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The ethics of placebo-controlled trials: Methodological justifications

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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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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].

Proponents argued that since it was anticipated that short course AZT might be less effective than the 076 regimen, an active controlled trial would be uninformative regarding the efficacy of short course AZT, and that there was a compelling public health need for a cheaper, less complex intervention [10].

This debate helped clarify conditions for ethically permissible PCTs in populations without access to existing effective treatments. Such trials can be justified if: (1) the research is intended to develop interventions to be implemented in the population from which trial participants are drawn, (2) the trial does not require participants to forgo treatment they would otherwise receive, and (3) there are compelling methodological reasons for using a placebo control [11].

3. Interpreting the justifications for placebo controls

Though debate continues, there is fairly widespread agreement that using a placebo control in these four cases, or something like them, can be ethically justifiable. However, how to interpret the conditions under which they apply remains unsettled, especially for the third and fourth cases.

First, there is no consensus regarding the level of risk to which participants may be exposed by forgoing treatment. For example, is exposing participants to the risk of a depression relapse too great a risk? It is not adequate to proscribe placebo use when it might lead to "*any* serious or irreversible harm," as CIOMS and the Declaration of Helsinki suggest. Not treating a finger cut or minimal risk procedures like skin biopsies can lead to irreversible scarring and carry a tiny chance of serious harm from infection. Instead, it seems sensible to allow participants to be exposed to the same degree of risk by forgoing treatment that is allowable when they undergo other research procedures. Interpretation of the risk condition for PCTs should therefore be assimilated to the more general—albeit still unsettled—question of what level of risks it is permissible to ask informed people to take on in research.

Second, although scientific justification is always needed for the choice of a trial design, justification for exposing people to risks associated with placebo use must be more compelling as the risk of not receiving treatment increases. However, what this means in practice needs elucidation. Only when we understand what reasons count as compelling reasons will we be able to judge the ethics of placebo use in the most controversial cases. The remainder of this analysis considers how researchers and research ethics committees might evaluate whether there are *compelling methodological reasons* for placebo use.

4. Compelling methodological reasons

The relative merits of different scientific designs are complex and contextual. Experts may therefore disagree about the facts underlying a claim that placebo use is scientifically required. In the HIV perinatal trials, commentators disagreed about whether or not active-controlled trials could reliably answer the relevant scientific questions [12]. The investigators of an Indian placebo-controlled trial of risperidone for the treatment of acute mania [13] criticized for unnecessarily exposing participants to the risks of non-treatment, [14] responded that a placebo group was necessary "because patients with mania generally show a high and variable placebo response, making it difficult to identify their responses to an active medication" [15].

However, even when the facts are not disputed, determining whether there are sufficiently compelling methodological reasons for using placebo is not straightforward. Sometimes a placebo control design is not strictly necessary to answer a scientific question, but without it the knowledge will be more difficult to obtain or less likely to result. For example, active-controlled trials typically require more participants for adequate power than PCTs. At what point does the added difficulty of enrolling the needed number of people constitute a compelling enough reason to justify a PCT? In other cases, a different trial design might be expected to yield *some* socially valuable knowledge, but not as much as a PCT. For example, an equivalence trial might yield data suggesting that a new intervention is comparable to an established one within certain parameters, but the addition of a placebo arm might provide additional information about its relative effectiveness. In certain non-inferiority trials, it is helpful to add a placebo arm for internal validity, for example [16]. Would it be acceptable for a government to fund a PCT to collect comparative or cost-effectiveness data in order to make decisions about health care coverage?

The ethical requirement that there be compelling methodological reasons for using placebo is motivated by the concern that participants might be *unjustifiably* exposed to the risk of no treatment. Hence, to assess these reasons, both the risks of placebo use and the social value of the knowledge that using placebo is expected to provide must be assessed relative to other possible trial designs. The importance of the *additional* social value gained by using a placebo control must justify the *additional* risks of using placebo. The following considerations should be helpful in making these assessments (Table 2).

First, a judgment about whether methodological reasons are sufficiently compelling depends on the study's social value, not on strict scientific necessity. That a placebo-controlled design is scientifically necessary to answer a particular question is insufficient to justify the design. A study's goals could always be re-described in a way that required the use of placebo, e.g., the goal could be described as determining whether an investigational drug is superior to placebo. However, whether study goals, so described, justify putting research participants at risk depends crucially on the social value expected from meeting those goals. It has been noted, for example, that placebo-controlled trials of "me-too" drugs may suffice to show they are safe and effective for approval by the FDA, but do not give clinicians information they need to understand the comparative clinical value of a drug [17]. The right description of a study's goals for the purposes of ethical analysis is one that links the scientific questions to the social value of the generalizable knowledge that justifies carrying out the research in the first place. Compelling methodological reasons for using placebo must show how the use of placebo allows realization of that social value in a way that other designs would not.

