

# Transnational Research Participant Protection

## A Canadian Example

This article reviews the Canadian system of governance of clinical research, highlights how it fails to provide research participants with appropriate protections, and outlines the steps that need to be taken by researchers to ensure appropriate risk management when conducting clinical trials in Canada.

Human research participants play a key role in clinical research. Indeed, the need to recruit research participants in a timely manner is a critical part of all clinical research planning. Research participant recruitment has been one of the main drivers of clinical trial globalization and harmonization efforts. The U.S. Food and Drug Administration (FDA) has been developing policies to broaden the acceptance of foreign data for new drug applications, and is in the process of establishing satellite offices in emerging regions such as China, India, Eastern Europe, and South America. Regulatory authorities within these emerging regions have been developing systems of governance of clinical research to help foreign regulators develop confidence in the integrity of the data arising from research conducted on their soil.

Despite this recent shift of clinical research to emerging regions, Canada remains a country of choice when it comes to conducting clinical trials. According to [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov), Canada ranks second in the world in terms of the number of clinical studies. (As of February 4, 2009, 5,673 studies were registered in Canada on [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov).)

There are many factors that support Canada's position as one of the major players in the conduct of clinical trials, including its developed research industry, the relative value of its currency, and its streamlined regulatory process. Because of its proximity to, and long-lasting relationship with, the United States, there is a general impression that the Canadian and U.S. systems for the governance of clinical research are similar. However, compared to its neighbor, there is no uniform regulatory framework in Canada that protects all research participants in a consistent manner irrespective of the source of research funding, the type of research, or the province where the research is conducted. Instead, there exists a patchwork of texts governing clinical research (laws, regulations, codes, guidelines, etc.), which, despite its questionable value as a legally binding standard of practice, gives the impression that a comprehensive system of research participant protection exists. Recent examples,<sup>1,2</sup> however, have shown that this is purely an illusion, and that the actual system relies essentially on the good faith of the actors involved in human research.

This article reviews the Canadian system of governance of clinical research and highlights how it fails to provide research participants with appropriate protections. Although it contains suggestions on how the system may be improved, the primary focus is on outlining the steps that researchers need to take to ensure appropriate risk management when conducting clinical trials in Canada. Although this article looks at the performance of clinical research in Canada, we believe that the proposed approach could assist sponsors and researchers, when conducting transnational research, in ensuring that

*There is no uniform regulatory framework in Canada that protects all research participants in a consistent manner.*

research participants benefit from the same level of protection as required under the UNESCO *Universal Declaration on Bioethics and Human Rights*.<sup>3</sup>

### **A Normative Patchwork Governing Human Research**

In Canada, human research is governed by laws and regulations originally adopted for other purposes. The law applies almost by accident to clinical research<sup>4</sup> and, indeed, there is no law in Canada that specifically oversees human research. Instead, the Canadian system governing clinical research resembles more of a legislative mosaic that draws upon elements of criminal, civil, and administrative law.

This patchwork approach to the governance of human research provides stakeholders with a heterogeneous legal framework that is often contradictory and inefficient. Because the laws were not written specifically to provide a framework for the conduct of clinical research, several loopholes exist that apply to both the principles governing the conduct of research and the protection of participants' rights, and to the rules and methods employed to enforce these principles.

Moreover, the Canadian federal and provincial governments have chosen to delegate the authority to regulate the conduct of clinical research to the research sponsors and the research ethics boards (REBs)—without clarifying the extent of their mandate or the standards by which they should operate. Researchers, funding agencies, research sponsors, academic institutions, and other stakeholders in clinical research were therefore invited to fill the gaps. As a result, the level of clinical research oversight varies considerably depending of what type of

research is being conducted (e.g., drug, device, fundamental), where the research is being conducted (e.g., different provinces and/or types of research settings), and who funds the research (i.e., public vs. private funding).<sup>5</sup> The most eloquent example of this situation is the fact that the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*,<sup>6</sup> the principal standard of practice in research ethics in Canada, applies only to clinical research funded by the three federal funding agencies, which represents just 50% of the overall health research conducted in the country.<sup>7</sup> With respect to drug clinical trials, federal funding accounts for less than 20%.<sup>8</sup>

*There is no law in Canada that specifically oversees human research.*

The end result is a system where the work of REBs is inconsistent, and where the obstacles to the regulatory and professional inspection process make the system ineffective and obscure.

