

Federal Regulation of REB Review of Clinical Trials: A Modest But Easy Step Towards An Accountable REB Review Structure in Canada

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Introduction: REB Review as Public Mandate

In 2000, a working group on the regulation of clinical trials, established by the Swiss Intercantonal Drug Regulatory Agency submitted a report on the regulation of clinical trials in the country, focusing in particular on the role and regulation of research ethics boards (REBs).¹ The working group had been established in the wake of a controversy surrounding a contract research organization, VanTx, and a private REB, the Freiburger Ethik-Kommission International (FEKI). This controversy hit the Swiss media after an Estonian newspaper reported that VanTx had been importing research subjects into Switzerland from foreign countries, and was often using highly questionable recruitment procedures. The report of the Working Group confirmed that serious problems were associated with the recruitment of subjects in phase I and II trials organized by VanTx. It found that VanTx had been flying subjects in from Estonia, Poland, Macedonia and the Slovak Republic, and that it had also targeted asylum seekers to participate in research in exchange for a participation fee. The report raised concerns about the consent procedures and about the focus on the recruitment of vulnerable people.² Interestingly, the report also revealed administrative concerns related to VanTx and

FEKI. The director of VanTx appeared to combine this function with his position as director of the local subsidiary of FEKI, the REB that was approving the questionable research of his company.³

Following the VanTx scandal, the Cantonal Authorities of Bale decided to intervene by introducing the requirement that any research involving human subjects had to be reviewed by a recognized regional ethics review board, thereby making it impossible for the local subsidiary of FEKI to continue its work. FEKI challenged that decision in court and argued that the government had no authority to regulate REB review. In 2003, the Swiss Supreme Court (Bundesgericht) confirmed that the cantonal authorities have the authority to assign exclusive authority to a regional research review board, thereby depriving private REBs within their jurisdiction of their authority to operate. The highest court ruled that the organization of research review is part of the cantons' legitimate exercise of state authority in matters of health protection. Although it did not rule out a role for private parties in this system, it explicitly stated that they could only do so under explicit delegation of authority from the health authorities. "A research ethics committee fulfills a control function with a mandate from the state," the court ruled, "and the exercise of such function should not be open to whoever is interested."⁴



This case is, even in the international context, one of the rare court decisions that touch on the role of REBs and their relation to state authority. It confirms that REBs are seen as having an important public mandate with respect to health protection, and is therefore interesting as an introduction to a legal analysis of the basis for regulatory authority over REBs in Canada.

In this paper, I will argue that a clear governmentally-enforced regulatory structure around REB review is not only needed, but also relatively easy to accomplish in at least one area. A clear, accountable and independent REB system is particularly needed, I will suggest, in the context of clinical research involving new drugs and medical devices. The federal government, I will maintain, should have no difficulty imposing a binding regulatory regime around REB review in the context of such clinical trials. Various recent controversies have illustrated the serious concerns associated with the increasingly competitive context in which clinical trials are conducted. Interestingly, these controversies also confirm that the federal government can legitimately impose a regulatory structure which clearly could be qualified as a *bona fide* exercise of their public authority over the protection of the health and safety of its citizens.

The Canadian Situation

In Canada over the last couple of years, various reports and commentaries have pointed to the need for more coherent regulation of REBs.⁵ The introduction of the Tri-Council Policy Statement in 1998 has provided impetus for further initiatives aimed at improving the coherence of REB review across the country. When the three major federal funding agencies launched the Tri-Council Policy Statement in 1998, they specified that institutions receiving federal funding had to comply with the first two sections of the TCPS (dealing with, among other things, the composition, structure and authority of REBs) by a specific date in order to continue to be eligible for funding. The funding agencies also started to negotiate with institutions about the signing of formal Memoranda of Understanding, to provide a stronger contractual basis for requiring the respect of the Tri-Council Policy for all forms of research undertaken within a federally funded institution. Most of the institutions were considered to comply with the first two sections of the TCPS by an extended deadline of December 1, 1999. However, until recently at least, the Tri-Council Ethics Secretariat continued to discuss the implementation of appropriate standards with

institutions which were deemed not to adhere to these minimal REB requirements. If the enforcement of adherence to the most minimal formal requirements and structures for REB review has proven relatively difficult in Canada, one can presume that coherence with respect to other aspects of REB review is far from achieved at this point.

In any event, as has often been emphasized, the Tri-Council Policy does not apply to research undertaken outside the context of funded institutions and can therefore not be seen as the single basis for a coherent uniform approach towards REBs in Canada. Even if the funding agencies are ultimately successful in promoting adequate REB review and making the REB system fully accountable and coherent within all funded institutions, this will only have a limited moral impact on REBs that function outside of these institutions. It can be expected that TCPS initiatives will be closely watched and likely followed by other funding agencies and by governmental agencies that are themselves involved in conducting research (e.g. research undertaken by various Ministries such as Defense and Health). For example, the REB that was set up by Health Canada to review its own research, and the REB that will be established to review protocols for stem cell research under the new *Assisted Human Reproduction Act*, would likely be influenced by the funding agencies' initiatives related to REBs. Other REBs outside these categories, or other organizations involved with research, will probably be influenced by the moral status that the TCPS has attained in Canada. But the real impact of the funding agencies' initiatives will be limited when it comes to research that is undertaken outside of academic health care centers and not funded by any of the federal agencies. Other initiatives may also promote a more accountable and coherent REB system. In the 2000 Law Commission of Canada Report on research governance, the late Douglas Kinsella discussed how the Canadian Medical Association Code of Ethics' requirements related to the duties of Canadian physicians who participate in research inspired the Alberta College of Physicians and Surgeons to implement its own REB structure for all research undertaken outside academic institutions.⁶ The work undertaken by the National Council on Ethics in Human Research, for example, may have an impact outside federally funded institutions. Initiatives undertaken with support of the NCEHR to implement a voluntary accreditation and certification system will also contribute to a more accountable REB system in Canada.⁷ Elsewhere in this journal, McDonald and Beagan argue that a much more evidence-based approach needs to be taken in order to determine how well research subjects are actually protected.⁸



