

## Substituting placebo for established, effective therapy: Why not?

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The answer to the question of “Why not?” would seem relatively straightforward: substituting placebo for established, effective therapy is always ethically questionable and usually ethically inappropriate, and therefore we should not do it. That position finds support in numerous guidelines, statements and codes.<sup>1-3</sup> A more vexing question would seem to be “Why?” In other words, given the acknowledged ethical concerns, why are placebo controls suggested when established, effective therapy exists and why, in some cases, is this type of control strongly endorsed by authoritative organizations, such as the International Conference for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use,<sup>4</sup> and how solid is the argument supporting that stance?

The fact that placebo comparator trials reduce the risk of unfavourable findings and require smaller sample sizes than active-control trials might be strong inducements, especially for those seeking registration and licensure of new products. However, expediency would seem insufficient to overcome ethical concerns without further support. A major source of that additional support comes from the notion that placebo-controlled trials possess assay sensitivity,<sup>5</sup> that is, they have the ability to distinguish an effective treatment from a less effective or ineffective treatment. This concept serves to elevate the argument from one that could be perceived as potentially self-serving to one that appears more methodologically grounded.

The theoretical claim that the use of placebo controls ensures assay sensitivity has become pivotal in a debate that has been characterized by some as pitting scientific against ethical concerns. We examine here the practical implications of assay sensitivity and note that it is not immune from the crucial assumption of effective blinding. If blinding is not effective, protection against expectation effects, biased assessment, contamination and co-intervention is lost. Contrary to what many seem to believe, assay sensitivity in and of itself does not guarantee the validity of a positive finding from a placebo-controlled trial and does not obviate underlying ethical concerns. However, this paper is not about ethics per se. Rather, we focus on why, despite ethical concerns, some still endorse and strongly advocate for placebo controls, especially when direct information about how proposed innovations compare with existing options is of clear benefit to health care payers, providers and patients.<sup>6</sup>

### Key points

- Some claim that placebo controls are needed in randomized controlled trials even when established, effective therapy exists.
- The justification for this ethically questionable practice has been grounded in an invocation of enhanced scientific credibility through a concept known as assay sensitivity, whereby placebo controls enable distinguishing an effective from an ineffective therapy.
- The practical importance of assay sensitivity is limited in the absence of evidence that blinding has been effective.
- Such evidence is usually lacking and frequently not sought.

### The use of placebos

The advent of the randomized controlled trial marked a major advance in our ability to evaluate new therapies. It also raised concern about the ethical appropriateness of asking individuals to accept that their treatment would be decided on the basis of chance.<sup>7</sup> Freedman<sup>8</sup> provided a simple yet powerful analysis of this problem. He noted that if there is a lack of consensus within the expert medical community as to the preferred treatment for the patient population under consideration (i.e., if there is clinical equipoise), then it is ethically acceptable for physicians, whatever their individual hunches, to offer prospective patients randomization in a corresponding trial. Explicit in Freedman’s analysis was the acknowledgement that those proposing a trial must ensure that patients are offered choices that do not knowingly disadvantage them.

Shapiro and Shapiro<sup>9</sup> defined a placebo as any treatment that is used for its ameliorative effect on a symptom or disease but that is ineffective for the condition being treated. In this definition of “placebo,” it would probably be more appropriate to replace the word “ineffective” with the term “not

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directly effective.” They defined a placebo effect as the non-specific psychological or psycho-physiologic therapeutic effect produced by a placebo. The proceedings of a US National Institutes of Health conference held in 2000 reflected the variety of questions and issues of interest in this area.<sup>10</sup> For more than a decade, a spirited debate regarding the appropriateness of certain types of placebo-controlled trials has taken place.<sup>11-13</sup> At this point, it seems useful to briefly review the reasons for using placebos.

### Reasons for using a placebo

Sick individuals can feel better for a variety of reasons. A person’s condition may improve because of the passage of time. It may improve because the person sought care when the condition became particularly troublesome, and it subsequently regressed to its typical state. Some patients may perceive that they are better because they expect that what is being done for them will make them better. Some may feel better as a result of ancillary treatment received along with their primary treatment. Others may sense improvement because they are told that they seem improved. And, of course, individuals may experience direct improvement because of the specific treatment they are given, rather than because of the effects associated with being treated.

When evaluating a new treatment, we wish to isolate the direct effects of the treatment from the indirect effects of being treated. This typically requires a comparator or “control.” The use of existing treatment as the control provides a means of accounting for all of the indirect effects listed above and permits a comparison of any additional effect of the new treatment. When there is no existing therapy that has been appropriately assessed and found to be effective, we typically employ a placebo in an attempt to obtain a “clean” comparison.