### **REB Inconsistencies**

Canadian regulators have established REBs as the first-line control mechanism of human research without providing guidance regarding their operational framework or the principles of ethics they should apply. For example, under Division 5 of *Food and Drug Regulations*, REBs are accountable to research sponsors and the sponsors are accountable to Health Canada.<sup>9</sup> Therefore, the authority, compliance, and accountability of the REBs are set by the sponsor, who has the duty to conduct the necessary verifications in order to ensure that REBs operate in accordance with good clinical practices (GCPs). Although Health Canada has adopted International Conference on Harmonization (ICH)-GCP<sup>10</sup> as a guidance document to assist sponsors in their verification duties, the ICH-GCP guideline is silent with respect to the REBs' authority or accountability. This situa-

tion is very different from the accountability imposed on institutional review boards (IRBs) and institutions in the U.S. under 21 CFR 56.121, where they may face disqualification if they do not comply with the applicable regulations.

The Canadian system places the sponsors of clinical research in a delicate situation. Not only have sponsors been entrusted with the duty of ensuring compliance without any clear guidance as to what to verify, they have also been put in a situation of structural conflict of interest, wherein the organizations that have a vested interest in the trial's data play a fundamental role in its regulation. For example, sponsors select the REB that will review the research; research institutions oversee the conduct of research within their walls and select the members of its REB; and commercial REBs whose survival depends on the financial support of sponsors and researchers are omnipresent. Although one may agree that conflicting interests can be managed, the fact that the choice, financing, establishment, and oversight of REBs is the responsibility of the organization that finances and conducts the research leaves the question of conflicting interests unanswered—particularly when the system has very little accountability and no uniform standards.

*The organizations that have a vested interest in the trial's data play a fundamental role in its regulation.*

### **Obstacles to the Professional and Regulatory Inspection Process**

The professional and regulatory inspection of clinical research and medical practice is ensured by provincial colleges of physicians and surgeons, and by the Health Products and Food Branch Inspectorate (HPFBI) of Health Canada. Currently, the provincial colleges have been reluctant to take an active role in the inspection of the clinical research

*The duty to inspect clinical research practices has rested, so far, almost entirely on the shoulders of Health Canada.*

activities of their members, since the investigators' duties differ from, and even contradict those of, the physician in clinical care. The duty to inspect clinical research practices has rested, so far, almost entirely on the shoulders of Health Canada. Unfortunately, the current system in Canada does not provide inspectors with the means to meet HPFBI's objectives "to ensure that the generally accepted principles of [GCPs] are met, validate the quality of the data generated, and verify compliance"<sup>11</sup> with the regulations.

Health Canada's inspection system has been the object of several criticisms<sup>12</sup> related primarily to its lack of transparency and its complacency in applying the regulations. Contrary to the United States, Health Canada publishes the results of its inspections only in a nonidentifiable manner. Furthermore, only the general results of routine inspections are published; investigations (i.e., specific responses to known or suspected instances of noncompliance) remain confidential. Considering the fact that, for the year 2006–07, Health Canada conducted 39 routine inspections of qualified investigators, and that it typically conducts 15 to 20 investigations annually, this means that nearly 50% of the inspection activities of Health Canada remain entirely secret. One would think that, in a system where the oversight of clinical research conduct has been delegated to sponsors, Health Canada would provide assistance to sponsors by disclosing the results of its inspections.

Finally, because of its statutes, HPFBI has limited options with respect to the enforcement of corrective measures related to observed issues of noncompliance. HPFBI's arsenal of sanctions focuses primarily on the study or product, rather than on the actors themselves. Health Canada could proceed,

for example, with the seizure and/or voluntary detention of products, or the suspension or cancellation of the clinical trial authorization. However, contrary to the FDA, Health Canada does not have the legislative authority to disqualify an investigator, an IRB/REB, or a research site. Therefore, if an inspection/investigation concludes that there were critical issues of noncompliance in an already completed or terminated clinical trial, HPFBI has no options to remediate the situation for future studies. The noncompliant investigator, research site, IRB/REB, or sponsor is allowed to conduct or participate in other studies in the future.

