

Research Governance Lessons from the National Placebo Initiative

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1. Introduction

For at least the last two decades, Canada has been an international leader in research ethics. Canadian scholars have written seminal articles that now fill standard texts in the field. For example, in the authoritative collection *Ethical and Regulatory Aspects of Clinical Research*, fully eighteen of 86 articles included in the volume were authored in Canada.¹ In the realm of research ethics policy, Canada's contributions are also many. The *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*² (TCPS), introduced a decade ago and currently under revision, is widely admired for its scope and substance. More recently the Canadian Institutes of Health Research *Guidelines for Research Involving Aboriginal People*³ attracted considerable interest as a potential roadmap for effective research partnerships between aboriginal communities and researchers.

The National Placebo Initiative (NPI) was established in 2002 with a mandate to broker consistent guidance on the use of placebos in clinical research in Canada. Although the recommendations set forth in its Final Report (2004)⁴ have the potential to renew Canada's role as an international leader in research ethics, they have yet to be acted upon by the Canadian Institutes of Health Research and Health Canada. In this paper we discuss the history of the placebo question in Canada, describe the recommendations made by the NPI, and attempt to identify some of the reasons for their lack of uptake.

2. Historical Background

Since the 1980s, Canada has been at the center of scholarly work on the ethics of randomized controlled trials (RCT).⁵ Early work focused on the ethics of randomization. It is widely acknowledged that the physician owes her patient a duty of care that requires the physician to act and advise in accordance with the patient's best medical interests. In a RCT, the participant is allocated by chance to an experimental or control treatment. How, critics asked, could offering a patient enrollment in a RCT ever be consistent with the physician's duty of care? Benjamin Freedman provided the most widely accepted answer to this question with his concept of "clinical equipoise."⁶ According to Freedman, a physician may legitimately offer a patient RCT enrollment provided that each of the treatment arms to which she may be allocated is consistent with competent medical care. In other words, clinical equipoise requires that at the start of a RCT "[t]here exist...an honest, professional disagreement among [the community of] expert clinicians about the preferred treatment."⁷

Generally, a placebo control is appropriate when there is no proven treatment for the study condition. However, once proven treatment exists, an active control (i.e., standard treatment) ought to be used. Not only does this ensure that patients enrolled in a clinical trial will not go untreated when a proven therapy is available, but comparison to an active control provides valuable information on comparative efficacy. If the new drug



eventually receives regulatory approval, information on comparative efficacy is essential for informed decision making by policy makers, clinicians, and patients.

Clinical equipoise has clear implications for use of placebo controls in RCTs. In a 1990 article in the journal *IRB*, Freedman laid out circumstances in which a placebo control may be used consistently with clinical equipoise, namely when:

1. there is no standard treatment;
2. standard treatment is no better than placebo;
3. standard treatment is placebo;
4. the net therapeutic advantage of standard treatment has been called into question by new evidence; or,
5. effective treatment exists but is not available due to cost or short supply.⁸

Two further circumstances in which a placebo control is licit are entailed by Freedman's list. First, a placebo control may be used in a population of patients who don't respond to standard treatment, provided no effective second-line treatment exists (there is no standard treatment). Second, a treatment added to a standard regimen might be compared to placebo provided that all patients in the trial receive the standard regimen (no one is denied standard treatment).

The impact of clinical equipoise on research ethics policy has been profound. The Tri-Council Working Group (1994-1998) appealed to clinical equipoise repeatedly in early drafts of the *TCPS* and used the concept to justify its restrictive stance on placebo controls. For instance, the April 1998 draft of the *TCPS* states: "The use of placebos in clinical trials is ethically unacceptable where clearly effective therapies or interventions are available." The commentary on this article goes on to say:

Researchers and REBs should be cautious concerning the use of placebos in clinical trials. Such use may be appropriate when a new or currently used intervention is in clinical equipoise with no intervention or a placebo, and when no clearly effective therapy is available for the study population. In the same vein, it is inappropriate to withhold a clearly effective intervention from patients for research purposes, unless it is being compared with another intervention that satisfies the criterion of clinical equipoise.

Given the widespread use of placebo controls in studies supporting applications for licensure of new drugs, this draft provision generated considerable controversy. Many agreed that Canada's research ethics boards would require more specific guidance in order to implement this provision effectively. In 1998, the National Council on Ethics in Human Research (NCEHR), a Canadian non-governmental organization dedicated to improving research ethics board review, sponsored a consensus-seeking roundtable that brought together representatives of universities, funding agencies, government (including Health Canada) and industry to discuss the issue.⁹ The meeting resulted in recommended language that was incorporated as article 7.4 in the final version of the *TCPS* (see Table 1).¹⁰

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Although Health Canada participated in the 1998 consensus-seeking roundtable, its Therapeutic Products Directorate (TPD), Canada's drugs regulator, chose not to endorse the *TCPS*, largely due to the language of article 7.4. Following the lead of the U.S. Food and Drug Administration, TPD chose not to accept the 2000 revision of the *Declaration of Helsinki* which (similarly) requires that "[a] new method should be tested against... the best current prophylactic, diagnostic and therapeutic methods." The reasons behind these policy decisions are undoubtedly complex. Central among them are two: first, that a RCT with a placebo control (as opposed to an active control) provides more reliable evidence of the efficacy of a new treatment; and, second, that proven treatment may ethically be withheld from research participants.¹¹ In place of the *TCPS* and the *Declaration of Helsinki*, TPD endorses the International Conference on Harmonization's *Guideline on Good Clinical Practice* (ICH GCP).¹² ICH GCP is widely interpreted to take a more permissive stance on the use of placebo controls.



