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Target Article

What Makes Placebo-Controlled Trials Unethical?

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The leading ethical position on placebo-controlled clinical trials is that whenever proven effective treatment exists for a given condition, it is unethical to test a new treatment for that condition against placebo. Invoking the principle of clinical equipoise, opponents of placebo-controlled trials in the face of proven effective treatment argue that they (1) violate the therapeutic obligation of physicians to offer optimal medical care and (2) lack both scientific and clinical merit. We contend that both of these arguments are mistaken. Clinical equipoise provides erroneous ethical guidance in the case of placebo-controlled trials, because it ignores the ethically relevant distinction between clinical trials and treatment in the context of clinical medicine and the methodological limitations of active-controlled trials. Placebo controls are ethically justifiable when they are supported by sound methodological considerations and their use does not expose research participants to excessive risks of harm.

Randomized controlled trials (RCTs) became the leading method of testing treatment efficacy in the 1940s. From the beginning, ethical concerns were voiced about clinical trials involving control groups not receiving proven effective or standard treatment. Debate over the use of placebo controls intensified following the publication in 1994 of a *New England Journal of Medicine* "Sounding Board" article by Rothman and Michels, "The Continued Unethical Use of Placebo Controls" (1994). The authors appealed to the Declaration of Helsinki in support of their claim that placebo-controlled trials are unethical whenever they are used to evaluate new treatments for conditions when proven effective treatments exist. They cited a range of recently published articles in the medical literature that violated the ethical guidance of the Declaration of Helsinki. Additionally, they pointed to the regulatory policy of the United States Food and Drug Administration as a major reason for the continued unethical use of placebo controls.

Recently the World Medical Association issued a "Note of Clarification" concerning the stance of the Declaration of Helsinki on the use of placebo controls (World Medical Association 2001). This statement marks a fundamental departure from the revision of October 2000 (World Medical Association 2000), which reiterated more clearly an absolute prohibition of placebo controls to test the efficacy of new treatments when proven effective treatments exist for a given condition. The "Note of Clarification" states that placebo-controlled trials may be ethically justifiable despite the availability of proven effective treatment in two circumstances:

> (1) Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method, or (2) Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm. (World Medical Association 2001)

This fundamental change in the Declaration of Helsinki, which has not been accompanied by an ethical rationale, makes it important to examine critically whether placebo-controlled trials can be ethically justified in conditions for which proven effective treatments exist.

The ethical reasoning underlying a prohibition of placebo controls in randomized clinical trials when proven effective treatments exist has been presented most clearly and persuasively by the late Benjamin Freedman and his colleagues (Freedman 1987; 1990; Freedman, Glass, and Weijer 1996a; 1996b). They have developed two arguments in support of this ethical stance. First, the use of pla-

1. The opinions expressed are those of the author and do not necessarily reflect the policies of the National Institutes of Health, the Public Health Service, or the U.S. Department of Health and Human Services.

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cebo-controlled trials in the face of proven effective treatments violates the physician's therapeutic obligation to offer optimal medical care to patients. Second, testing new treatments against placebo when proven effective treatments exist lacks scientific and clinical merit. Linking these two arguments is the principle of clinical equipoise, first formulated by Freedman, which has become a widely accepted axiom governing the ethics of randomized controlled trials. Freedman and his colleagues characterize the ethical and scientific force of clinical equipoise as follows:

> That principle can be put into normative or scientific language. As a normative matter, it defines ethical trial design as prohibiting any compromise of a patient's right to medical treatment by enrolling in a study. The same concern is often stated scientifically when we assert that a study must start with an honest null hypothesis, genuine medical uncertainty concerning the relative merits of the various treatment arms included in the trial's design. These principles allow for testing new agents when sufficient information has accumulated to create a state of clinical equipoise vis-à-vis established methods of treatment. At the same time they foreclose the use of placebos in the face of established treatment, because enrolling in a trial would imply that a proportion of enrollees will receive medical attention currently considered inferior by the expert community. (Freedman, Glass, and Weijer 1996b, 253)

Although these two arguments against placebo-controlled trials have intuitive plausibility, we contend that they are both mistaken. We attempt to demonstrate that they fail to withstand critical scrutiny in light of the ethically fundamental distinction between clinical research and clinical care, methodological considerations pertaining to the scientific validity of clinical trials, appropriate ethical standards of risk-benefit assessment for clinical research, and sound public policy for drug development. In the process of this critique, we argue that the principle of clinical equipoise conflates the ethics of clinical research with the ethics of clinical medicine and provides erroneous ethical guidance on the use of placebo-controlled trials.

