

# Giving and taking: ethical treatment assignment in controlled trials

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## Summary

The current version of the Declaration of Helsinki states that ‘the benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention(s) . . .’. This wording implies that it is acceptable for patients to be assigned to receive an unproven new intervention and to be denied a best current proven intervention. We assert that patients being invited to participate in controlled trials cannot, ethically, be expected to forego proven beneficial forms of care. Patients being treated in controlled trials should not knowingly be disadvantaged compared with similar patients being treated in usual clinical care, where they have access to beneficial care. In this article, we have tried to separate for discussion ‘the withholding of effective care from trial participants’, ‘informed consent to treatment’, ‘blinding’ and ‘use of placebos’.

## Keywords

Ethics, Equipoise, Placebo, Informed Consent, Blinding

## Introduction

More than a decade ago, an article by Jeremy Howick opened with an important statement:<sup>1</sup> ‘A resilient issue in research ethics is whether and when a placebo-controlled trial (PCT) is justified *if it deprives research subjects of a recognized treatment*’ (our emphasis). Howick’s wording makes clear that he recognised a crucial point: that use of placebos does not *necessarily* involve withholding or withdrawing effective treatments. He went on to discuss in detail the reasons why placebo-controlled trials would often compare unfavourably with trials in which an active treatment was used as a comparator.

In a commentary responding to the paper, one of us pointed out that, contrary to widespread belief, placebo-controlled trials do *not* necessarily involve withholding effective therapy, but that trials using

active controls frequently *would* do so. Senn<sup>2</sup> illustrated this using the example of placebo-controlled ‘add on trials’ in HIV research: all trial participants had received standard elements of care as well as either a new pharmaceutical or a matching placebo.<sup>3</sup>

The use of placebo can act as ‘a false ethical trigger’: the key ethical issue is not whether placebos are being used but whether an agreed effective therapy is being withheld. This can be a problem for trials using placebo or active controls.

Inconsistent statements about use of placebos in successive editions of the World Medical Association’s<sup>4</sup> Declaration of Helsinki have been unhelpful. These have varied over time since they were first mentioned in 1996.<sup>5</sup> In 1996 and 2000, the Declaration asserted that placebos could only ethically be used if no proven treatment was available. In the 2004 and 2008 versions of the Declaration, however, the use of placebos was declared acceptable for ‘compelling and scientifically sound methodological reasons’, as long as ‘extreme care’ had been taken ‘to avoid abuse of this option’.

The latest revision of the Declaration<sup>4</sup> states that ‘the benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention(s) . . .’. This wording is presumably intended to ensure that participants in clinical trials will not be denied forms of care known to be effective; yet, it actually encourages withholding such forms of care. The wording implies that it is acceptable for patients to be assigned to receive an unproven new intervention and to be denied best current proven intervention. Except in circumstances comparable to those illustrated using the add-on trial above, patients who are being invited to participate in controlled trials cannot, ethically, be expected to forego proven beneficial forms of care.

The confusion in the wording of the Declaration of Helsinki results from an inappropriate focus on *what is given* rather than *what is withheld* in clinical trials. The Declaration should make crystal clear that all potential participants in clinical trials should be

offered proven beneficial interventions when these exist. Because the Declaration does not do this, it fails to illustrate the circumstances in which using placebos is not only ethical but actually highly desirable. By blinding the patient and (usually) the investigator to which treatment is being given to which patients, placebos can help to reduce biases and mistaken conclusions about the effects of treatments.

In this article, we offer an alternative perspective on ethics. Instead of making a judgement about the ethical acceptability of a trial by asking whether clinicians would be indifferent as among the alternatives *within* the trial when compared with each other, they should instead ask whether each of the trial arms is justified given the usual standard of care *outwith* the trial. In what follows, we show that this offers a very different perspective on what is and is not ethically acceptable.

### Benchmarking using standard of care

In arriving at decisions about whether patients should participate in controlled trials, patient views and decisions matter most. Trialists should run clinical trials in the hope that patients will wish to understand as much as possible about what is going on, and researchers should be prepared to share every last detail of trial protocols with them if this is what patients say they want.<sup>6-8</sup> They should also make clear to patients the treatments to which they are entitled if they decide not to participate in trials.

