The Ethics of Using a Placebo-Control

in Clinical Trials

By

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“The ends justify the means.” This phrase is the basis of Consequentialism, which says to do the greatest good to the most amount of people. This applies to the field of medical research, where the goal is to find new ways to help more people. However, is it ethically just to withhold treatment from some patients by giving them placebo, while treating another group of patients? This has been happening since clinicians have started researching medications by using human patients in clinical trials. In this paper, we will look at the ethical issues involved in withholding treatment from some patients during clinical trials.

We will first look at the Declaration of Helsinki and use it as background information as to what has been said about ethics in clinical research, then apply what is learned to the use of placebos in clinical trials. In 1964, the topic of ethics in clinical trials was a major issue during the 18th World Medical Association General Assembly in Helsinki, Finland. In June of that year, the WMA Declaration of Helsinki was adopted with the subtitle Ethical Principles for Medical Research Involving Human Species. Although it has been amended multiple times since 1964, the general principles remain the same. According to Paragraph 1, “The Declaration of Helsinki [was developed] as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects.”

The introduction (Paragraphs 1-9) of the Declaration of Helsinki discusses why it was written and begins to describe some of the principles discussed later. The WMA recognized that even the best therapeutic options must be continuously improved on and challenged and that “medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.” As previously stated, the Declaration of Helsinki recognizes the need for experimentation but says that even with informed consent, it is the duty of the physician to care for the patients and the physician should dedicate all their knowledge toward beneficial outcomes for the patient. The Declaration quotes the World Medical Association Declaration of Geneva stating “The health of my [physician’s] patients will be my first consideration,” and the International Code of Medical Ethics which states that “A physician shall act only in the patient’s
interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient.”¹ Finally, this Declaration takes the needs of vulnerable populations into account by requiring “Special attention...for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.”¹ With a continuing description of the Declaration of Helsinki, we will see how these statements from the Introduction fit into the Ethical Principles outlined.

The next section in the World Medical Association Declaration of Helsinki (Paragraphs 10-27) outline the “Basic Principles for all Medical Research.” Paragraph 13 discusses the experimental procedure when dealing with human subject in clinical trials. It states that,

…design and protocol...should be clearly formulated in an experimental protocol [and] submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence...The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events, [and] should also submit to the committee information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.¹

The experimental protocol that is submitted must contain a statement of ethical considerations involved, as well as indicate that it is in compliance with the Declaration of Helsinki.

Paragraph 16 says that before beginning a clinical trial involving human subjects, the physicians or researchers running the trial must carefully assess all predictable risks and burdens that some subjects may incur versus the possible benefits to the subjects or others. Continuing into Paragraph 17, the researcher should not participate in any studies in which the risks have not been assessed or there are risks that cannot be managed. It also states, “Physicians should cease any investigation if the risks are found to outweigh to potential benefits or if there is conclusive proof of positive and beneficial results.”¹ This is seen in many studies, where statistically significant results are seen before the trial’s endpoint, and the trial is stopped so that all patients may receive the superior treatment option. Paragraphs 18 and 19 state that trials should only be carried out on human subjects if the importance of the outcome of the trial outweighs any potential risks, and if the subjects of the trial will benefit from the results of the research.
The final Paragraphs in the Basic Principles section talk about the subject, the researcher’s obligations to the subjects, and publication of findings. One of the most important principles stated in the *WMA Declaration of Helsinki* is, “the subjects must be volunteers and informed participants in the research.”\(^1\) It goes on to state, “each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations or the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail.”\(^1\) After the subject receives this information, they have the right to abstain from the study. Subjects, once enrolled in a study, also have the right to withdraw consent at any time without reprisal from the researcher. According to the *Declaration*, the researcher is required to respect the patient’s confidentiality and privacy, and minimize the effects that the study will have on a patient’s integrity. Finally, when it comes to publishing a study, the researcher is also ethically bound. Researchers must preserve the accuracy of results of the study by publishing both positive and negative data that was collected. All conflicts of interest, including affiliations and sources for funding, must also be included in the publication.