But will this be sufficient? The initiatives undertaken in Canada to introduce an accreditation system fit the traditional self-regulatory model, in which those involved in medical research undertake to impose specific standards of research ethics review and introduce a quality label for REBs and, in the case of certification, research ethics members. These initiatives, in the current context, would not be binding. Although they may promote the quality of REB review and may lead to the establishment of a standard of practice that most REBs will aim at, I would argue that they would not be sufficient to safeguard the public interest. I have developed elsewhere the argument that REBs have an official mandate to protect research subjects and the public, and that this public mandate should be reflected in a clear regulatory framework that can be enforced through state authority.

Clinical Trials and the Need for a Strong REB System

Two categories of concerns can be distinguished in the context of the commercialization of clinical trials. First, commercial pressures may have an impact on the protection of human research subjects. The pressure on pharmaceutical companies to develop new drugs has turned recruitment of research subjects into one of the major challenges in drug development for pharmaceutical sponsors.⁹ As a result, a variety of recruitment strategies are increasingly used, targeting both researchers and research subjects. Sponsors offer various recruitment incentives to researchers, who may receive considerable financial benefits from recruiting research subjects and from doing so as fast as possible.¹⁰ Research participants are also offered significant amounts of money, even though such payments are generally frowned upon by various research ethics guidelines and policies. Discussing the potential result of these practices in much detail exceeds the scope of this paper, but it is fair to say that concerns have been raised that commercial competition for research subjects has led to inappropriate recruitment practices. For example, some controversies suggest that financial interests may push researchers or research subject recruiters to disrespect the inclusion criteria, either

by falsifying test results on subjects or by repeating clinical tests until the results are reconcilable with the inclusion criteria. In some instances, financial incentives may also undermine appropriate informed consent procedures. These practices can negatively affect the safety and well-being of research subjects, and can also have an impact on the reliability of the research outcome. If inclusion criteria are not respected, the scientific quality of the study is affected and the representativeness of the outcome may be undermined. The safety of human subjects can further be compromised by the potential commercial interest in keeping subjects in the clinical trial even when there are reasons to either halt the trial, or to take individual subjects out of the trial. This will particularly be the case if researchers receive financial benefit from keeping subjects in a clinical trial until the trial ends. The various financial incentives to include patients in clinical trials can also be particularly problematic if it leads researchers to push patients in need of treatment towards participation in placebo-controlled studies.

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A second category of concerns related to commercial involvement in clinical trials involves research integrity. Various empirical studies have indicated that research funded by industry tends to lead to an outcome that is favourable to the sponsor.¹¹ Although these empirical studies do not establish a clear causal link between the source of funding and the outcome of research, they do raise concerns about the potential bias in industry-funded research. This concern should be combined with the increasing dominance of industry over clinical trials related to drug development. Clinical trials have gradually moved outside academia in the last decades and into a highly specialized clinical trials industry. In addition, the percentage of industry funding in research has steadily increased, making academic centers increasingly dependent on research funding, thus influencing the type of research undertaken in academic centers. If industry-funded research is the sole or very dominant source of information on the safety and efficacy of a new compound, and if, as various studies suggest, these studies show a bias in favour of products produced by the sponsor, there is reason to be concerned about the reliability of much of the evidence that supports drug approval applications and that is



often used in the development of clinical practice guidelines.

An interesting example of how industry interest are more and more directly using clinical trials as part of a marketing effort, raising questions about the impact of commercial interests on the outcome of the results, is the recently exposed history behind much of the scientific literature related to the safety and efficacy of sertraline hydrochloride, better known under its brand name Zoloft.¹² David Healy and Dinah Cattell analyzed the literature that discussed the efficacy and safety of this compound. They found that most of the scientific articles on sertraline were prepared by *Current Medical Directions Inc*, a medical communications agency specialized in the development of communication strategies for drug sponsors. The publication of these articles in the most respected academic journals, such as the *Journal of the American Medical Association*, the *American Journal of Psychiatry* and the *Archives of General Psychiatry*, provided immediate credibility to analyses which were largely prepared within the context of a marketing strategy. Interestingly, those studies that were organized by the communications firm were much more likely to be published in journals with the highest impact factor than the few more independent studies.

