:525-42), with the majority of those trials now taking place in the community, rather than academic medical centres. Sponsors, specialized private firms and site management organizations manage the trials.

The agencies that award research grants in Canada have long recognized the potential conflict of interest that arises when trial participants are paid, or when doctors are paid to recruit patients. The profit motive can conflict with “participant protection and the scientific validity of clinical trials,” states the *Draft 2nd edition of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (www.pre.ethics.gc.ca).

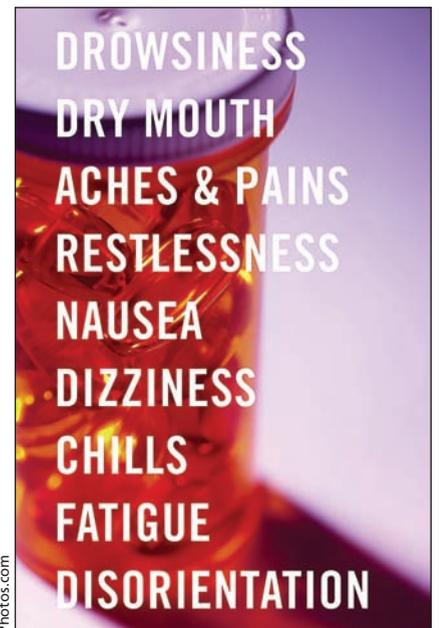
The document, which updates the 1998 policy, also expands its discussion of conflict-of-interest issues (page 379). It makes clear that institutions, not just individual researchers, can be compromised. It also stipulates that institutions must make sure that real, potential or perceived conflicts do not compromise the research, and suggests they establish central conflict-of-interest committees to identify and manage conflicts.

The statement’s chapter on clinical trials leaves considerable latitude in interpreting its provisions. While it prohibits finders’ fees offered to those recruiting patients for trials, it allows for “reasonable” payments from sponsors to researchers.

It further warns that payments associated with phase 4 postapproval marketing trials “may compromise physicians’ professional integrity by skewing pre-

scription practices and encouraging finders’ fees.” And it advises research ethics boards to scrutinize trial budgets to ensure that no inappropriate payments are made, such as bonus fees or incentives to recruit quickly. But the strictures are a “general guide,” rather than an outright prohibition.

The statement constitutes definitive Canadian policy regarding research ethics within the nation’s universities, according to a 2008 report by the Experts Committee for Human Research Participant Protection in Canada. The committee was established by the Sponsor’s Table, a group of organizations including the 3 granting councils — the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada and the Social Sciences and Humanities Research Council of Canada — that make up the Tri-Council, as well as Health Canada, Canada’s Research-Based Pharmaceutical Companies (Rx&D), the Royal College of



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Concerns have been raised that Canadians aren’t adequately informed about the number of adverse events associated with clinical trials.

Physicians and Surgeons of Canada, and the Canadian Association of Research Ethics Boards.

Similar concerns about conflict of interest and dubious recruitment practices have been raised south of the border. A report by the US Office of the Inspector General states that “disturbing recruitment practices” have developed because of the increasingly commercial, competitive research environment. According to *Recruiting Human Subjects: Pressures in Industry-Sponsored Clinical Trials* (2003), these practices include:

- misrepresentation of the true nature of the research
- patients being influenced to participate because of trust in their doctors
- recruitment of ineligible participants because of pressures to enrol and
- breaches of confidentiality when third parties search medical records.

No similar report has been written on patient recruitment practices in Canada, where most Canadian research institutions “have a far better idea of what happens to research funds than what happens to research subjects,” according to the Law Commission of Canada in a 365-page report, *The Governance of Health Research Involving Human Subjects*, released in 2000.

Little has changed since. The pharmaceutical industry spent at least \$1 billion on clinical trials in Canada last year, according to submissions that brand-name pharmaceutical companies

made to the Patented Medicine Prices Review Board, as well as estimates by the Canadian Generic Pharmaceutical Association on member outlays for phase I trials, which are required to obtain market approval from Health Canada. (The \$1 billion estimate does not include spending on phase 4 trials, which involve drugs that have already received market authorization.)

