

ÉTHIQUE MÉDICALE/MEDICAL ETHICS ON THE ETHICS OF PLACEBO-CONTROLLED TRIALS

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Georges EPHREM*

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The most classical form of clinical trials entails the inclusion of both intervention and comparison groups. If the choice of the intervention agent is expected to be the novel therapy (whether a new agent or a new use of it by dosage or disease) the debate lingers with regards to the comparison group. In the early days of clinical trials where therapies were nascent comparing a new product to placebo was acceptable as it was the only comparison available. As the armamentarium of proven treatment options increased the issue of the ethical soundness of using placebo as a comparison arose. This led to the advent of two schools of thought [1]: *Placebo orthodoxy* and *Active-control orthodoxy*. The former advocates that the use of a placebo control is always better than the use of an active control whereas the latter believes that if an effective therapy exists, the use of a placebo should be prohibited in all cases [2]. In this article we will present both positions and then appraise the ethical soundness of placebo-controlled trials.

This debate has ethical ramifications through the various medical ethics codes, and the Universal Declaration of Human Rights. It also has moral (Nuremberg Code, declaration of Helsinki), regulatory (FDA, OHRP, IRBs), and sometimes legal dimensions (laws). This plethora of references is beneficial when they reinforce each other but becomes problematic when they disagree causing loopholes and creating controversies. An example would be to reconcile one of the principal precepts of medical ethics “maximizing benefit and minimizing harm” and the FDA’s encouragement to have some form of placebo comparison in the conducted studies [2].

Fortunately there are situations where such a dilemma is avoided. The best example is a disease with no proven therapies. Comparing a new drug with placebo is then a reasonable and ethically sound choice [3-4]. The case is also made that sometimes therapies are not available in a given location such as developing countries. Therefore the use of placebo would not be a deviation from the available standard of care [5]. No withholding of otherwise available care is occurring and hence no ethical breaches are at hand. The picture gets shadier when there are no strongly proven therapies or when the comparison is placebo despite the presence of proven treatment options.

The proponents of placebo use argue that this approach provides sound clinical validity in that it allows the evaluation of the absolute impact of an intervention which is clearly identifiable and less complicated to interpret compared to an active-control approach. The estimation of effect by comparison of two treatments poses the question of assay validity [4-5]. If the measurement process (whether the unit or the method or the design) is not precise enough the difference in effect size might go unnoticed. In the case of a non inferiority study one may erroneously conclude that both treatments have similar impacts. Some go even further by stating that this may be an implicit reason for applying less stringent efforts when conducting non inferiority studies as the desired result is the failure to reject the null hypothesis. The placebo-orthodoxy adepts point that a non inferiority study shows exactly this, that two treatments are fairly similar. This similarity can be in efficacy or in the lack of it. The adoption of a placebo as control clarifies the comparison. The use of a placebo as the comparison arm instead of another therapy allows by the differential of effect size that is hypothesized to decrease the sample size required to achieve the proper power of a study. This indirectly decreases harm by having fewer people subjected to the potential side effects of the treatment being tested [1]. The placebo in general has dismal (if any) side effects and is not harming patients from that perspective. It is even hypothesized to have up to a 30% benefit, i.e. the “*placebo effect*.” In the defense of having control subjects at least temporarily deprived of any therapy the advocates of placebo control state that there is no rigorous assessment or estimation of the risk/benefit ratio, especially when we include the long-term dimension of it. In foregoing the short-term benefit of immediate treatment the control subjects (or other patients) will gain the long-term benefit of the discovered therapies through placebo-controlled trials [5]. All these arguments are finally coupled with the delegation of ethical burden to the patient through the *informed consent process*. Indeed the final decision to participate or not remains in the hands of the subjects. Through the informed consent process the subject is made aware of the fact that he/she may be getting a placebo even though proven therapy exists [4]. Regardless of the overall appraisal of the quality of information during the consent process the ethical concern is considered mitigated (if not waived) by the proponents of this approach.

*Beth Israel Medical Center, Department of Medicine, New York City, NY, USA.

Correspondence to: *Georges Ephrem, MD. Beth Israel Medical Center. Department of Medicine. 350 East 17th Street. Baird Hall, 20th floor, Suite 53. New York. NY 10003 USA.* e-mail: g.ephrem@gmail.com

This perspective on research is fairly vocal. There is a deeply entrenched conceptualization of placebo as the “gold standard” comparison for being the “negative-negative.” This is seen for example in the Code of Federal Regulations under which the FDA operates. It states that “*an active treatment study may include additional treatment groups ... such as a placebo control*”. For some disorders, it is even required [2]. Even the Declaration of Helsinki which is viewed as a pro-active-control document states that “*the use of placebo, or no treatment, is acceptable in studies where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm*” [1-2].