The last section of the *WMA Declaration of Helsinki* most directly applies to the ethical use of placebos as a control in clinical trials. This section is entitled, “Additional Principles for Medical Research Combined with Medical Care.” Paragraph 29 states,

> The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.\(^1\)

This statement was further clarified in the 2002 World Medical Association General Assembly in Washington. According to the Clarification, placebo should only be used when other treatment options do not exist, but may be acceptable in cases where use is necessary to determine safety or efficacy of a new treatment, or when investigating a new therapeutic option for a minor condition and placebo or no treatment will not place the subject at any additional risk. Finally, the *Declaration of Helsinki* states that at the conclusion of the trial, all patients should be given whichever treatment option was determined to be superior.

With this background information about the *World Medical Association Declaration of Helsinki*, we are now able to look at how the principles apply to clinical research today, and whether or not the use of placebos as a control is ethically just. The randomized clinical trial was a major breakthrough in the field of medical research. It allows for a way to divide a large population of patients into two groups, one of which is treated with the new medication while the other is a control group. “For conditions having no effective treatment, the control regimen to which the new treatment is compared is usually either observation or
administration of placebo. In some cases, untreated or placebo control groups are used even though effective treatment exists for the condition. It is in these latter groups that ethical issues arise.

Placebo-controlled trials have been in place for many years and have greatly influenced medical research.

The first placebo-controlled trial was probably conducted in 1931, when Sanocrysin was compared with distilled water for the treatment of tuberculosis. Ever since then, placebo-controlled trials have been controversial, especially when patients randomly assigned to receive placebo have forgone effective treatments.

There are two main sides to this argument as described by Ezekial J. Emanuel and Franklin G. Miller in *The Ethics of Placebo-controlled trials – a middle ground*. These groups are the Placebo Orthodoxy, which advocates placebo-controlled studies, and the Active-Control Orthodoxy, whose members are proponents of only using already effective treatment options as controls. Advocates of placebo-controlled trials argue for the ethical use of these trials even if other treatment options have been proven effective “because of the methodologic limitations of trials in which active treatment is used as the control.” Placebo groups ensure validity, and without these, the differences between investigational and standard treatment options can be misleading or uninterpretable. Also, new treatments may not be as effective as the standard treatments, but they may have fewer side effects or prove more effective in particular patient subpopulations. These medications would not be approved without the use of placebo-controlled trials to prove that they are more effective than no treatment. Although typically for placebo-controls, the Placebo Orthodoxy proponents “acknowledge that [placebo-controlled trials] are unethical in some circumstances, especially when withholding an effective treatment might be life-threatening or might cause serious morbidity.”

A few problems are present with the placebo orthodoxy. First, they argue that these trials are ethically acceptable if the patient “will not be harmed” by receiving placebo during the trial. This explicitly excludes the use of placebo in trials where the investigational treatment can cure a deadly disease, but what about patients that may be harmed by temporary, but reversible, conditions. According to the above statement, if there is any harm that a patient may experience, there should not be a placebo control arm. Second, the use of placebo-controlled trials can permit intolerable suffering on the part of the study participants. In the ondansetron clinical trials for chemotherapy-induced vomiting, a placebo group was used even though metoclopramide had already been proven effective. They stated that vomiting induced by chemotherapy is not life-threatening and will not cause irreversible disability to patients, and therefore it was ethical to use placebo in these trials. However, when justifying the need for a new medication, it was stated that “uncontrolled nausea and vomiting
frequently results in poor nutritional intake, metabolic derangements, deterioration of physical and mental condition, as well as the possible rejection of potentially beneficial treatment."³ These two statements are contradictory, but it seems as though giving placebo would cause harm to the subjects of the study, and is therefore considered to be unethical. The final flaw in the placebo orthodoxy is that its proponents tend to focus on physical harm, not psychological or social. It is important to address these other areas when evaluating the risk-benefit ratio of a drug, especially if this is an antidepressant, or drug for another neurological disorder.

