Editorial

Placebo Controlled Trials: Interests of Subjects versus Interests of Drug Regulators

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Abstract

The use of placebo-controlled trials in situations where established therapies are available is considered ethically problematic since the patients randomised to the placebo group are deprived of the beneficial treatment. The pharmaceutical industry and drug regulators seem to argue that placebo-controlled trials with extensive precautions and control measures in place should still be allowed since they provide necessary scientific evidence for the efficacy and safety of new drugs. On the other hand, the scientific value and usefulness for clinical decision-making may be much higher if the new drug is compared directly to existing therapies. As such, it may still be unethical to impose the burden and risk of placebo-controlled trials on patients even if extensive precautions are taken. A few exceptions do exist. The use of placebo-controlled trials in situations where an established, effective and safe therapy exists remains largely controversial.

Keywords: randomised controlled trial, placebo, research ethics, ethics, institutional review board, ethics committee
A critical question arising from this scenario is whether the need for new products, products that are better than the placebo but not proven to be better than existing products, reflects the need of the all-powerful big pharmaceutical industry or the need for public health.

**Placebo- versus Active-controlled Trials**

Freedman (4) was among the authors who rejected the use of a placebo for the sole purpose of scientific curiosity or the desire to achieve a clean biological analysis of a specific drug effect.

A lack of assay sensitivity in active-controlled trials (ACTs) as compared to placebo-controlled trials (PCTs) has been mentioned in ICH-E10, section 1.5 (5). Several authors (6, 7, 8) have rebutted the assay sensitivity argument in a very convincing way.

Another argument brought up in favour of PCTs was that ACTs do not measure the absolute effect size (ICH-E10 section 2.1.6.2) (5). Howick (7) convincingly argued that this operates on the false assumption of ‘additivity’.

Howick (7) also argued against the notion that ACTs are less ethical because they usually involve a larger sample size (ICH-E10 section 2.4.7.2) (5). If a PCT is designed to detect a difference that is the same size as the equivalence margin, it will require a sample size that is equally as large as an ACT. Moreover, further studies requiring more samples are needed to determine how the new treatment compares with the best existing treatment.

For the industry, it is easier to demonstrate the superiority of a new drug over a placebo than it is to demonstrate the superiority of a new drug over an existing treatment. Of course, the question remains, if it is not superior to an existing drug, then why do we need the new drug? Indeed, it may be increasingly difficult to produce new drugs that are superior to the existing ones; however, from a patient/society point of view, one could argue as to why new drugs are needed that are not superior to the existing ones.

Drug regulators (2, 3) may be more inclined to approve or disapprove new drugs based on the results of placebo-controlled trials than on trials comparing two active substances (new and standard). The pharmaceutical industry is an extremely strong driving force for local economies and one might question the amount of pressure this industry can or does impose on legal drug regulators who are directly responsible to the governments of their respective countries.
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Drafting of the article: THS, HVR
Critical revision of the article for important intellectual content: THS, HVR
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Summary

The use of placebo-controlled trials when an effective and safe therapy exists remains largely controversial. We argued in this article that PCTs, compared to ACTs, might have an unacceptable risk/benefit ratio for clinicians and patients, although PCTs may be useful for industry and drug regulators.

Competing Interests

All authors are medical members of the IRB or human research ethics committee of the Universiti Sains Malaysia.

Placebo-controlled Trials and the Difference Position

In most countries, medical doctors are bound by the Declaration of Geneva (9), which states that ‘the health of my patient will be my first consideration,’ and/or the International Code of Medical Ethics.

Miller and Brody (10) argued that the ethics of research, which governs the researcher–subject relationship, are fundamentally different from the ethics of therapy, governing the physician–patient relationship. This is also known as the ‘difference position’. In practice, even if we adopt the ‘difference position’, it is easy to recognise that, in clinical trials, the physician and the researcher are the same person and the patient and the subject are also the same person. Therefore, the ethical norms will be competing at best, where the immediate interests of the therapy and the patients ought to prevail.

Physician-researchers have a fiduciary duty to the patient-subjects, including a duty of care. Extending this argument to the application of placebo-controlled trials, the need for competent care would support restrictions on the use of placebo controls in clinical research. Accordingly, clinical equipoise requires the adoption of an active control (comparator intervention) in clinical trials investigating new treatments for serious conditions for which a proven treatment exists (11). This is also known as the ‘similarity position,’ which recognises the unified ethics between that of research and that of therapy.
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