Can patients be invited to participate in trials from which proven effective forms of care are being withheld, sometimes being replaced by placebos? The default answer is 'No'. Patients being treated in controlled trials should not knowingly be disadvantaged compared with similar patients being treated in usual clinical care and so having access to effective care. Predictably, the outcome of the care of patients treated within the formal structure of controlled trials is reflected in similar outcomes to those experienced by similar patients receiving similar treatments in usual clinical care.<sup>9</sup>

The general rule that patients cannot ethically be invited to participate in trials from which proven effective forms of care are being withheld does not preclude informed potential trial participants deciding to forego beneficial treatments, at least in the short term, if this seems likely to lead to improved knowledge of how to protect their health and/or the health of others. For example, SJS takes effective medication to reduce the symptoms associated with hay fever; he would be willing to participate in a placebo-controlled trial of an insufficiently tested

new drug for hay fever. Some years ago, Chalmers indicated<sup>10</sup> that he would welcome participation in a placebo-controlled, randomised, crossover statin withdrawal trial to assess whether statins were responsible for his muscle pains. Recently reported research resolved his uncertainty.<sup>11</sup>

In brief, although the assumption must usually be that known beneficial forms of care cannot ethically be withheld from participants in controlled trials, informed participants may decide to forego beneficial care within research if they are satisfied that this seems likely to lead to an increase in worthwhile knowledge. In the rest of this article, however, except for a brief discussion where we explicitly mention this, we shall not address such situations but instead consider those in which the disease is serious and possibly life-threatening.

### The role of placebos in rigorous testing of treatments

Unfortunately, the quite reasonable conclusion that effective treatment should not be withheld when the condition is serious has led many, including the World Medical Association,<sup>4</sup> to argue that the use of placebos in such circumstances is therefore unethical. However, this focus on placebos is unhelpful in two ways. If interpreted literally, as referring to any trial in which a placebo is used, it would preclude so-called add-on trials, in which all participants receive a known effective therapy and, in addition, either a new or inadequately tested intervention, or a matching placebo. If the World Medical Association's statement is interpreted instead, as referring to trials in which some patients receive *only* placebo, it would encourage the belief that provided that this does not happen, all is well. However, it would then permit so-called *active controlled trials*, in which a new treatment is compared against an established one. Such trials are not always ethical, however. We shall illustrate this in due course taking the example of a trial for HIV infection. Whether or not placebos are given is not a useful basis for judging the ethics of a trial. To judge whether a proposed clinical trial is ethically acceptable, each arm of the trial should be compared with the treatments to which patients are entitled if they are not participants in the trial.

In fact, withholding proven treatment is a quite separate and more important issue than whether or when to use a placebo as a control when assessing the effects of an active treatment.<sup>12,13</sup> Placebos are intended to be indistinguishable from active treatments. Although they have been used mainly in research assessing pharmaceuticals, they have

been used for at least 200 years in assessing other interventions, including surgery.<sup>14–16</sup>

Placebos are used in controlled trials to reduce biased inferences about the effects of treatments.<sup>17</sup> Biased inferences can result from health professionals, patients and researchers knowing which patients have received which treatments.<sup>18</sup> The use of placebos helps to prevent biases by reducing assessment and allocation and cointervention biases. The former can arise if participant or observer assessments are influenced by expectation or prejudice. The latter can arise if participants are handled differently according to the treatment to which they have been allocated (apart, of course for the treatment itself). If biases are reduced by using placebos and other ways of blinding, misleading and potentially harmful inferences about the effects of treatments can be reduced.<sup>19</sup> Effective blinding with placebos can also make concealed, unbiased allocation of patients to the arms of the trial<sup>20</sup> easier to guarantee. When neither physicians nor patients know which treatments are being given, unconscious subversion of allocation schedules is not possible.

