Institutional Oversight of Clinical Trials and the Drug Approval Process

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Abstract
The institutional and federal bodies responsible for regulatory review and oversight of clinical trials in Canada serve distinct yet complementary functions in ensuring that clinical trials provide scientifically rigorous and ethically sound evaluation of new therapeutic products. To date, academics and reformers alike have discussed reform priorities for federal and institutional review in isolation, as if their guiding purposes are distinct. This article identifies the overlapping objectives of federal and institutional review, argues for the importance of coordination of institutional and federal oversight structures, and identifies potential points of coordination.

Keywords
Clinical trials; Drugs--Testing--Law and legislation; Canada
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PAUL B. MILLER

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I. INTR O D UC TIO N ................................................................. 680

II. CLINICAL TRIALS .................................................................... 681
    A. General background on clinical trials .................................... 681
    B. The importance of clinical trials ........................................... 685

III. REGULATORY OVERSIGHT OF CLINICAL TRIALS ............. 689
    A. The emergence of regulatory oversight structures in the United States ................................................. 689
    B. Recent calls for regulatory reform ........................................ 694
       1. Calls for reform of institutional review ............................ 696
       2. Calls for reform of federal review ................................. 701

IV. EXPLORING THE RELATIONSHIP BETWEEN INSTITUTIONAL AND FEDERAL REVIEW ........................................ 709

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I. INTRODUCTION

The institutional and federal bodies responsible for regulatory review and oversight of clinical trials in Canada serve distinct yet complementary functions in ensuring scientifically rigorous and ethically sound evaluation of new therapeutic products. The principal mandate of institutional Research Ethics Boards (REBs) is to protect the rights and welfare of research subjects through initial and ongoing review for compliance with predetermined substantive and procedural norms. The Therapeutic Products Directorate of Health Canada (TPD) is responsible for ensuring the relative safety and efficacy of new therapeutic products by conducting pre-marketing and post-marketing reviews, and, more recently, by overseeing the conduct of clinical trials. To date, academics and reformers alike have approached federal and institutional review as though their guiding purposes are entirely distinct. The TPD’s recent—if forced—recognition of its responsibility for the oversight of ongoing clinical trials in Canada provides an opportunity to question the prevailing approach. This article seizes the opportunity to do so.

The argument will proceed as follows. Part I explains the purpose of clinical trials and their importance to clinical medicine. Part II establishes the importance of regulatory oversight of clinical trials, reviews the emergence of the institutional and federal oversight structures, then presents and assesses recent recommendations for regulatory reform. Part III employs a case study to advance an argument

1 Save for biologics. Review and approval of biologics is the responsibility of the Biologics and Genetic Therapies Directorate.
for the importance of coordination of institutional and federal oversight, and identifies potential points of coordination.

II. CLINICAL TRIALS

A. General background on clinical trials

Clinical trials are experiments that evaluate the safety and efficacy of experimental therapeutic products. The most common form of clinical trial is the randomized controlled trial (RCT).\(^2\) RCTs can vary considerably in the details of scientific design (e.g., whether single, double, or triple blinding\(^3\) is used, or whether placebo and/or active controls\(^4\) are employed). Common to all RCTs, and central to their superiority as a means of generating credible scientific evidence, are the controlled conditions\(^5\) under which the experiment is undertaken, the statistical analysis of the study data to determine the extent to which they can be generalized, and the random assignment of the experimental and control modalities to subjects.\(^6\) The most common therapeutic interventions tested by way of the RCT are pharmaceuticals.\(^7\) The

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\(^3\) In single-blinded trials, subjects do not know which modality they are receiving (i.e., experimental treatment, standard treatment and/or placebo) until the completion of the trial. In double-blinded trials neither the subject nor the investigator knows who is receiving which modality until the completion of the trial. In triple-blinded trials, neither the patient, nor the researcher, nor the person analyzing the data knows who is receiving which modality until the completion of the trial. The binding process is used as a control against bias.

\(^4\) A placebo is an inert substance with known properties. When used in RCTs, the placebo is a control, or baseline, against which to measure the safety and efficacy of the experimental treatment. Active controls are also used as a baseline, but they are substances and/or interventions of proven (or at least accepted) therapeutic merit. Generally, *either* placebo or active controls are employed in RCTs—the former enables the trial to generate data as to the absolute safety and efficacy of the experimental treatment, and the latter enables the trial to generate comparative data as to the safety and efficacy of the experimental and accepted treatment(s).

\(^5\) For example, inclusion criteria for the enrollment of subjects ensure that they share relevant characteristics, and that the phases of the research are conducted in similar institutions according to predetermined procedures explained in the study protocol.

\(^6\) For an excellent treatment of the arguments for and against RCTs, grounded in a more wide-ranging analysis of the history and philosophy of the experimental sciences, see Deborah G. Mayo, *Error and the Growth of Experimental Knowledge* (Chicago: University of Chicago Press, 1996), in particular, c. 5 at 128.

\(^7\) Levine, *supra* note 2.
analysis provided here addresses the oversight of clinical trials of pharmaceuticals.8

Larger RCTs—the sort that would generate evidence sufficient to support an application for federal marketing approval—can be conducted only subsequent to smaller experiments that give evidence of sufficient promise. The very first tests of the experimental treatment are pre-clinical animal studies. These are essential to ensuring the safety of human subjects in clinical trials given that approximately one in one thousand tested substances survives pre-clinical screening.9 The U.S. Food and Drug Administration (FDA) and the TPD classify clinical trials of pharmaceuticals according to four categories or “phases”10.

1. Phase I trials are those in which the experimental drug is first introduced to humans (usually healthy volunteers) in order to develop its pharmacological profile. The profile includes data as to the absorption, metabolism, and excretion of the drug, the safe dosage range, the relative efficacy of different routes of administration, and the side effects.

2. Phase II trials are generally the first in which the experimental drug is introduced to patients with the condition the drug is expected to ameliorate. These trials involve limited numbers of closely monitored subjects and are intended to establish a safe dosage. They also give a preliminary indication of the drug’s efficacy.

3. Phase III trials are large-scale studies of the experimental drug. Most are RCTS. Often, thousands of patients are enrolled in any given Phase III trial. These trials are intended to generate data as to the safety and efficacy of the experimental drug that can be generalized for the patient population. Phase III trials are conducted with the hope that favourable data will accrue in support of the pharmaceutical manufacturer’s application for TPD marketing approval.

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8 Note that the oversight bodies discussed below oversee a wider range of human subjects research. REBs review all research involving humans that comes within the funding mandates of the three major Canadian public funding agencies (Canadian Institutes of Health Research, Social Sciences and Humanities Research Council, and Natural Sciences and Engineering Research Council). The TPD assesses the quality, safety, and efficacy of medical devices and disinfectants, in addition to pharmaceuticals.


10 See Levine, supra note 2 at 6-7.
4. Phase IV trials are primarily post-marketing or "surveillance" studies, which are conducted in order to determine whether the drug has long-term side effects. Other Phase IV studies include testing of the drug on other populations (e.g. children) or for indications other than those for which approval was granted.

According to Arnold Relman and Marcia Angell, only one in five substances that enter Phase I testing in the United States will survive the FDA marketing approval process.\(^{11}\) Citing a study by Joseph DiMasi and his colleagues, American pharmaceutical manufacturers claim that research and development costs 802 million U.S. dollars for each drug that ultimately makes it to market.\(^{12}\) Industry critics, including Relman and Angell, dispute these figures.\(^{13}\) They claim that research and development costs are closer to 266 million U.S. dollars per new molecular entity\(^{14}\) approved, once opportunity costs are factored out and tax savings are factored in. Data from Statistics Canada put gross investment in health research in Canada at $5.7 billion in 2004, an increase of $463 million since 2003 and a remarkable $3.6 billion since 1994.\(^{15}\) Data cited in the 2004 Annual Report of the Patented Medicine Prices Review Board indicate that the brand-name pharmaceuticals industry invested $1 billion in health research in Canada in 2004,\(^{16}\) fully

\(^{11}\) Relman & Angell, supra note 9.


\(^{14}\) New molecular entities are "drugs whose active ingredients are newly discovered or synthesised molecules." The research and development costs for so-called "me too" drugs are much less. Relman & Angell, ibid. at 28-30.


half the corporate investment in health research in 2004 as measured in light of Statistics Canada figures.\(^\text{17}\)

In a Regulatory Impact Analysis Statement accompanying the new clinical trials regulations in 2001, the TPD indicated that it reviewed “over 800” applications for approval to proceed with clinical trials in 1998, and that it has witnessed a 20 per cent average annual increase in clinical trials conducted in Canada.\(^\text{18}\) If this rate of increase had remained stable, the TPD would have received approximately 1,658 applications to conduct clinical trials in 2002. Evidently, the rate of increase has jumped significantly, for, as of January 2002, the TPD estimated that approximately 4,000 clinical trials would be conducted in Canada in 2002.\(^\text{19}\) No similar estimate has since been made for subsequent years. Given that no federal officials in the United States or Canada collect data on human subjects enrolled in clinical trials, reliable estimates of the numbers of subjects enrolled per annum are impossible to make. Very rudimentary estimates put the figure at approximately 18,000,000\(^\text{20}\) in the United States and between 100,000\(^\text{21}\) and 1,800,000\(^\text{22}\) in Canada. Parexel’s *Pharmaceutical R&D Statistical Sourcebook* suggests a median number of 4,186 enrolled patients per clinical trial in the United States in 2001, with median numbers for the period from 1998 to 2001 ranging from a low of 3,840 to a high of 5,435.\(^\text{23}\) Assuming that the average (4,637) holds for Canada, and that the TPD’s prediction of numbers of trials for 2002 was roughly accurate, existing estimates of

\[^{17}\text{Statistics Canada, supra note 15.}\]
\[^{18}\text{Regulations Amending the Food and Drug Regulations (1024 – Clinical Trials), P.C. 2001-1042, C. Gaz. 2001.II.1116 at 1139 [Regulations].}\]
\[^{19}\text{Health Products and Food Branch Inspectorate, Health Canada, Inspection Strategy for Clinical Trials (Ottawa: Health Canada, 2002) at 6 [Inspection Strategy]. Note that not all of these trials will necessarily be financed by the pharmaceuticals industry.}\]
numbers of subjects enrolled in clinical trials per annum in Canada may be conservative.