### The Need for Reform in Canada

For these reasons and several others, it is clear that the current system of oversight of clinical research in Canada is based not on accountability, but rather on the good faith of various stakeholders. The fact that, until recently,<sup>13</sup> no major clinical trial incident had occurred in Canada cannot be interpreted as an indicator of the system's effectiveness. Experts have called for reform of the Canadian governance of clinical research.<sup>14</sup> For a great majority, such reform implies the adoption of legislation that would provide both a substantive and procedural framework within which sponsors, researchers, institutions, and REBs would operate, making them all accountable for their actions. Until such reform takes place, given that Canada remains a preferred location for the conduct of clinical trials, there are behaviors that sponsors can adopt in order to secure the value of their investment and the integrity of their data, and that research facilities and investigators can use to preserve their reputations. Such behaviors stem from the adoption of a comprehensive human research protection program.

### Ensuring Proper Risk Management

Since research and development necessarily involve risk, this risk must be managed through careful planning,

which necessitates the development of a human research protection program (HRPP). Development of an HRPP implies that the persons responsible for the conduct of a clinical trial

- adopt principles and standards toward the protection of research participants;
- develop a structure by which employees, partners, and suppliers understand the set principles and standards, know their responsibilities, and are accountable for maintaining the pre-established standards; and
- develop a process by which compliance with the requirements of the human research protection program is enforced and enhanced.<sup>15</sup>

In practice, the development and respect of an HRPP poses challenges, especially in an environment where time and resources are often limited. Nevertheless, the challenge can be met even within such restrictions. For instance, you can select partners and suppliers who have already developed an HRPP, which can be verified through an audit or, if resources do not permit it, through an independent source. Several academic centers have published their standard operating procedures (SOPs) on their websites, allowing for a paper audit. You may also develop a questionnaire for sites and REBs to complete (see Tables 1 and 2). Such questionnaires could request copies of SOPs, certifications in clinical research, and copies of recent regulatory inspections (typically going back three to five years).

*Experts have called for reform of the Canadian governance of clinical research.*

The Quebec Ministry of Health has established a system of accountability, unique within Canada, where institutional REBs under its jurisdiction (including every hospital in the province) must provide an annual report

**Table 1** Summary of Elements to Consider when Evaluating a Research Ethics Board (REB)

REB Evaluation Domains	The REB Has Written Policies and Procedures Describing
<b>Authority and Relationship</b>	<ul style="list-style-type: none"> <li>• The authority under which the REB is established and empowered.</li> <li>• The relationship between the REB and other research departments or institutions.</li> <li>• The authority of the REB to approve, modify, disapprove, place restrictions on, suspend, and terminate studies.</li> </ul>
<b>Laws, Regulations, Guidelines, and Ethical Principles to be Followed</b>	<ul style="list-style-type: none"> <li>• The laws and principles that govern the REB in assuring the protection of the rights and welfare of participants.</li> </ul>
<b>REB Membership</b>	<ul style="list-style-type: none"> <li>• Member qualification and diversity.</li> <li>• Member and chairperson selection and appointment.</li> <li>• Responsibilities and length of term/service for all members.</li> <li>• Members' training and evaluation.</li> <li>• Use of consultants.</li> <li>• Management of REB members' conflict of interest and undue influence.</li> </ul>
<b>REB Functions and Operations</b>	<ul style="list-style-type: none"> <li>• Full board and expedited review processes.</li> <li>• Modifications to approved studies.</li> <li>• Management of unanticipated problems, serious adverse events, protocol deviations, noncompliance, and waivers.</li> <li>• Continuing review process.</li> <li>• Appeal of REB decisions process.</li> </ul>
<b>Elements of Ethics Review</b>	<ul style="list-style-type: none"> <li>• Submission requirements.</li> <li>• Scientific review.</li> <li>• Ethical review.</li> <li>• Financial and conflict of interest review.</li> </ul>
<b>REB Communications and Records</b>	<ul style="list-style-type: none"> <li>• Content and means of communications with investigator/sponsor.</li> <li>• Record retention requirements.</li> <li>• REB minutes requirements.</li> </ul>
<b>Research Participant Resources</b>	<ul style="list-style-type: none"> <li>• Management of participant questions, concerns, and complaints.</li> </ul>

of their research activities, unanticipated events that occurred over the year, and a copy of their SOPs. Moreover, there are organizations accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP) that offer clinical research and/or ethics review services in Canada.

Compliance with the HRPP can be easily integrated into the routine monitoring of the trial. For sites conducting research in Canada, the development of an HRPP is vital, as investigators are ultimately responsible for the well-being of research participants. A site should clarify with the sponsor what the reporting requirements will be for unanticipated events and how these events will be managed. Furthermore, if the site is located in the community and will rely on the services of a commercial central REB, the site should review, with the sponsor, the criteria used to select the REB and assess whether the criteria meet the principles and standards of the site's HRPP.