What we don't know about research participants

No one knows how many Canadians take part in clinical trials. Observers estimate the annual number to be in the hundreds of thousands, perhaps even as many as a million. But no government body tracks — or will release — those numbers. Although Health Canada oversees the vast majority of clinical trials in Canada, the department told *CMAJ* it does not have the mandate to require sponsors to report the number of enrolled participants. Although some sponsors submit this information, Health Canada says the data are not captured in its tracking system. “Nor can it be easily retrieved.”

Academic experts aren't amused.

“What I find to be one of the most challenging issues is the lack of coherent information,” says Trudo Lemmens, a University of Toronto law professor who has written extensively about clinical trials.

The potential for patients to be co-

erced into phase 2 or 3 trials, or to be subject to undue influence, is recognized in clinical trial policies and regulations, he notes.

Regulatory reporting obligations concerning adverse events also implicitly recognize the inherent risk in participation, Lemmens adds. “But we have no clear information about how many people are involved ... or how many people are harmed. There is no transparency.”

In 2008, Health Canada received 21 580 reports of adverse events related to clinical trials, both international and domestic. About 10%, or 2158 reports, concerned clinical trials in Canada.

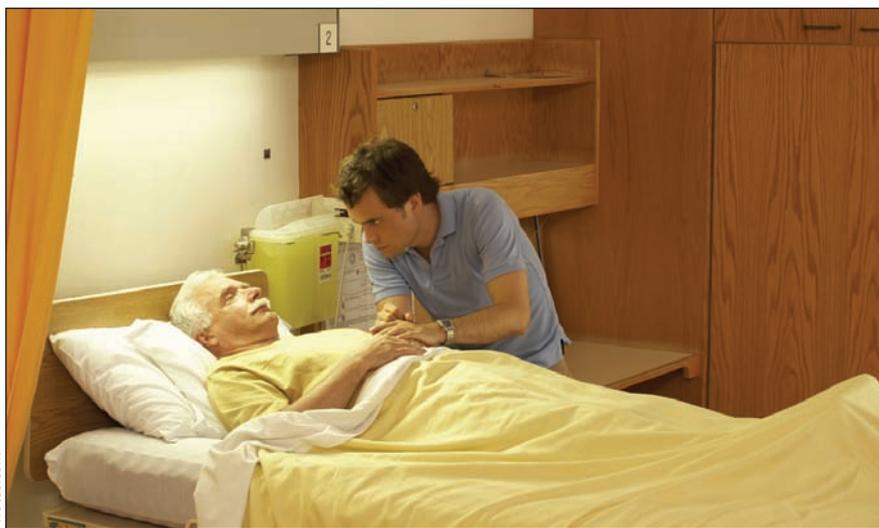
But reports about serious adverse events, which clinical trial managers must submit to researchers, ethics boards and institutions, often “lack context, informed analysis or explanation of their significance to the safety of participants,” states the recent Tri-Council ethics policy.

As a consequence, there is “no way of knowing how well research participants in Canada are protected,” Dorothy Pringle, former dean of nursing and professor emerita at the University of Toronto, recently concluded (*Can J Nurs Leader* 2008;21[4]:1-5).

It raises questions about whether patients, while being wooed to participate in trials, are being provided with an accurate sense of the risks, or the frequency of adverse events in Canada.

As it stands, they are now primarily reliant on media coverage.

Some tragedies have become public, thanks to the US Food and Drug Administration (FDA) or a measure of investigative reporting. For example, in 2002, a 4-year-old boy who was participating in a clinical trial at the Children's Hospital of Eastern Ontario in Ottawa, Ontario, died after he was administered a powerful drug at a dose “22 to 25 times higher” than what was specified in the protocol. His death became public because of an FDA inspection, the results of which were posted on the agency's website. (The FDA was involved because the US National Cancer Institute financed the trial.) Meanwhile, it was Bloomberg News, a US wire service, that broke a story about trial participants who contracted latent tuber-



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The potential for patients to be coerced into participating in trials or be subject to undue influence is considerable, some experts say.

