Contemporary Clinical Trials 36 (2013) 510–514

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

The ethics of placebo-controlled trials: Methodological justifications

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ARTICLE INFO

Article history:
Received 15 May 2013
Revised 3 September 2013
Accepted 4 September 2013
Available online 12 September 2013

Keywords:
Ethics
Placebo control
Randomized controlled trial

ABSTRACT

The use of placebo controls in clinical trials remains controversial. Ethical analysis and international ethical guidance permit the use of placebo controls in randomized trials when scientifically indicated in four cases: (1) when there is no proven effective treatment for the condition under study; (2) when withholding treatment poses negligible risks to participants; (3) when there are compelling methodological reasons for using placebo, *and* withholding treatment does not pose a risk of serious harm to participants; and, more controversially, (4) when there are compelling methodological reasons for using placebo, *and* the research is intended to develop interventions that can be implemented in the population from which trial participants are drawn, *and* the trial does not require participants to forgo treatment they would otherwise receive. The concept of *methodological reasons* is essential to assessing the ethics of placebo controls in these controversial last two cases. This article sets out key considerations relevant to considering whether methodological reasons for a placebo control are compelling.

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1. Introduction

Randomized, placebo-controlled trials (PCTs) are widely considered to be the most rigorous method of evaluating the efficacy of treatment or prevention interventions. To be ethical, clinical research requires balancing rigorous science with the protection of human subjects. Most people accept the use of placebo controls in trials for conditions with no effective treatment. However, PCTs raise ethical concerns when a proven effective treatment exists, since randomizing subjects to a placebo exposes them to the potential harms of non-treatment [1]. The choice of a PCT design over other designs, such as active-controlled superiority or non-inferiority trials, therefore requires ethical justification. In this paper, we review ethically acceptable uses of placebo in randomized controlled trials and analyze how and when *methodological reasons* are compelling enough to justify placebo use.

2. Permissible use of placebo

There are four cases in which a placebo control design, when scientifically appropriate, is also considered ethically acceptable (Table 1). First, PCTs are acceptable when there is no proven effective intervention for the condition under study, or when placebo is compared against an investigational treatment added on to established treatment. This includes trials of treatments shown to be efficacious in some populations but where the data cannot be extrapolated to the population of interest. Use of placebo in this case is typically not ethically controversial.

Second, placebo is acceptable "when withholding an established, effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms," as noted in the Council of International Organizations of Medical Sciences' (CIOMS) *International Ethical Guidelines for Biomedical Research Involving Human Subjects* [2]. For example, it would be acceptable to use a placebo in testing a treatment for allergic

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1551-7144/$ – see front matter. Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.cct.2013.09.003

Table 1
When is it permissible to use a placebo control?

Condition	Variants	Examples
1. No proven effective intervention for condition under study.	No treatment exists.	Trial of a new medication to prevent Alzheimer's dementia [23]
	Trial tests add-on treatment	Trial of a new agent against placebo added to standard chemotherapy for ovarian cancer [24]
	Data on existing treatment cannot be extrapolated to the population of interest.	Trial to test whether an existing anti-depressant is efficacious in the treatment of PTSD [25]
2. No or negligible harms from delaying or forgoing treatment.	Not treating is an acceptable option for the condition under study.	Trial of medication for male pattern baldness [26]
	Negative consequences of not receiving treatment are negligible.	Trial of medication for symptom relief of allergic rhinitis [27]
3. Compelling methodological reasons for use of placebo; *and* Participants are not at risk of excessive harm.	High expected placebo response OR	Trial of new analgesic [28]
	Fluctuating outcomes AND	Trial of new treatment for psoriatic arthritis [29]
	Mixed data on effectiveness of standard treatment	Trial of new anti-depressant [30]
4. Compelling methodological reasons for use of placebo; *and* Participants are not deprived of interventions they would otherwise receive; *and* Research intended to develop interventions that will benefit the host population.		Short course AZT for prevention of mother to child HIV transmission [31]
		Trial of rectal artesunate as initial treatment for severe malaria patients en route to referral clinics [32]

rhinitis, a common headache, or male pattern baldness. In other words, placebo is permissible when the negative consequences of going untreated are negligible or no treatment is an acceptable alternative.

A third justification is sometimes invoked to justify placebo controls in trials of new treatments for conditions whose response to both established treatments and placebo is highly variable [3]. For example, depression has fluctuating symptoms and a high placebo response rate. It is not uncommon to have inconsistent evidence of the efficacy of approved anti-depressants—showing superiority to placebo on some endpoints in some trials but not others [4]. Demonstrating equivalence or non-inferiority of an investigational compared to an approved anti-depressant treatment may mean that the new drug is as efficacious as the established anti-depressant or that neither the established nor the investigational drug performed better than placebo in this trial. Similar phenomena can arise with anti-psychotics, treatments for mania, and analgesics. In such cases a placebo control may be necessary in order to establish the efficacy of a new treatment.

However, the fact that a placebo control is necessary to demonstrate efficacy is not sufficient to justify it. Sometimes the risks of forgoing treatment—for example, for a life-threatening condition—are so high that it would not be ethical to ask participants to accept them. Unlike for the previous justification, the risks of forgoing or delaying treatment need not be negligible. However, as with any research study, there are limits to the level of risk to which participants may be exposed, risks must be minimized, and risks must be justified by the value of the expected knowledge. Accordingly, the CIOMS guidelines permit placebo use:

> When use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects [2].

Likewise, the Declaration of Helsinki allows placebo controls:

> Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm [5].

Finally, some guidelines permit PCTs under certain unusual conditions in developing countries [6]. Sometimes an effective treatment is not available to a population for economic or logistic reasons. Researchers and policy makers may seek to develop a less expensive or easier to administer treatment that could be made available. They may expect that the newer treatment will be less effective than the existing alternative, or there may be reasonable doubts about extrapolating data from other populations to the developing country patients. Comparison to placebo may then be scientifically necessary to evaluate the efficacy of the new intervention in that context.

This last justification was articulated for PCTs of "short course" AZT for the prevention of mother to child HIV transmission in developing countries in the late 1990s. An intervention proven effective in the U.S. for reducing perinatal transmission using Zidovudine (AZT), the "076 regimen," had become the standard of care in developed countries. Although the original U.S. trial showed that AZT given intravenously prenatally, during delivery, and postpartum reduced the HIV transmission rate from mother to newborn by approximately two-thirds, [7] it had little prospect of implementation in the developing countries where the majority of perinatal HIV infections occurred: they lacked necessary infrastructure, many women did not receive prenatal care, and the drugs were too expensive.

These trials were controversial. Critics argued that placebo use was unnecessary to test the efficacy of short course AZT and that the trials represented an unethical "double standard" [8,9].