being younger and having fewer traditional coronary risk factors.

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Placebo tribulations

Charles Weijer's[1] recent indictment of the Canadian research review process is unsupported. On the basis of the meagre information given, it is impossible to determine whether the protocol in question violates the *Tri-Council Policy Statement* (TCPS).[2] That guideline enunciates a strong presumption against placebo use when "standard therapies" are available. It does not state an exceptionless rule, and, indeed, the policy discusses some of the exceptions. Demonstrating that the protocol violates the TCPS statement is crucial to Weijer's accusation that Canadian researchers, research ethics boards (REBs), universities and federal funding agencies are shirking their responsibilities.

Health Canada cannot dictate decisions on particular cases to REBs, but nothing is wrong with it promulgating general policy on research ethics. The passage Weijer quotes contains nothing but statements of general principles. Not a single one of them is objectionable, idiosyncratic or even at odds with the TCPS statement. I know of no national or international guideline that specifies that the judicious use of placebo controls in clinical trials is unethical. (There is, of course, great controversy over what counts as a judicious use.) Benjamin Freedman agreed with the TCPS that REBs should reject trials with inconclusive designs.[3]

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In his commentary, Charles Weijer poses interesting and challenging questions regarding placebo-controlled clinical drug trials.[1] However, it is unfortunate that he chooses to make negative and unsubstantiated assertions about for-profit research ethics boards (REBs), lumping them all together.

He states that the failures of university teaching hospital REBs are attributed to "lack of clarity … regarding the need for adherence to the *Tri-Council Policy Statement*" while for-profit REBs are assailed because of "obvious conflicts of interest doing ethics reviews." Why is the latter an "obvious" conflict of interest? Getting paid for work does not necessarily compromise judgement.

We would suggest that the members of most for-profit REBs are guided, or should be, by the same ethical standards as are the members of university teaching hospital REBs. For example, the members of the latter are subject to the same conflicts of interest because university teaching hospitals receive "overhead" funds whenever a study is done at that institution. Moreover, the voting members of university teaching hospital REBs regularly review studies submitted by their colleagues and thus potentially have more conflicts of interest than do the members of for-profit REBs. Our institutional review board (IRB) is totally independent, without a research arm, and is well positioned to pass judgement on the merits of a particular study. We are completely independent of outside pressures and able to consider the safety of the patient foremost, providing the study has scientific merit.

We would like to point out that our IRB rejected an unethical study involving an angiotensin-converting enzyme (ACE) inhibitor versus an angiotensin-II blocker versus placebo in diabetics with proteinurea, although 7 Canadian university teaching hospital boards approved it. Only 1 university teaching hospital REB rejected it. What's even more worrisome is that this particular study had been running for more than 2 years before it was sent to us, and each of the approving university teaching hospital REBs had extended the approval. None shut it down despite incontrovertible evidence of the ACE inhibitor's nephroprotective effect during the continuing review period.

We also restricted approval of a study with a new thrombolytic agent to 3 months due to safety concerns, although a university teaching hospital REB approved it for 1 year. Why did we restrict it? Because we knew of an exsanguinating hemorrhage with the study compound that occurred at the hospital REB's sister hospital. The bleeding could not be stopped, and the case was discussed during the university's cardiology department rounds. Despite this occurrence, the REB apparently did not review their approval or require changes to the consent form, despite information from their own investigators that the study drug might cause life-threatening bleeding.

How do we know about the hospital REBs' decisions? Because in each instance we were told by the sponsor or the principal coordinating investigator when we refused to approve these studies that "you are the only one to refuse!"

In several other cases, we have rejected unethical studies that other REBs have not (see the complete letter at www.cmaj.ca).

Weijer should also consider the well-publicized ethical problems at presti-

gious US academic institutions such as Duke, Virginia Commonwealth, Johns Hopkins, Pennsylvania and the Fred Hutchinson Cancer Institute, not omitting the sad Poisson breast cancer trial at the University of Montreal.

In the US, the FDA inspects both the private and university teaching hospital REBs. Yet, all the above major problems found by Food and Drug Administration or Office for Human Research Protections inspections have been at academic institutions.

Legitimate differences of opinion will always exist in a free society. Improving the protection of human research subjects is everyone's concern and responsibility — whether a particular study is vetted by an REB in the university/public study sector or private sector.

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Charles Weijer has elegantly discussed the ethical issues regarding the use of placebo controls in clinical therapeutic trials.[1] However, can one speak of placebo-controlled trials when the patient is told that he or she might receive an inactive drug or procedure? A placebo is defined in the *Shorter Oxford Dictionary* of 1811 as "a medicine given more to please than to benefit the patient."[2] Thus a placebo is a pharmacologically inert drug or a dummy procedure prescribed with therapeutic intent. Patients in modern-day clinical therapeutic trials are, by this definition, not given a placebo and cannot be under current guidelines.

The prescribing of a placebo implies deception. Conversely, allocating an inert therapy to a patient who has been instructed that it is inert, with their consent, is quite a different matter. Inert controls provide a greater delta of response than placebo controls.

Currently, the use of placebo therapy is denounced by most ethicists,[3,4] but practising physicians caring for patients find it more acceptable. Why is it deceitful to prescribe a placebo when most modern drugs, especially antirheumatic drugs, are only marginally better and certainly more toxic?[5] Most alternative therapies can be considered super-placebos[6] and are certainly very popular with patients. The greatest placebo is the doctor, a fact appreciated by William Osler.

I hope that the recent National Conference on Appropriate Placebo Use in Clinical Trials, held in Ottawa, was not only attended by scientists, ethicists and policy-makers, but also patients and their families. It is, after all, the patient who is at the end of the final common pathway.

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[The author responds:]

The point of my commentary[1] is simple: 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*.[2,3] Effective regulation of research requires change at a variety of levels, including the researcher, institution, funding councils, and Health Canada. It is not surprising that a strong emotional response has been evoked in the letters to the editor. When something is broken, some will continue to insist — however implausibly — that it is working just fine.

Grenier claims that I have not provided sufficient information to determine if the trial in question falls into one of the exemptions laid out in article 7.4. This is not the case. I invite readers to compare the text of my article with article 7.4a-g. This protocol qualifies for none of the listed exemptions.

Corman and colleagues are correct that university and hospital REBs are subject to conflicts of interest because their institutions receive money to conduct research, and researchers often dominate REBs. This is yet another aspect of the current system that needs to be fixed. In 1993, Paul McNeil proposed that REBs ought to be composed of equal numbers of community and institutional representatives, and the REB chair must be a community member.[4] The problem with for-profit REBs cannot, however, be fixed. The REB is a social oversight mechanism charged with the public's trust to protect research subjects. This trust will surely be eroded when the regulatory system contains elements that exist to turn ethics reviews into profit. Corman and colleagues helpfully provide other examples supporting my point that Canada's research regulatory system is broken.

Buchanan reasonably asks whether a placebo given in the context of a modern clinical trial is really a placebo because research participants are informed that they may receive a placebo. A fascinating literature is available on so-called revealed placebo use in medical practice.[5] It is unclear that deception is key to achieving a placebo effect. In any case, placebo use in clinical trials is not fully revealed because subjects are only informed that they *may* receive a placebo, not that they *will* receive one.

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