B. The importance of clinical trials

Clinical trials are of obvious economic importance, in both the United States and Canada. Clinical trials provide the evidentiary foundation for every pharmaceutical manufacturer’s application for marketing approval of its products. On the strength of sales of its products, the pharmaceuticals industry has become an economic powerhouse and is an increasingly important sector of industrial economies. According to Angell, Americans spend 200 billion U.S. dollars per year on prescription drugs. The American pharmaceutical industry realizes incredible profits, with some reports of average profits (18.3 per cent of revenues) ranking well above the median for all other industries (3.3 per cent of revenues). Likewise, Canadian spending on pharmaceuticals is significant. The Canadian Institute for Health Information (CIHI) reports that Canadians spent $21.8 billion on prescription and non-prescription drugs in 2004. Spending on prescription drugs is estimated to have accounted for $18 billion of that figure. Overall drug spending is increasing at a staggering rate, with 2004 levels representing an increase of 8.8 per cent from 2003. Spending on prescription drugs is increasing at an even higher rate, with 2004 levels representing an increase of 10.2 per cent from 2003. In 2004, Canadians spent nearly twice the amount previously spent on prescription and non-prescription drugs in 2001 ($12.3 billion), and five times the amount spent in 1985 ($3.8 billion). According to CIHI, total drug spending in Canada has increased at an average annual rate of 9.7

\[ 24 \text{ Angell, supra note 13 at 3.} \]
\[ 25 \text{ Relman & Angell, supra note 9. See also Angell, ibid. at 10-13. Note, however, that it has been contended that reported profits are inflated. See U.S., Office of Technology Assessment, \textit{Pharmaceutical R&D Costs, Risks and Rewards} (Washington: United States Government Printing Office, 1993) at 73-104.} \]
\[ 26 \text{ Canadian Institute for Health Information, \textit{Drug Expenditure in Canada, 1985-2004} (Ottawa: Canadian Institute for Health Information, 2005) at i.} \]
\[ 27 \text{ Ibid. at 7.} \]
\[ 28 \text{ Ibid. at 3.} \]
\[ 29 \text{ Ibid. at 7.} \]
\[ 30 \text{ Ibid. at 3.} \]
per cent over the past twenty years, a rate which well exceeds inflation and population growth rates.\textsuperscript{31} For its part, Canada’s Research-Based Pharmaceutical Companies (Rx&D), a Canadian trade organization representing brand-name pharmaceuticals companies, emphasizes the sector’s contribution to the Canadian economy. It claims that the pharmaceutical industry is responsible for 24,000 jobs and $8.3 billion in research and development investment since 1993.\textsuperscript{32}

More important than the economic impact of clinical trials is their primacy of place within evidence-based medicine (EBM). Michel Foucault once argued that despite clear ties to the sciences, clinical medicine for a long time did not qualify as a science because of its questionable epistemic foundations: “[I]t involve[d] a scarcely organized mass of empirical observations, uncontrolled experiments and results, therapeutic prescriptions, and institutional regulations.”\textsuperscript{33} While it has long been accepted that some degree of uncertainty is inevitable in medicine,\textsuperscript{34} over the past ten to fifteen years the EBM program has been heralded as a means of reducing avoidable risk, uncertainty, and waste in medical care.\textsuperscript{35} Responding in part to disturbing evidence of geographical variation in medical practice patterns,\textsuperscript{36} proponents of EBM have argued that teaching students and physicians to adopt an informed, critical perspective on the evidentiary basis for their clinical decisions helps to achieve the ideals of medically appropriate and economically

\textsuperscript{31} Ibid. at i.


efficient care. The point is not merely to teach physicians the importance of basing patient care on evidence; rather, it is also to teach them to discriminate between alternative courses of action through a process of comparison based on a hierarchical categorization of different forms of evidence. As an early guide to EBM put it, optimistically invoking Kuhn:37

A new paradigm for medical practice is emerging. Evidence-based medicine de-emphasizes intuition, unsystematic clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision-making, and stresses the examination of evidence from clinical research. Evidence-based medicine requires new skills of the physician, including efficient literature-searching, and the application of formal rules of evidence in evaluating the clinical literature.38

Physicians currently trained in EBM are taught to base their clinical decisions on evidence in the following order of preference (from most to least preferred): systematic reviews of RCTs; individual RCTs published in peer-reviewed journals; uncontrolled trials (e.g. observational studies); and anecdotal reports of peer observations.39 The evidence that emerges from completed clinical trials thus sits at the apex of the evidentiary pyramid established by EBM. Indeed, the clinical trial’s rise to prominence must be recognized as intimately interrelated with the emergence of EBM.40 When the founders of EBM identified variations in practice patterns, they argued that the cause was faulty

37 Thomas S. Kuhn, The Structure of Scientific Revolutions, 2d ed. (Chicago: University of Chicago Press, 1973). Kuhn would likely have been wary of the (common) suggestion that the “revolution” in medicine ushered by EBM can be understood in terms of his discussion of paradigms in his theory of the dynamics of theory change in science. Kuhn was himself trained in the natural sciences (theoretical physics), and was candid about the limitations of his work with respect to the social and human sciences. He seems to have included medicine in the latter category. See Thomas S. Kuhn, “The Natural and the Human Sciences” in The Road Since Structure (Chicago: University of Chicago Press, 2000) 216. See also Eugenie Gatens-Robinson, “Clinical Judgment and the Rationality of the Human Sciences” (1986) 11 J. Med. Philos. 167.

38 “Evidence-Based Medicine: A New Approach to Teaching the Practice of Medicine” (1992) 268 J.A.M.A. 2420 at 2420 (“Evidence-Based Medicine”).


40 “The foundations of the paradigm shift lie in developments in clinical research over the last 30 years. In 1960, the randomized clinical trial was an oddity. It is now accepted that virtually no drug can enter clinical practice without a demonstration of its efficacy in clinical trials.” “Evidence-Based Medicine,” supra note 38 at 2422. See also Marks’ superb treatment of the history of clinical research: Harry M. Marks, The Progress of Experiment Science and Therapeutic Reform in the United States, 1900-1990 (New York: Cambridge University Press, 1997).
clinical decision making based on outmoded—and, indeed, potentially dangerous—adherence to experience, opinion, and habit. Further, in retrospect, it was only logical for EBM's progenitors to look to clinical trials for a firmer foundation for clinical decision making. Well before the variations in practice patterns became well publicized, controlled clinical trials had garnered recognition for their ability to produce reliable, verifiable evidence on the safety and efficacy of new and established treatments.41

While the intertwined successes of EBM and RCTs have been the subject of considerable debate,42 there can be little doubt that they have become a firmly entrenched part of medical education. Likewise, reliance upon clinical trials for the production of medical knowledge has become fixed. Still, much work remains. Clinical trials of new therapeutic products are being conducted in ever increasing numbers, and the efficacy of many established therapeutic interventions is in need of validation. Some suggest that the efficacy of as many as 50 per cent of therapeutic interventions have now been validated by way of clinical trial;43 others suggest the figure is closer to 20 per cent.44 In either case, the current directions of medical science and pharmaceutical product development are aligned.45 Given the confluence of academic confidence and industry interest in clinical trials, it seems reasonable to predict that the numbers of clinical trials conducted per annum will increase exponentially. With evidence suggesting bias in the results of

41 Marks, ibid.
44 Noah, “Medicine’s Epistemology,” supra note 33 at 388.
45 Regulatory agencies led the way in establishing the clinical trial as the evidentiary benchmark for therapies employed in clinical medicine. Beginning in the 1960s and 1970s, the FDA required pharmaceuticals manufacturers to prove efficacy through submitting the results of multiple clinical trials with their applications for marketing approval. See Harold Edgar & David J. Rothman, “New Rules for New Drugs: The Challenge of AIDS to the Regulatory Process” (1990) 68 Milbank Q. 111.
industry-sponsored clinical trials\textsuperscript{46} and industry influence over the development of clinical practice guidelines,\textsuperscript{47} the public interest in the integrity of EBM and clinical science demands that the institutional and federal regulatory oversight structures be improved.

III. REGULATORY OVERSIGHT OF CLINICAL TRIALS

A. The emergence of regulatory oversight structures in the United States

Today, few people would seriously question the need for some form of regulatory oversight of the conduct of clinical trials, and scrutiny of the conclusions reached by clinical trials. Though it was not always the case, the public stake in the conduct of clinical trials is now almost universally recognized to be extremely high. The institutional ethics review and the federal therapeutic products approval structures emerged first in the United States, largely in response to public crises of confidence in the conduct of science.\textsuperscript{48}

In retrospect, the importance of establishing a scientific basis for manufacturers’ claims as to the merits of their therapeutic products seems obvious. However, it was not always recognized as such. The


\textsuperscript{48} I am not suggesting that there have not been troubling research scandals of our own in the Canadian research community. But by and large, the Canadian institutional and federal review structures were not developed in response to Canadian controversies. Rather, these structures were developed subsequent to, and modelled closely on, those that emerged in the United States.
public has a strong appetite for products promising to cure or prevent diseases, alleviate pain, and increase vitality. As high levels of spending on pharmaceuticals attest, the public appetite for therapeutic products has not waned with time. Arguably, the public's tolerance of risk has changed concomitantly with the rise of university-based scientific medicine. At one time, self-selected quack therapies were widely accepted as the best medicine had to offer. But with the rise of professional medicine and increased faith in the capabilities of scientific medicine to test and verify therapeutic products, the public has grown more risk-averse to therapeutic products, and more concerned about scientific validation. Consumers now want to know that products will deliver the therapeutic benefits promised, and that the costs of consumption, in terms of possible side effects, are acceptable.