It is common to use placebos in assessing the effects of new pharmaceuticals when they are given in addition to standard therapy. The simplest way to ensure blinding of the new treatment is to give patients in the control arm a placebo as ‘add-on’ to the standard therapy. Even if a new pharmaceutical is to be investigated as an alternative to an existing pharmaceutical, placebos to each will have to be used in so-called double dummy trials.<sup>21</sup> In fact, it is a commonplace of drug development that pharmaceutical companies must be prepared to supply their rivals with placebos to make such blinding possible.

To run trials as double-blind, it will often be helpful to use placebos. The use of placebos does not, of itself, indicate what is being given and what is being withheld. But compared with standard practice, what is given and what is withheld is key to judging whether the trial is ethical, so this should be addressed and discussed directly with potential participants. Inappropriate focus on placebos only confuses the issue.

### Comparison with standard practice

To decide whether a trial is ethical, what is proposed to give to patients allocated to each arm should be compared with standard best treatment. Compared with standard treatment, any proposed trial arm can be discussed in terms of any of four strategies: Substitution, Augmentation, Maintenance, and/or Elimination (SAME). If patients, whichever the trial arm to which they have been assigned, are allocated

something instead of standard of care, we have ‘Substitution’. Adding a new treatment to standard of care is ‘Augmentation’. Assigning control patients to standard best care alone is an example of ‘Maintenance’. Withdrawing an element of standard care involves ‘Elimination’. Note that Substitution involves both Elimination and Augmentation.

The trial of nevirapine in HIV infection reported by D’Aquila et al.<sup>3</sup> provides an illustration. All patients received zidovudine and didanosine. This was a standard treatment at the time and all patients can be regarded as having been maintained on it. Since patients in both arms received these treatments, there was no point in blinding them and so the drugs were given ‘open label’ (unblinded). In addition, patients in the intervention group were *augmented* by the addition of nevirapine. To blind the nevirapine, the standard zidovudine and didanosine combination was *augmented* by giving patients in the control arm placebo to nevirapine. The trial was, quite properly, described as ‘A Randomized, Double-Blind, Placebo-Controlled Trial’.

Suppose instead that the trialists had decided to compare nevirapine with the combination of zidovudine and didanosine. The experimental arm would then have consisted of nevirapine alone. Thus, nevirapine would have been substituted for zidovudine and didanosine, and patients on the experimental arm would have been denied the benefit of these treatments. Of course, placebos to all three treatments would have had to have been used to blind the trial. The arms would have been AZT & DDI & placebo to nevirapine (control) and placebo to AZT & placebo to DDI & nevirapine (intervention). The trial would have been described as ‘*active controlled*’.

In this case, the placebo-controlled trial does not raise an ethical problem that use of an active controlled trial would have done: is it ethical to eliminate from patient treatment elements that have been proven to be effective? Taking ‘placebo’ to raise an ethical flag here is thus a mistake. Comparison of all arms to standard therapy is needed.

Many placebo-controlled trials use the placebo as an add-on to a known beneficial form of care, so these do not pose ethical problems. For those other trials where use of a placebo involves elimination of some aspect of standard care, either this practice should involve the patient in an agreed temporary inconvenience or systematic reviews of existing evidence, and surveys of clinical practice should have shown that there are important uncertainties about the effects of supposedly standard treatments. For example, a systematic review of existing controlled trials revealed uncertainty about whether giving corticosteroids to people who had sustained acute

traumatic brain injury reduced or increased mortality. Surveys of clinical practice showed that this uncertainty was reflected in very varied clinical practice: some clinicians prescribed steroids routinely for traumatic brain injury; others did not do so because they were sceptical about the value and safety of the treatment. A large placebo-controlled comparison addressed the uncertainty and showed that steroids increased mortality.<sup>22</sup> The detailed criteria for concluding that there is sufficient uncertainty about the effects of a treatment to justify further research will vary from case to case. However, a combination of systematic reviews of existing research evidence combined with demonstrated variations in clinical practice provide the ethical foundation for additional research. A difficult ethical issue arises when clinical trials are not the first to address a particular question but may be replication or confirmation studies. This is addressed separately in Appendix 1.