Argument from Therapeutic Obligation

It is claimed that the use of placebo controls in clinical trials when proven effective treatments exist violates the duty of physicians to offer optimal medical care. Because patients who enroll in RCTs are seeking treatment, they should not be randomized to treatment known to be inferior. When existing treatments have been proven effective in previous RCTs, it is unethical to test an experimental or novel treatment against placebo, which is known to be inferior to standard treatment. Instead, new, promising treatments should be tested against standard, proven effective treatment. What makes it ethical to conduct an RCT comparing a new treatment with a standard treatment, but not with a placebo, is that experts in the clinical community are uncertain or in a state of disagreement about whether the new treatment is as good as or better than standard therapy. This state of uncertainty in the clinical community is known as "clinical equipoise" (Freedman 1987). Use of placebo controls in the face of proven effective treatment violates clinical equipoise because it is already known that the placebo is inferior to standard treatment.

Underlying both clinical equipoise and the therapeutic obligation of physicians is the principle of therapeutic beneficence, central to medical ethics. Physicians should promote the medical best interests of patients by offering optimal medical care; and the risks of prescribed treatments are justified by the potential therapeutic benefits to patients. Placebo-controlled trials of new treatments in conditions for which proven effective treatments exist contravene the principle of therapeutic beneficence. Placebo controls in this situation are contrary to the medical best interests of patients. Patients randomized to placebo forgo proven effective treatment or treatment with a novel intervention considered to be as good as or better than standard treatment. Accordingly, they are exposed to risks associated with lack of treatment that are not justified by potential medical benefits.

Critique of Argument from Therapeutic Obligation

The argument from therapeutic obligation and the principle of clinical equipoise as applied to placebo-controlled trials confuse the ethics of clinical medicine with the ethics of clinical research. Physicians in clinical practice have a duty to promote the medical best interests of patients by offering optimal medical care. In RCTs, however, physician-investigators are not offering personalized medical therapy for individual patients. Rather, they seek to answer clinically relevant scientific questions by conducting experiments that test the safety and efficacy of treatments in *groups* of patients. The process of treatment in RCTs differs radically from routine clinical practice. Treatment

is selected randomly, not by an individualized assessment of what is best for a particular patient. Patient volunteers and physician-investigators often do not know who has have been assigned to the experimental treatment and who to the control treatment, which may be a placebo. Protocols governing RCTs frequently restrict flexibility in dosing and use of concomitant medications. These features of research design are implemented to promote scientific validity, not to promote therapeutic benefit.

Owing to these fundamental differences in purpose and process, the ethics of clinical trials is not identical to the ethics of clinical medicine. Specifically, the obligations of physician-investigators are not the same as the obligations of physicians in routine clinical practice. Investigators have a duty to avoid exploiting research participants, not a therapeutic duty to provide optimal medical care. Accordingly, enrolling patient volunteers in placebo-controlled trials that withhold proven effective treatment is not fundamentally unethical as long as patients are not being exploited. Patients may be seeking medical benefits by enrolling in clinical trials; however, they are not being exploited if

1. they are not being exposed to excessive risks for the sake of scientific investigation; and
2. they understand that they are volunteering to participate in an experiment rather than receiving personalized medical care directed at their best interests.

Given the distinction between clinical trials and medical therapy, as a rule it is undesirable or ethically hazardous for physician-investigators to enroll in their studies individuals with whom they have an ongoing doctor-patient relationship, either for primary or specialty care. Physicians may properly perform the dual roles of treating physician and investigator; the ethical problem arises when these dual roles are undertaken simultaneously with the same patients. Conflicts between patient welfare and scientific investigation, inherent in clinical research (Miller, Rosenstein, and DeRenzo 1998), are compounded and the potential for exploitation is increased when investigators have an ongoing physician-patient relationship with research participants. We do not, however, suggest that combining these dual roles simultaneously is always unethical. The duality of roles may be acceptable if clinical trials pose only slight risks to participants or if they offer the possibility of therapeutic benefit for patients who have exhausted all standard therapy other than supportive or palliative care.