Recognition of the need for reliable scientific evidence of the safety and efficacy of pharmaceuticals, of the fact that clinical trials represent the best available means of generating that evidence, and of the necessity of regulatory scrutiny of the results of clinical trials came long before clinical trials achieved privileged epistemic status within clinical medicine. As has often been the case in the history of regulatory responses to public health and environmental risks, the establishment of modern regulatory structures for the oversight of therapeutic products was not the achievement of a prescient government. In the United States, where modern regulatory structures for the oversight of therapeutic products first developed, public fears generated the political will for increased regulatory intervention. The FDA ballooned in size and power largely in response to the public fear and outrage provoked


50 On the historical and philosophical context for the increase in public faith in, and expectations of, scientific medicine, see Guenter B. Risse, "Medicine in the Age of Enlightenment" in Wear, ibid., 149.

51 This demand, however, is not uniform in all consumers. As the market for herbal remedies, nutritional supplements and other alternative health products attests, the public still has a considerable appetite for self-selected products whose claims of therapeutic merit have not been scientifically validated.


by the thalidomide scandal. In 1962, the U.S. government deemed that the public interest would be best served by a publicly funded administrative agency with the expertise required to protect the general population. With a public mistrustful of the motives of drug manufacturers, and demanding the protective intervention of the government, the expanded FDA received a Congressional mandate to evaluate drugs for safety and efficacy as a condition of marketing approval. Unable to meet its new mandate through review of traditional supporting materials (largely physician anecdotes and uncontrolled observational studies), the FDA began to champion approval based on sound science. For the FDA, sound science meant that the manufacturer’s statements regarding the indications, safety, and efficacy of its product must be supported by evidence from multiple well-designed clinical trials.

The history of the institutional ethics review system reveals a similar dynamic of scandal and regulatory response. Whereas the emergence of the modern FDA was a response to public fears over the safety of therapeutic products and mistrust of industry, the institutional review system emerged in response to public outrage over disregard for the rights and welfare of human research subjects and growing mistrust of scientists.

Public sensitivity to the potential for abuse of research subjects was heightened internationally with the widely publicized revelations of Nazi scientists’ horrific experiments on non-consenting subjects. Yet, in North America, public pressure for the regulatory oversight of research only reached its breaking point following revelations of the

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56 Prior to 1962, the FDA conducted post- rather than pre-marketing approval, based solely on safety data submitted by manufacturers: Lasagna, supra note 54 at 324. See Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780.

57 Edgar & Rothman, supra note 45 at 117-18.

abuse of subjects by North American scientists. The pressure mounted with the 1966 publication of an article by Harvard medical professor Henry Beecher, which chronicled twenty-two trials in which U.S. researchers risked “the health or the life of their subjects” without obtaining consent or permission. Beecher stated that these trials were but a small sampling of those he collected, and that given the ease with which they were collected, one could only conclude that the rights and welfare of subjects were being routinely ignored in clinical research in the United States. By all accounts, Beecher’s article attracted a great deal of media attention and, in consequence, provoked considerable public outcry and feelings of mistrust.

The Beecher article was preceded by two disturbing studies sponsored by the National Institutes of Health (NIH). In one, a chimpanzee kidney was transplanted into a non-consenting patient; in the other, live cancer cells were injected into non-consenting indigent patients at the Brooklyn Jewish Chronic Disease Hospital. Already concerned about the potential for liability and public outrage in connection with these cases, the director of the NIH needed little prompting when asked by a congressman for the NIH’s response to the Beecher article. Efforts slowly mounted towards development of a uniform policy for the protection of human subjects in NIH-sponsored research. The first step was a directive issued in 1966 from then Surgeon General William H. Stewart that required all institutions receiving public funding to give written assurance of “independent assessment” of the risks and benefits, and the adequacy of the consent process for


63 Ibid. at 100.
each experiment. The directive was vague both as to what would count as “independent review,” and as to the standards for assessing the adequacy of consent procedures and the acceptability of risk-benefit profiles. Random audits revealed widespread non-compliance.\textsuperscript{64}

The current institutional review system did not emerge until two further widely publicized research scandals came to light. The first of the two infamous studies was conducted over a period of more than fifteen years at the Willowbrook State School for the Retarded in New York. Incoming residents of the school (most suffering from severe mental retardation) were admitted on the condition that their guardians consent to their enrolment in the study. Each child was injected with a mild dose of hepatitis to help discover a prophylaxis. The second study, conducted by physicians from the Public Health Service over forty years, involved four hundred African-American men from Tuskegee, Alabama. The men were afflicted with syphilis and over the course of the study were observed, but not treated, so that scientists could trace the natural history of the disease.\textsuperscript{65} Aside from being denied penicillin when it became available, the subjects were not informed of their illness, and were misled as to the purpose of the examinations and invasive interventions they were asked to accept.\textsuperscript{66} Over the course of the study approximately twenty-eight men died, and one hundred became blind and insane as a result of untreated syphilis.\textsuperscript{67}

Unsurprisingly, the Tuskegee study made front-page news. The U.S. Department of Health, Education and Welfare (DHEW) responded immediately by establishing an advisory panel to investigate the adequacy of its protections for human research subjects. The final report of the panel concluded that existing protections were inadequate, and argued that there was need for “prior and ongoing review” of human subjects research.\textsuperscript{68} Most importantly, the panel advised Congress to establish “a permanent body with the authority to regulate

\textsuperscript{64} Ibid. at 101.


\textsuperscript{66} Jones, \textit{ibid.} at 7-11.

\textsuperscript{67} Ibid. at 13.

at least all federally supported research involving human subjects." In 1973, Senator Edward Kennedy successfully introduced the *National Research Act*, which provided that the DHEW would establish regulatory protections for human subjects, and a national commission (the latter was eventually named the National Commission for the Protection for Human Subjects of Biomedical and Behavioural Research). The DHEW issued its regulations in 1974, ushering the institutional review system into existence by requiring each institution receiving federal funding to establish an institutional review board, and by establishing detailed substantive and procedural norms to be followed and enforced by IRBs.

Over the course of the past thirty years, the regulatory system in the United States has not remained static. But, more recent controversies—including notably those surrounding revelations about the U.S. government's secret Cold War radiation experiments, and the widely publicized death of eighteen-year-old Jesse Gelsinger in a gene therapy trial—failed to yield the far-reaching change brought by earlier controversies. Rather, regulatory change has been relatively incremental in nature and limited in scope. Pressure for major systemic reform is instead coming from other sources.

**B. Recent calls for regulatory reform**

While there has been a steady flow of reports recommending the reform of institutional and federal review structures in the United

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70 "Government Standards" in *Human Radiation Experiments, supra* note 59, 97 at 103. Over the course of the 1970s, the National Commission issued seventeen voluminous reports that would have considerable impact on the structure and content of federal regulations.

71 Institutional research ethics review was not carried out in Canada in a systematic way until the Medical Research Council of Canada mandated it for institutions receiving MRC funding. Medical Research Council of Canada, *Guidelines on Research Involving Human Subjects* (Ottawa: Minister of Supply and Services Canada, 1987). The Canadian ethics policy was not, and still is not, legislated as it is in the United States.


States and Canada from the 1970s through the mid 1990s, the last seven to eight years have seen a veritable throng of such reports. These reform movements differ from developments giving rise to the federal and institutional review structures because they have been primarily generated by "inside" parties in an environment generally devoid of public scandal. Reports recommending reform of the institutional review system have emerged almost biannually in the United States for the past decade, generated in large part by government inspection agencies and by advisory bodies composed of academic experts in bioethics. Though fewer in number and more modest in scope, similar reports are beginning to emerge and attract attention in Canada. Recommendations for reform of the federal review structure have come about in a different way. In the United States, much of the pressure for reform comes from the steady lobbying efforts of patient advocacy groups and industry. In Canada, these interest groups have also been vocal. Given the sheer volume of American reports and the present uncertainties concerning their impact on policy reform, the discussion

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below will review and assess only the most important recommendations for reform that have emerged in Canada.

1. Calls for reform of institutional review

Released in 2000, the McDonald Report to the Law Commission of Canada is the most recent, and thus far the most important, call for reform of the Canadian system for institutional review.\(^7\) Containing analyses by leading Canadian figures in health law and policy and bioethics, the McDonald Report identifies a number of significant weaknesses in the Canadian system, and advances several recommendations for reform.

By far the most prominent recommendation of the McDonald Report is for national coordination and oversight of the institutional review system. One of its key findings was that "Canada's complex, decentralised, multisourced arrangements for governing HRIRIHS [Health Research Involving Human Subjects] pose major ethical challenges in terms of consistency, transparency and accountability."\(^7\) The argument underlying the recommendation is that there is no way of ensuring uniformly high quality REB review, in accordance with existing regulation and policy, where national coordination and oversight are lacking. National standards for accreditation and education require a national agency to promulgate and enforce these standards. Adequate enforcement of Canadian research policy by REBs cannot be assured unless some entity is responsible for auditing reviews. Resource-related problems are often too large, far-reaching, and expensive to be managed at the institutional level. The coherent development of research ethics policy and the effective resolution of interpretation and implementation problems require coordination.


\(^7\) Michael McDonald et al., The Governance of Health Research Involving Human Subjects (Ottawa: Law Commission of Canada, 2000) [McDonald Report].

