Randomized Controlled Trials: Ethical and Scientific Issues in the Choice of Placebo or Active Control

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Abstract

The use of control group in clinical trials has been universally acclaimed by researchers to effectively help discriminate between the actual effects of an intervention and those arising from other factors. However, the choice of the control that provided both scientific and ethical acceptability among researchers has been a source of intense debate. We conducted a literature search on the use of placebo and active controls in clinical trials and X-ray the arguments for and against both choices in randomized control trials and concluded by highlighting the scenarios where the use of placebo is justified.

Keywords: Active control, placebo control, randomized controlled trials, research ethics

Résumé

L’utilisation de groupe témoin dans les essais cliniques est universellement accepté par les chercheurs pour distinguer entre les effets réels d’une intervention et ceux provenant d’autres facteurs. Cependant, les choix de témoin qui a fourni l’acceptabilité scientifique et éthique parmi les chercheurs, a été une l’objet d’intense débat. Nous avons mené une recherche documentaire sur l’administration de placebo et d’essais actifs dans les essais cliniques et examiner les arguments pour et contre les deux choix en essais contrôlé randomisé, et conclure en soulignant des scénarios où l’administration de placebo est justifié.

Mots-clés: Essai actif, groupe placebo, essais contrôlés randomisé, éthiques de recherche

INTRODUCTION

Randomized controlled trial (RCT) is regarded as the “gold standard” in the evidence-based evaluation of new treatments and interventions and is different from other study designs because they are performed under very rigorous conditions.

A high-quality RCT uses randomization, placebo, and double-blind design to minimize bias by isolating the effect of an intervention from other potential causes and ensuring that confounders are evenly distributed between the treatment group and comparator group. These give the assurance of the highest certainty that the observed treatment effects could be attributed to the intervention, rather than to external factors.¹

The choice between placebo and active controls in clinical trials affects the quality of the result as well as the ethical and scientific acceptability by both the public and regulatory bodies. It has, therefore, continued to generate discuss among researchers.

In this essay, we reviewed the arguments for and against placebo-controlled trials (PCTs) and concluded by highlighting the scenarios where the use of placebo is ethically justified.

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The word placebo comes from the Latin word, placere, which means, “I shall please.” It is “an epithet given to any medicine more to please than to benefit the patient.”[2] In the context of RCTs, a placebo is not merely devoid of active pharmaceutical ingredients but is designed to resemble the test treatment with respect to physical characteristics such as color, weight, taste, and smell.[3] Therefore, a placebo though may resemble the test treatment, it is not expected to add real medicinal benefit (physiological effect) aside the psychological benefit to the clinical subjects.[4]

On the other hand, an active control trial is one in which an investigational drug is compared with an established treatment that has a known degree of effectiveness, with the aim of either demonstrating that the test treatment is as good as or is superior to the active treatment.[3]

The arguments for and against the questions raised by PCTs are highlighted below.

The ethical creeds and placebo controversy
The critique of PCT is often hinged on the World Medical Association’s (WMA) Declaration of Helsinki (DoH) which states that “the benefits, risks, burdens, and effectiveness of a new intervention must be tested against those of the best proven intervention(s).”[5]

In PCTs, the new intervention is not tested against the best proven one, and therefore, the study participants are denied the best available treatment at that time and possibly exposed to further harm or risk. In the words of Glass and Waring, “PCTs ignore well-established ethical and legal standards of care, which defines the duty of physician toward their patients.”[6]

However, latter part of paragraph 33 of the DoH justified the use of placebos in the following statement: “…The use of placebo or no treatment is justified where no proven intervention exist; or where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subjected to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention…….”[5]

The Belmont Report also emphasized that for a research to be considered ethical, it must be based on respect for persons/autonomy, beneficence/nonmaleficence, and justice.[7] In this regard, a physician is expected to do no harm by minimizing the risk while enhancing the benefits of subjects’ participation in clinical trials. In PCTs, there is a reasonable chance that the participants who receive placebo may be exposed to some risk or harm if they are denied the best available treatment and this contradicts the ethical principle of beneficence/nonmaleficence in clinical research.