Whereas bias related to the source of funding may reveal an unconscious and indirect impact of industry on results of clinical trials, there are also concerns about more direct interference. The substantial profits associated with bringing new blockbuster drugs to the market and the commercial pressure to do so quickly have been invoked to explain a variety of other practices in which pharmaceutical sponsors increasingly engage, and which more directly threaten, the integrity of medical research. In addition to the recruitment of research subjects, commercial sponsors increasingly control the design of the study, the gathering of data, the analysis of the results and the subsequent publication process. Clinical trials or other forms of research involving drug products are in and of themselves increasingly part of a complex marketing scheme. Various recent controversies have raised concerns about how these practices diminish the reliability of the results of clinical trials.¹³

Since research integrity is a crucial component of the drug approval system as well as of the establishment of appropriate clinical practice, these concerns not only affect the safety and well-being of research subjects, but also the safety of the future consumers of health care products and the costs of the health care system. Research subjects and consumers can be directly harmed when scientific research is compromised by the impact of commercial interests on research.

This short discussion of the challenges related to the commercialization of clinical trials should provide sufficient background information for a further discussion of the role of REB review and the need for more stringent regulation of such review in the context of clinical trials. Two issues must be kept in mind. First, the commercialization of clinical trials has created pressures which may affect the individual behaviour of those involved in medical research. Second, on a more structural level, the safety, health and well-being of research subjects and consumers

is threatened by some aspects of the commercialization of medical research. The question that I will address further in this paper is: what are the implications of these developments in terms of the authority and role of the drug regulatory authorities in the regulation and oversight of REBs? I will not discuss in this paper other regulatory changes that, in my view, are urgently needed to strengthen the review of the safety and efficacy of new drugs and medicinal products.¹⁴

REB Review and Clinical Trials Regulations

The first thing one has to recognize is that the movement of clinical trials outside academic centres has significantly reduced the impact that the granting agencies possess on this form of research. Clinical trials are increasingly undertaken by specialized contract research organizations (CROs), which either conduct these trials in their own research centres, or engage physicians in private practice to enroll patients and perform some of the research tasks. The protocols supporting these clinical trials are generally reviewed by private commercial REBs, which have boomed over the

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last decade in both Canada and the U.S. Some CROs have set up their own internal REB to review in-house studies. But most of these clinical trials are reviewed by non-institutional REBs, often referred to as “independent review boards”, which operate as independent for-profit entities of which the sole commercial activity is the review and monitoring of medical research.

Commercially-sponsored research undertaken outside of the federally funded institutions is submitted to regulatory oversight and REB review to the extent that it involves clinical trials that aim at the approval of drugs or medical devices in Canada. In that case, the sponsor has to obtain an authorization to import or sell a drug for clinical trial purposes from Health Canada’s Therapeutic Products Directorate.

The 2001 *Clinical Trials Regulations* explicitly refer to REB review as part of the requirements for clinical trials that are part of the drug approval process.¹⁵ The regulations first mention the REBs in the definition section. According to the regulations, an REB is:

- ... a body that is not affiliated with the sponsor, and
- (a) the principal mandate of which is to approve the initiation of, and conduct periodic reviews of, biomedical research involving human subjects in order to ensure the protection of their rights, safety and well-being;
- and
- (b) that has at least five members, that has a majority of members who are Canadian citizens or permanent residents under the Immigration Act, that is composed of both men and women and that includes at least
 - (i) two members whose primary experience and expertise are in a scientific discipline, who have broad experience in the methods and areas of research to be approved and one of whom is from a medical discipline or, if the clinical trial is in respect of a drug to be used for dental purposes only, is from a medical or dental discipline,
 - (ii) one member knowledgeable in ethics,
 - (iii) one member knowledgeable in Canadian laws relevant to the biomedical research to be approved,
 - (iv) one member whose primary experience and expertise are in a nonscientific discipline, and
 - (v) one member who is from the community or

is a representative of an organization interested in the areas of research to be approved and who is not affiliated with the sponsor or the site where the clinical trial is to be conducted. (comité d’éthique de la recherche)¹⁶

The language used in this definition confirms the traditional view that REBs have a public mandate to protect the “rights, safety and well-being” of Canadians. This mandate is shared with many official governmental agencies. Similar terms are found back in documents supporting, for example, Health Canada.¹⁷

When sponsors want to sell or import a drug for use in a clinical trial, their request for authorization to Health Canada must include the name and contact information of the REB that approved the study (C.05.005(c)(x)), as well as the name and contact information of any REB that previously rejected the protocol and the reasons for this rejection (C.05.005(d)). REB review is also required when amendments are made to a previously authorized study (C.05.008(1)(c)(ii)). Reference to REB review is also made under the section describing sponsors’ obligations with respect to good clinical practices. The regulations impose on sponsors a general duty to “ensure that a clinical trial is conducted in accordance with good clinical practices” (C.05.010) and give as one of the examples the duty to obtain approval by an REB before commencing a clinical trial at a particular site (C.05.010(d)). REB review is thus clearly part of the regulatory procedures that are required in order to obtain permission to conduct clinical trials involving a drug or medical device that is not yet approved for use in Canada.

Clinical Trial Regulations and the ICH-GCP

There are, however, no further references to what REB review specifically entails and what the power and regulatory authority of these REBs is. The precise content of the “good clinical practices” that are connected to REB review in the regulations refers to documents with a weaker regulatory status. For instance, more information on good clinical practice can be found in “Good Clinical Practices”(GCP) guideline, also known as the ICH-GCP Guideline, which Health Canada introduced into its framework as a “guidance document”. The ICH-GCP is an international guideline that was adopted as part of a harmonization effort of clinical trials by the drug regulatory agencies of the U.S.A., Europe



and Japan.¹⁸ The goal of this harmonization effort is to streamline the approval of drugs in these jurisdictions. Canada had observer status at the conference where these guidelines were adopted.