### Placebos in clinical trials

As noted, various codes of medical and research ethics have addressed the issue of using placebos in clinical trials.<sup>1-3</sup> There is certainly agreement about placebo usage in the absence of existing therapy. Similarly, the use of a placebo is relatively uncontroversial in investigations of the effect of adding therapy to an existing therapeutic regimen. However, except in cases of minimal risk such as rhinitis, there is considerable disagreement when placebo is proposed as a control for a trial of a new therapy in the presence of established, effective therapy.

Established, effective therapy can be used as a comparator in a clinical trial in several ways. In a superiority trial, the objective is to determine whether the new treatment is superior to the existing treatment. Because regulatory approval of a new drug typically does not require demonstrating superiority to an already approved drug and because demonstrating superiority to an existing agent is more difficult, the majority of superiority comparisons in drug trials are done in the context of placebo-controlled trials. Established, effective therapy can also be used in equivalency trials, where the question is whether the new treatment is essentially equivalent (within a prespecified

tolerance) to the existing treatment, and in non-inferiority trials,<sup>14</sup> where the question is whether the new treatment is not worse than (although perhaps better than) the existing treatment, again within a prespecified margin.

## Regulatory and industry perspective

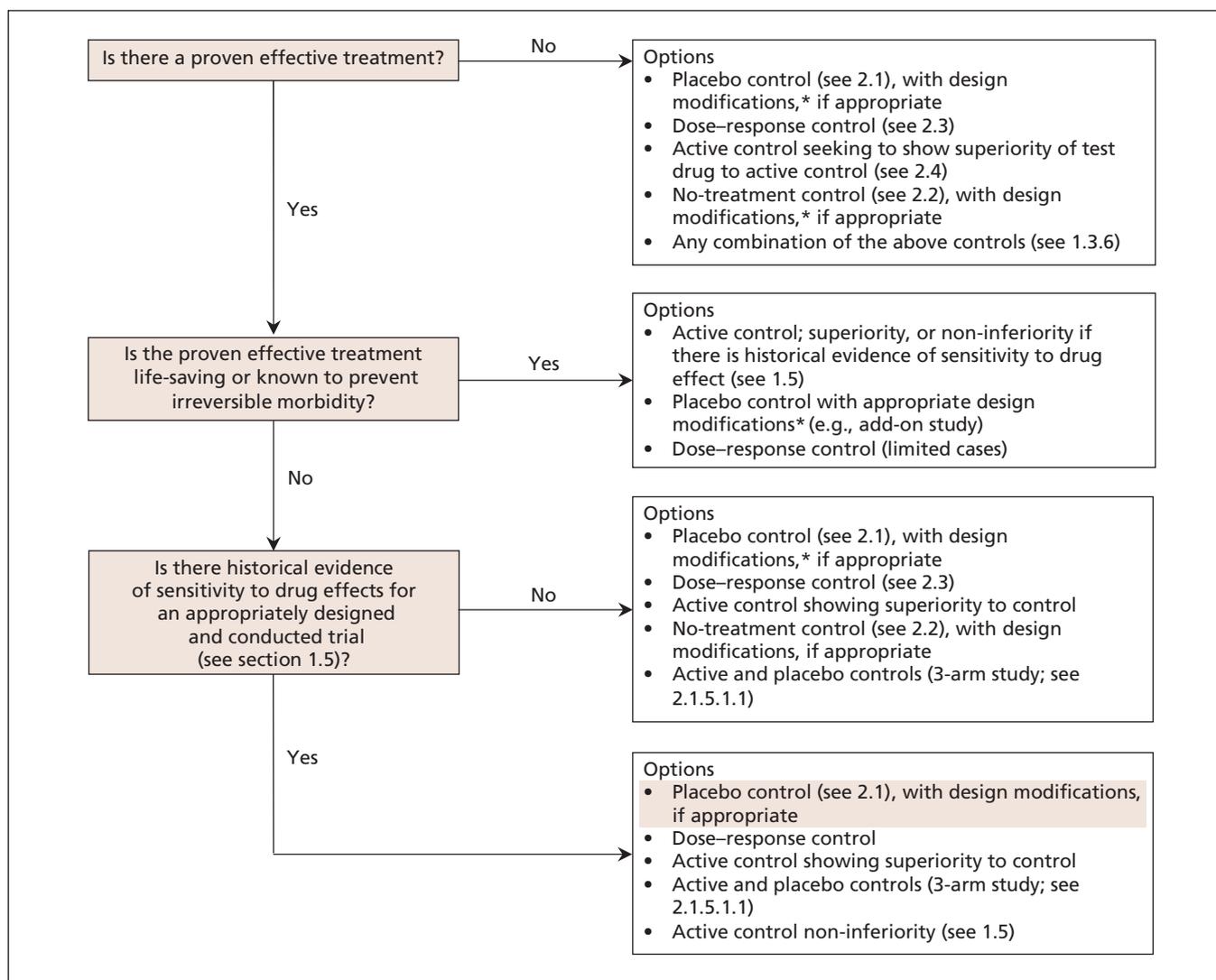
The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, an organization comprising the regulatory authorities of the United States, Europe and Japan and representatives from the pharmaceutical industry, aims to harmonize international practices for drug approval. The organization has put forward a series of publications on clinical trial practice, including one that deals with the choice of control groups in clinical trials.<sup>4</sup> This document suggests the use of placebo controls for essentially all situations except when proven effective treatment is life-saving or known to prevent irreversible morbidity. The figure in that document, described as a decision tree for choosing among different types of control groups, summarizes the recommendations regarding placebo usage, placing placebo control at the top of the list of options even when proven effective treatment exists (Figure 1).