### A common unethical use of placebos

Many, probably most, uses of placebos are ethical because they help to protect us from mistaken (often misleadingly optimistic) inferences about the effects of treatments. Indeed, failure to use placebos to prevent mistaken inferences about the effects of treatments might itself be regarded as unethical. By contrast, one currently quite common use of placebos – the so-called placebo run-in period, in which all patients are given placebo – is not ethical.<sup>23</sup> Such use seems always to involve deception – there would hardly be any point otherwise.

It is useful to distinguish between consented and unconsented deception. The critical test of what form of deception is involved is to ask ‘Can the description to the approach to deception be shared with the trial participant?’ When placebo is being given as one of two or more random alternatives, the answer is ‘Yes’. Any participant who agrees to enter the trial has agreed, knowing the form of deception involved. If all participants are being given a placebo in a given period, the ‘answer’ is ‘No’, unless one is prepared to nullify the point of using a placebo. Thus, any deception would be without consent.

### The need for clearer ethical analysis of the use of placebos in research

In this article, we have tried to separate ‘the withholding of effective care from trial participants’, ‘informed consent to treatment’, ‘blinding’ and ‘use of placebos’. As with other aspects of medical research ethics,<sup>24</sup> we think that it is important to disentangle these factors and their interactions.

Instead of reiterating misplaced concern that the use of placebos necessarily implies that trial participants must forego benefit, the next revision of the Helsinki Declaration should consider ethical issues more broadly, asking instead:

- Has a standard of care been established?
- Is the trial being judged against this standard?
- Is any possible sacrifice of benefit acceptable?
- Are the risks acceptable?
- Is informed consent being sought in a way that respects patients’ autonomy?

#### Declarations

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## Appendix 1. Ethical issues in trial replication

The fundamental shift of determining ethical admissibility by comparing the arms of the clinical trial to standard of care rather than to each other solves an ethical problem presented by replication. If one or more previous trials suggest that a new treatment is beneficial, it will be increasingly difficult to remain uncertain about the ethics of additional trials. However, the standard of care comparison offers an alternative perspective.

Consider circumstances in which a health problem is serious and a partially effective treatment already exists but there are reasons to hope that a new treatment may be effective. In many cases – HIV infection being one we have cited above – a placebo-controlled add-on trial would be chosen, with the experimental arm consisting of the existing treatment plus the experimental one and the control arm consisting of the existing treatment plus placebo to the new treatment. If the trial shows the control arm to be superior, the new treatment will no longer be pursued. This would also be the case if there is no good evidence of superiority of the new treatment. By stopping further study of the new treatment, future patients in the centres involved in the first trial will receive the standard or care. This does not raise any ethical issue.

If, however, the experimental treatment proves superior, then there are many circumstances under which it will simply be impossible for all future patients to receive the new treatments: it may not have a license, even if a license will be rapidly granted it will not be manufactured in sufficient quantity and

even if approved, many physicians may be unconvinced by the results of a single trial.

Carrying out further trials may therefore be justified to convince those who need to be convinced, and to obtain clearer evidence. In fact, regulators such as the Food and Drug Administration and the European Medicines Agency commonly require two large phase III studies to show statistically 'significant' superiority of an experimental treatment to grant a license.

There is a technical point regarding meta-analysis that does not appear to have been generally appreciated by the evidence-based medicine movement. The standard of two trials being significant implies (if only two trials have been run) that the regulator's type one error rate, using the usual standard for

significance of 5% two-sided despite requiring superiority of the experimental treatments, is  $1/40 \times 1/40 = 1/1600$  or  $1/800$  two sided.<sup>25</sup> If this requirement were to be replaced by a meta-analysis or a single large trial, the confidence level ought to be  $1 - 1/800 = 99.875\%$  (or 99.9% to three significant figures). Very few meta-analyses employ this standard.

Be that as it may, our position is that until it is generally agreed that a treatment is standard of care and until it is available generally, it is legitimate for trialists who believe it may be useful to study it as an experimental treatment. In some cases, a treatment may have become registered or adopted in one country, but the regulators or physicians of other countries may require further evidence. In that case, the treatment can be studied in such countries.