

Placebo trials and tribulations

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The most divisive debate within psychiatric research today involves the proper role of placebo controls in clinical trials that test the effectiveness of new drugs. Canada's *Tri-Council Policy Statement* carefully defines the conditions under which placebo controls may be used legitimately.¹ Article 7.4 stipulates that "[t]he use of placebo controls in clinical trials is generally unacceptable when standard therapies or interventions are available for a particular patient population." This is not an idiosyncratic position. Indeed, the most recent revision of the *Declaration of Helsinki* (paragraph 29) similarly prohibits the use of a placebo control when effective therapy exists for the medical condition being studied.² But ethical guidelines are only as good as their application in practice. Are Canada's researchers, research institutions and government abiding by these requirements?

Unfortunately, at least in some cases, it appears that the answer is no. Consider the following ongoing clinical trial for which I served as an external reviewer for a local research ethics board (REB). The study is a multicentre, randomized controlled trial comparing a new selective serotonin reuptake inhibitor, paroxetine, and placebo in the treatment of major depressive disorder. Given the existence of proven, effective treatment for major depressive disorder,³ the local REB concluded that the use of a placebo control was inappropriate and, in accordance with the *Tri-Council Policy Statement* and paragraph 29 of the *Declaration of Helsinki*, rejected the study. The local REB's decision placed it in the minority of Canadian REBs that had considered the same study: 16 other REBs approved the protocol for use by 19 investigators.⁴

In order to explain this disparity, each of the many levels of Canada's regulatory system that is designed to protect research subjects must be examined. The first level of protection for research subjects is provided by the clinical investigator and by each subject's own physician. When may the responsible physician offer trial enrolment to her or his patient? Clinical equipoise provides the most widely accepted answer to this question.⁵ According to this concept, there must exist at the start of the trial a state of honest, professional disagreement in the community of expert clinicians as to the preferred treatment. Under these circumstances a state of clinical equipoise is said to exist, and the physician may offer trial enrolment to his or her patients legitimately.

Placebo controls may be used when there is no available treatment for a disorder, or when an adjunctive treatment is being tested, so that all participants receive the standard treatment.⁶ Second-generation treatments, however, must be tested against the best available therapy.⁶ In the case of depression, the effectiveness of drug treatment is well established.³ In such cases, the scrupulous clinician cannot offer participation in a placebo-controlled trial ethically to his or her patients.³

The second level of protection for Canada's research

subjects is the research institution, be it a university or hospital. Research institutions that receive funds from the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council or the Social Sciences and Humanities Research Council must uphold the ethical standards for research laid out in the *Tri-Council Policy Statement*.¹ Lack of compliance may be associated with serious consequences: "The Councils will consider funding (or continued funding) only to individuals and institutions which certify compliance with this policy regarding research involving human subjects."¹ The REB's role is to ensure that research meets the standards set by the *Policy Statement*.

The protocol described earlier was approved by REBs from a number of Canada's leading universities and their teaching hospitals. This suggests a lack of clarity on a national level regarding the need for adherence to the *Tri-Council Policy Statement*. The funding councils themselves may have perpetuated this state of affairs. To date, the councils have failed to caution or suspend funding to any institution for failing to adhere to the *Policy Statement*.

The third level of protection for Canada's research subjects is the government. All research for the licensing of new drugs, including the protocol described here, is conducted under the aegis of Health Canada's Therapeutic Products Directorate (TPD), which was part of the Therapeutic Products Programme (TPP) until April 2001. The TPD does not officially endorse the *Tri-Council Policy Statement*. Rather, new drug research must comply with the guidelines of the International Conference on Harmonization (ICH), an international standard-setting body for the licensing of new drugs.^{7,8} Obviously, any discrepancy between ICH guidelines and the *Policy Statement* will translate into a double standard for Canadian research subjects.

Further problems are posed by the fact that the ICH documents give conflicting guidance about the conduct of placebo-controlled trials. At one point, ICH guidelines take a relatively permissive stance on the use of placebo controls, allowing them when effective treatment exists as long as subjects are not exposed to the risk of death or permanent morbidity (Section 2.1.3).⁷ At another point, however, ICH guidelines require that "[c]linical trials should be conducted in accordance with ... the Declaration of Helsinki ..." (Section 2.1) and, thus, prohibit the same trials that other ICH guidelines permit.⁸ Clearly, this regulatory conflict must be resolved.