\(^7\) Ibid. at vii.
While the need for national coordination and oversight was the dominant and recurring theme, the McDonald Report advanced other important recommendations. The report advocated greater investment in resources for REBs, in response to the concern that REBs do not have adequate financial and human resources to rigorously protect human subjects. REBs need greater financial resources to sponsor educational programs, compensate ad hoc consultants, and generally cover mounting administrative costs. Lack of human resources—principally science experts—also represents a concern, inasmuch as the sound assessment of many substantive conditions for the approval of research (e.g. risk/benefit assessment, adequacy of inclusion and exclusion criteria, and determination of scientific value and validity) requires scientific expertise. Based on interviews with REB members across Canada, the McDonald Report concluded:

The need for an infusion of resources cannot be overstated. At the various sites across the country the story is the same: overburdened REB members are stretched to the breaking point ... As the work becomes increasingly complicated with globalization, advances in technology and commercialization, REBs are struggling to find committee chairs or even members.

The McDonald Report's second most important recommendation proposed a coordinated effort to ensure the independence of REBs. Until recently, it has been tacitly accepted that the benefits of local review outweigh any possible negative effects owing to potential conflicts of interest. The McDonald Report found that the tacit assumption no longer holds due to new financial pressures placed upon institutions and researchers at a time when industry investment in research is proportionally high. Indeed, the report concluded that "those with vested interests in its outcomes — researchers, research

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81 McDonald Report, supra note 78 at xii.

institutions and research sponsors—dominate the research process and its governance. The issue of REB independence is particularly notable in Canada because “we lack the strong counterbalance provided in the US by independent federal governance of research ethics approval and by the significant level of research support provided by NIH and other US agencies.”

Though the McDonald Report set them aside, important questions have been raised by scholars about the operation of for-profit REBs in Canada and the United States. As Trudo Lemmens and Benjamin Freedman note, for-profit REBs suffer from an inherent conflict of interest that is inconsistent with their public mandate; their clients—predominantly members of the pharmaceuticals industry—have a clear vested interest in securing ethics approval. The McDonald Report recommended that stakeholders, including federal and provincial governments, “take greater steps ... to insulate REBs and parallel bodies from pressures that potentially compromise their independence.” Given the increasing reliance on for-profit REBs in the review of community-based studies, the report ought to have recommended that they be barred or made subject to specific regulation.

That being said, the overall message of the McDonald Report is important and strikingly clear: confidence in the ability of REBs to protect the rights and welfare of research subjects will only come with cooperative government oversight, investment, and participation in the institutional review system. The influence of that unalloyed message is reflected in the adoption of many of the McDonald Report recommendations in the final report of the Senate Standing Committee.

83 McDonald Report, supra note 78 at xi.
84 Ibid. at xii. For an account of how the University of Toronto has confronted these and other challenges in the absence of a strong national oversight system, see C. David Naylor and The Research Committee and Clinical Study Agreements Working Group of the Toronto Academic Health Science Council, “Early Toronto Experience with New Standards for Industry-Sponsored Clinical Research: A Progress Report” (2002) 166 Can. Med. Assoc. J. 453.
85 McDonald Report, supra note 78 at 10.
87 McDonald Report, supra note 78 at 311.
on Social Affairs, Science and Technology (the Kirby Report\textsuperscript{88}), and in recent efforts by Health Canada to investigate reform options.

The Kirby Report addressed issues relating to the protection of human subjects in its chapter on health research. There, it noted that generally Canadian REBs "seem to operate to a high standard," but that "serious gaps" in the Canadian institutional review system have come to light.\textsuperscript{89} Among these, the report mentioned the fact that Canada has "no oversight mechanism to ensure compliance" with existing research ethics policies.\textsuperscript{90} It further noted that there are "no standard training requirements for Canadian REB members," and that there is "no process of certification [or] accreditation" of REBs and REB members.\textsuperscript{91} The Kirby Report acknowledged concerns about the independence of REBs, stating that it is essential that they "operate free from institutional or researcher pressures."\textsuperscript{92} Finally, it also recognized that there is a "basic need for more resources" for REBs.\textsuperscript{93}

On the basis of these findings, the Kirby Report recommended that Health Canada begin the collaborative development of "a joint governance system for health research involving human subjects for all research that the federal government performs, that it funds, and that it uses in its regulatory activities."\textsuperscript{94} It added further that the development of this system should be guided by a set of priorities. These include establishing national, updated standards for the approval of research; providing for education and certification of REB members; and


\textsuperscript{89} Ibid. at 224.

\textsuperscript{90} Ibid.

\textsuperscript{91} Ibid. at 225.

\textsuperscript{92} Ibid.

\textsuperscript{93} Ibid.

\textsuperscript{94} Ibid. at 226. Note that this recommendation in effect calls for national coordination and oversight to meet the gaps found in the system, but it does not specifically recommend legislation, nor does it call for an extension of the requirement for REB review to all privately sponsored research. It is also noteworthy that the recommendation applies only to governance of health research. If acted upon only in respect of health research, important questions as to the governance of other forms of human subjects research (now covered, along with health research, by the Tri-Council Policy Statement, infra note 164) will need to be addressed.
establishing an accreditation system for REBs that is “at arm’s length from government, but clearly accountable to government.”

The ultimate impact of the recommendations advanced by the McDonald Report, and affirmed in the Kirby Report, is not yet clear. There were some early signs of movement within the federal government. Health Canada recognized many of the flaws in the Canadian system, promised improvements, and engaged in widespread consultation to determine Canadian priorities for reform. The promise of improvement also received official government recognition in a throne speech delivered by former governor general Adrienne Clarkson in 2002. The mounting pressure for regulatory reform might have gained momentum under the government’s “Smart Regulation” initiative: a resulting consultation draft championed a number of themes that resonate with calls for reform of the governance system in Canada. In particular, commitments to transparency, public accountability, and policy coherence seem to herald change to the existing “complex, decentralised, multisourced arrangements for governing HRIHS”—a system the McDonald Report rightly criticized as posing “major ethical challenges in terms of consistency, transparency and accountability.” However, former prime minister Paul Martin failed to act on the promise contained within the throne speech. This may not be surprising given that he championed increased industry

95 Ibid. at 227.


97 Health Canada, Towards a National System of Oversight for the Governance of Research Involving Humans (Discussion Workbook) (Ottawa: Health Canada, 2002). Though, as shall be discussed below, it appears that Health Canada’s interest in improving governance is as much a reflection of its recognition of potential liability in the wake of a 1999 audit by the auditor general as anything else. See infra note 131.


100 Ibid. at vii.
investment in Canada through the commercialization of basic science.\textsuperscript{101} Indeed, some interpreted the “Smart Regulation” initiative as fundamentally pro-industry and anti-regulation in motivation.\textsuperscript{102} If this interpretation is correct, it could be predicted that early signs of movement within Health Canada have ceased. Though the Conservative Party policy declaration suggests more of the same, highlighted as it is by pro-industry promises of tax credits\textsuperscript{103} and faster drug approvals, it remains to be seen what the government of Prime Minister Stephen Harper will do.\textsuperscript{104} One can only hope that the urgent need of research subjects for better regulatory oversight will not be sacrificed at the altar of industry profit.

2. Calls for reform of federal review

The two most prominent groups pushing for reform of federal processes in the recent past have been the pharmaceutical industry and patient advocacy organizations. Both are well organized, experienced in lobbying, and have a proven track record of bringing their respective agendas to bear on pharmaceuticals’ policy development.\textsuperscript{105}

The demands for policy reform by patient advocacy groups have been less visible once important victories were won, first in the United States in the late 1980s and soon thereafter in Canada, by groups


\textsuperscript{104} Ibid. at 20.

representing HIV/AIDS patients. In a strange alliance, the voices of the HIV/AIDS advocacy groups joined with those of industry representatives to decry delays in drug approval times. Though the resulting policy changes fell short of industry aspirations, they were wide-ranging and did much to expedite access to promising new treatments. Perhaps the most important policy development in Canada was the initiation of the Special Access Program, through which patients with serious or life-threatening conditions (for whom conventional treatments have failed) can, through their physician, gain access to drugs not approved for sale in Canada. The establishment of priority review, or fast-tracking of potentially life-saving drugs to reduce the targeted review time from 300 days to 180 days, represents another important development. Similarly, the “Notice of Compliance with Conditions” policy is critical, because it allows for the marketing of potentially life-saving drugs on

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107 See Edgar & Rothman, supra note 45.


110 Therapeutic Products Directorate, Priority Review of Drug Submissions (Ottawa: Health Canada, 2002) at 2. Note that these review times are targets, and are reportedly rarely met. Furthermore, the criteria for priority review are vague.
the condition that the manufacturer supply additional evidence of the efficacy of the drug within a given time frame. 111

While patient advocacy groups have campaigned for, and won, policies providing improved access to new treatments, industry lobbying efforts have been, and continue to be, focused on the need for improved “efficiency” in the federal approval process. When the pharmaceutical industry demands “improved efficiency,” it hopes to achieve shorter review times. Delay, for whatever reason, is costly, and for that reason industry representatives continue to press for shortened review times. 112 The position advanced by Rx&D in a 2002 policy report is typical. 113 The Rx&D report warned that Canada stands to lose its place among world leaders in pharmaceuticals research if Canadian policies, including those on drug approval, are not “improved.” Taking on the mantle of improving patient access, it suggested that “formidable delays and barriers to patient’s access to innovative therapies... stand out as impediments to R&D investment growth.” 114 The report claims that the “time taken for the review of drug submissions is unnecessarily lengthy” and promises that “timely approvals would encourage more research to be undertaken in this country.” 115 It emphasized these complaints by raising the issue of international competitiveness, suggesting that a “key factor” in the consolidation of American dominance in pharmaceuticals research and development is the “streamlining of the FDA’s review and approval procedures.” 116 Rx&D also cleverly suggested that it should be invited by government into the policy development process, in doing so noting that “other jurisdictions have already undertaken joint industry-government consultations that yielded recommendations and detailed action plans aimed at enhancing their global competitiveness in

111 Therapeutic Products Directorate, Notice of Compliance with Conditions: Revised Policy (Ottawa: Health Canada, 2002). Unfortunately, these conditions are not made public, so there is no way to determine whether manufacturers are complying with them.