*Sponsors need to be aware that variations in the governance of clinical research exist from one country to the next.*

### Conclusion

Human research participant recruitment, which is essential for successful clinical research and development, has been a driver for the recent globalization of clinical trials. Despite numerous efforts toward the harmonization of standards of clinical trials at the international level, sponsors need to be aware that variations in the governance of clinical research exist from one country to the next, and they must evaluate the potential impact of these variations on their investment in the research and on the integrity of the data.

This article used Canada as an illustration of such variations. Despite the proximity of the U.S. and Canada, and their significant collaborative research projects, the two countries' systems of governance of clinical research differ significantly concerning the protection of research participants. In Canada, this protection is based primarily on the good faith of stakeholders, whereas in the U.S. these same stakeholders are legally accountable to the FDA. In order to alleviate problems that might be caused by such inconsistencies while conducting transnational research, and to ensure that research participants benefit from the same level of protection worldwide, careful planning is important. Such planning necessitates the development of an appropriately rigorous HRPP.

### Acknowledgement

Research for elements of this article was funded by the Quebec Bar Foundation.

**Table 2** Summary of Elements to Consider when Evaluating an Investigator and Research Facility

Investigator and Site Evaluation Domains	Elements Required
<b>Training and Expertise</b>	<ul style="list-style-type: none"> <li>• The principal investigator has a valid medical license.</li> <li>• The principal investigator has expertise relevant to the area of the research project.</li> <li>• The principal investigator has additional training relating to the protection of research participants.</li> <li>• The research staff is aware of its obligations with regards to participant protection.</li> <li>• None of the investigators have been barred from conducting research by a professional or regulatory agency.</li> </ul>
<b>Competing Interests</b>	<ul style="list-style-type: none"> <li>• The principal investigator and/or his/her relatives do(es) not have financial or nonfinancial interests that could potentially influence the conduct or outcome of the research.</li> </ul>
<b>Research Resources</b>	<ul style="list-style-type: none"> <li>• The principal investigator has a practice affiliation in which there are sufficient resources (staff and materials) available to successfully complete the study.</li> <li>• Medical resources are readily available for participants in need of emergency care.</li> <li>• The research facility has policies and/or practices to safeguard the privacy of participants and the confidentiality of study data.</li> </ul>
<b>Recruitment Process and Consent Process</b>	<ul style="list-style-type: none"> <li>• The principal investigator has the potential for recruiting the required number of suitable participants.</li> <li>• Sufficient time will be devoted to the consent discussion.</li> <li>• The participants will have the opportunity to ask questions prior to making a decision.</li> <li>• Sufficient time will be allowed for the participant to make a decision.</li> <li>• The circumstances in which consent will be obtained minimize the possibility of coercion or undue influence.</li> </ul>