The TPD relies on arms-length review by the REBs to ensure that research is conducted ethically. In some cases, these REBs are not affiliated with any institution (and as such are not bound by the *Tri-Council Policy Statement*) and charge for ethics review. These "for profit" REBs are neither accredited by government nor are they subject to government oversight despite the obvious conflict of interest posed

by “for profit” ethics review.⁹ At least 2 of the REBs that reviewed the protocol described here are “for-profit” REBs.⁴

The TPD must itself avoid the appearance of conflict of interest. After the local REB rejected the protocol under discussion, it received a copy of a letter from the then TPP written to a project manager at a research centre and forwarded by a researcher at the same centre that stated the following:

We believe judicious use of placebo controlled trials to establish unequivocally the efficacy of a new drug, together with a comprehensive risk management protocol and appropriate informed consent, is ethical. To use an inconclusive trial design when a conclusive trial design is possible, is unethical.¹⁰

REB review must be independent and it was, therefore, inherently improper for the TPP to tell an REB what is ethical. The facts of this case are problematic for 2 reasons. First, whether a particular practice is ethical or not is a matter set forth in national and international guidelines to be interpreted by REBs. The TPP should not have promulgated idiosyncratic views. Second, though the letter from the TPP made its way to the REB indirectly and the TPP may not have been aware of the investigator’s intention to so distribute it, the TPP ought to have made it clear that this action by the investigator was inappropriate and should have reassured the REB that the TPP had no intention of interfering with the REB review process. I raised this issue in a letter to the TPP’s then Acting Director General, Dr. Robert Peterson, dated Sept. 27, 2000.¹¹ I wrote, “For the TPP to attempt to influence the decision of a particular REB, or for it to even appear to do so, is a violation of proper procedure, and undermines the REB’s role as a societal mechanism to protect Canadians in research.”¹¹ To date, I have not received a reply.

The placebo-controlled trial is a litmus test for the adequacy of Canada’s regulatory system for research. The case discussed here reveals the need for change at all levels. Clinician investigators must reaffirm their commitment first and foremost to the well-being of their patients. REBs must follow the ethical guidance given by the *Tri-Council Policy Statement*. The funding councils must enforce these standards. Finally, the TPD must formally adopt the *Policy Statement* to ensure that all Canadians who give of themselves to further research are afforded the highest level of protection.

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The World Medical Association recently offered a “Note of clarification on paragraph 29” that seems to allow for limited use of placebo controls when “compelling and scientifically sound methodological reasons” exist or when subjects will not be placed at “any additional risk of serious or irreversible harm.” The interpretation of this development is hindered by the fact that these “clarifications” of paragraph 29 in fact contradict it. Nonetheless, Dr. Delon Human, Secretary General of the WMA, seems to suggest that research on common psychiatric conditions would not fall into these exceptions. According to Human, the exceptional use of placebo controls is only acceptable “where research is done to find more effective treatments for a *minor condition*, such as baldness or allergic rhinitis. For this type of clinical situation there would be *no additional risk or irreversible harm* for the control group, who would be receiving placebo (no treatment)” [emphasis added] (www.wma.net/e/press.html [accessed 2002 Feb 4]). The reader should note that all the events discussed in this commentary occurred before the note of clarification was published.

This article arose from a solicited manuscript submitted to the *Journal of Addiction and Mental Health (JAMH)*, a publication of the Centre for Addiction and Mental Health at the University of Toronto, in May 2000. The author received an extensively edited and revised version of the paper for approval. In Dr. Weijer’s view, the alterations so fundamentally altered his criticism of placebo-controlled trials in psychiatric research that he felt compelled to withdraw the manuscript.

CMAJ became aware of the manuscript when these events were reported in the *Globe and Mail* last year (2001 May 1; Sect A:6). We invited Dr. Weijer to submit the paper to us. An edited version approved by the author is published here.