113 Canada’s Research-Based Pharmaceutical Companies, Improving Health Through Innovation: A New Deal for Canadians (September 2002), online: Innovation in Canada <http://innovation.gc.ca/gol/innovation/site.nsf/vDownload/SectorReports_e/$file/Pharmaceuticals-e.pdf> [Improving Health].

114 Ibid.

115 Ibid.

116 Ibid.
pharmaceuticals." In the interim, the Rx&D report outlined specific policy recommendations that advance its members' agenda, which include the establishment of review time targets; the direction of increased government resources to improved review "efficiency"; and the pursuit of cooperative agreements with other countries that would enable the TPD to "take much better advantage of the scientific evaluation" carried out by its counterparts.118

Although it does not appear that the government responded publicly to the Rx&D report, years of industry pressure seem to have secured a number of policy changes within the TPD. Due to the cutback in federal appropriations in the early to mid 1990s, between 1994 and 1998 the TPD introduced a government-wide cost-recovery program, which requires manufacturers to pay fees ranging from $250 through $300,000 per product submitted for review.119 This program came with a commitment from Health Canada that the funds would be allocated in part to improving the efficiency of the review process.120 According to Joel Lexchin,121 this commitment increased the already considerable leverage of the industry. The passing of the User Fees Act122 in 2004 only strengthened perceptions of industry influence.123 Several aspects of the bill give the pharmaceutical industry considerable influence by establishing government performance measures tied to the payment of user fees.

The TPD had also, for some time prior to the Rx&D report, been engaged in international collaborative efforts designed to reduce review times.124 The initiatives undertaken by the TPD include its pursuit of Mutual Recognition Agreements (MRA) with counterpart agencies in other countries. MRAs provide that each signatory country will

117 Ibid. at 2.
118 Ibid. at 13.
120 Improving Health, supra note 113 at 11.
recognize the other's testing and inspections. Canada has, to date, ratified MRAs with the European Community and Switzerland, Australia, and the European Economic Area (Norway, Liechtenstein, and Iceland). Some scholars view the MRAs as particularly striking, potentially risky, and arguably undemocratic concessions to industry pressures to minimize regulatory scrutiny and oversight of new therapeutic products. These are among the many concerns associated with Canada's participation in the International Conference on Harmonization (ICH), which has recently been endorsed in strong terms by the External Advisory Committee on Smart Regulation. MRAs implicitly cede control over the establishment and enforcement of regulatory standards for the safety and efficacy of therapeutic products. Such concessions are inseparable from broader ICH-led efforts to harmonize international standards and processes for drug approval. These efforts are especially troubling because ICH proceedings are dominated by regulatory agencies and pharmaceutical industry associations to the exclusion of advocacy groups, the medical profession, and the lay public.

In addition to calls for reform advanced by patient advocacy groups, industry representatives, and others, the TPD has also been

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125 MRAs are potentially risky to the extent that multiple reviews are more likely to uncover flaws in the evidence submitted in support of manufacturers' claims. See Robyn Lim, "Rapacuronium: Premarket Drug Evaluation Can Be Very Effective for the Identification of Drug Risks" (2003) 96 Anesth. Analg. 631.

126 MRAs imperil democratic values to the extent that the foreign agencies whose assessments Canada will accept are not accountable to the Canadian public.


129 Abraham, "International Harmonisation," supra note 127.

forced to respond to criticism by the auditor general of Canada (AG). 131 In 1999, the AG audited a clinical trial of an anti-malarial drug (mefloquine), which was sponsored by Health Canada and the Department of National Defence. The audit found that the subjects in the trial, who were members of the Canadian Armed Forces, had not provided written consent, and that there was no ongoing monitoring of the safety and efficacy of the treatment provided over the course of the trial. The AG found Health Canada culpable: “Once Health Canada approved the conditions for the clinical trial of the drug, it made no attempt to monitor the study to ensure that the trial was adhering to the protocol with its reporting requirements and procedures to protect patients’ well-being.” 132 The AG faulted Health Canada for its failure to establish “procedures for monitoring the conduct of these studies.” 133 The audit recommended that Health Canada develop and implement monitoring procedures immediately, noting that under the Food and Drug Regulations, “Health Canada has the responsibility to review and approve the trial design and protocol.” 135

This call for reform marks a turning point of considerable importance, both because of its direct impact on policy and because it unequivocally states that the federal government is responsible for a more active role in the approval and oversight of clinical trials. 136 This public interest mandate had previously been left to REBS, researchers, and research sponsors. Indeed, Health Canada officially responded to the audit by disowning responsibility, claiming it “rests with the sponsor of the clinical trial ... as well as associated institutional research ethics


132 Ibid.

133 Ibid. at para. 14.

134 Food and Drugs Act, R.S.C. 1985, c. F-27.

135 Supra note 131 at para. 18.

boards." Health Canada soon reversed course. The TPD drafted an inspection strategy for random auditing of ongoing clinical trials in August 2001 and implemented a final policy in January 2002. The policy anticipates the annual inspection of 2 per cent of all clinical trial sites and has resulted in two reports revealing important research ethics deficiencies. Most significantly, in 2001, Health Canada promulgated revised clinical trial regulations, which, until the 2001 revision, had been essentially unchanged since instituted in the 1960s.

Highlights of the revised regulations include improved requirements relating to federal approval and oversight of clinical trials, provisions for the inspection/monitoring system, and the clear grant of authority to Health Canada to deny approval to or terminate the conduct of clinical trials. The regulations also require that sponsors of clinical trials obtain REB approval. Most telling about the current state of affairs, however, are the vague remarks about REBs in the accompanying Regulatory Impact Analysis Statement. These remarks indicate that, despite its recognition of the role of REB review, the federal government is still uncertain of its ability to rely on REBs and of the relationship between federal and institutional levels of review. Consider, for instance, that while the new regulations "recognise the important role played by REBs in their oversight of the conduct of clinical trials," the statement repeats familiar concerns about REB

137 Office of the Auditor General, supra note 131 at para. 18.
138 Inspection Strategy, supra note 19.
139 Ibid. at 6.
141 Regulations, supra note 18.
142 The changes include detailed provisions for application information, notice of amendments to study design and protocol, record keeping, and the prompt reporting of adverse reactions.
143 Regulations, supra note 18 at para. C.05.006.(1)(c): "[F]or each clinical trial site, the sponsor has obtained the approval of the research ethics board in respect of the protocol referred to in paragraph C.05.005(a) and in respect of an informed consent statement referred to in paragraph C.05.005(b)."
144 Ibid., Regulatory Impact Analysis Statement at 17.
review. The most notable concerns are that "at the present time, there is no accreditation system in Canada for REB," that "some Canadian REBs have limited resources and experience with the review of drug clinical trials," and further, that REBs presently "follow one or a number of federal or provincial guidelines [with some following] foreign guidelines." The federal government's uncertainty about its relationship to REBs is clearly indicated by its suggestion that "clarifications are required to better define the roles and responsibilities of the various players in the review of clinical trials."

These developments suggest that Health Canada has realized that it shares responsibility for the oversight of clinical trials, and understands the imperative to work more closely with REBs. They also reveal that Health Canada is troubled by the current state of REB review and is unsure of the relationship between institutional and federal review structures. Despite the clear need for coordinated assessment of REB and TPD review policies and practices, recommendations to date for reform of federal and institutional review have consistently and without exception failed to recognize the issue.

Recommendations for reform of the institutional review system, while calling for national oversight and coordination, have consistently failed to assess the inadequacies of REB review from a systemic perspective. The ultimate impact of the pervasive problems in institutional oversight of clinical trials on the ability of federal officials to assess the safety and efficacy of therapeutic products remains unknown. Potential avenues for the coordination of institutional and federal approval and oversight efforts remain to be explored. To be fair to those engaged in reform efforts in Canada, it should be noted that these failings coincide with gaps in the more extensive reform literature in the United States and in the academic research ethics literature.

Reform efforts focused on federal drug approval and oversight processes have been no better in this respect. Many of the reforms adopted to date reflect the respective interests of powerful interest groups, most notably patient advocacy groups and industry. The former

145 Ibid. at 4.
146 Ibid. at 4, 12, and 14.
147 Ibid. at 18.
148 Ibid. at 11.
have demanded, and largely won, improved access to new and experimental treatments. The latter continue to press for shorter review times. Perhaps unsurprisingly, in consideration of their respective agendas, neither has called for the coordination of institutional and federal approval and oversight processes. The AG’s audit has stimulated important policy development as well as reflection within the federal government on the relationship between federal and REB review. These developments, however, have not attracted mention, let alone sustained reflection in the most recent examination of the federal drug approval process—namely, that conducted by the Romanow Commission. The Romanow report does advance some progressive recommendations for reform of the national approval of pharmaceuticals, but it simply does not recognize the role of the federal government and REBs in overseeing the very clinical trials that form the evidentiary basis of the approval process. This is peculiar, given that the Romanow Commission otherwise demonstrated great sensitivity to the importance of securing the informational and evidentiary foundations of health care delivery.

