

Pan-Canadian Study on Variations in Research Ethics Boards' Reviews of a Research Project Involving Placebo Use¹

*Johane Patenaude, Julien Cabanac
and Johane de Champlain*

Introduction

In Canada, since 1996, researchers have abided by ethical norms² intended to protect research subjects without unduly hindering the functioning of research projects. To this end, research ethics boards [REBs] have been entrusted with the responsibility for overseeing the protection of research subjects under the terms of recognized norms, including the *Tri-Council Policy Statement* [TCPS].³ One of the objectives of TCPS policy was “to harmonize the ethics review process. The Agencies expect that REBs will benefit from common procedures within a shared ethical framework”.⁴ Moreover, since 1997, when reviewing clinical trials, REBs have also been able to turn to the *Good Clinical Practice* [GCP] guidelines.⁵

Since these norms were implemented, the need has emerged to review, modify, and harmonize them. In the fall of 2001, Health Canada and the Canadian Institutes of Health Research [CIHR] set up the National Placebo Working Committee “to help determine the appropriate use of placebos in clinical trials in Canada.”⁶ One of this group’s objectives was to harmonize *Good Clinical Practice (E10)*⁷ [GCP (E10)] with the TCPS,⁸ in particular as it related to the diversity of terms employed regarding placebo use in clinical trials.

GCP (E10) allows for the possibility of offering a placebo in these situations:

2.1.3 Ethical Issues.... In cases where an available treatment is known to prevent serious harm, such as death or irreversible morbidity in the study population, it is generally inappropriate to use a placebo control. There are occasional exceptions, however, such as cases in which standard therapy has toxicity so severe that many patients have refused to receive it. In other situations, when there is no serious harm, it is generally considered ethical to ask patients to participate in a placebo-controlled trial, even if they may experience discomfort as a result, provided the setting is noncoercive and patients are fully informed about available therapies and the consequences of delaying treatment.⁹

Like GCP (E10), article 7.4 of the TCPS forbids the use of a placebo “when standard therapies or interventions are available for a particular patient population”. However, exceptions to this prohibition are identified:

Consistent with clinical equipoise, a placebo may be used as the control treatment in a clinical trial in the following circumstances: (a) There is no standard treatment; (b) Standard therapy has been shown to be no better than placebo; (c) Evidence has arisen creating substantial doubt regarding the net therapeutic ad-



vantage of standard therapy; (d) Effective treatment is not available to patients due to cost constraints or short supply (this may only be applied when background conditions of justice prevail within the health care system in question; for example, a placebo-controlled trial is not permissible when effective but costly treatment is made available to the rich but remains unavailable to the poor or uninsured.); (e) In a population of patients who are refractory to standard treatment and for whom no standard second-line treatment exists; (f) Testing add-on treatment to standard therapy when all subjects in the trial receive all treatments that would normally be prescribed; or (g) Patients have provided an informed refusal of standard therapy for a minor condition for which patients commonly refuse treatment and when withholding such therapy will not lead to undue suffering or the possibility of irreversible harm of any magnitude.¹⁰

REBs' ethical review of the acceptability of placebo use is based on two factors: their familiarity with the principal sets of norms for Canada, namely the TCPS and GCP (E10), and how they interpret these norms. At present, the great divergences among REBs' decisions result in the approval in some institutions of research projects for clinical trials involving placebo use that are rejected by others. For researchers, this inconsistency can mean differing requirements to modify a research project from one REB to another, a circumstance that is extremely undesirable in the context of multicentre research. Several studies¹¹ have assumed the existence of significant divergences in the way REBs apply purportedly shared norms.

Our study is intended to document these potential divergences. Our objective is not to forge a normative approach to revisit the legitimacy of placebo use. Rather, we wish to know whether Canadian REBs proceed homogeneously in their reviews, or whether, on the contrary, divergences exist that make substantive change to existing norms appropriate.