The other side of the argument presented by Emanuel and Miller is the Active-Control Orthodoxy. Proponents of this side argue that whenever a proven effective therapeutic option exists, it should be used as the control. Placebos are inappropriate due to the fact that new treatment options do not need to be proven effective versus no treatment, but versus the currently used standard. Finally, they “criticize the placebo orthodoxy for placing the demands of science ahead of the rights and well-being of study participants.”³

As with the placebo orthodoxy, there are also a few problems with the active-control orthodoxy. First, there are some clinical trials where the use of placebo controls present nonexistent or very small harm and discomfort to the patient. In trials for such minor problems, such as headache or baldness, where patients rarely seek medical attention, why is it unethical to give them placebo? Another argument against the active-control orthodoxy is the placebo response. According to Dr Jeffrey Kahn, “we know that placebos actually work, that is, they have a positive effect.”⁴ It has been shown in various trials that substantial proportions of patients will have measurable and clinically meaningful improvements when receiving placebo instead of conventional treatment. An example of this is that 30-50% of patients with depression, and 30-80% of patients with chronic stable angina have shown response to placebos in clinical trials.⁵

As seen from the title of their paper, Emanuel and Miller propose a “middle ground” to attempt to satisfy both the placebo and active-control proponents. Both sides agree that...

if effective, life-saving, or at least life-prolonging treatment is available, and if patients assigned to receive placebo would be substantially more likely to suffer serious harm than those assigned to receive to investigational drug, a placebo-controlled trial should be prohibited.³

The disagreement between the groups centers on whether it is ethically just to use placebo controls when there is another available treatment proven to be effective, or if there is some potential harm to subjects receiving the placebo. When the risks of using placebo equal the risks of an active control, the use of
placebo for these studies should be ethically justified. However, when effective treatment does exist, there must be a compelling reason to use placebo in the place of that treatment. Emanuel and Miller give a list of criteria that must be met in order to provide scientific rationale for placebo control use. These include; a high placebo-response rate, a disease with off and on symptoms or frequent remissions, and existing therapy options that are only partly effective or that have serious adverse effects. Once these criteria have been met, the risk of using placebo control must be assessed by determining that participants in the placebo group are not more likely to die, have morbidity, disability or harm, suffer reversible but serious harm, or experience severe discomfort than those in the active-control group. Finally, once a placebo-controlled trial is proposed,

The institutional review board must ensure that the following safeguards are instituted to minimize harm: participants at increased risk of harm from nonresponse are excluded; the placebo period is limited to the minimum required for scientific validity; subjects will be carefully monitored, with inpatient observation when appropriate; rescue medications will be administered if serious symptoms develop; and there are explicit and specific criteria for the withdrawal of subjects who have adverse events.3

According to Emanuel and Miller in The Ethics of Placebo-Controlled Trials – a Middle Ground, these safeguards, along with informed consent and a statement of risks for those who may not receive the investigational treatment, should help the two sides of the placebo argument see things on a more even level.

The paper by Emanuel and Miller shows just some of the multiple disagreements that arise between groups arguing for and against the use of placebo-controlled trials. As previously stated, there is an agreement among clinicians that non-treatment or placebo use in clinical trials for life-threatening conditions is not an option. If there are clinically effective treatment options available, the control group will normally receive this other treatment in use as a comparison to the medication being studied. Once again, the ethical issues arise in studies where there is no life-threatening problem. Even though there is no immediate harm in delaying the treatment in these patients, should a proper treatment option be withheld from this group? Why can’t a currently available treatment be used as a control in these cases like they are in patients with life-threatening conditions?

The answer to this question is not as simple as it seems. There are many arguments that say “that placebo-controlled trials may be ethically conducted when effective therapy exists as long as omission of such treatments would not increase risk for death or irreversible morbidity and patients are fully informed about their alternatives.”2 It does not seem very likely that some patients with a disease choose to be in a study where they might not receive the actual treatment, but some patients do. The patients realize that there is a chance to
receive the treatment, and understand that if the drug is proven clinically effective, they will receive a better drug in the future to help their condition. As stated in the *Declaration of Helsinki*, “at the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.”¹ Since all patients will eventually get the best treatment available, it does not seem unethical to perform a placebo-controlled trial, especially when the patient has given informed consent for the study.