IV. EXPLORING THE RELATIONSHIP BETWEEN INSTITUTIONAL AND FEDERAL REVIEW

To date, recommended reforms for the regulatory oversight of pharmaceuticals development—whether focused on institutional or federal bodies—have consistently failed to adopt a systemic perspective. This is despite the significant outstanding questions about the relationship between federal and institutional approval and the

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149 These include the establishment of a national drug agency, independent from industry and government, and recommendations that the national approval process include assessment of the comparative safety and efficacy of new and standard treatments; the devotion of more resources to reduction of review delays; and that the national authority take on an expanded role in dissemination of “objective and reliable knowledge” about pharmaceuticals to health professionals and the public. Commission on the Future of Health Care in Canada, “Chapter 9 – Prescription Drugs” in Building on Values: The Future of Health Care in Canada, Final Report (November 2002) 189 at 199-205.

150 “Chapter 3 – Information, Evidence and Ideas” in Commission on the Future of Health Care in Canada, ibid., 75. It was this sensibility that motivated the commission’s strong recommendation in this chapter (ibid. at 77-82) for the establishment of electronic personal health records. Personal health records are important, but they are just one significant part of the information armamentarium that physicians must bring to bear in caring for patients. Equally, if not more significant, is the scientific evidence in support of treatment alternatives (e.g. that provided by clinical trials).
oversight of clinical trials, and the ultimate impact of such oversight on the final federal reviews for marketing approval.

This section reviews the relationship between the assessments conducted by REBs and the TPD, and indicates the importance and promise of future coordination of REB and TPD review, arguing that REBs and the TPD can work better by working together. Though future reform efforts should consider the potential for coordination more widely, the illustration provided here focuses on the risk assessment and evaluation functions carried out by REBs in the approval and oversight of clinical trials, and by the TPD in conducting its reviews for marketing approval.

A. Risk assessment and evaluation: a case study

1. Risk assessment and evaluation by the TPD

The principal mandate of the TPD is the evaluation of the safety and efficacy of therapeutic products.\(^{151}\) It fulfils its mandate in large part by conducting detailed scientific risk-benefit assessments of new therapeutic products.\(^{152}\) Traditionally, the interests protected by the TPD are the interests of the Canadian public. The TPD protects the welfare interests of Canadians by ensuring that we consume products for which there is sound, reliable evidence of acceptable levels of safety and therapeutic benefit. In working to fulfil its mandate, the TPD must engage in a delicate balancing act. It must release a product to market only when the evidence shows that the risks the product poses are acceptably offset by its benefits. At the same time, it must not unduly delay products of considerable benefit from reaching Canadians in need of them.

The TPD's risk-benefit assessment shapes its performance of its particular responsibilities. Most evidently, the assessment provides the

\(^{151}\) Of course, in the wake of the AG's audit, the TPD has also accepted responsibility for overseeing the conduct of clinical trials through inspections. But the nature of the risk-benefit assessment to be conducted in these inspections, and the relationship between these inspections and those conducted by REBs, remains unclear. Recognition of this "new" responsibility opens up the very grey zone of overlapping REB-TPD responsibility that stands in need of exploration and clarification.

\(^{152}\) See generally Richard A. Merrill, "Risk-Benefit Decisionmaking by the Food and Drug Administration" (1977) 45 Geo. Wash. L. Rev. 994.
foundation for its evaluation of the “quality, safety and effectiveness” of pharmaceutical drugs as part of the Notice of Compliance (NOC) approval process. It also forms the basis of the TPD’s review of the accuracy of risk-benefit information provided to Canadian consumers (e.g. in packaging inserts, and, more indirectly, through advertisements directed at physicians). Risk assessment is also conducted on an ongoing basis as part of post-marketing surveillance activities conducted by the Marketed Health Products Directorate in coordination with the TPD and the Biologics and Genetic Therapies Directorate. On the basis of adverse event reports received from physicians, the results of Phase IV clinical trials, or alerts from other countries, the TPD may revise its assessment of the safety of marketed products and revoke marketing approval accordingly.

The TPD uses a range of evidence in conducting its risk-benefit assessment. Much of this evidence comes from materials submitted by the manufacturer in support of its application for an NOC. An American commentator suggests that the FDA receives on average 100,000 pages of supporting material with each submission. The most important information consists of the results of Phase III clinical trials. Other important forms of evidence in the supporting materials include the results of animal studies, Phase I and II clinical trials, the protocol(s) according to which the clinical trial(s) were conducted, records (including adverse event reports), information as to the chemical composition of the compound, and the manufacturer’s summary. The TPD may also conduct its own literature review, searching for results of clinical trials other than those submitted by manufacturers, such as interim results from ongoing clinical trials released in peer-reviewed journals. Another potentially important source of evidence is the “two-way” alert system the TPD has established with a number of its counterparts around the world. The alert arrangements are part of the mutual recognition agreements and memoranda of understanding the

\[\text{153} \text{ As shall be discussed below, there are important policy implications flowing from a basic distinction between risk assessment and risk evaluation. That is, “a fundamental distinction must be made between measuring risk, an objective but probabilistic pursuit; and judging the acceptability of that risk (judging safety), a matter of personal and social value judgment.” William W. Lawrence, Of Acceptable Risk: Science and the Determination of Safety (Los Altos: William Kaufmann, 1976) at 8, cited in Fraiberg & Trebilcock, supra note 52 at 847.}\]

\[\text{154} \text{ Dunbar, supra note 105 at 683.}\]
TPD has entered into under its international strategy. They provide that the signatories will promptly exchange important safety information. It remains unknown whether the alert system has been used, and if so, to what extent.

The scrutiny undertaken by the TPD in the course of conducting its risk-benefit assessment is comprehensive. TPD scientists must determine whether, taken in sum, the evidence is sufficient to support manufacturers' claims (e.g. by considering whether the Phase III trials are sufficiently large or the results sufficiently supportive). They must also look for flaws in the design of the study that would indicate that the results are not reliable. Pharmacologists and chemists independently study the compound and its ingredients to determine whether there are any concerns with the toxicity of the ingredients, deficiencies in the manufacturing process, and so on. On the basis of its investigations, the TPD issues a final risk-benefit assessment. In light of the nature of the evidence assessed by the TPD, this is an “absolute” risk-benefit assessment. The evidence generally does not reveal, and the TPD therefore does not base its approval on, information as to the comparative safety and efficacy of the new drug as against standard treatments. Phase III clinical trials, which are the most important source of information, are most often designed with placebo (inert) rather than active controls (e.g. standard treatment(s)). As a result, the data is indicative only of the absolute safety and efficacy of the new drug.

While the basis and process of the TPD's risk-benefit assessment activities are fairly transparent, the standards and process according to which it makes its ultimate risk-benefit evaluation are less clear. The risk-benefit evaluation is the final determination, based on the assessment, as to whether the risks and benefits are acceptably balanced. This is a point of concern, for while risk assessment is widely accepted as a scientific endeavour (requiring expert scrutiny of complex scientific

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155 International Policy Division, supra note 124 at 15-21.

156 Other study design constraints (e.g. sample size, exclusion criteria) limit the generalizability of the results of Phase III trials. Some of these constraints are inevitable while others are the subject of decision. The latter are implicated in the debate between explanatory and pragmatic approaches to study design. See Daniel Schwartz & Joseph Lellouch, “Explanatory and Pragmatic Attitudes in Therapeutic Trials” (1967) 20 J. Chronic Dis. 637; Mike Pringle & Richard Churchill, “Randomised Controlled Trials in General Practice: Gold or Fool's Gold?” (1995) 311 Brit. Med. J. 1382; and Marshall Godwin et al., “Pragmatic Controlled Trials in Primary Care: The Struggle Between External and Internal Validity” (2003) 3 BMC Med. Res. Methodol. 28.
information, and calculation of the probability and magnitude of possible harms and benefits), it is well established that risk evaluation is a matter of politics and morals.\textsuperscript{157} Fraiberg and Trebilcock, among others,\textsuperscript{158} note that determination of acceptable risks and benefits is a value judgment, requiring moral and political deliberation and choice.\textsuperscript{159} Where scientists are making both the risk assessment and evaluation determinations without public input or representation—as they appear to be doing at the TPD—important questions of democratic legitimacy ought to be raised and addressed.\textsuperscript{160} These questions are arguably more pressing as the TPD and its counterparts come under increasing pressure to “privatize” drug approval by contracting it out to external scientists.\textsuperscript{161} These scientists are less accountable to the public than government-employed scientists. More troubling, in view of very pervasive ties between industry and clinical scientists,\textsuperscript{162} is the possibility that the

\textsuperscript{157} See Abraham, \textit{supra} note 53.


\textsuperscript{159} Fraiberg & Trebilcock, \textit{supra} note 52 at 857-71.

\textsuperscript{160} See generally Sheila Jasanoff, \textit{The Fifth Branch: Science Advisors as Policymakers} (Cambridge: Harvard University Press, 1990), in particular c. 8 at 152.

\textsuperscript{161} See Elizabeth M. Rutherford, “The FDA and Privatization: The Drug Approval Process” (1995) 50 Food & Drug L.J. 203; Elizabeth C. Price, “Teaching the Elephant to Dance: Privatizing the FDA Review Process” (1996) 51 Food & Drug L.J. 651; and Henry I. Miller, “A Proposal for FDA Reform” (2002) 1 Nature Rev. Drug Disc. 642. The key arguments advanced in favour of privatization are improved efficiency and “more informed” reviewers. Though concerns over privatization have historically been more pronounced in the United States, industry-led calls for privatization of regulatory functions have found recognition in the report of the External Advisory Committee on Smart Regulation, \textit{supra} note 128 at 66. Among other things, the External Advisory Committee recommends that regulatory capacity be built in “the private sector” and that government tap federally funded research networks “to supplement their in-house scientific knowledge.” (\textit{Ibid.} at 66-67). According to the committee, “By tapping into these existing resources, Canada will be in a better position to inform its regulatory decision making with cutting edge science and conduct scientific peer reviews when needed.” (\textit{Ibid.} at 67).

public interest in rigorous, independent risk assessment and evaluation will be compromised.\textsuperscript{163}

2. Risk assessment and evaluation by REBs

The mandate of REBs is to ensure that the rights and welfare of research subjects are protected. REBs ensure that clinical trials within their institution are initiated and conducted in compliance with predetermined substantive and procedural norms.\textsuperscript{164} The risk assessment and evaluation conducted by REBs is increasingly recognized as an essential component of the protection they provide,\textsuperscript{165} but they also enforce a wide range of norms derived from principles of justice\textsuperscript{166} and respect for persons.\textsuperscript{167} Although the principal mandate of REBs is to protect research subjects, many of the risk-related norms they enforce have implications for the public interest in pre-market evaluation of new drugs.