The ICH-GCP begins by enumerating some general principles, such as the primordial importance of respecting the rights and well-being of research subjects and the need for a careful weighing of risks and potential benefits of clinical trials. It also contains rules about the responsibilities and role of various parties involved in clinical research. For example, it discusses the required qualifications for researchers, how they ought to conduct research and their reporting obligations. The ICH-GCP specifies the duties of sponsors with respect to the management of the trials and the monitoring and reporting of adverse events, and also elaborates on the content of the protocol and the investigator's brochure. The ICH-GCP contains many of the substantive rules with respect to the REB review of clinical trials, rules which are often similar to the ones enumerated in the Tri-Council Policy Statement. It is worth noting, however, that the Tri-Council Policy Statement combines in one policy document a clear reference to the obligation to obtain ethics approval for all federally funded research with substantive details of how this review should take place and what the content of the review should be. In contrast, the detailed rules about REB review that we find in the ICH-GCP are not part of Health Canada's *Clinical Trials Regulations* that impose REB review for all clinical trials conducted in the context of drug development in Canada.

The legal status of the ICH-GCP in Canada is ambiguous, since it is not part of the formal regulations enacted by the government. Guidance documents are intended to provide assistance to industry and health care professionals on how to comply with the regulations. They also can be used by regulatory agents to establish whether good clinical practices are respected in the research that supports an application. As Health Canada states, "Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate scientific justification."¹⁹

In Canada, clinical trials which are part of the drug approval process are thus submitted to a formal regulatory requirement to undergo REB review. The Clinical Trial Regulations of 2001 specify the composition of these REBs, but contain neither further substantive details as to the scope and

content of REB review, nor any further procedural requirements related to REB review.

This soft regulatory approach towards REB review contrasts sharply with the importance attached to it in the context of clinical trials. The Regulatory Impact Statement that accompanies the 2001 regulations confirms that Health Canada recognizes REB review as a fundamental part of the drug regulatory process. Various references are made in this Regulatory Impact Statement that highlight how important REB review really is. The text explicitly states that REB review "... helps to ensure that conflict of interest situations are avoided and that the health and safety of trial subjects remain the paramount concern." Interestingly, it refers to the REBs' role with respect to initial review, but also indicates that REBs are responsible for "periodic reviews."²⁰

Clearly, REB review and monitoring by REBs of on-going research is seen as a part of the good clinical practices that the regulatory agency wants to see respected. And yet, although the ICH-GCP rules with respect to REB review can be used to determine whether an REB is acting in accordance with good clinical practice, there is no clear regulatory power to hold these REBs accountable for violations of these rules. The 2001 Regulatory Impact Statement also explicitly recognizes that there is currently no accreditation system for REBs and that Health Canada is looking into implementing such system in conjunction with CIHR and the NCEHR. It seems remarkable, though, that three years after the introduction of these new regulations, no clear regulation-based authority and no clear regulatory guidance has been given to REBs. At the same time, Health Canada's Health Product and Food Branch Inspectorate is now inspecting REBs as part of the compliance review of clinical trials. In its *Summary Report of Inspections of Clinical Trials in 2003-2004*, the agency reports that it visited 5 REBs which approved the 45 clinical trials it inspected.²¹ The report points out how inspectors made observations about regulatory deficiencies in systems and procedures, membership and records among some of the REBs inspected. It can be argued that Health Canada is thus enforcing the ICH-GCP requirements related to REB review through its inspection process. In principle, Health Canada has the authority to suspend clinical trials if good clinical practice, is not respected.²² If REB review does not take place in accordance with the ICH-GCP, it could be argued that good clinical practice is not being respected and that a trial authorized by an inappropriately functioning REB ought to be suspended. So far, no clinical trial seems to have suspended on this basis. A firmer regulatory structure for



REB review, with also clear regulatory sanctions attached to non-compliance, would provide a much more solid legal basis to intervene. It is also clear, in light of the high number of clinical trials undertaken in Canada that the review remains very sporadic.

Federal-Provincial Jurisdiction and REB Review

Concerns about encroachment on the jurisdiction of the provinces may have made the federal government reluctant to engage in the development of a clear regulatory structure surrounding REB review. This may explain why ambiguous references are made when it comes to the authority of these REBs, and to the obligatory nature of REB review. Concerns about the issue of federal and provincial jurisdiction in this area are not surprising. Some issues that are typically covered in research ethics guidelines, for example those dealing with the behaviour of physician-researchers, may indeed fall within the category of the regulation of the profession, which is traditionally seen as falling under provincial jurisdiction. Provincial governments would have the jurisdiction to enact regulations related to the involvement of various professionals in the context of research.²³ They could develop a regulatory structure, enacting requirements for participation in research and establishing supervision of the behaviour of health care professionals. They could also impose a system of accreditation or licensing on researchers, and could mandate specific administrative bodies, such as REBs, to fulfill a role in this context. Provincial power over the accreditation of physician-researchers and other health care workers such as nurses could also affect REBs, since some of these professionals are represented on REBs. Provincial regulations of health care professionals and of researchers could impact on REB membership requirements. Provinces could for example determine what research ethics training requirements these professionals have to fulfill in order to be qualified.²⁴

It is clear, however, that the federal government considers REB review to be a fundamental part of the protection of human subjects in the context of clinical trials undertaken as part of the drug approval process. As the Regulatory Impact

Statement points out, the revised clinical trials regulations “provide Federal recognition of the important service provided by REBs.”²⁵ There is no doubt that the regulation of pharmaceuticals falls under the jurisdiction of the federal government. Both the criminal law power and the Peace, Order and Good Government (POGG) powers can be invoked in this context.²⁶ Martha Jackman discusses in a 2000 article in the *Health Law Journal* how the Supreme Court has dealt with the use of both the criminal law power and the POGG clause to justify federal jurisdiction in areas related to the protection of health. The 1983 decision in *R. v. Wetmore*, in which the Supreme Court confirmed that the

Food and Drugs Act is a legitimate exercise of the federal government’s criminal law power.²⁷ In the 1982 case of *R. v. Schneider*²⁸ the court also found that jurisdiction over health could be found under POGG as health was a matter of national concern.