Methodology

Between January 2003 and June 2003, a mock research protocol based on real protocols was submitted to Canadian biomedical REBs that volunteered to participate. This mock protocol was accompanied by a brief questionnaire designed

to elicit the decision-making criteria that underlay the REBs' review processes. Participating REBs were requested to follow their usual method of operation in the processing and ethical review of the documents.

The mock protocol presented a double-blind, Phase II multicentre study designed to evaluate the safety and antiviral efficacy against hepatitis B of three doses of the medication under study. The project provided for 85 patients with hepatitis B to be divided into four groups: three groups of 25 patients receiving 10, 20, and 50 mg doses respectively, and one group of ten patients receiving an inert substance. All participants would have previously been receiving treatment with a standard medication, the only one recognized so far for the treatment of hepatitis B. Patients agreeing to participate would have to suspend this treatment for the twelve weeks of the study. Standard treatment was said to be efficacious for most patients but weakly efficacious for over 15% of patients. The mock protocol specified that the medication under study had proven to be teratogenic and genotoxic in rats, dogs, and rabbits. It was also specified that Phase I studies lasting 14 days had been conducted on a group of patients receiving 5 mg doses of the medication and that the only side effects reported so far had consisted of nausea and vomiting.

REBs that participated in the study were requested to review this mock research project involving numerous ethical issues, including placebo use. In the present report, only our findings relating to the issue of placebo use will be addressed.

The findings presented below in no way claim to have predictive value or significant statistical validity. Rather, they are intended to reflect, as faithfully as possible, the decisions made by participating REBs, along with their decision-making criteria, when they reviewed a single research project involving placebo use.

Findings

Forty-seven Canadian biomedical REBs agreed to review the mock protocol.

Our findings are presented in the table below (Table 1).



Table 1: Distribution of the 47 REBs' Decisions

	Project Approved	Decision Deferred	Project Rejected	Total
With no explicit consideration of the placebo arm	5	3	2	10 (21%)
With explicit consideration of the placebo arm	5	9	23	37 (79%)
Total	10 (21%)	12 (26%)	25 (53%)	47 (100%)

Ten of the 47 REBs approved the research project; two unconditionally, seven with minor conditions, and one with a major condition (elimination of the placebo arm). Twelve REBs deferred their decision, noting either their wish to submit the research project for outside expert opinion or making their decision dependent on the researchers' responses to certain questions and 25 REBs rejected the research project, most of them citing the unacceptability of placebo use in the context described in the mock protocol.

Nearly all of the 37 REBs (79%) that explicitly considered the placebo arm in conducting their ethical review expressed acute concern about withdrawing medication that was recognized as standard. This concern was also shared by the five REBs that approved the research project.

Ten REBs (21%) did not explicitly mention the placebo arm as figuring in their decision making. Five of these approved the research project, three deferred their decision and two rejected the project. The answers given do not allow for a determination of whether the placebo issue was discussed.

Of the ten REBs that approved the research project, half explicitly addressed the placebo issue: one approved the project while rejecting the placebo arm; two expressed their concerns while nevertheless approving the research project; and two were prepared to accept the risk flowing from suspension of treatment for twelve weeks. One of these last two (which we will refer to as REB α) explicitly justified its choice to approve placebo use without treatment:

It is acceptable that the placebo-taker has no continuing therapy whatsoever, because the accepted/standard treatment is so ineffective; the impact (on a chronic Hepatitis B sufferer) from this number of weeks of therapy is so small; and the potential gain (over the long term) is so significant for the placebo-taker (and everyone else in the trial) if a superior treatment is found by this trial.

Of the 25 REBS that rejected the research project, some specified that the inclusion of placebo use without treatment was their main or indeed the only reason for rejection.

Analysis

It would be reasonable to view these divergent decisions by REBs as *prima facie* indications of significant variation in the way ethical rules around placebo use are applied. And yet, that is not our opinion.