Like the TPD, REBs are called upon to assess \textit{and} evaluate the risks and benefits of clinical trials. Of course, the evidence upon which REBs conduct their risk assessment is much more limited in nature than that available to TPD reviewers, given that it is conducted \textit{ex ante}. While


\textsuperscript{166} These include ensuring that subject selection criteria are fair (that women, children, and minorities are not excluded from study participation without reason), and that adequate, but not excessive compensation, is provided to research subjects.

\textsuperscript{167} These include ensuring that consent documents and procedures are accurate and that subjects' privacy and confidentiality are well protected.
the results of Phase III clinical trials are not generally available for scrutiny, the results of pre-clinical animal studies and any previous clinical trials (e.g. Phase I and Phase II trials) will be submitted to the REB by the principal investigator as supporting material in the study justification. Important information will also be contained in the protocol itself (e.g. dosage and procedures for patient monitoring). If the REB reviewer has lingering questions about the evidence on which the risk assessment is to be made, he or she may also conduct a literature review to determine whether there have been any other clinical trials completed or important interim results reported. Given the well-noted workload problems from which REBs suffer, however, it is unlikely that such literature reviews are routinely conducted.

While it can be argued that REBs appear to receive adequate evidence upon which to make their risk assessments, it can also be said that their capacity for conducting them rigorously is questionable. Like the TPD, REBs’ risk assessment requires scrutiny of highly complex scientific information, and the calculation of the probability and magnitude of potential harms and benefits. As Health Canada itself recognized in the Regulatory Impact Analysis Statement accompanying the new clinical trials regulations, many REBs have limited experience reviewing clinical trials. Even REBs that do have this experience may not have the necessary range of expertise in their membership to assess the complex information contained in protocols submitted by investigators from disparate specialities. Further, and in contrast to the TPD, REBs do not have the financial resources to call in outside experts to conduct assessments on their behalf.

While REBs are not as well situated as the TPD to assess risks, they are comparatively better situated to evaluate them for at least three reasons. First, REB evaluation of risk does not raise obvious problems of legitimacy, because rules governing their composition require that their membership include lay people and other non-scientists (including lawyers, ethicists, and clerics). Second, to fulfil their overall mandate,

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168 Article 1.3 of the Tri-Council Policy Statement, supra note 164, sets out composition requirements as follows: “The REB shall consist of at least five members, including both men and women, of whom: (a) At least two members have broad expertise in the methods or in the areas of research that are covered by the REB; (b) At least one member is knowledgeable in ethics; (c) For biomedical research, at least one member is knowledgeable in the relevant law... and; (d) At least one member has no affiliation with the institution, but is recruited from the community served by the institution.” This is not to say that the situation is ideal. Many have complained that scientists
REB members must routinely engage in debate over the ethical, legal, and social issues raised by new technologies. Third, and perhaps most importantly, REB risk evaluation is governed by standards which are clearly stated and increasingly debated by the public.169

At least some of these points of difference between REBs and the TPD with respect to risk evaluation and assessment highlight potentially fruitful avenues of coordination: The standards governing REB evaluation of risk are a case in point. While many are clearly designed to protect subjects, some have important, if yet largely unrealized, implications for the type and quality of evidence generated by clinical trials, and thus for the NOC review conducted by the TPD.

Canadian REBs are required to evaluate the risks and benefits of a protocol according to an elaborate framework.170 Any given clinical trial protocol generally calls for a number of interventions involving the subject. Generally, clinical trials employ a mixture of therapeutic procedures, for which the evidence must support the promise of therapeutic benefits to research subjects (e.g. the experimental drug) and non-therapeutic procedures, which are administered solely to address the research question (e.g. extra blood draws). The framework holds that the presence of the potential for therapeutic benefit to subjects (i.e. therapeutic warrant) founds a morally significant distinction between therapeutic and non-therapeutic procedures and, as such, requires an evaluation of the risks associated with each according to distinct standards. Clinical trials may proceed only when both sets of standards are satisfied. Where implemented, these standards prefigure

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170 Tri-Council Policy Statement, supra note 164 at 1.5 and 7.1-7.6. See also Weijer, supra note 165.
the type of clinical trials conducted, and accordingly have a direct impact on the development of new therapeutic products and the federal drug approval process.

In evaluating the risks associated with non-therapeutic procedures, REBS must be satisfied that three standards are met: the risks associated with the non-therapeutic procedures must be minimized; the risks must be reasonable in relation to the knowledge to be gained from the study; and, with research involving vulnerable subjects, the risks must fall below a threshold of permissible risk called "minimal risk." These standards allow socially beneficial interventions to be carried out, and provide subjects special protection from exposure to risk in the absence of therapeutic benefit. Yet the latter two standards clearly have a wider impact by placing a limitation on the pursuit of the interests of scientists, the industry, and the public at large in the generation of scientific knowledge. In meeting the risk-knowledge standard, for example, the REB weighs risks to subjects against the interests of others in the generation of knowledge. Depending on the importance of an intervention to the overall study design, the evaluation may have a significant impact on the quality or significance of results generated by the trial.

The standard for REB evaluation of the risks of therapeutic interventions has even greater potential impact. REBs must determine that therapeutic interventions meet the requirement of clinical equipoise. That is, they must find that at the start of the study there exists within the relevant community of clinical scientists a state of "honest, professional disagreement as to the preferred treatment." The basic idea underlying clinical equipoise is that research subjects ought not to be at risk of receiving inferior treatment solely to test a promising, but unproven, experimental treatment. The upshot of the requirement is that clinical trials can proceed only where the relevant community of experts is in a state of significant disagreement as to the relative therapeutic merits of the therapeutic interventions to be


compared (i.e., the experimental treatment and the control(s)). The object of the clinical trial is to resolve this disagreement by providing compelling evidence of the relative therapeutic merits of the experimental treatment and the control(s).

The requirement for clinical equipoise has important implications for the design of clinical trials, and thus the evidence they produce. Where proven standard treatments for the subject's condition exist, clinical equipoise requires that the experimental treatment be compared against one or more of the standard treatments (as an active control). Where no proven standard treatment exists, or where it is consistent with the standard of care not to offer treatment (e.g., for minor conditions like allergic rhinitis), a placebo-controlled trial may proceed. It follows that, wherever possible, clinical trials must be designed to give comparative rather than absolute evidence of safety and efficacy. The implications for the drug approval process are important: if REBS consistently enforced the clinical equipoise requirement, the clinical trials submitted to federal authorities (and ultimately relied upon by physicians practicing EBM) would provide optimally useful data with which to determine the safety and efficacy of treatments.

B. Identifying the potential for coordination

1. Standard setting

The caveat is that, if applied consistently, the requirement for clinical equipoise would have important implications for federal drug approval and physicians practicing EBM. While it is not exactly clear what Canadian REBS are doing, it is evident that they are not consistently applying the clinical equipoise requirement. This can be adduced from the fact that clinical trials in Canada involving pharmaceuticals commonly continue to be placebo-controlled.173

173 Charles Weijer, "Placebo Trials and Tribulations" (2002) 166 Can. Med. Assoc. J. 603. While I have found no evidence on the proportion of placebo-controlled trials conducted in Canada, the fact that such trials are common can be safely deduced in consideration of the resources devoted to the National Placebo Initiative, a joint effort of Health Canada and the Canadian Institutes of Health Research, online: <http://www.cihr-irsc.gc.ca/e/5466.html>. For indirect evidence, see Joel Lexchin, "New Drugs with Novel Therapeutic Characteristics: Have They Been Subject to Randomized Controlled Trials?" (2002) 48 Can. Fam. Physician 1487.
The reason for the divergence between policy and practice lies in the lack of coordination between institutional and federal oversight and approval policies and practices. While it is unclear what standards the TPD employs in evaluating the risks and benefits of new therapeutic products, the standard is evidently not clinical equipoise, for the TPD continues to issue NOCs on the basis of placebo-controlled clinical trials of drugs even when proven standard treatments exist. Canadian REBs likely approve these trials because of unclear and possibly inconsistent guidance.

While the trial design implications of the clinical equipoise condition contained in the Tri-Council Policy Statement are pretty clear, matters were muddied somewhat when, in enacting the new clinical trials regulations, the federal government endorsed the ICH guideline rather than the Tri-Council Policy Statement. The Tri-Council Policy Statement and the ICH guideline do not contain inconsistent standards for risk evaluation. The problem is that the ICH guideline does not establish any clear standards for risk evaluation (though it says such evaluation must take place), and, further, has a permissive clause on the use of placebo controls.

The clear conflict between the Tri-Council Policy Statement and REB practice, and the possible conflict between the former and the ICH guideline, underscores the need for a coordinated effort at setting standards. In view of the considerable implications of the risk evaluation standards, this effort should be open and transparent, and should consider the implications for research subjects and the public at large.