A related ICH document (E-10) explicitly permits a placebo control in the face of proven treatment, provided that there is no risk of irreversible harm or death to the participants, appropriate measures are taken to ensure their safety, and proper informed consent is obtained.¹³

The emergence of conflicting international guidance on placebo controls has resulted in significant confusion and frustration for researchers, research ethics boards (REBs), sponsors, and regulators. For although the TCPS and ICH GCP are consistent on many fundamental ethical requirements, the documents differ significantly in their stance on the use of placebo controls in RCTs.

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3. The National Placebo Initiative

In the fall of 2001, the Canadian Institutes of Health Research (CIHR), Canada's leading funder of health research, and Health Canada jointly launched the NPI with the aim of reconciling conflicting views on placebo use in clinical trials. The main objective of the NPI was to "make recommendations to Health Canada and CIHR regarding a common placebo policy that can be used to inform; a Canadian appendix to the international regulatory guidance document *ICH E-10: Choice of a Control Group and Related Issues in Clinical Trials*; and a revision of section 7 on clinical trials in the *Tri-Council Policy Statement*."¹⁴ This was timely as a number of international organizations, including the World Medical Association (WMA) and the Council for International Organizations of Medical Sciences (CIOMS), were in the process of revising their respective guidelines with special attention to the proper use of placebo controls. CIOMS released its revision late in 2002, while WMA issued a series of clarifications and a major revision in October 2008.¹⁵

The National Placebo Working Committee (NPWC) consisted of twelve members representing various stakeholders, including researchers, the pharmaceutical industry, regulators, research ethics boards, patients, and the public at large. Over a two-year period the NPWC engaged in extensive consultations with scientific, ethical, legal, and regulatory experts, as well as leading figures in the research ethics board (REB) community. Opportunities for broader stakeholder and public involvement in this initiative included a national conference, focus groups, citizen town hall meetings, and online distribution of the Draft Report of the NPWC for comment.

In July 2004 the *Report of the National Placebo Working Committee on the Appropriate Use of Placebos in Clinical Trials in Canada* (the Final Report) was delivered to Dr. Robert Peterson, Director General of the Therapeutics Products Directorate at Health Canada, and to the Ethics Office of CIHR. The Final Report presents a consensus view on key aspects of the placebo debate. It also flags for further work a number of issues on which consensus was not reached. The key policy recommendations on which consensus was achieved centered on changes to TCPS article 7.4 to further clarify the circumstances in which the use of a placebo control is permissible (see Table 1).

Changes to policy were then to be made by both CIHR and Health Canada. In the case of CIHR, it would endorse the Final Report and bring forth its recommendations to the Interagency Advisory Panel on Research Ethics (PRE), which is charged with amending and updating the TCPS. PRE would then, in consultation with the other major funders, issue a revision of the TCPS based on the recommendations. Health Canada, for its part, would endorse the Final Report and use its recommendations as the basis for a draft Canadian appendix to ICH E-10. The result would be a common standard for placebo use in clinical trials in Canada.

After being presented with the Final Report, CIHR and Health Canada diverged significantly in their reaction. CIHR referred the Final Report to its Standing Committee on Ethics (SCE). After some discussion, in November 2004 the SCE endorsed the main recommendations with minor amendments. The SCE's approval was then communicated to Dr. Alan Bernstein, the President of CIHR.



Health Canada's response was dramatically different. Dr. Robert Peterson, Director General of TPD, contacted the chair of the SCE in early 2005 to discuss concerns, which were outlined in a subsequent letter. These included a concern that public consultation on the final recommendations of the NPI was not as extensive as it should have been. A second concern related to the then recent withdrawal of Vioxx from the market. The suggestion was that Vioxx may not have received regulatory approval in the first place had adequate placebo controlled Phase III trials been conducted. The implication was that Health Canada's endorsement of the Final Report would further restrict the use of placebos, thus opening the door to more large-scale adverse events with drugs. In light of these concerns Health Canada asked the SCE to consider modifying or even withdrawing its recommendations to the President.

The SCE reviewed the letter carefully but concluded that the stated concerns did not warrant either modification or withdrawal of its endorsement of the Final Report, and informed Health Canada accordingly. To date, Health Canada has not endorsed the NPI's Final Report, and neither CIHR nor Health Canada has made the recommended policy changes.