The issue of informed consent in trials has been debated and written about to a great extent. As shown previously, the *Declaration of Helsinki* declares that the subjects must be volunteers and adequately informed. They are informed about the methods of the trial and possible benefits and adverse effects. They are also given the right to abstain from the trial or withdrawal at any time. The *Declaration* also gives guidelines as to how consent should be obtained, whether it be from the patient, or a patient representative or guardian.¹ Many patients receive the information about the trial and decide to take part in it because of various reasons, including: “interest in being treated and monitored by the specialists performing the trial, curiosity about the scientific process, lack of enthusiasm for existing therapies, or simple altruism. The perceived scientific value of the trial may contribute to this decision.”⁷

The opposite side of the argument uses the *Declaration of Helsinki* to argue against the use of placebo-control groups in clinical trials. The opposition to placebo use in clinical trials uses the following line from the *Declaration*: “In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method.”¹ This states that no matter if a patient agrees with the clinical trial, it is against the Declaration to perform a placebo-controlled trial. Unfortunately, if taken literally, this brief excerpt from the Declaration of Helsinki would actually bar all clinical trials. If an “effective treatment exists, the patient receiving the investigational treatment instead of the established therapy is clearly not getting the best proven treatment.”⁶

Informed consent, as stated earlier, has been a widely debated topic. Informed consent is a requirement in all trials, especially placebo-controlled, but the information given is rarely monitored. There is a lot of concern as to whether the consent given for trials is as informed as it should be. However, “these concerns apply as much to the patient’s decision to forgo known effective treatment and risk exposure to a potentially ineffective or even harmful new agent in an active-control trial as to a decision to accept possible persistence of symptoms in a placebo-controlled trial.”⁶ As the previous quote states, even if the information given to the patients is not as complete as we would hope, the same amount of information is given no matter if it is a placebo-controlled or active-control trial.
Many of the arguments regarding the ethics of clinical trials are based on two key aspects, respect for the patient’s autonomy, and beneficence on the part of the researcher. The respect for autonomy means that the patient’s should be fully informed about the methods of the trial and pros and cons of participating in the trial, and then allowed to give their consent without coercion from the researcher. Beneficence on the physician’s part deals with the physician respecting their relationship with the patient and looking out for the good of each individual. These two ethical aspects should be assessed for every clinical trial. The respect of autonomy can be checked by testing the adequacy of the information that is provided to the information in order for them to give their informed consent. As for the beneficence, each researcher or physician needs to be looked at. Is there any reason why the researcher or physician would not act in the best interest of the patient, such as a conflict of interest?²

Now that both sides of the argument have been presented, we will look at some reasons as to why “in these times of raised ethical consciousness, placebo treatments are still commonly used in medical research in circumstances in which their use is unethical.”⁸ We will not only discuss why these trials are still used, but will also look at some of the trials that have been completed using placebo as a control group. Even though the Declaration of Helsinki explicitly states that placebo-controlled trials should not be used if a currently effective treatment is available, “studies that breach this provision are still commonly conducted, with the full knowledge of regulatory agencies and institutional review boards.”⁸ Although many trials are published, there are a large amount of trials conducted to gain approval for new drugs that are never released to the public, so there is no way to estimate exactly how many trials are conducted with use of placebo-controls.

We will now look at six different clinical trials in which placebos were used despite other effective treatment options. The first trial was to study the efficacy of ivermectin, which is used to treat onchocerciasis or river blindness. The researchers split the participants into two groups, those who received ivermectin, and those who received placebo. They included a placebo-controlled group even though the drug diethylcarbamazine had been the standard of treatment for decades. The researchers possibly took advantage of the trial subjects due to the fact that most of the participants were illiterate Liberian seamen.