In section 2.1.4 of the document,<sup>4</sup> advocacy of placebo controls is more direct: “Even when the primary purpose of a trial is comparison of two active agents or assessment of dose-response, the addition of a placebo provides an internal standard that enhances the inferences that can be drawn from the other comparisons.”

## Critical examination of assay sensitivity

The broad endorsement of placebo controls by the International Conference on Harmonisation centres on the notion of assay sensitivity. Section 1.5 of the document discussing choice of control groups defines the assay sensitivity of a clinical trial as “the ability to distinguish an effective treatment from a less effective or ineffective treatment,”<sup>4</sup> which is essentially the same definition as provided in the peer-reviewed literature. The absence of assay sensitivity decreases the chances of demonstrating superiority and increases the chance that equivalency or non-inferiority trials will conclude that a new treatment is similar to or no worse than its active treatment comparator. Finding that the new treatment is essentially as efficacious as the existing therapy in a two-arm equivalency or non-inferiority trial may reflect the fact that both therapies were ineffective in the current trial. In a superiority trial, the new treatment needs to be shown to be superior, so the absence of assay sensitivity works against finding in favour of the new treatment. The claim is that demonstrating superiority to a placebo provides calibration that is absent in an active-control non-inferiority trial.

The practical benefit of assay sensitivity for placebo-controlled trials depends on a crucial assumption: effective blinding. If blinding of the placebo arm is ineffective, protection against expectation effects, biased assessment, contamination and co-intervention is lost. Superiority of the new



**Figure 1:** Basic logic for choice of control group, as proposed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. The shading highlights the recommendations regarding use of placebo in the presence of proven effective treatment. \*Add-on, replacement, early escape, brief placebo period and randomized withdrawal. Reproduced, with permission, from International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (E-10).<sup>4</sup> The section numbers appearing in the figure refer to section numbers in the source document.

treatment to placebo could be a consequence of the loss of this protection. Alternatively, an ineffective new treatment would spuriously appear to be superior merely because a “placebo-type effect” has appeared only in the experimental drug treatment arm. Ultimately, in the absence of evidence of effective blinding, we cannot be sure that a difference between the experimental and placebo arms is not merely a manifestation of the fact that individuals know that the treatment they received (as patients) or assessed (as investigators) is an inert substance.

Effective blinding is often difficult to achieve and cannot be assumed. In an attempt to obtain direct evidence about the success of blinding, we studied a random sample of placebo-controlled trials in leading general medical journals and in leading psychiatric journals.<sup>15</sup> Only 4 (2%) of

the 191 trials that we evaluated reported assessment of blinding among both participants and outcome assessors or investigators: 1 of the 97 trials in the general medicine literature and 3 of the 94 trials from the psychiatric literature. Seven of the 97 general medicine articles and 8 of the 94 psychiatric articles provided any blinding assessment, an overall rate of 8%. Notably, these were simply reports of having assessed blinding, not reports of successful blinding. Among these 15 trials, the authors of only 5 studies claimed that blinding had been successfully maintained. Furthermore, for only 3 of these trials did the authors actually provide data to support this claim. Thus, of the 191 trials examined, only 3 provided data in support of a claim of successful blinding and the appropriateness of at least one of those claims is in question.