If there is no argument about the use of placebo in instances where no established therapies are available, its adoption in the other situations is becoming less defensible as we go along. One such situation is the conduction of placebo-controlled trials in developing countries. Such settings are attractive in view of their deficit of legislation when it comes to such an issue but also in that there may be less oversight and concern with regards to the ethical dimension. In Lebanon for example there is a new law that is being drafted that will deal with research ethics. This draft tackles the issue of experimental therapies and the need to have proper registration of trials and adequate IRB approval and supervision. There is no mention of the placebo-control dimension or of the ethical dimension of trials. It is either implicitly or inadvertently deferred to the IRBs or maybe plainly omitted. The ethical ramifications are just too meaningful to ignore. This dimension is tantamount in the active-control perspective. By withholding any therapy from the comparison group, we are not being faithful to the principle of maximizing benefit and, depending on the clinical situation, that of minimizing harm. How can someone defend the choice of giving anti-hypertensive medications to a group of patients and placebo to the other when we know the repercussions of high blood pressure on morbidity and mortality and we have numerous established therapeutic options available?

The use of placebo breaches another ethical principle guiding scientific research: *clinical equipoise*. Ideally a therapy is being tested as it is hypothesized to provide benefit to the health of a person. The presumption that both the intervention and comparison subjects may benefit is not met when placebo is used as the comparison. To take it one step further, the current version of the Declaration of Helsinki permits the use of placebo as a control as long as “*serious or irreversible harm*” is avoided. This is a vague term that entrusts the assessment of the degree of risk to the subjectivity of an investigator or an IRB committee far from any standardized criterion. One might argue that this violates the principle of justice as there are no guarantees that subjects are treated in an equal fashion. Why would one situation be considered serious versus another? And how can we justify temporary or reversible harm especially if we

are aiming to uphold the ethical principle of doing no harm? As we expect those previously established therapies to have been rigorously vetted, the harm/benefit ratio is assumed to still be in favor of the patients’ welfare when they receive the existing treatment. As for the perspective of privileging the long-term benefit over the short one, the same argument presented by the placebo advocates that we can’t properly assess the long-term risk/benefit ratio is in favor of not disregarding the short-term repercussions of our actions.

The argument that no clear advances can be achieved by the conduct of non inferiority trials is an overstatement. Important therapeutic advances in which new treatment was no more effective than established treatment are numerous [5]. The quality with which the research is conducted is a requisite regardless of the type of control the study uses. Hence the assumption that less stringent efforts are deployed in non inferiority studies does not hold. Besides, the scope of comparative studies encompasses non inferiority as well as superiority ones, and can be extended to include the knowledge brought by meta-analyses.

The issue of placebo-controlled studies remains a controversial one with ardent protagonists from each school of thought. This debate has clear repercussions on the current guidelines and codes we use. In an age where advances in statistics, computational power, and analytical sophistication allow us to obtain decently satisfactory answers from head-to-head comparison studies, it is hard to make an ethically sound case for placebo-controlled studies in the presence of a proven intervention. We therefore advocate restricting the recourse to placebo-controlled trials to the sole situations where no proven therapy is available. We also encourage the adoption of legislative measures to properly guide and monitor such activities as the current regulations, unfortunately, still allow for too many loopholes that can lead to potentially flagrant breaches of ethical principles of conducting research.

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REFERENCES

1. Emanuel EJ, Miller FG. The ethics of placebo-controlled trials – a middle ground. *N Engl J Med* 2001 Sep 20; 345 (12): 915-19.
2. Rothman KJ, Michels KB. The continuing unethical use of placebo controls. *N Engl J Med* 1994 Aug 11; 331 (6): 394-8.
3. Temple R, Ellenberg SS. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 1: ethical and scientific issues. *Ann Intern Med* 2000 Sep 19; 133 (6): 455-63.
4. FDA, HHS. International Conference on Harmonisation; choice of control group and related issues in clinical trials. *Fed Regist* 2001 May 14; 66 (93): 24390-1.
5. Ellenberg SS, Temple R. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 2: Practical issues and specific cases. *Ann Intern Med* 2000 Sep 19; 133 (6): 464-70.