Conversely, a placebo-controlled design might be justified in some cases even if it were not scientifically necessary. For example, the Bucharest Early Intervention Project (BEIP) randomized abandoned children in Romanian institutions to foster care or continued institutional care, even though the

Table 2
Evaluating compelling methodological reasons.

- The importance of the *additional* social value gained by using a placebo control must justify the *additional* risks of using placebo.
- Three key points regarding methodological reasons:
  - In order to justify placebo use, it is neither necessary nor sufficient that a placebo control is scientifically required.
  - In order to justify placebo use, it need not be impossible to attain the study's goals using an alternative trial design.
  - There are multiple sources of social value that can justify a PCT.
- These conclusions apply to all choices of trial design, not just placebo-controlled trials.

existing consensus among U.S. childcare experts was that foster care was superior. The BEIP investigators established a foster care program in Bucharest and their results were anticipated by policy-makers who were interested in applying them in Romania [18]. The tight connection forged between the project and Romanian policy-makers suggests that this study had sufficient social value to justify its design [19].

Social value is a fundamental, but under-analyzed, concept in research ethics. Here, we interpret social value in a simple way: social value comprises the benefits from the research, including generalizable knowledge, for the sake of which it is acceptable to ask people to take on risks and burdens. Recommended benchmarks for ensuring social value include defining who will benefit from the research and in what way they will benefit [20]. So, for example, justifications for PCTs in populations that lack access to existing treatments should include the intention to develop interventions *for those populations*—the social value and benefits from the research should redound to people in the population from which participants are drawn. For instance, when Discovery Labs proposed conducting a placebo-controlled trial of a new artificial surfactant for respiratory distress syndrome (RDS) in Bolivia, one of the (several) criticisms of the proposed study was that the company sought data in order to market its drug in high-income countries, not to develop a product that would help premature Bolivian infants with RDS [21].

Second, in order to justify the use of a placebo control it does not need to be impossible to answer the socially valuable question using another trial design. As noted, to be powered to detect a particular effect size, a PCT requires fewer participants than would an active controlled trial. In certain studies, especially those for low prevalence diseases, it might be *possible*, but unlikely, to enroll enough participants to complete an active-controlled trial, or an active-controlled trial might complete accrual only after many years [22]. A placebo-controlled study might be able to detect the treatment effect earlier and with fewer participants. Mere possibility does not always tell us the most sensible way to answer a socially valuable scientific question.

Third, these examples indicate that there are different ways in which one trial design may have greater social value than another. Most often, a study will have social value because, as designed, it will achieve its goals, such as determining whether a new treatment is effective or changing health policy for the better. Sometimes, a study as designed will be expected to have more social value than alternative designs because it is more likely to achieve its goals. For example, the BEIP, as designed, was thought to be more likely to influence Romanian policy than other designs, though, of course, alternative studies *might* have affected policy and the PCT *might* not have had the desired effect. Alternatively, a study design may contribute to social value because it has fewer opportunity costs than alternative ways to achieve those goals. For example, if an alternative trial design is more expensive than a PCT, then an opportunity cost might be paid in not being able to use that money to conduct other socially valuable research studies.

A cautionary note: achieving the goals of a study and having lower opportunity costs are both potential sources of social value. However, not all gains that result from one's choice of trial design count. To constitute *social value* they must be gains of a type for which it is acceptable to ask people to take on risks or burdens through research participation. We would judge, for instance, that the advantage to a pharmaceutical company of reducing costs by using placebo instead of an active control is generally not the sort of advantage that should count. However, a substantially greater probability that a PCT rather than an active-controlled trial could enroll sufficient participants to complete an important and timely study could be a relevant consideration.

Finally, these considerations are not limited to the justification of placebo-controlled trials. Researchers' choice of trial design should always be justified whenever there is a choice between different trial designs which pose different levels of risk and which are likely to differ in their contribution to the social value of the research. PCTs are just the most controversial case.

5. Conclusions

Most commentators agree that placebo-controlled trials are permissible in the four cases summarized in Table 1. A key issue in the ethical justification of PCTs, especially for categories in which non-treatment poses more than negligible risk, is what counts as a compelling methodological reason supporting placebo use. Here, we have argued that any *additional* risks of using placebo must be justified by the *additional* social value gained relative to other trial designs, and suggested some important considerations for evaluating whether these reasons are sufficiently compelling to justify a placebo-controlled design.

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