## Practical implications of assay sensitivity

Randomized clinical trials represent our strongest tool for therapeutic evaluation. Within the realm of the randomized controlled trial, claims of assay sensitivity for placebo-controlled trials have helped make them “the gold standard.” The claim of assay sensitivity has also been used to rationalize placebo-controlled trials of limited clinical relevance and appropriateness, trials for which clinical equipoise does not exist. A frequent supporting argument has been that the need for greater scientific rigour trumps ethical concerns. However, it is difficult to see how an investigator can defend the use of a placebo control in the presence of established, effective therapy on the basis of a claim that assay sensitivity will guarantee the validity of a positive finding. To do so, the investigator must either provide evidence that blinding is unnecessary, which seems strange in the context of a placebo-controlled trial, or provide evidence that blinding will be maintained, and there is little supportive evidence for the latter claim.<sup>15</sup> The inclusion of existing, effective therapy as a third arm does not ameliorate the situation.

Some people might argue that it is only the reporting of blinding that is in question; many investigators may have assessed blinding but have chosen not to publish the results or have been dissuaded from doing so. We are skeptical, at least with regard to reports of successful blinding. Such reports would lend strength to a trial’s conclusions, and investigators would likely be eager to share such findings. Moreover, both the original CONSORT statement<sup>16</sup> and its 2001 revision,<sup>17</sup> widely endorsed guidelines for the reporting of randomized trials, encouraged authors to provide information about blinding when it had been assessed. Of course, the potential for unblinding also exists in an active-control trial. However, when individuals who are receiving or assessing an active control become unblinded, they become unblinded to the fact that treatment is an active agent that is currently in clinical use or one that is believed to be as good or perhaps superior.

In terms of the potential consequences of the lack of effective blinding, Thomson<sup>18</sup> presented striking data from a review of 75 placebo-controlled trials of antidepressants. The 75 trials were published between 1958 and 1972, and 7 of them had used an active placebo designed to mimic the side effects of the anticholinergic drugs under investigation. In only 1 (14%) of these 7 trials was the drug found to be superior to placebo. However, among the 68 trials using an inactive placebo, the drug was found to be superior in 43 (63%).

Trials of antidepressants have been a particularly contentious area, with some arguing that the use of placebo control leads to enrollment of less severely impaired patients, that is, patients deemed better able to forego available therapy. There is also concern about higher dropout rates and shorter periods of follow-up in such studies and the consequent limitation on the information that the trials provide.

## Moving forward

The International Committee of Medical Journal Editors, in its statement on clinical trial registration,<sup>19</sup> has stated, “In

return for the altruism and trust that make clinical research possible, the research enterprise has an obligation to conduct research ethically and to report it honestly.” However, current reporting practices make it difficult to know whether blinding has been effective. In the past, we faced a similar situation for randomization and allocation concealment. Now, we expect researchers to provide explicit details about those aspects of a trial, and we should expect the same to support claims about blinding.

This is not only an editorial responsibility. It applies as well to investigators’ choices in planning a trial. Investigators need to consider the evidence that they will provide to assure critics that any biases resulting from loss of blinding will be assessed and controlled. Similarly, those charged with the review and funding of the proposed research should be actively looking for this information. There is ongoing debate about the information that we should seek and when it should be requested. This debate is driven in part by the legitimate concern that post-treatment assessments of blinding, obtained by simply asking individuals to guess what treatment was received, are confounded by differential treatment efficacy. We can of course accompany simple requests regarding treatment “guess” with requests for the reasons for that “guess,” to help distinguish such situations. Some, such as Dave Sackett,<sup>20</sup> have suggested that rather than attempting to directly assess blinding, we should focus on assessing the bias-generating consequences of the loss of blinding, such as co-intervention and contamination. Although more work is needed on these issues, the lack of consensus on an accepted method does not mean that it is preferable to leave a vacuum. Unfortunately, the 2010 revision of the CONSORT statement<sup>21</sup> has eliminated the item on how the success of blinding was assessed, although the empirical evidence cited for doing so<sup>22</sup> is weak.

When appropriate, placebo controls certainly have an important role.<sup>23</sup> However, decisions about their use, especially in circumstances where there is existing effective therapy, should not be based on routine invocation of a claim of assay sensitivity. Placebo-controlled trials, especially those with subjective outcomes, are particularly susceptible to the risk of bias resulting from ineffective blinding. The fact that a placebo-controlled trial, because it is a superiority trial, has the theoretical property of assay sensitivity does not mean that it is to be preferred to a well-designed, active-control trial. Attempting to use such arguments to sidestep the serious challenges posed by the use of a placebo when established, effective therapy exists does neither trialists nor trial participants credit.

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