Article 7.4 of the TCPS reads, "The use of placebo controls in clinical trials is generally unacceptable when standard therapies or interventions are available for a particular patient population." Our findings show that all 37 (79%) of the 47 participating REBs that considered the placebo arm (some of which approved the project) reached the conclusion that this element presented an ethical problem because it entailed suspending currently used treatment. The explanation provided by REB α shows that it approved the project because it believed, whether rightly or wrongly, that the



existing therapy was not efficacious,¹² that the risk of harm was minor, and that the benefits to be reaped, for both the subjects and other patients, were significant. Thus, this REB's application of the regulation appears to coincide with that of the 36 others. It is only its different understanding of the therapeutic effect of the standard treatment that has led to different conclusions. We will return below to risk/benefit considerations.

Thus, these findings do not demonstrate the presence of variability or significant divergences in applying article 7.4 of the TCPS. What, then, is to be made of the perceived inconsistencies¹³ between GCP (E10) and the TCPS? The truth is that the divergence between article 7.4 of the TCPS and regulation 2.1 of GCP (E10) that some have adverted to appears not to be reflected in our findings. In effect, REBs that addressed the question of placebo use all respected the main position of the TCPS and none save REB α appear to have seen a justification for making an exception.

REB α justified its approval on the basis of the major inefficacy of the standard treatment and the possibility of achieving better treatment, linked with a low level of risk for the specified period of treatment suspension. It is possible that the distinctiveness of the REB α 's views puts in evidence potential divergences in interpretations of norms and in interpretations of allowable exceptions under the norms. Unfortunately, our findings are too fragmentary to assert this with confidence as REB α did not indicate whether it had relied on any specific normative source. Consequently, the criteria for the acceptability of placebo use presented by REB α could as easily refer to the allowable exceptions under the TCPS as to those under GCP (E10).

However, while the 47 REBs' review reports do not broadly diverge in their application of the regulations, they are not homogeneous. Note that 21% of participating REBs approved the research project,¹⁴ while 25.5% deferred their decisions and 53% rejected it. Furthermore, of the 37 REBs that rejected the project or deferred their decisions, five (13.5%) remained silent on the question of the placebo arm, while the majority considered this question crucial. We must conclude, then, since the regulations are being applied in a generally homogeneous fashion, that the divergences in REBs' decisions arise from a different quarter. One explanatory hypothesis relies on REBs' spontaneous assessment of the risk incurred by subjects. Under this hypothesis, an REB that considers that it is confronting a significant or non-negligible risk would be less inclined to look for guidelines allowing exceptions to the placebo-use rejection guideline.

This approach could explain why the 37 REBs that invoked considerations about placebo use referred to the main statement in article 7.4 of the TCPS ("The use of placebo controls in clinical trials is generally unacceptable when standard therapies or interventions are available for a particular patient population.") without having recourse to the allowable exceptions under this regulation.

Undoubtedly, there is no single explanation for the existence of divergent decisions. Thus, the 21% of REBs that did not address the placebo issue is not comprised exclusively of REBs that approved the research project. One rejected the project for a set of reasons unconnected to placebo use:

- A process needs to be established for how to un-blind due to potential toxicities.
- The risk for harmful weight gain with HIV testing needs to be clearly identified in the consent form.
- The family doctor needs to be informed of patients' participation in this study.
- The sample size is too small to make the study significant.
- The number of subjects varies throughout the study.
- Concern was expressed that results from the following studies are still pending:
 1. The pharmacokinetic data from a dose proportionality study of enteric-coated tablets at 5.20 and 50 mg.
 2. The food effect study.

This example illustrates the problem inherent in looking for a single explanation for the origin of disparities among REBs' decisions. REBs may well, knowingly or unknowingly, use the same norms in reviewing a research project, yet each may choose to highlight one aspect of the project over others. This could explain some of the divergences in the decisions made by REBs reviewing the same research project.

Do these divergences entail a lower level of protection for research subjects? It is not the purpose of our study to engage this question, but it ought to be addressed in light of the decision-making practices of those responsible for interpreting and applying existing norms. The existence of variation among REBs' decisions despite the relatively homogeneous use of norms confirms that a mere statement of norms is not the sole determinant of REBs' decisions.