While there is no doubt that drug regulation falls under federal jurisdiction, the question

will be whether it is appropriate to consider research ethics review as a fundamental part of the regulatory regime. In the context of the distribution of powers between the federal and provincial governments, federal regulation of REB review could still be seen as an inappropriate encroachment on provincial jurisdiction if there is no clear connection between the aims and purpose of federal drug regulation and REB review. It is therefore interesting to evaluate whether REB review could be seen as a coherent part of the drug regulatory system, and whether it could be justified under the criminal law power of the federal government.

As Martha Jackman points out, the Supreme Court assigned the federal government a wide scope of power to enact criminal sanctions in the area of health protection.²⁹ The only requirement imposed is that “the legislation must contain a prohibition accompanied by a penal sanction and must be directed at a legitimate public health evil.”³⁰ I have mentioned earlier that clinical trials have increased considerably in the last decades. It is definitely an important social activity in which a large number of Canadians are participating and, as argued earlier, one which exposes research subjects to considerable risks. The various official references to the role of REBs with respect to the protection of the “rights, health and well-being of subjects” resonate with the lan-

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guage used in federal regulatory regimes to justify the use of criminal law. In addition, the discussion of the impact of commercialization on medical research shows that there are public health concerns related to the safety and efficacy of pharmaceutical products. If, as TPD points out, REBs play a crucial role with respect to conflicts of interest, they are definitely a crucial component of the drug regulatory regime, and more particularly, a crucial review body that should contribute to avoiding inappropriate influence by commercial interests on the research process and research outcome.

An interesting reference is also made in the *Wetmore* case, by Laskin C.J. (as he then was), to the fact that federal regulation of the pharmaceutical industry could be justified under the federal trade and commerce power.³¹ Clinical trials, in particular multi-site trials, are part of the commercial development of drugs and pharmaceuticals, which are developed, traded and sold across the country. It could be argued that good clinical practices and the REB review associated with these good clinical practices can be regulated by the federal government as part of the regulation of this inter-provincial trade and commerce. This would enable the federal government to enact legislation without the need to invoke its criminal law power, thus making it possible to develop a regulatory regime that uses more administrative sanctions than criminal law.

It would also be interesting to consider a POGG basis to justify federal regulation of research ethics review, for example if one wants to avoid having to justify the use of criminal law sanctions. The POGG clause has been accepted as a basis for federal jurisdiction in the area of health in cases of emergency and in cases of “national concern”. While the emergency concern could be used to regulate research and REB review in the context of epidemics such as SARS, the “national concern” basis is the most likely candidate for federal jurisdiction over research and REB review. In *R. v. Crown Zellerbach Canada Ltd.*, Le Dain J., writing for the majority of the Supreme Court, specified that in order to justify federal jurisdiction based on this ground, an issue must “have a singleness, distinctiveness and indivisibility” and its impact on provincial jurisdiction must be reconcilable with the constitutional division of power.³²

Using the “national concern” doctrine, federal regulation of pharmaceuticals, with REB review of clinical trials as an indivisible part of it, could likely be justified under this rubric. Concerns raised by recent controversies in the context of pharmaceuticals could be invoked to argue that there is something distinct and indivisible about drug research and

development, and that a federally organized REB review system is part of the regulatory regime needed to address these national concerns. The use of the POGG ground could perhaps also make it possible to support the argument that a comprehensive REB review system has to be developed on the federal level, covering not only clinical drug trials but also other forms of research.

For all of these reasons, it seems obvious that the federal government can clearly regulate REB review in the context of clinical trials that are part of drug development. In fact, one specific aspect is currently explicitly regulated as part of the 2001 *Clinical Trials Regulations*, i.e. the need for REB approval. It seems inconsistent to recognize the importance of REB review, to stipulate even that REBs are *the* crucial administrative bodies that ensure that conflicts of interests are avoided, and then leave all details of REB review other than membership issues up to the good will of these often commercially focussed REBs.

In June 2003, the House of Commons Standing Committee on Health discussed the absence of a regulatory framework for REBs. In a report on the regulation of prescription drugs in Canada, it mentioned that several witnesses had expressed concern about the “uneven standards and inconsistent operations among research ethics boards across the country”, and about the lack of a national body mandated to provide oversight for research. It did not make any clear recommendation about the need to develop a comprehensive REB framework for all forms of research. It seemed to recognize implicitly, however, as I discussed here in this paper, that the federal jurisdiction over the regulation of REBs is clear in the context of clinical trials. It recommended that “Health Canada develop standards that establish an accreditation process for research ethics boards assessing clinical trials.”³³ In light of this clear recognition of the importance of a coherent REB system, especially for the review of clinical trials, it is surprising that the supporting documents for Health Canada’s new Health Protection Legislative Renewal initiative, aimed at developing new all-encompassing federal health protection legislation, make no reference to the need for a tighter REB system.³⁴ In the documents supporting this renewal, the agency recognizes that under the current legislative and regulatory scheme, “enforcement and compliance mechanisms are inadequate,” but it does not mention the need for a coherent REB review system. This may be related to the general purpose of the documents announcing this initiative. It can be hoped that if this legislative renewal moves ahead, federal oversight over REB review will be included in its initiatives.



