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*

Background

A controversy exists about the ethics of placebo-controlled trials. Whenever a proven intervention exists, the Declaration of Helsinki 2013 (1), article 33, explicitly discourages the involvement of a placebo in human research but allows an exception in rare occasions when compelling reasons for the use of a placebo exist. Clinicians and Institutional Review Boards (IRBs) may find such compelling reasons to be extremely rare or non-existent. Drug regulators and industries, on the other hand, have repeatedly supported and stated compelling reasons to conduct placebo-controlled trials even in the presence of proven efficacious therapies.

This article aims to explore each of the above viewpoints and correlate them to recent literature on the topic.

Perspective of the Clinician

A new drug needs to be shown to be superior to, or at least non-inferior to, existing proven effective therapies before a clinician will start to use it. In this regard, placebo-controlled trials do not address the question of superiority or non-inferiority and would therefore offer limited clinical value to clinicians. In addition to limited merit, the danger of administering a placebo for a condition with available efficacious therapies is high. As such, placebo-controlled trials have an unfavourable risk/benefit ratio.

Exceptions include the use of add-on therapies where either the new therapy or the placebo is added to the existing standard of care and situations where an established way of treating patients has been around for a long time but has never been founded on rigorous high-quality research. Examples of such exceptions also include medications prescribed off-label.

Perspective from Drug Regulators and Industry

Drug regulators, such as the European Medicines Agency (EMA), have generated multiple explicit statements defending the use of placebo-controlled trials, even in the presence of proven efficacious treatments (2, 3). These statements have been used by the sponsors of clinical trials in an attempt to convince IRBs of the acceptability of certain trials.

It seems that well-respected drug regulators support the industry in their call that placebo-controlled trials are necessary, even if other effective therapies have been established. 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.

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.

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.

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