The Council for International Organizations of Medical Sciences guideline for biomedical research involving human subjects reechoed the WMA DoH in its guideline 11 where it states that “Placebo may be used: When there is no effective intervention; when withholding an established effective intervention would expose subjects to, at most, temporary discomfort, or delay in the relief of symptoms; when use of an established effective intervention as comparator would not yield scientifically reliable results and the use of placebo would not add any risk of serious or irreversible harm to the subjects.”[8]

Despite these clarifications, there still exist some lacunae in all these provisos and these further make the subject more confusing. The DoH warned that extreme care must be taken to avoid the abuse of placebo in clinical trials. Further questions that many may ask are: When do we really say the proviso is abused? At what point can we conclude that there is no effective intervention or treatment? Are PCTs scientifically and methodologically superior to active controls? Are placebos actually inert and powerless? How well does informed consent and independent review validate the use of placebos in clinical trials? The rest of this article explores the answers to these questions.

The potential for abuse of placebo control trials
Increasing globalization has seen many of the big pharmaceutical companies conducting clinical trials in developing countries where the use of PCTs is commonly exploited. In developing countries, the Institutional Review Boards are weak and not entirely independent; and investigators are keen to get international recognition by participating in multinational, multicenter trials.[4] In these situations, the decision of no effective intervention or treatment may be confused by conflict of interests of the persons making the decision. Furthermore, the distribution of the benefits and burden of clinical research must be fair and equitable, but this is not the case in most PCTs in developing countries, where, due to dysfunctional health system and out-of-pocket payments of medications, the new medications developed are often beyond the reach of poor participants.[7]

The concept of clinical equipoise versus therapeutic misconception
The proponents of the PCTs contend that a placebo may be used in the context of clinical equipoise – which is defined as “a genuine state of uncertainty in the expert medical community about the comparative therapeutic merits of each arm of the clinical trial.”[9] Freedman contends that clinical equipoise is
a condicio sine qua non in the conduct of an ethically valid clinical research, and in this case, once the trial participant gives a proper and well-informed consent, then the process can be adjudged ethical.\[10\] However, Miller and Brody argued that the concept of clinical equipoise is flawed because it is at variance with the objective of clinical research, which is fundamentally different from clinical care.\[10\] They contend that there is always obfuscation about the real motive of clinical research, hence, a “therapeutic misconception.” Therapeutic misconception is a false belief that the purpose of research is therapeutic for the subject. The purpose of clinical research is to benefit future patients and not for patient care, and though a patient enrolled in clinical trials may benefit from the trial, such can be best described as a “side effect” as this was not the original intention. The physician – researcher is primarily obligated to science and secondarily obligated to patient care.

Temple and Ellenberg argued that it is not always possible for the patient to receive the best proven therapy even when an active control is used, and hence, “...the requirement that all patients receive the best proven diagnostic and therapeutic method...” would bar not only PCTs but also active-control and historical-controlled trials. When effective treatment exists, the patient receiving the investigational treatment instead of established treatment is clearly not getting the best-proven treatment.\[11\]

The concept of equipoise and false belief of therapeutic benefit for the patients or subjects has further come into attack in the conduct of Phase 1 clinical trials. Phase 1 clinical trials are conducted in healthy volunteers, except for trials in oncology and HIV where disease patients are used. The purpose of Phase 1 trial is to gain insight in the safety and tolerability of the new medicinal product. Here, graded doses of the test substances are given to the subjects until the maximum dose that induce the first symptom or sign of toxicity is achieved, with the hope that toxicity is reversible.\[12\] At this point, the physician-investigator cannot genuinely claim knowledge of the likely nature and severity of this toxicity and can never claim to be at equipoise about the risk benefit of the medicinal product and clearly does it for the public good and not that of the subject. In Phase 1 oncology trials, many of patients who enroll have limited life expectancy\[13\] and as few as 4.2%-6.3% derive any benefit from the study.\[14\]

In further justifying the use of placebo, some ethicists have contended that all failures to use effective therapy are not equal, and that placebo/or untreated controls may be used in the following situations: Where the treatment does not affect the patient’s long-term health; and in the study of drugs for illnesses that may be self-limiting or have fluctuating course with exacerbation and remission. Even in such situations, it is with the proviso that the patient is fully informed of the existence of a therapy, and he/she must be able to explore, with the investigator, the consequences of deferring such therapy.\[11\]