Conclusion

This analysis has indicated that REBs fulfill an important public function and that Health Canada has recognized that REB review is a fundamental part of the protective regime surrounding clinical trials. REBs, I have argued, are not only expected to ensure that the health, safety and well-being of individual research subjects are not negatively affected by participation in clinical trials, but they are also asked to make sure that conflict of interests do not negatively affect the conduct and outcome of clinical trials. The current reliance on largely unregulated REBs with respect to conflict of interest review becomes more problematic in light of the growing concerns over the commercial impact on research.

I began this article by discussing the VanTx case as a paradigm of clearly inappropriate research recruitment practices, vetted through what hopefully everyone would consider an inappropriate administrative review structure. There is no indication that administrative review structures with such inherent and extreme conflicts of interest currently exist in Canada, even though various commercial REBs operate within the country. But there is little in the current regulatory system that would prevent a similar situation. The only regulatory requirement that we have in the *2001 Clinical Trials Regulations*, is the need for REB review, and the stipulation about its membership. The definition stipulates that REBs are bodies “not affiliated with the sponsor”, but there is no further specification of what that means. The regulatory impact statement refers to good clinical practice guidelines, and Health Canada has introduced the ICH-GCP guidelines as a guidance document, but it is not part of a directly enforceable regulatory structure. The ICH-GCP also refers to national regulations that could specify requirements for REBs, which Canada currently does not have. Within Canada, there is therefore no restriction on who can establish an REB, who becomes a member, how members are trained and selected, and so on. As long as the very minimal requirements of membership and approval are met, there is not strict regulatory ground to reject an REB decision.

It is also problematic that although REBs are considered so important for ensuring that conflicts of interest do not affect clinical trials, there are no regulations to prevent conflicts of interests in REBs. In the context of the growing concerns about research integrity and the impact of commercial interests on drug safety and efficacy, it seems crucial that an administrative body that plays a role in evaluating these concerns is itself protected from conflicts of interest. As has been discussed elsewhere, both institutional and commercial REBs are currently affected by serious conflicts of interests.³⁵ Commercial REBs are increasingly relied upon to

deal with clinical drug trials. Whereas most institutional REBs are now at least part of a “soft” regulatory system emanating from the funding agencies, private REBs are currently not submitted to a clear regulatory structure. These commercial REBs are fully integrated within a commercialized research scene and in fact owe their development and success to the commercialization of research, in which REBs have gained a more important role.

The language used in the promotional material of these REBs confirms that their primary clients are the commercial sponsors and that satisfying the needs of these clients is crucial to their success. One Ontario-based private REB praises on a website its ability “to expedite research at private practices in Canada.” It states proudly that it “has implemented streamlined procedures to minimize the administrative burden to both the sponsor and the Investigator.”³⁶ Some of the private REBs are actively participating in efforts to introduce a voluntary accreditation system in Canada, but a voluntary system seems insufficient in the context of the fundamental public role that REBs play. No one ought to be opposed to the development of more efficient and “streamlined” REB review, but one should be willing to ask the question whether we can leave the protection of the rights and physical well-being of human subjects up to boards that operate in a largely unregulated competitive research review environment where minimizing administrative burdens and expediting review is one of the key arguments to attract more business.

The lack of public accountability of private REBs has at least been recognized by the College of Physicians and Sur-

“The current reliance on largely unregulated REB's with respect to conflict of interest review becomes much more problematic in light of the growing concerns over the commercial impact on research.”



geons of Alberta, which has set up a centralized Research Ethics Review Committee to oversee the research activities of all the physicians and surgeons in Alberta.³⁷ This initiative is laudable, and seems an appropriate response by a professional organization that is confronted with a lack of adequate oversight over some important activities of its members that may affect the health care of patients. The Alberta approach provides an interesting alternative that should be considered in other provinces that are currently relying on the work of private commercial REBs. However, relying solely on provincial professional organizations will result in even more patchwork regulation, without sufficient coherence and without guarantees that all forms of research will be submitted to sufficient oversight. The Alberta initiative is in fact an interesting recognition of the fact that professional organizations are sounding the alarm. It indicates that at least one organization has felt the need to impose a provincial review structure for members of their profession, in the absence of solid governmental regulations. Professional organizations would likely welcome a more coherent Canada-wide approach.

It is true that while it seems easy to defend jurisdiction of the federal government over REB review of clinical trials that are part of drug development, it is more difficult to argue that this gives the federal government jurisdiction to regulate all forms of REB review. For this reason, it would be useful to start with a solid federal regulatory structure around REB review of clinical trials. Further thought should also be given to the possibility of using the model of the *Personal Information Protection and Electronic Documents Act*,³⁸ which would provide the provinces with the option of implementing a coherent REB review structure for all forms of research while satisfying the federal requirements of REB review in the context of clinical trials. The various federal and provincial bodies, including the funding agencies, should be involved in concrete discussion about how to develop a coherent REB system. The federal government could create the momentum for new initiatives by indicating its clear intention to regulate REB review in the context of clinical trials, where it seems to have clear jurisdiction.