## References

1. Evans D. December 15 2005. SFBC drug testers have tuberculosis after exposure at center. *Bloomberg* online; available at [www.bloomberg.com/apps/news?pid=10000039&sid=a900ZzPRlkaE&refer=columnist\\_evans](http://www.bloomberg.com/apps/news?pid=10000039&sid=a900ZzPRlkaE&refer=columnist_evans).
2. Evans D. January 3, 2006. A history of problems at SFBC. *International Herald Tribune*; available at [www.ihf.com/articles/2006/01/03/business/sfbcweb.php](http://www.ihf.com/articles/2006/01/03/business/sfbcweb.php).
3. United Nations Educational, Scientific and Cultural Organization (UNESCO). October 19, 2005. *Universal Declaration on Bioethics and Human Rights* Available at [http://portal.unesco.org/en/ev.php-URL\\_ID=31058&URL\\_DO=DO\\_TOPIC&URL\\_SECTION=201.html](http://portal.unesco.org/en/ev.php-URL_ID=31058&URL_DO=DO_TOPIC&URL_SECTION=201.html), section 21.
4. See Dickens BM. 2000. Governance relations in biomedical research. In McDonald M, et al. *The Governance of Health Research Involving Human Subjects* (HRIHS). Ottawa, Law Commission of Canada; available at [http://epe.lac-bac.gc.ca/100/200/301/lcc-cdc/governance\\_health\\_res-e/index.html](http://epe.lac-bac.gc.ca/100/200/301/lcc-cdc/governance_health_res-e/index.html).
5. Hirtle M. 2003. The governance of research involving human participants in Canada. *Health Law Journal* 11: 137.
6. See Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada. 1998. *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*. Ottawa, 1998 (with 2000, 2002, and 2005 amendments); available at [www.pre.ethics.gc.ca/english/policystatement/policy\\_statement.cfm](http://www.pre.ethics.gc.ca/english/policystatement/policy_statement.cfm).
7. Parliamentary Information and Research Service. October 5, 2006. *Federal Funding for Health Research*. Available at [www.parl.gc.ca/information/library/prbpubs/prb0627-e.pdf](http://www.parl.gc.ca/information/library/prbpubs/prb0627-e.pdf), p. 11.
8. Lexchin J. 2008. Clinical trials in Canada: whose interests are paramount? *International Journal of Health Services* 38(3): 525.
9. Regulations Amending the Canadian Food and Drug Regulations: (1024 Clinical Drugs) Division Five Drugs for Clinical Trials Involving Human Subjects, section C.05.010 d).
10. Health Canada. 1997. *Guidance for Industry - Good Clinical Practice*. Consolidated Guideline ICH Topic E6. Available at [www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/efficac/e6-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/efficac/e6-eng.php).
11. Health Canada, Health Products and Food Branch Inspectorate. 2002. *Inspection Strategy for Clinical Trials*. Available at [www.hc-sc.gc.ca/dhp-mps/alt\\_formats/hpfb-dgpsa/pdf/compli-conform/insp\\_strat-eng.pdf](http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/compli-conform/insp_strat-eng.pdf), p. 4.
12. For a review of these criticisms, see, for example, Shuchman M. 2008. Clinical trials regulation—how Canada compares. *Canadian Medical Association Journal* 179(7): 635; House of Commons, Report of the Standing Committee on Health. April 2004. *Opening The Medicine Cabinet: First Report on Health Aspects of Prescription Drugs*. Available at <http://cmte.parl.gc.ca/Content/HOC/committee/373/heal/reports/rp1282198/healrp01/healrp01-e.pdf>, p. 3.
13. 20 people test positive for TB after Quebec trial. 2006. *CTV.ca News* (March 10, 2006); available at [www.ctv.ca/servlet/ArticleNews/story/CTVNews/20060310/tb\\_trial\\_ap\\_060310/20060310?hub=Health](http://www.ctv.ca/servlet/ArticleNews/story/CTVNews/20060310/tb_trial_ap_060310/20060310?hub=Health); and Munro M. 2004. Death of four-year-old is a tragic reminder of the dangers of clinical research. *Canada West News Service* (February 26, 2004); available at [www.michenerawards.ca/english/ryan.htm](http://www.michenerawards.ca/english/ryan.htm).
14. See, for example, Lemmens T. 2005. Federal regulation of REB review of clinical trials: a modest but easy step towards an accountable REB review structure in Canada. *Health Law Review* 13 (2&3): 39; Downie J. 2005. The Canadian agency for the oversight of research involving humans: a reform proposal. *Accountability in Research* 13: 75.
15. Association for the Accreditation of Human Research Protection Programs (AAHRPP). Human Research Protection Program Plan. Available at [www.aahrpp.org/Documents/D000147.pdf](http://www.aahrpp.org/Documents/D000147.pdf). **ACRP**

**Martin Letendre, LLB, LLM**, is the director of ethics and legal affairs at ethica Clinical Research Inc., a Canadian full-service contract research organization that conducts and manages ethical clinical research on three continents. He has been responsible for the creation of ethica Clinical Research Inc.'s Government Affairs and Legal departments, its successful accreditation by AAHRPP, and the expansion of its ethics review services in Latin America. He can be reached at [mletendre@ethicaclinical.ca](mailto:mletendre@ethicaclinical.ca). Please direct all correspondence pertaining to this article to him.

**Sébastien Lanctôt, LLB, LLM, DESSci, DCL**, is a professor with the Faculty of Law of the University of Sherbrooke, where he conducts research in civil liability and insurance law. He has recently authored, codirected, and coauthored several books on insurance law and participated in the elaboration and publication of a civil law encyclopedia. Since 2003, he has been an active member of the Canadian Genetics and Life Insurance Task Force. He can be reached at [Sebastien.lanctot@USherbrooke.ca](mailto:Sebastien.lanctot@USherbrooke.ca).