4. Lessons for Research Governance in Canada

Although the NPI – to date at least – has failed to harmonize Canadian guidelines on the use of placebos in clinical trials, this recounting is instructive in several respects. The Canadian struggle with the proper role of placebo controls in clinical trials has mirrored international developments. Ever since the publication of ICH GCP in 1996, there has been an on-going struggle on the placebo issue between ICH GCP and the World Medical Association's *Declaration of Helsinki*. The *Declaration of Helsinki* is viewed by many as the authoritative international statement on research ethics. Indeed, it is even referenced in the ICH GCP as the source document for ethical principles. Nevertheless, ICH GCP and related documents of ICH (such as E-10) have not adopted the standard on placebo controls articulated in the *Declaration of Helsinki*. The division in international standards provides an opportunity for regulatory agencies to choose to which standard they will adhere. On October 27, 2008 the US FDA formally abandoned its use of the *Declaration of Helsinki* for international clinical trials. In its stead, the FDA will take direction only

from the ICH GCP.¹⁶ The FDA's move seems hazardous precisely because it undermines the global reach of the Declaration of Helsinki. Commentators worry that it will undermine international ethics standards and may lead to a balkanization of research ethics.¹⁷

Canada's proximity to the largest drugs market in the world undoubtedly places Health Canada in a precarious position. Clearly, regulatory harmonization between Health Canada and the U.S. FDA has advantages. Information about new drugs gathered in the FDA licensure process could very usefully inform Canadian review of the same products, and could expedite review in some cases. Beyond this, regulatory harmony

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enhances Canada's ability to compete for and attract international clinical trials, resulting in knowledge and economic benefits. But these benefits come at a cost. Health Canada's decision not to endorse the *Declaration of Helsinki* only further undermines the document and exacerbates worries about the erosion of international standards in research ethics. Further, harmony with FDA standards comes at the price of perpetuating conflict in the Canadian governance of clinical trials. We believe Health Canada has been remiss in its failure to endorse the entirety of TCPS, thereby promoting a single ethical standard to protect Canadians in research.

The experience of the National Placebo Initiative highlights the importance of the authority and independence of national ethics bodies. In retrospect, NPI did not have the mandate required to get the job done. In merely relying on CIHR and Health Canada to follow its recommendations, it was in a sense too easy for the funders to simply ignore recommendations with which they did not agree. CIHR and Health Canada ought to



Table 1

<p>TCPS Article 7.4</p> <p>The use of placebo controls in clinical trials is generally unacceptable when standard therapies or interventions are available for a particular patient population. 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 <u>A</u> above). Consistent with clinical equipoise, a placebo may be used as the control treatment in a clinical trial in the following circumstances:</p> <ol style="list-style-type: none"> 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 advantage 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. 	<p>NPWG Recommendations regarding use of placebo</p> <p>Amendments to Tri-Council Policy Statement, Article 7.4</p> <p>Article 7 should be amended to read:</p> <p>"The use of an active treatment comparator in a clinical trial of a new therapy is generally the appropriate study design when <i>established effective therapy or therapies exist</i> for the population and indication under study." Additionally,</p> <p>"A placebo comparator is acceptable in the following situations:</p> <ol style="list-style-type: none"> a) There are no established effective therapies for the population and for the indication under study, b) Existing evidence raises substantial doubt regarding the net therapeutic benefit of available therapies, c) Patients are refractory to the available therapies by virtue of their past treatment history or known medical history d) The study involves adding a new investigational therapy to established effective therapies, (established effective therapy + new therapy vs. established effective therapy + placebo) e) Patients have determined that the response to the established effective therapies for their condition is unsatisfactory to them,"* f) Patients have previously refused established effective therapies for their condition."* <p>*For articles (e) and (f) the determinations of response satisfaction and refusal of treatment must take place outside of the context of recruitment for the clinical trial and prior to the offering of trial participation to the potential subject, and be documented in a standardised manner. Under these conditions, study subjects would not necessarily be considered "refractory" to the available therapies since the choice to discontinue available therapies is based on their own opinion and values, not those of the clinicians responsible for their care. As such, regulatory approval of the therapy under investigation would not necessarily be restricted.</p>
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have been required to respond publicly within a set time frame to recommendations that were not implemented. The wisdom of the NPI being funded by CIHR and Health Canada must also be questioned. The NPI was in some respects a successor to a successful consensus-seeking roundtable on placebos funded by the National Council on Ethics in Human Research. NCEHR does not fund research, and does not have the conflicts of interest that arise when research sponsors assume responsibility for research governance.

In our view, the experience of the NPI highlights the urgent need for the creation of an independent body to set national research ethics policy. Recent moves to create a "Sponsor's Table for Human Research Participant Protection in Canada," a group of organizations with an interest in human research protections in Canada, seem only to intensify conflicts of interest and undermine independence by placing the control of research governance in the hands of federal, provincial, and private sector sponsors of research.¹⁸ We are likely to achieve progress in the governance of research in Canada only when control of the ethical standards for research is wrested from those who have a mandate to fund and promote research. An independent body given the necessary authority to set national policy is the right avenue to create a unified and effective standard to protect all Canadians in research.

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Endnotes

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