The next trial involved secondary treatments for rheumatoid arthritis. All participants in the study received an approved primary treatment, then split into an investigative secondary treatment and a placebo group, even though many medications have been proven effective as secondary treatments. These participants who received placebo were put at risk for serious and irreversible degenerative changes that could have possibly been prevented.

Ondansetron, as previously described, was involved in trials with a placebo-control group when it was being investigated for approval. Drugs such
as metoclopramide, phenothiazines, substituted benzamides, corticosteroids and benzodiazepines have all been proven effective in the treatment of chemotherapy-induced emesis. Although these drugs have been proven effective, none of them were used as active-controls in the ondansetron trial.

The final three trials we will look at are not for specific medications, but for multiple drugs in three different classes. The first class is antidepressants. Although effective antidepressant compounds have been available for decades, many new medications are still compared to placebo. This was seen in the 1992 trial of paroxetine (Paxil) in which half of the seriously depressed patients used in the trial were given placebo. The next class is the drugs used in treatment of congestive heart failure. Although angiotensin-converting-enzyme inhibitors are the accepted standard of treatment in congestive heart failure, most of the newly examined drugs are tested against placebo. The third and final class is for antihypertensive drugs. Many drugs have been proven clinically effective in the treatment of hypertension, however most drug trials are still using placebo controls.

We have seen a few of many trials that have unethically used placebo-controls, but why are they still conducted? One of the main reasons to conduct placebo-controlled trials is to gain FDA approval. “The Code of Federal Regulations under which the FDA operates is ambiguous about the acceptability of placebo controls.” On one hand, the FDA discourages the use of placebo, stating that if an effective therapy exists, it is contrary to the interest of the patient to use placebo or no treatment. On the other hand, the FDA regulations go on to suggest that both placebo and active-treatments controls should both be used in a study. Aside from the regulations, FDA officials consider placebo-controlled trials to be the gold standard in clinical trials. Placebo trials seem to be necessary according to the FDA in to two different types of clinical trials. “The FDA demands the inclusion of a placebo group when new-drug applications are submitted for fixed-dose combinations of NSAIDs with codeine [and] for the clinical evaluation of disease-modifying antirheumatic drugs.” It has been seen at least once that the FDA has refused to approve a drug when a placebo-controlled trial was not completed. A new beta-blocker, was rejected because a placebo-control group was not used, even though it was proven to have an effect similar to propranolol, an already approved medication.

Besides FDA necessity, there are three main arguments of why placebo-controlled trials are still used. First, placebo groups are used to establish a reference point to allow the investigators to determine whether an investigational medication is superior to no treatment. This new drug may be worse than the current standard, but it may still be effective. Second, inferior treatment options may be advantageous to some patients with respect to cost, less adverse effects, or quality of life. Finally, placebo-controls are used to bolster statistical significance. Since the FDA relies heavily on statistical significance, this is important in clinical trials. When a new drug is compared to placebo, the effects
of the new drug appear large and may show statistical significance even in small trials.

After looking at the arguments for whether or not the use of placebo-controlled trials is ethical, a decision is still hard to come by. Many trials are discontinued if serious adverse events are shown or a drug is shown to be superior or inferior to the current regimen. With these standards set, it seems as though placebo-controlled trials would be discontinued before they can do serious harm to a patient. Also, with informed consent from the subjects of a study, the ethical burden is placed on the subject of the study. It seems that the main reason for continued use of placebo-controlled trials is the fact that the FDA indirectly requires such a trial to be completed before an investigational drug will be approved. The change needed to cease the use of placebo-controlled trials needs to come from the FDA and other regulatory agencies. The FDA has the ability to review data from all trials, even those not published, so the FDA needs to conduct an ethical review of all trials, and should ignore all new drug applications that involved the unethical use of placebos.


References

1. World Medical Association Declaration of Helsinki; Ethical Principles for Medical Research Involving Human Subjects. www.wma.net/e/policy/b3.htm