In the meantime, Health Canada should increase its monitoring activities of REBs, as part of its inspection of clinical trials sites and trial sponsors. Health Canada regularly inspects such sites to ensure that good clinical practices are respected. If REB review is seen as a fundamental part of good clinical practice, it seems logical that an inspection of good clinical practice should include control of the work of REBs. The National Council on Ethics in Human Research

currently conducts site-visits of REBs. These visits can contribute greatly to the promotion of more stringent and coherent REB practices in Canada, but they do not create an enforceable system. The site-visits are only taking place after an invitation by the institutions in which these REBs operate. Health Canada's visit of REBs as part of the compliance assessment of clinical trials is in this context promising. A clear regulatory structure of REBs would, however, seem crucial to give the review system more teeth and to promote its accountability.

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1. Groupe de travail 'Réglementation des essais cliniques', *Rapport Final à l'intention de l'Office intercantonal de contrôle sur les médicaments* (Berne/Fribourg, September 2000).
2. For example, the consent forms were written in English and German, languages which many of the research subjects may not have understood.
3. *Supra* note 1 at 15-17.
4. Swiss Bundesgerichts, Second Public Law Division, *Freiburger Ethik-Kommission International v. Regierungsrat des Kantons Basel-Landschaft* (2A.450/2002), (4 July 2003), online: http://www.srv.bger.ch/cgi-bin/AZA/MapProcessorCGI_AZA?mapfile=pull/ConvertDocFrameCGI.map&ri=fr&lang=fr&ds=AZA_pull&d=04.07.2003_2A.450%2f2002&pa=1%7e2a%2b450%2b2002%4073%7e&. For a commentary on this case, see Alfred Jost, "Arr t du 4 juillet de la II me cour de droit public du Tribunal fédéral, *Freiburger Ethik-Kommission International c. Bâle-Campagne* (2A.450/2002)" (2003) 1 *Revue suisse de droit de la santé* 13.
5. See e.g. Michael McDonald (research director), *The Governance of Health Research Involving Human Subjects* (Ottawa: Law Commission of Canada, 2000) [*Governance Report*]; Michael McDonald, "Canadian Governance of Health Research Involving Human Subjects: Is Anybody Minding the Store?" (2001) 9 *Health L.J.* 1; Kathleen Cranley Glass & Trudo



- Lemmens, "Research Involving Humans" in Jocelyn Downie, Timothy Caulfield & Colleen Flood, eds., *Canadian Health Law and Policy*, 2d ed. (Toronto: Butterworths, 2002) 459.
6. T. Douglas Kinsella, "Research Involving Humans: Current Regulatory Status of the Canadian Medical Profession" in McDonald, *Governance Report*, *supra* note 5, 155-169.
 7. See e.g. Ken Davey, Barbara McGillivray & Richard Carpentier, "Protecting Human Research Participants in Canada" (2004) 7:2 *Royal College Outlook* 21. See also, *Final Report of the Task Force Established by the National Council on Ethics in Human Research To Study Models of Accreditation for Human Research Protection Programs in Canada* (National Council on Ethics in Human Research, 2002) online: <http://www.ncehr-cnerh.org/pdf/publications/task_force/NCEHR_Task_Force_Rpt.PDF>.
 8. See Brenda Beagan & Michael McDonald, "Evidence-Based Practice of Research Ethics Review?" (2005) 13:2 & 3 *Health Law Review*.
 9. See Trudo Lemmens & Paul B. Miller, "The Human Subjects Trade: Ethical and Legal Issues Surrounding Recruitment Incentives" (2003) 31 *Journal of Law, Medicine & Ethics* 398 at 399-401 and the references there.
 10. See Timothy Caulfield's article in this issue on competitive recruitment incentives. See also Lemmens & Miller, *ibid*.
 11. For two recent meta-analyses of various studies supporting this argument, see Joel Lexchin *et al.*, "Pharmaceutical Sponsorship and Research Outcome and Quality: Systemic Review" (2003) 326 *British Medical Journal* 1167; and Justin E. Bekelman, Yan Li & Cary P. Gross, "Scope and Impact of Financial Conflicts of Interest in Biomedical Research" (2003) 289 *Journal of the American Medical Association* 463.
 12. David Healy & Dinah Cattell, "Interface Between Authorship, Industry and Science in the Domain of Therapeutics" (2003) 183 *British Journal of Psychiatry* 22.
 13. See e.g. the controversies related to the safety of VIOXX and the safety and efficacy of SSRIs. Eric J. Topol, "Failing the Public Health—Rofecoxib, Merck, and the FDA" (2004) 351 *New England Journal of Medicine* 1707; Editorial, "Vioxx: an unequal partnership between safety and efficacy" (2004) 364 *The Lancet* 1287; Matthew Herper & Robert Langreth, "Merck's Missing Vioxx Study", online: *Forbes* <http://www.forbes.com/home/sciencesandmedicine/2004/10/14/cx_mh_1014vioxx.html>. See in general Marcia Angell, *The Truth About the Drug Companies: How They Deceive Us and What To Do About It?* (Random House: New York, 2004). I discuss the implications of these controversies and the interaction between REB review and drug regulation in more detail in "Leopards in the Temple: Restoring Integrity to the Commercialized Research Scene" (2004) 32 *Journal of Law Medicine & Ethics* 641. See also more references there.
 14. For a discussion of other required changes, in addition to a clearer regulatory structure around REB review, see *ibid*.
 15. S.O.R./2001-203 [*Clinical Trial Regulations*].
 16. *Ibid.*, C.05.001.
 17. See e.g. Health Canada, "Health and Safety First! A Proposal to Renew Federal Health Protection Legislation", online: Health Canada <<http://www2.itssti.hc-sc.gc.ca/HPCB/Policy/LegislativeRenewal.nsf/vwProposalWeb?OpenView&Expand=1&Count=2000&>>
 18. Trudo Lemmens, Marie Hirtle & Dominique Sprumont, "A Comparative Analysis of Research Ethics Review Mechanisms and the ICH Good Clinical Practice Guideline" (2000) 7 *European Journal of Health Law* 265; to view the guidelines see online: International Committee on Harmonisation <http://www.ich.org/UrlGrpServer.jsr?@_ID=276&@_TEMPLATE=254>.
 19. Health Products and Food Branch, "Guidance for Industry, Good Clinical Practice: Consolidated Guideline ICH Topic E6", online: Therapeutic Products Directorate <http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/e6_e.html>.
 20. Health Canada, "Regulatory Impact Statement" (22 June 2001), online: Health Products and Food Branch Inspectorate <http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/food_drug_reg_amend_1024_gcp_entire_e.html>.
 21. Health Canada, Health Products and Food Branch, *Summary Report of Inspections of Clinical Trials in 2003-2004* (December 14, 2004), available online at: <http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/gcp_inspection_sum_rep_2003-2004_e.pdf>
 22. Anne Tomalin, "New Clinical Trial Legislation in Canada" (September 2001) *Regulatory Affairs Focus* 1 at 2.
 23. See *Landers v. N.B. Dental Society* (1957), 7 D.L.R. (2d) 583 (N.B.C.A.) in which the New Brunswick Court of Appeal affirmed that provinces can enact de-