Conclusion

In Canada, variation among REBs' decisions appears to be an accepted though hitherto undocumented fact.¹⁵ The case of clinical trials involving placebo use is no exception to this phenomenon.

As with all norms that REBs are responsible for applying, those regarding placebo use entail the REB's familiarity with Canadian norms, interpretation of what may constitute a risk to subjects within the given context, and appropriate application of the norms. Our findings indicate that the gap between REBs' decisions does not result from unfamiliarity with the general guidelines, specifically those of article 7.4 of the TCPS. Variations among decisions may derive from divergent interpretations of the concepts of risk and standard treatment and from interpretations of the allowable exceptions to the guideline on acceptable placebo use.

These variations could justify the concerns of the National Placebo Working Committee¹⁶ and the troubling observations made earlier by C. Weijer.¹⁷ It is therefore legitimate to wonder to what point would it be useful to make Canadian guidelines specific or to harmonize them with international ones, as is proposed by the National Placebo Working Committee's final report. Our findings suggest that the present state of the guidelines is not always implicated in REBs' decision-making disparity. Harmonization of national with international guidelines is perhaps desirable, but it would not necessarily contribute to an advance in the quality of REBs' work nor constitute the harmonization of ethical review processes that is desired by the drafters of policies. Before changing the guidelines or increasing their number, it would perhaps be appropriate to understand why REBs diverge. Our exploratory study confirms the existence of certain divergences among REBs' decisions that are not attributable to the formulation of the ethics guidelines. It will be necessary to achieve a fuller determination of the origin of these divergences¹⁸ before changing existing guidelines with the view of making Canadian research ethics more homogeneous.

Pending such studies, it is doubtless appropriate to turn to the requirement of the *Regulations Amending the Food and Drug Regulations (1024 – Clinical Trials)*,¹⁹ under which, when a research project is rejected, reasons for the rejection must be circulated to other REBs to whom the project has been submitted. Such a procedure might contribute to a more thorough conduct of their analyses by all REBs involved in multicentre research projects and to the better

protection of research subjects. As well, it could be made part of a national framework for the governance²⁰ of pan-Canadian research.

Johane Patenaude is an Associate Professor, Department of Surgery, Faculty of Medicine and Health Sciences, Université de Sherbrooke, Québec; Julien Cabanac is a Lawyer at Bérubé & Pion, Law Office, Québec; and Johane de Champlain is a Research Professional, Centre de recherche clinique, Faculty of Medicine and Health Sciences, Université de Sherbrooke, Québec.

1. The authors thank the Canadian Institutes of Health Research for funding this study.
2. Medical Research Council of Canada, Natural Sciences and Engineering Research Council of Canada & Social Sciences and Humanities Research Council of Canada, *Code of conduct for research involving humans: draft document* (Ottawa: Medical Research Council of Canada, 1996).
3. Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada & Social Sciences and Humanities Research Council of Canada, *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*. 1998 (with 2000, 2002 and 2005 amendments), online: Intergency Panel on Research Ethics <<http://www.pre.ethics.gc.ca/english/policystatement/policystatement.cfm>> [TCPS]. Since 2003 the online version has been the official version.
4. *Ibid.* at Goals and Rationale of the Policy, B.3.
5. Health Canada, *Good Clinical Practice: Consolidated Guideline ICH Topic E6* (Ottawa: Public Works and Government Services Canada, 1997) online: Health Canada <http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/e6_e.pdf>.
6. National Placebo Initiative, *Final Report of the National Placebo Working Committee on the Appropriate Use of Placebos in Clinical Trials in Canada* (Health Canada & Canadian Institute of Health Research, July 2004) at iii, online: Canadian Institutes of Health Research <http://www.cihr-irsc.gc.ca/e/documents/National_Placebo_Initiative_Final_Report_July_27_2004.pdf> [NPI] (in 2002, the Canadian Institutes of Health Research have also undertaken the creation of new norms and guidelines in other fields: *Human Pluripotent Stem Cell Research: Guidelines for CIHR-Funded Research* (4 March 2002), which have been superseded by: *Updated*