Subjects participating in a randomized PCT must be carefully and frequently monitored; there must be an escape mechanism put in place for any patient who suffers adverse consequences related to the lack of therapy; the clinical trial duration should be as short as possible.\[14\]

**Primum non nocere and placebo-controlled trials in surgery**

The physician’s dictum as he conducts his affairs with his patients must be *primum non nocere* (first, do no harm). However, this dictum poses a serious dilemma in placebo-controlled surgical trials. The need to rigorously evaluate innovative surgery procedure has seen many researchers advocating for placebo control surgical trials, especially in trials where primary outcome is subjective.\[15\] In a placebo (sham) operation or surgery, a procedure is performed on a control group to ensure that they experience the same incidental effects of the operation or procedure as do those participants who had a true operation performed.\[15,16\] Sham surgery has helped unravel the ineffectiveness of otherwise well-established surgical procedures and has contributed in understanding treatments for Parkinson’s disease, osteoarthritis, treatment-resistant depression.\[15-17\]

Opponents of sham operation argue that the potential harm to the subjects who received placebo surgery violate the dictum of *primum non nocere*. The sham operation is associated with risk of anesthesia, sedation, and pain and therefore contradicts the provision of the DoH and the concept of clinical equipoise. However, PCTs in surgery can be considered justifiable if the risk is not excessive and the subject has clearly been told of the experimental nature of the surgery.\[15-17\]

**Placebo-controlled trials in psychiatry**

PCTs in psychiatry deprive many of the patients enrolled in such studies effective treatments for as long as the trial lasts. For proponents of PCT, a proper and well-informed consent validates the experimental nature of the study. However, the question is, “how well is a ‘well-informed’ consent, especially in a psychiatric patient?” Mental illness compromises the patients’ capacity to understand and their ability to make reasoned decision about participation.\[4,18\] Therefore, acceptable risk-benefit ratio and informed consent cannot justify randomized PCT in psychiatric subjects.

**The methodological superiority of placebos: Assay sensitivity in clinical trials**

The concept “bad design is bad ethics” is a well-known mantra in medical ethics. Proponents of PCTs have always argued against the methodological limitations of active-controlled designs – their lack of assay sensitivity in noninferiority trials. Assay sensitivity is the ability of a clinical trial to distinguish an effective treatment from less effective or ineffective treatment.\[3\] Active-control trials are nearly always designed as noninferiority or equivalent trials. Unlike in a superiority trial (often used with placebo-controlled designs), a lack of assay sensitivity in a noninferiority trial may lead to an erroneous conclusion of efficacy.\[3\] Superiority designs provide stronger evidence to the effectiveness of a drug,
limited only by statistical uncertainty of the result; however, in noninferiority design, equivalence could mean that both treatments are effective in the study, or that both treatments were ineffective in the study.[11] To get about this, active control studies must make use of historical evidence of sensitivity in choice of noninferiority margin, and the design must be similar to those of the previous trials in terms of eligibility criteria, concomitant, etc. The PCTs also measure “absolute” efficacy and safety of a pharmacological product, in contrast to the active-control, which measures efficacy and safety relative to other treatment and also requires large sample sizes to demonstrate efficacy.[3,19]

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CONCLUSION

PCTs, when conducted in the context of sound ethical framework of scientific validity, fair subject selection, favorable risk-benefit ratio, and respect for subjects, independent ethics review and well-informed consent are better than studies with active controls in determining the clinical efficacy and safety profiles of new drugs. Therefore, they are acceptable in the initial assessment of an investigational drug or disease with spontaneous tendency to improvement, in diseases with significant psychological component, or in situations where it causes only temporary discomfort and serious risk of irreversible harm is absent.

Regulatory consideration

The US Food and Drug Administration (FDA) is the world’s leading national regulatory agency and has been at the forefront of regulation of clinical research. In its guidance document, the FDA contend that “PCTs are necessary to control for placebo effect of investigational medicinal product, and that blinding and randomization of groups to inert treatment controls for all potential influences on the actual or apparent course of the disease other than those arising from the pharmacological action of the drug.”[19] It is faster for an investigational medicinal product to reach regulatory approval if they are placebo-controlled because of the ability to minimize bias, high efficiency and high assay sensitivity in demonstrating superiority inherent in the design.

Conflicts of interest

There are no conflicts of interest.

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