- tailed regulations for dentists, imposing a licensing scheme accompanied by penalties. See the discussion of this case in Martha Jackman, "Constitutional Jurisdiction Over Health in Canada" (2000) 8 Health L.J. 9 at 112.
24. For a discussion of the developments and initiatives in Newfoundland, see further in this journal: Daryl Pullman, "Research Governance, Bio-politics and Political Will: Recent Lessons from Developments in Newfoundland and Labrador," (2005) 13:2 & 3 Health Law Review. Quebec is the Canadian province which seems to have moved the furthest towards a comprehensive official policy on REB review. See Minist re de la Santé et des Services sociaux, Direction générale de la planification et de l'évaluation, *Plan d'action ministériel en éthique de la recherche et en intégrité scientifique* (Minist re de la Santé et des Services sociaux, Direction des communications : 1998) available online at: <http://ftp.msss.gouv.qc.ca/publications/acrobat/f/documentation/1998/98_759.pdf>.
 25. Health Canada, "Regulatory Impact Statement", *supra* note 20.
 26. See André Braën, "Health and Distribution of Powers in Canada" Commission on the Future of Health Care in Canada, Discussion Paper No. 2, (July 2002) at 10-14; Martha Jackman, *supra* note 23 at 99-105.
 27. [1983] 2 S.C.R. 284 [*Wetmore*].
 28. [1982] 2 S.C.R. 112.
 29. *Ibid.* at 100-101.
 30. *RJR-MacDonald Inc v. Canada (A.G.)*, [1995] 3 S.C.R. 199 at 246.
 31. *Wetmore*, *supra* note 27 at 288-289. See Jackman, *supra* note 23.
 32. [1988] 1 S.C.R. 401 ¶ 33.
 33. House of Commons Standing Committee on Health, *Opening the Medicine Cabinet: First Report on Health Aspects of Prescription Drugs* (April 2004), online: Parliament of Canada <<http://www.parl.gc.ca/committee/CommitteePublication.aspx?SourceId=76297>>
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 35. See Leslie Francis, "IRBs and Conflicts of Interest" in Roy S. Spece, David S. Shimm & Allen E. Buchanan eds, *Conflicts of Interest in Clinical Practice and Research* (New York: Oxford University Press, 1996) 418; Mildred K. Cho & Paul Billings, "Conflict of Interest and Institutional Review Boards" (1997) 45:4 *Journal of Investigative Medicine* 154; Trudo Lemmens & Benjamin Freedman, "Ethics Review for Sale? Conflict of Interest and Commercial Research Review Boards" (2000) 78 *Milbank Quarterly* 547; and Institute of Medicine, *Responsible Research: A Systems Approach to Protecting Research Participants*, Daniel D. Federman, Kathi E. Hanna & Laura Lyman Rodriguez, eds. (Washington: National Academies Press, 2003) at 84-86.
 36. Online: Canadian Shield Ethics Review Board <<http://www.cserb.com>>
 37. See Kinsella, *supra* note 6; and Timothy Caulfield *et al.*, "Research Ethics and the Role of the Professional Bodies: A View from Canada" (2004) 32 *Journal of Law Medicine & Ethics* 365.
 38. S.C. 2000, c. 5, online: Privacy Commissioner <http://www.privcom.gc.ca/legislation/02_06_01_01_e.asp>.