The ethical irrelevance of the therapeutic obligation and the principle of clinical equipoise are concretely illustrated in the case of placebo-controlled trials that carry little or no risk from placebo assignment, despite withholding proven effective treatment. Consider a placebo-controlled trial of a new treatment for allergic rhinitis. There exist proven effective treatments for this condition. Nonetheless, it is difficult to see what could be morally wrong about a short-term trial comparing a novel treatment for allergic rhinitis with a placebo (Emanuel and Miller 2001). Trial participants randomized to placebo may be more likely to suffer from mild to moderate discomfort associated with untreated allergic rhinitis. But individuals with this condition often forgo treatment, and short periods without treatment pose no risks to health. Many would probably consider this example to be a valid exception to an absolute prohibition of placebo-controlled trials in the face of proven effective treatments. Notice, however, the significance of recognizing an exception in this case and in comparable clinical trials. If it is ethically justifiable to conduct a placebo-controlled trial of a new treatment for allergic rhinitis, then *what counts ethically is not denial of treatment but lack of substantial risk to participants.* Furthermore, if placebo-controlled trials can be ethical when they pose low risk to research participants, then it is an open question whether they are justifiable in conditions such as depression and anxiety disorders, migraine or tension headaches, stable angina, and asthma. In patients with these conditions, randomization to placebo poses more serious risks of discomfort or temporary functional disability from lack of standard treatment but low risk of irreversible harm, provided that clinical trials implement appropriate safeguards for screening eligible participants, monitoring their condition, and withdrawing them from the trial and initiating standard treatment (Emanuel and Miller, 2001).

Freedman and his colleagues have not acknowledged any exception to clinical equipoise: "Finally, attempting to justify a study by saying that it does not cause too much harm to too many people fails to take account of the physician's or investigator's responsibility to each individual patient or subject" (Freedman, Glass, and Weijer 1996b, 254). Physician-investigators do have an obligation to each research participant. However, that obligation

is not one of therapeutic beneficence. Rather, it is an obligation not to exploit participants for the sake of scientific investigation. Defenders of clinical equipoise might object that placebo controls in the face of proven effective treatment are wrong even if they do not pose any risks of serious or lasting harm. This, however, begs the question at issue. If there is no therapeutic obligation in the context of RCTs, then there is no wrong per se in using placebo controls that involve withholding proven effective treatment.

The implications of adopting clinical equipoise for the ethics of clinical research in general, especially research without any prospect of medical benefit, deserve attention. If physician-investigators are subject to a therapeutic obligation in the case of clinical trials, which makes RCTs ethical only when they conform to clinical equipoise, it is puzzling that physician-investigators can ethically perform any research procedures that pose risks but no compensating therapeutic benefits to patient volunteers; for example, studies of pathophysiology that administer biopsies or lumbar punctures, or imaging procedures that use ionizing radiation. In other words, why should therapeutic beneficence govern clinical trials but not the whole of clinical research?

Weijer offers an answer to this question by presenting an ethical framework for the evaluation of the risks and benefits of clinical research that draws on a fundamental distinction between therapeutic and nontherapeutic procedures (Weijer 2000). Procedures "administered with therapeutic intent" must pass the test of clinical equipoise. Procedures not administered with therapeutic intent are subject to an ethical requirement of minimizing risks and are justified by their potential to generate scientific knowledge. According to this framework, the principle of therapeutic beneficence applies to therapeutic procedures but not to nontherapeutic procedures.

We contend that this distinction is dubious. The most plausible candidates for therapeutic research procedures are experimental (or standard) treatments evaluated in clinical trials. However, as we noted above, the intent or purpose of administering treatments in clinical trials is not to provide personalized therapeutic benefit but to test hypotheses concerning safety and efficacy of treatments in groups of patients. Personalized attention characteristic of medical therapy is lacking in clinical trials that provide treatment according to a scientific protocol. This makes it misleading to characterize such treatment as therapeutic in intent.