Currently, the debate over risk evaluation standards is largely focused on the issue of appropriate placebo use. The field of debate is occupied, on the one hand, by those who assert that the widespread use of placebo controls is inconsistent with the ethical and legal duties of researchers to subjects, and, on the other, by those who argue that the practice is justified on the grounds that placebo-controlled trials are

174 ICH, Consolidated Guideline, supra note 164.
175 ICH Harmonised Tripartite Guideline: Choice of a Control Group and Related Issues in Clinical Trials (ICH E10).
methodologically superior to, and cheaper than, active-controlled trials.\textsuperscript{177} A national working group on the use of placebo controls (the National Placebo Initiative, struck jointly by Health Canada and the Canadian Institutes of Health Research) has recently produced a final report which contains an illuminating and very persuasive case for a restrictive stance on the use of placebo controls in Canadian research.\textsuperscript{178} Despite the fact that debate over risk evaluation standards ultimately underlies the placebo debate, the working group was not given the mandate to issue recommendations on such standards (e.g. clinical equipoise).

The recommendations of the National Placebo Initiative provide a compelling starting point. However, a coordinated effort to address the standards issue could usefully broaden the debate by encouraging the adoption of a systemic perspective. Such a perspective would consider the implications of the standards governing REB review for drug approval and EBM. Ensuring that TPD standards of evidence for the efficacy of therapeutic products are in conformity with the requirement of clinical equipoise would be consistent with the Romanow commission's proposed mandate for a national drug agency (which would replace the TPD and related bureaux within Health Canada). Among other things, the commission recommended that the drug approval process involve "[comparison of] the efficiency of new prescription drugs to existing drugs on the market or to other therapeutic approaches that could be used."\textsuperscript{179} As the Romanow commission noted, "this is critically important information for policymakers and health care providers to guide their decisions on including prescription drugs in insurance plans or in choosing the most effective medication or treatment."\textsuperscript{180} The Romanow commission was concerned to move drug approval in this direction in light of mounting evidence of the considerable cost,\textsuperscript{181} and the questionable therapeutic


\textsuperscript{178} National Placebo Initiative, \textit{Final Report of the National Placebo Working Committee on the Appropriate Use of Placebos in Clinical Trials in Canada} (Ottawa: Health Canada and the Canadian Institutes of Health Research, 2004).

\textsuperscript{179} Commission on the Future of Health Care in Canada, \textit{supra} note 149 at 200.

\textsuperscript{180} Ibid.

\textsuperscript{181} Canadian Institute for Health Information, \textit{supra} note 26.
Clinical Drug Trials

progress, associated with many new drugs. If the authorities responsible for drug approval are to assess new drugs on a cost-benefit basis, and to disseminate useful information on the comparative safety and efficacy of treatments, they will have to work with REBs and other stakeholders to determine the feasibility of system-wide adoption and enforcement of the clinical equipoise requirement.

2. Information sharing

The accuracy of risk assessment and evaluation depends in large part on the quality and extent of information before the reviewer. Both REB and TPD risk assessment and evaluation can benefit from mutual sharing of information.

The prospects for information sharing are many. Considering the excessive workloads under which they operate, REBs would benefit greatly if the TPD granted them access to its information on the risk-benefit profiles of pharmaceuticals. The TPD could also play an essential role in the REBs' effort to ensure that research subjects are safe by relaying alerts, adverse event reports, and notices of termination of studies in other countries. Realizing these benefits would require a reversal of TPD policy, which currently goes to great lengths to maintain the secrecy of commercially sensitive information. Such a policy reversal would lend substance to the rhetoric of transparency and accountability which now dominates the regulatory reform movement in Canada, and would be a natural consequence of the international movement toward clinical trials registries.

The TPD may likewise benefit from information sharing arrangements with REBs. Notice of REB refusal to approve clinical trials

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183 While no such information would be available for new molecular entities, the greatest proportion of new pharmaceuticals coming to market are "me too" drugs. Sometimes, these have pharmacological profiles similar to their competitors' drugs.

184 See Lexchin, "Secrecy," supra note 121.

185 Sibbald, supra note 102; External Advisory Committee on Smart Regulation, supra note 128.

186 Infra note 191.
may prove particularly helpful, considering that nothing currently prevents sponsors of clinical trials from “shopping” their ethically and/or scientifically deficient protocols to different REBs across the country. Notices of refusal, particularly when many in number, may alert federal reviewers that something may be amiss with clinical trial evidence eventually submitted in support of an application for an NOC.

Though commonly thought unachievable in light of the contrary interests of the pharmaceuticals industry, the informational holy grail would be the establishment of a comprehensive and mandatory national electronic clinical trials registry, accessible to REBs, the TPD, physicians, and ideally, the general public. The registry would be an electronically searchable database containing comprehensive information on all completed and ongoing clinical trials. Because trials conducted outside Canada can be used to support drug approval, it would be essential that such a registry be linked to others internationally. A mandatory national registry linked with registries around the world would make it much easier for all to obtain some of the most important evidence on which they must base their decisions. It would further enable communication about evidence between REBs and the TPD. Because the potential benefits of a mandatory national clinical trials registry are significant, it merits intensive feasibility studies.

At present, the prospects for the establishment of a clinical trials registry may be improving, at least if recent developments in the United States are any indication. Former New York State Attorney General Elliott Spitzer recently filed suit against GlaxoSmithKline, charging “repeated persistent fraud” for its failure to disclose unfavourable results of clinical trials in which Paxil® was being tested for the treatment of depressed adolescents. In the aftermath of public controversy following the suit, the American Medical Association

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187 Lemmens & Freedman, supra note 86.
(AMA) and the Association of American Medical Colleges (AAMC) issued calls for the Department of Health and Human Services to establish a national clinical trials database. AAMC President Dr. Jordan Cohen said “the association believes a mandatory public clinical trials registry would be a significant step toward strengthening the reliability and credibility of clinical research, which is so vital to advancing medicine and improving health.”

If mounting momentum towards the establishment of registries proves successful; it may be hoped that Health Canada will follow suit by instituting a mandatory Canadian database, and exploring possibilities for sharing results collected in other national and international databases. REB and TPD review would be vastly improved under this scenario.

3. Resource sharing or pooling

Resource sharing or pooling is yet another potential point of mutually beneficial coordination between REBs and the TPD.

Risk assessment suffers when REBs lack the requisite expertise. Accurate risk assessment requires the analysis of complex scientific information and the calculation of the probability and magnitude of harms and benefits. Where REBs do not have the capability to conduct risk assessments properly, their ultimate risk evaluation will be skewed, regardless of the conceptual coherence of their standards. One possible remedy would be for the TPD and REBs to establish a resource pooling arrangement, whereby scientists (including those at the TPD) who are


willing to be called in for ad hoc reviews could be identified in a coordinated way. TPD participation would be essential, given its experience in calling upon outside experts for their own reviews. Of course, as indicated above, independence is an important concern with respect to reviews conducted by external scientists. Measures to ensure the independence of the reviews would be required, and the consultation ought only to include risk assessment, not evaluation. An alternative arrangement would have the TPD enter into a resource sharing arrangement with REBs, whereby it would volunteer its own scientists for REB review in exchange for access to scientists from REBs whose expertise it could use. As an effective means to integrate the institutional cultures of REBs and the TPD, this alternative may be most attractive.

A resource-sharing arrangement between the TPD and REBs may also partially resolve problems of democratic legitimacy created when risk evaluation is dominated by scientists. Such an arrangement might allow the TPD to call on lay and other non-scientist members of REBs to consult on policy development affecting risk evaluation, or participate in the evaluation of potentially controversial new treatments. REB members will generally have relevant expertise and valuable experience in bringing public concerns and perceptions to bear on the evaluation of the risks and benefits of new technologies and treatments.

V. CONCLUDING REMARKS: DIRECTIONS FOR REFORM OF RESEARCH GOVERNANCE

Recognition of the relationship between REB and TPD review and of the importance of coordination in policy making and implementation helps identify priorities for systemic reform of the governance of clinical trials in Canada. The case for systemic reform is complicated, as is the task of comprehensively identifying reform priorities. Nonetheless, without making any pretence to comprehensiveness, the following steps and reforms are essential to the realization of a system of national governance operating in accord with the ideal of coordinated review.

\footnote{For more comprehensive recommendations, see Jocelyn Downie & Fiona McDonald, "Revisioning the Oversight of Research Involving Humans in Canada" (2004) 12 Health L.J. 159.}
First, a major summit aimed at clearly identifying problems with the status quo and priorities for reform of the governance of human subjects research should be held in Canada. The summit should be jointly convened by representatives of federal and provincial/territorial governments, and should include representatives of stakeholders including health professionals, public research institutions, the pharmaceuticals industry, patients, REB members and administrators, lawyers, bioethicists, and members of the lay public.

Second, it is critical for the federal and provincial/territorial governments to reach an agreement on (1) the need for a national governance strategy and structure; (2) the costs and benefits of developing this structure, available resources, and cost sharing; and (3) the basic principles for reform.

Third, legislation should be drafted to establish an office within Health Canada with departments responsible for (1) the establishment and maintenance of a mandatory national clinical trials database; (2) the accreditation and oversight of federal and institutional review bodies; and (3) the coordination of resource sharing between federal and institutional bodies.

Fourth, there is also a need for the establishment, preferably through legislation, of (1) consistent, mutually supportive, national procedural and substantive standards for federal and institutional review of research; (2) meaningful penalties for non-compliance with the above-mentioned standards by institutions, researchers, and research sponsors; and (3) enforcement and compliance mechanisms.

Clinical trials have privileged evidentiary status within the drug approval process and within clinical medicine. The ongoing discovery and improvement of medical treatments through clinical science depends heavily on the maintenance of public trust and confidence in the scientific and ethical integrity of research. Institutional and federal oversight bodies play essential roles in ensuring that the conduct of clinical science merits the public's trust. For REBs and the TPD to fulfill their respective roles in safeguarding the rights and welfare of patients and the Canadian public at large, the government must recognize and respond to the need for a national governance structure in which the federal and institutional review of clinical research is coordinated and harmonized.