

## ***Should the Food and Drug Administration Limit Placebo-Controlled Trials?***

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### ABSTRACT

Randomized placebo-controlled trials are often used in clinical research, though there are ethical concerns regarding their use. The Food and Drug Administration (FDA) has rejected international stances on placebo-controlled trial use in favor of the bioethical principles of autonomy, beneficence, nonmaleficence, and justice. The FDA permits placebo-controlled trials in three circumstances: when there are no established treatments available, when their use would be of negligible harm to the patient, and when there are compelling reasons for their use. However, in some cases, the FDA's approval of placebo-controlled trials violates bioethical principles. Ultimately, the FDA should overhaul its practices regarding the use of placebo-controlled trials.

**Keywords:** Food and Drug Administration, Placebo-Controlled Trials, Bioethics, Declaration of Helsinki, International Ethical Guidelines for Biomedical Research Involving Human Subjects, Belmont Report

### INTRODUCTION

Randomized placebo-controlled clinical trials (PCTs) are considered the most rigorous method of understanding the efficacy of an intervention and, as a result, are widely used in clinical research.<sup>1</sup> However, there are ethical concerns regarding placebo controls, including their use in the study of deadly diseases or when effective treatments already exist, though poor oversight and lax rules have largely permitted PCT research, even under those conditions.<sup>2</sup> The FDA prefers PCTs for most interventional research and considers them essential to test the efficacy of drugs. Between 2006-2011, 40 percent of FDA-approved clinical trials used a placebo alone for comparison. The FDA has been lagging in altering its policies

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regarding PCTs, only advising against PCT research in select oncological cases for the first time in 2019 in a nonbinding guidance. It is our belief that the FDA should change its approach and prohibit the use of placebo controls in clinical trials where effective treatments already exist.

#### I. Brief History of PCTs and the FDA

In contemporary research practices, PCTs are used to evaluate whether an intervention is effective by comparing it to a control group that received a treatment designed to have no real effect (placebo). Throughout the 20<sup>th</sup> century there have been numerous bioethical tragedies, including but not limited to the Holocaust and the Tuskegee Syphilis Study.<sup>3</sup> These and other transgressions have become an impetus for establishing ethical research standards preventing human exploitation in the name of science. The Declaration of Helsinki, adopted in 1964, a nonbinding instrument, restricts the use of PCTs. Clause 33 of the Declaration of Helsinki states that new medical interventions should be tested against previously demonstrated interventions and placebos should be used only if there is no existing intervention with narrow exceptions. Clause 33 says the effectiveness of a new intervention must be tested against those of the best current proven intervention (s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable;  
or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.<sup>4</sup>

The FDA has largely ignored this and deemed placebo controls the gold standard, stating that “PCTs are necessary to control for placebo effect of investigational medicinal product.”<sup>5</sup> The FDA has even refused to approve drugs that are tested against established treatments instead of against placebos, notably atenolol.<sup>6</sup> By stretching the “methodological” exception and failing to define harm reasonably, the FDA does not meet the spirit behind Helsinki’s conditions for allowing PCTs. When the Declaration of Helsinki was revised in 2000 to increase restrictions, the Director of Medical Policy for the FDA’s Center for Drug Evaluation and Research considered it “unpardonable” and abandoned any compliance with it in 2008.<sup>7</sup> The FDA’s past statements and actions have supported its belief that drug approval hinges on the use of placebos.

While the FDA has rejected the Declaration of Helsinki’s stance on placebos, it has remained faithful to the guidelines of other bioethical codes such as the International Ethical Guidelines for Biomedical Research Involving Human Subjects and the Council for International Organization of Medical Science’s guidelines for biomedical research involving human subjects. The International Ethical Guidelines for Biomedical Research Involving Human Subjects permits PCTs if the consequences are negligible, when methodologically advantageous, and when responses have been historically erratic.<sup>8</sup> The Council for International Organization of Medical Science’s guidelines for biomedical research involving human subjects echoed the Declaration of Helsinki in guideline 11, stating that a ““placebo may be used: When there is no effective intervention; when withholding an established, effective intervention would expose to, at most temporary discomfort, or delay in relief symptoms; when use of an established, effective

intervention as comparator would not yield scientifically reliable results and the use of the placebo would not add risk of serious or irreversible harm to subjects.”<sup>9</sup> The Belmont Report notes three ethical principles: beneficence, respect for persons (autonomy), and justice. The *Common Rule* requires IRBs for human research and reflects principles noted in the Belmont Report. The Belmont Report covers three applications of its principles: Informed consent, selection of research subjects, and risk-benefit assessments.<sup>10</sup> In 1979, Beauchamp and Childress established the four principles approach to bioethics including autonomy, beneficence, nonmaleficence, and justice. While PCTs were not mentioned in these reports, the principles in them permit placebo controls as long as subjects are informed of the risks of participating and risks are minimized. The FDA has since followed that approach. These guidelines have made PCTs ethically ambiguous, and there are moral counterpoints to be made.