Box 1: Further information about participation in clinical research

- Should I enter a Trial? *ECRI guidelines*: www.ecri.org/patients/references/Pages/Clinical_Trials_Patient_Reference
- The Alliance for Human Research Protection: www.ahrp.org/cms/content/view/18/87/
- Citizens for Responsible Care and Research: www.circare.org
- U.S. National Cancer Institute guide to clinical trials: www.cancer.gov/clinicaltrials/learning

culosis from other participants after a firm running a trial of an immunosuppressant drug failed to screen participants for tuberculosis at a phase 1 site in Montréal, Quebec, in 2005 (www.irforum.org/forum/read/2/111/111Vt).

Health Canada's response to the Montréal trial has been less than transparent. Years later, the department still has not released any information about what, if any, penalties it levied against the research organization contracted to organize the trial.

By contrast, the FDA has proved far more willing to act with alacrity or intervene during a trial. In December 2008, for example, it shut down all new enrolments in clinical trials at a veterans' hospital in Seattle — not because of harm done to patients, but because of deficiencies in documenting patient safeguards.

A "patchwork" of guidelines

Protection of research participants in Canada has been the source of controversy for years, in part because there is no single ethics policy or regulatory framework that governs all domestic clinical trials. The Tri-Council Policy Statement, for example, applies only to research conducted at institutes funded by the 3 granting councils, or research funded by other organizations that voluntarily adopt the policy. The International Council on Harmonization Guidance E6: Good Clinical Practices, and Health Canada's clinical trial regulations govern research conducted in other settings. Several provinces have also developed their own research ethics standards and policies.

This "complex patchwork" of regulations and guidelines govern, in an uneven and fragmented fashion, Canada's "non-system" for protecting Canadians who enter clinical trials, says the Experts' Committee report, *Moving*

Ahead (www.hrppc-pphrc.ca/english/movingaheadfinalreport2008.pdf).

The system in Canada is based "on the good faith of the actors," says Martin Letendre, director of ethics and legal affairs for ethica Clinical Research Inc., a Canadian-based contract research organization.

By contrast, the FDA has far greater powers of enforcement than Health Canada, says Letendre, whose company manages trials in the US and Canada, and is accredited by the US Association for the Accreditation of Human Research Protection Programs. No similar accreditation program exists in Canada.

"There are a lot of bodies involved" in oversight in Canada, agrees Dr. Jeff Blackmer, executive director of the Canadian Medical Association's Office of Ethics. "But no one body that is saying: 'This is our responsibility, and we will both oversee the process and fund the process'."

Paying for harm

Still, patients are constantly being urged to participate in trials, at least in part because Canada is actively promoting the development of a clinical trials industry (Box 1).

Trials, after all, yield economic benefits and employ highly trained Canadians, so governments are keen to attract them. In an online document aimed at attracting clinical trials, Ontario promotes itself as "Expert Efficient Effective," boasting that it has "everything in place to get clinical trials up-and-running successfully." That includes generous research and development tax advantages for companies that will locate in the province to conduct trials.

Ontario even states that its public health care system can help "offset the fees" for diagnostic and therapeutic interventions, such as blood chemistry

and magnetic resonance imaging scans required during clinical trials.

But if patients are harmed in trials, there is a risk that the treatment costs will be off-loaded to that same public health care system, which raises "very serious issues," the Law Commission report warned.

Toronto lawyer Margaret Kerr, who works on contracts for clinical trials, says she is not aware of any government or hospital directive ensuring that such costs are not off-loaded. "Trial sponsors, in addition to expecting that public health insurance will cover the cost of medical care that may be needed as a result of clinical trial participation, sometimes push for the contract to require that research participants' private health insurance picks up the tab for any needed medical care before the sponsor itself will have to contribute to the cost," she wrote in an email to *CMAJ*.

By contrast, the European Union's Clinical Trial Directive stipulates that trials cannot commence unless provision has been made for insurance to cover the liability of the investigator and the sponsor. Many other countries also require the sponsors of clinical trials to put specific obligations in place with respect to health insurance for participants, says Lemmens. Countries interpret the directive differently — some require additional insurance to cover injuries and potential disability resulting from trial participation; some offer coverage through the public system — but Canada has no clear requirement, he adds.