Guidelines for Human Pluripotent Stem Cell Research (June 7, 2005), online: Canadian Institutes of Health Research <<http://www.cihr-irsc.gc.ca/e/1487.html>>; see also Canadian Institutes of Health Research, *Guidelines for Protecting Privacy and Confidentiality in the Design, Conduct and Evaluation of Health Research: Best Practices Consultation Draft* (Ottawa, April 2004) which have been superseded by: *CIHR Best Practices for Protecting Privacy in Health Research* (September 2005), online: Canadian Institutes of Health Research <http://www.cihr-irsc.gc.ca/e/pdf_22427.htm>;

Canadian Standards Association, *Model Code for the Protection of Personal Information CAN/CSA-Q830-96*, reprinted in *Personal Information Protection and Electronic Documents Act*, S.C. 2000, c. 5, Sch. 1).

7. International Conference on Harmonisation, *ICH Harmonised Tripartite Guideline, Choice of Control Group and Related Issues in Clinical Trials E10* (ICH Steering Committee, 20 July 2000), online: International Conference on Harmonisation <<http://www.ich.org/cache/compo/276-254-1.html>>.
8. NPI, *supra* note 6 (“[T]he task of the National Placebo Working Committee has been to recommend a single ‘Canadian approach’, which hopefully will be acceptable to Canadian regulators, both Health Canada and the federal funding agencies following the *Tri-Council Policy Statement*” at 4)..
9. *Supra* note 7 at 13-14; see also NPI, *supra* note 6 at iii, 29; Patricia Huston & Robert Peterson, “Withholding proven treatment in clinical research” (2001) 345:12 N.Engl. J. Med. 912; Robert Temple & Susan S. Ellenberg, “Placebo-Controlled Trials and Active-Control Trials in the Evaluation of New Treatments. Part 1: Ethical and Scientific Issues” (2000) 133:6 Annals Intern. Med. 455.
10. *Supra* note 3 at sec. 7D.
11. G. Moutel, N. Leroux & C. Hervé, “Analysis of a survey of 36 French research committees on intracytoplasmic sperm injection” (1998) 351:9109 Lancet 1121; Johane Patenaude & Julien Cabanac, “Quelle recherche, quelle évaluation? Le cas de la distinction entre soin expérimental et soin innovateur” (2000) 2 :2 éthique publique 89. One recent study demonstrated disparities between REBs in different countries that all adhere to the principles of the Declaration of Helsinki, see Hilary Hearnshaw, “Comparison of requirements of research ethics committees in 11 European countries for a non-invasive interventional study” (2004) 328:7432 BMJ 140.

Other studies that report on disparities among REBs have used a retrospective methodology, see Seema Shah *et al.*, “How do institutional review boards apply the federal risk and benefit standards for pediatric research?” (2004) 291:4 Journal of the American Medical Association 476; Rita McWilliams *et al.*, “Problematic variation in local institutional review of a multicenter genetic epidemiology study” (2003) 290:3 Journal of the American Medical Association 360; Henry Silverman, Sara Chandros Hull & Jeremy Sugarman, “Variability among institutional review boards’ decisions within the context of a multicenter trial” (2001) 29:2 Critical Care Medicine 235; A.H. Ahmed & K.G. Nicholson, “Delays and diversity in the practice of local research ethics committees” (1996) 22:5 Journal Medical Ethics 263.