## II. FDA-PCT Conditions

The FDA has permitted PCT use under three conditions. The first condition is when there is no proven intervention for the medical condition under the study. This means treatment has either not been found for a disease or has not yet been translated into clinical practice and is not controversial. The second condition is when there is negligible harm to the patient from delaying or forgoing an available treatment. In this scenario, a placebo is not suspected to cause damage and the available treatment is meant for mild conditions that pose low-risk adverse effects, which is said to justify its use. The final condition is when there are compelling methodologic reasons for the use of the placebo. This scenario is for situations where outcomes fluctuate for complex reasons making other research methods likely to be unreliable. This condition for PCT use is also justified when it is not possible to administer the intervention to the experimental group because of economic, social, or administrative factors, in which case it is believed to be better to have results of some kind than none at all.<sup>11</sup> We will argue each condition is unethical to the current degree it is practiced.

### III. Condition One: Lack of Established Treatment

Placebo use in cases where no established treatment exists would not typically be considered unethical. However, placebos continue to be used in numerous clinical trials approved by the FDA, many of which already have standard interventions.<sup>12</sup> In addition, the lack of head-to-head drug trials, in favor of placebo, has had no benefit on clinical guidelines and practices. The direct comparison of drugs in head-to-head trials gives physicians and buyers a better understanding of the effectiveness of a drug and allows for the creation of more robust clinical guidelines. Instead, under the PCT model, the market is saturated with a plethora of drugs to choose from. While each one may be better than placebo, it can be difficult to understand how each treatment compares to another, which may be harmful to patients. A recent study has shown that nearly 90 percent of new drugs do not perform better than existing options.<sup>13</sup> There is an ethical cost to be considered when devoting financial resources and effort to create new drugs that are inferior to existing treatments and have not led to changes to clinical practice. While the FDA claims to follow the bioethical principles of beneficence and nonmaleficence, its choice of approving treatments through placebo controls, despite the existence of standard interventions, counters these guidelines.

### IV. Condition Two: Negligible Harm from Delayed Treatment

The International Ethical Guidelines for Biomedical Research Involving Human Subjects argues that placebos are acceptable if there is only “temporary discomfort or a delay in relief of symptoms,” a stipulation that the FDA follows. However, what constitutes temporary is arbitrary, as there is no absolute reference of time prescribed, nor is there a defined proportion relative to total life expectancy available.

For example, many patients in trials for terminal illnesses have a limited therapeutic window and a reduced life expectancy, so they value time differently from someone with a non-terminal illness. Additionally, there is no consensus of what constitutes harm when withholding treatment; placebos are often used in trials for major depressive disorder, yet this population has statistically higher rates of self-harm and suicide without treatment compared to the general population.<sup>14</sup> Serious risks can be incurred due to a placebo intervention by not offering experimental treatment, without excusing the psychological harm withholding a treatment may have on a patient should it be unblinded. Nevertheless, the FDA has used the umbrella term of “temporary discomfort” to justify the widespread use of PCTs, but the vagueness of this language results in human suffering.

#### V. Condition Three: Compelling Methodological Reasoning

Finally, the FDA authorizes placebo use in cases where for compelling scientifically sound methodological reasons, the use of placebo is necessary to determine the efficacy or safety of an intervention, and the parties who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. The condition includes cases where PCT is believed to be necessary to demonstrate efficacy, such as in trials of psychoactive drugs where evidence is inconsistent due to disease heterogeneity and demonstrating equivalence to an established treatment is insufficient. There are also arguments that PCTs, while not necessary, may be beneficial in generating socially valuable knowledge. However, whether a placebo control demonstrates efficacy is not sufficient to justify its use. When considering the ethical use of PCTs, investigators must weigh the social value gained against the risks of no treatment in the control. Unfortunately, the risk-benefit analysis is often controversial. For example, in 2001, the FDA initially responded positively to a placebo-controlled trial of Surfaxin in infants with acute respiratory distress syndrome in Latin America. However, the trial was deemed exploitative by a public watch group when it was revealed that the drug was already FDA-approved in the United States, and the manufacturer of that drug was undertaking another study with the same drug in Europe without any placebos. To justify withholding treatment from a vulnerable population in a developing country, the manufacturer stated that they would be providing a drug that would otherwise be unavailable to many participants, and the risks would be compensated by upgrades to the host country’s medical infrastructure. Despite the FDA’s initial approval and the manufacturer’s attempt to quell public outcry, objections by the public led to the removal of the placebo arm from the trial. While the FDA believes there may be methodologically compelling reasons to utilize PCTs, they have demonstrated a lack of judgment necessary to balance the gains against their inherent losses, requiring the public to step in.

#### CONCLUSION

Based on the ambiguous bioethical guidelines that the FDA follows, and the moral justifications described in this paper, its preference of PCTs is unethical. We suspect the overreliance of PCTs has resulted in harm to research participants and the general population, which is why the FDA should change its policy. We propose that PCTs be used only for diseases that lack an established treatment, as decreed by Clause 33 of the Declaration of Helsinki. Other measures that would satisfy Clause 33, the Belmont Report, and the *Common Rule* are the use of large retrospective observational trials for comparison rather than a prospective placebo group. Ultimately, it is ethically necessary that the FDA modify their practices regarding drug approval and more stringently scrutinize PCTs as well as adopt more favorable approaches to other comparative models.

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