Apotex, Canada's largest generic drug manufacturer, runs about 80 phase 1 trials in Canada each year at its own testing facilities, and another 50 or 60 at contract research organizations. Dr. Jeremy Desai, executive vice president of research and development, says his company provides any necessary follow-up care if a patient suffers harm while involved in a clinical trial.

"If anyone does develop some adverse event after one of our trials, a physician would be assigned to make sure the right follow up and process is used," he says. Asked if there is any off-loading to the public health care system, Desai says: "Not at all. Our physicians would follow up each case."

The company, which primarily con-



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The demand for participants in clinical trials continues to escalate. There are now websites exclusively devoted to recruiting trial participants and websites devoted to informing people about opportunities to earn extra cash by participating in studies. Included is PaidClinicalTrials.org, a public-service database outlining all trials reported to the US National Library of Medicine, US Department of Health & Human Services and the US National Institutes of Health Services.

ducts “bioequivalence” phase 1 trials to test generic versions of already patented pharmaceuticals, often is simultaneously seeking market approval in many countries. So it operates in a “highly regulated environment” subject to inspections and oversight by the FDA, Health Canada and the European Medicines Agency, Desai adds.

With such internal industry pressure to conduct more clinical trials and ensure profit margins, payments to participants have become more and more common, as firms are constantly hunting for research participants.

And in phase 2 and 3 trials, patients themselves are often eager to participate, in hopes that a new drug can provide a cure for their conditions.

As Jack Corman, president of IRB Services, a private research ethics board that companies can pay to use instead of an institutional REB, notes, phase 1 trials have become “a societal necessity ... a necessary evil.”

Moreover, he adds, payment is altogether appropriate when a normal healthy volunteer is “asked to ingest an ingredient never tested in man” while confined in a college-dorm-like setting for much of a trial.

Clinical trials are also a necessary evil for many patients, particularly those with life-threatening illnesses

grasping at any possibility of relief. They want access to trials of promising new medications, so some patient advocacy groups promote trials.

Research participant activism

In the past, some patient groups and healthy volunteers have used their collective strength to try to improve conditions for participants. In 1988, Canadian AIDS activist Chuck Grochmal declared that unless AIDS patients were given access to new experimental drugs through compassionate programs, they would boycott or disrupt clinical trials. And participants launched Guinea Pig Zero, a consumers’ review of US phase 1 trial sites detailing pay rates and food quality, in 1996.

Today, some participants withhold their involvement until they receive written guarantees that trial results will be disclosed publicly within a specified time frame, says Wendy Armstrong, a representative of PharmaWatch and a consumer advocate based in Edmonton, Alberta. Research participants also want more control over trial parameters. In a United Kingdom survey, for example, patients wanted to identify quality-of-life outcomes, rather than having clinicians define them, she adds.

But many participants may not

know what questions to ask or how to promote their own interests. According to a recent Canadian article, obtaining informed consent involves a standard process that “can be inadequate, with study participants frequently not understanding even basic information fundamental to giving informed consent” (*Implement Sci* 2008;3:38).

The tendency among patients to have an optimistic bias and therapeutic misconceptions about trials has been extensively documented. Many patients have been shown, for example, to be unaware of the implication of randomization. Others believe researchers will make decisions based on what treatment would provide the best care for patients rather than in the interests of their research project.

Michael MacDonald, director of the Centre for Applied Ethics at the University of British Columbia, has long argued that there is more accountability — and more money spent — overseeing research involving animals in Canada than research involving humans.

So it is noteworthy that the *Moving Ahead* report recommended the formation of a Canadian Council for the Protection of Human Research Participants. “We advocated a similar model to the Canadian Council for Animal care, only with 3 times the budget,” said Corman, a member of the experts’ committee.

Thus far, though, no such council has been created. — Ann Silversides, *CMAJ*

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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); an article on the rising costs of trials (*CMAJ* 2009;180[3]:277-8); and an article on drug development costs (*CMAJ* 2009;180[3]:279-80). Upcoming articles will explore registration, ethical oversight, patient safety, reporting and the push for reforms.