12. *Supra* note 3 at sec. 7D (See exceptions (b) and (c) under article 7.4: “Clinical equipoise is widely regarded as the moral foundation of the randomized-controlled trial. In order for a clinical trial to proceed ethically, a state of clinical equipoise must exist at the trial’s inception (see A above). Consistent with clinical equipoise, a placebo may be used as the control treatment in a clinical trial in the following circumstances: ... b) Standard therapy has been shown to be no better than placebo; c) Evidence has arisen creating substantial doubt regarding the net therapeutic advantage of standard therapy; ...”. <<http://www.pre.ethics.gc.ca/english/policystatement/section7.cfm>>.
13. “Indeed, the perceived discrepancies between the wording of *Tri-Council Policy Statement*, Section 7 and *ICH E-10* were at least part of the rationale for the formation of the National Placebo Working Committee”, NPI, *supra* note 6 at 63; M. Hirtle, T. Lemmens & D. Sprumont, “A comparative analysis of research ethics review mechanisms and the ICH good clinical practice guideline” (2000) 7:3 European Journal of Health L. 265; Joan C. Bevan, “Towards the regulation of research ethics boards”, (2002) 49:9 Canadian Journal of Anesthesia 900, online: Canadian Journal of Anesthesia <<http://www.cja-jca.org/>>.
14. It is nevertheless not obvious why REBs deferred their decisions or rejected the project. Their responses often presented a list of reasons without specifying, where relevant, the degree of significance of any given reason. It is thus possible that a combination of criteria motivated a given rejection. It is also possible for an REB not to have presented all the major aspects of its decision making, because it viewed the list of reasons as already sufficiently long or complete to motivate the decision. This is an approach that is in



fact commonly used by REBs. It would therefore be a mistake to conclude that a problem that is not mentioned by REBs in this study was necessarily neglected or considered to be of little importance by them. For this reason, for the purposes of our analysis, we are limiting ourselves to assuming that those reasons that REBs specified do express concerns of theirs but are refraining from drawing any firm conclusions about “what was left unsaid”.

15. NPI, *supra* note 6 at 61.
16. “The issues are complex from a medical and scientific perspective and can lead to potential oversights in the deliberations regarding trial design and options and the informed consent process”, *ibid.* at 56.
17. Charles Weijer, “Placebo trials and tribulations” (2002) 166:5 Canadian Medical Association Journal 603; see also “Placebo tribulations – author reply” (2002) 167:5 Canadian Medical Association Journal 456 (“Canada’s regulatory system for the protection

of research subjects is broken and needs to be fixed. Proof of this failure is found in the approval by 19 out of 20 research ethics boards (REBs) of a placebo-controlled trial that clearly violates article 7.4 of the *Tri-Council Policy Statement* and paragraph 29 of the *Declaration of Helsinki*.” at 456).

18. Ezekiel J. Emanuel *et al.*, “Oversight of human participants research: Identifying problems to evaluate reform proposals” (2004) 141:4 *Annals of Internal Medicine* 282.
19. Canada S.O.R./2001-2003 (“C.05.008....(c) before the sale or importation of the drug, the sponsor submits to the Minister: ... (ii) the name, address, and telephone number and, if applicable, the facsimile number and electronic mail address of any research ethics board that has previously refused to approve any amendment to the protocol, its reasons for doing so and the date on which the refusal was given.”).
20. NPI, *supra* note 6 at 59, 65.

Upcoming Events

4th International DNA Sampling Conference: Genomics and Public Health
June 4-7, 2006 Montreal, Quebec
www.humgen.umontreal.ca/events/dnasampling

Access and Privacy Conference 2006
Sharing New Perspectives June 7-9 2006, Edmonton, Alberta.
www3.extension.ualberta.ca/accessandprivacy/index.asp

The Public's Health & The Law in the 21st Century — 5th Annual Partnership Conference
June 12-14, 2006 Atlanta, Georgia
www.cdc.gov/phlp/Conference2006.asp — or contact Briana Grovhoug Kennedy at 404-639-5082

6th International Conference on Priorities in Health Care — September 20-22, 2006, Toronto, Ontario
www.healthcarepriorities.org

Halifax 6: The Canadian Healthcare Safety Symposium — October 19 -21, 2006, Vancouver, BC
www.buksa.com/main/conferences.asp

4th National Health Law Conference — November 8-11, 2007, Banff, Alberta (details forthcoming)