Nevertheless, let us grant for the sake of argument that treatments evaluated in RCTs are therapeutic procedures. Application of Weijer's framework for ethical evaluation of the risks and benefits of clinical research leads to the conclusion that clinical equipoise is irrelevant to placebo-controlled trials. Weijer illustrates his ethical framework with four examples, including "Study A: Placebo-controlled trial of a drug for people with acutely symptomatic schizophrenia." After noting that "In study A, a novel antipsychotic is compared with placebo," he makes the surprising claim that "Both of these procedures are therapeutic interventions" (Weijer 2000, 354). No rationale is provided for describing a placebo control as a therapeutic procedure. Despite the possibility that placebo interventions may produce therapeutic benefit, placebo controls are properly classified only as nontherapeutic procedures employed to test the efficacy of novel treatments (Levine 1986, 204). The goal of a placebo-controlled trial is not to test the therapeutic efficacy of placebos. Placebo controls are sham treatments—that is, they are not treatments at all but control interventions designed to mimic a treatment subject to experimental evaluation. Accordingly, placebo controls under Weijer's framework should be assessed ethically not under the principle of clinical equipoise, but under the risk-benefit standards governing nontherapeutic procedures. With respect to the specific example of a placebo-controlled trial in schizophrenia, we think it would be difficult to justify the risks of symptom exacerbation from withholding antipsychotic treatment for those randomized to placebo.

Just as it is ethically justifiable to conduct nontherapeutic studies that pose some, but not excessive, risks of harm without the prospect of medical benefit, so it can be ethical to use placebo controls in scientifically valuable RCTs that involve withholding proven effective treatment, provided that the risks are not excessive and participants give informed consent. We conclude that the argument from therapeutic obligation against placebo-controlled trials fails. Placebo-controlled trials are not unethical just because they withhold proven effective treatment.

A Challenge and Response

The position that placebo-controlled trials may be ethically justifiable despite the existence of proven effective treatment, provided that risks to participants are not excessive, may be challenged on two grounds. What counts as excessive risk? And, who

decides? In the case of placebo-controlled trials, the answers to these questions about risk-benefit assessment are no different in principle than in the case of clinical research without any prospect of medical benefit for participants. Risks of placebo-controlled trials must be minimized, consistent with the possibility of a valid test of study hypotheses. In addition, risks that are not compensated by medical benefits to participants should not exceed a tolerable threshold, which may vary somewhat depending on the value of the anticipated scientific knowledge. Risks of concern include death, irreversible damage, temporary disability, and short-lived but severe discomfort. However, there is no reasonable way to formulate exactly the probability, severity, and duration of potential harm that would make the risks of placebo controls excessive. It calls for judgment. Such risk-benefit judgments are made by research sponsors, investigators, and, most important, by institutional review boards (IRBs) and research participants. If IRBs are properly empowered to make risk-benefit assessments for nontherapeutic research, they should also be responsible for determining when placebo-controlled trials are methodologically necessary or desirable and their risks tolerable, despite the existence of proven effective treatment. Finally, once proposed placebo-controlled trials have been reviewed and approved by IRBs, patients make their own judgments about whether they are prepared to accept the risks of trial participation.

The Argument from Scientific and Clinical Merit

It is also argued that placebo-controlled trials in the face of proven effective treatment lack scientific and clinical merit (Rothman and Michels 1994; Freedman, Glass, and Weijer 1996a; 1996b). The purpose of RCTs is to answer clinically relevant scientific questions about the safety and efficacy of treatments, with the ultimate aim of improving treatment. When proven effective treatments exist, there is no scientific or clinical value in testing a novel treatment against placebo. Instead, we want to know whether the new treatment is as good as or better than standard therapy, not whether it is better than "nothing" or no treatment.

This argument fails to come to grips with the methodological limitations of active-controlled trials, especially when they are designed to test the equivalence or "noninferiority" of an experimental and a standard treatment (Temple and Ellenberg 2000a; 2000b). There are powerful methodological considerations in favor of placebo-controlled trials both in the initial efficacy testing of experimental treatments and in the comparative evaluation of new and standard treatments. No new treatment should be introduced into clinical practice unless the expert community can be confident that it is effective. Superiority to placebo in a double-blind RCT is generally considered to be the most rigorous test of treatment efficacy. Accordingly, new treatments should be tested initially against placebo before being approved or validated, unless the use of placebo controls poses substantial risks of serious harm from withholding proven effective treatment.

In addition to their superior rigor, two-arm placebo-controlled trials generally require fewer research participants than active-controlled trials, making them more efficient. The reason for this is that the anticipated difference between the new treatment and placebo typically is greater than that between the new and standard treatments (Leon 2001). The efficiency of placebo-controlled trials is ethically relevant because they permit rigorous testing with less cost than active-controlled trials, and they expose fewer research participants to potentially toxic or ineffective experimental treatments (Leon 2000). How many initial placebo-controlled trials should be conducted, given the need to replicate scientific findings, and how many subjects should be included are matters of debatable judgment. From an ethical perspective, initial placebo-controlled trials of new treatments for conditions with already existing proven effective treatments should not enroll any more patient volunteers than is necessary to achieve a convincing demonstration of efficacy.

As the argument from scientific and clinical merit correctly asserts, once a new treatment has been shown to be better than placebo, it is important to evaluate its comparative efficacy by testing it against an existing standard treatment in an RCT. Nevertheless, there remain strong methodological reasons for including placebo controls in many trials comparing new and standard treatments in disorders with high rates of placebo response where standard treatments are only partially effective and not consistently found to be superior to placebos in clinical trials (Emanuel and Miller 2001). Under these conditions, if a two-arm active-controlled trial between the new and the standard treatment shows no statistically significant difference between them, two inferences are possible. Either both the new and the standard treatments were effective in the study sample; or neither the new treatment nor the standard treatment were effective (Temple and Ellenberg 2000a;

2001b). Without a placebo control to validate the efficacy of the two treatments being compared, it may be difficult, if not impossible, to determine which inference is correct. Such active-controlled trials lack "internal validity." It follows that there are sound methodological reasons for including placebo controls in three-arm trials comparing new and standard treatments in conditions with high rates of placebo response where standard treatments are only partially effective, such as depression and anxiety disorders.

It might be objected that this appeal to methodological considerations in favor of placebo-controlled trials gives science priority over ethics (Rothman 2000). This objection rests on a false dichotomy. Scientific validity is an essential ethical requirement of clinical research (Emanuel, Wendler, and Grady 2000). No person should be subjected to risks of research participation in studies that lack scientific validity. It follows that sound methodological considerations in favor of placebo-controlled trials and against active-controlled trials are ethically relevant.

The argument from scientific and clinical merit also adopts the false premise that placebo-controlled trials test whether new treatments are better than nothing or no treatment. Despite the recently published meta-analysis of clinical trials with placebo and "no treatment" arms (Hrobjartsson and Gotzsche 2001), which cast doubt on the power and pervasiveness of the placebo effect, the jury remains out on whether the use of placebo controls is associated with therapeutic benefit. But even if placebo interventions in themselves are entirely lacking in therapeutic benefit, placebo controls are typically combined with interventions that have therapeutic potential. These include clinical attention from investigators and members of the research team, the therapeutic milieu of research hospitals, especially in the case of inpatient clinical trials, and ancillary treatments or rescue medications that are often provided to research participants randomized to placebo. Though participants randomized to placebo may receive treatment that is less than optimal, this is not the same as no treatment.

Conclusion

We conclude that both the arguments from therapeutic obligation, invoking clinical equipoise, and from scientific and clinical merit fail to establish that placebo-controlled trials are unethical or pointless whenever they evaluate treatments of conditions for which proven effective treatments exist. It does not follow that placebo-controlled trials are ethically innocuous. Placebo-controlled trials raise ethical concerns insofar as they have the potential to exploit research participants by exposing them to excessive risks from placebo assignment or by enrolling them without adequate informed consent. Additionally, they should not be conducted unless they have scientific merit. Reasonable ethical criteria for the justification of placebo-controlled trials have been presented elsewhere (Emanuel and Miller 2001; Miller 2000).

If our critique is sound, it has important implications for the ethics of clinical research. Appeal to the principle of clinical equipoise should be abandoned; or the scope of the principle should be limited so that it does not apply to placebo-controlled trials. Placebo controls should be evaluated according to the same ethical standards that apply to research procedures that pose risks without compensating medical benefits (Emanuel, Wendler, and Grady 2000). ■

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