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PERSPECTIVES

A Call to Revise *the Declaration of Helsinki's* Placebo Guidelines

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Since its introduction in 1964, the World Medical Association's *Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects* has enshrined the importance of safeguarding the well-being of human subjects in clinical research. *The Declaration* has undergone seven revisions, often in response to requests for clarification. I want to argue that *the Declaration* is in need of another revision in light of recent discoveries in placebo research.

Paragraph 33 of the current version (last amended in 2013) states that in a clinical controlled trial, an experimental intervention (the active arm) must be compared against best proven treatments. Placebos can be used as a control in specific situations, including:

1) Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
2) 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
3) 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.

The basic idea is that the use of placebo controls is permissible only if there are no existing treatments for the ailment being investigated. In cases where effective treatments do exist, the use of placebo controls is permissible only if there are compelling scientific reasons to do so and the harm to subjects is minor or reversible. Paragraph 33 in essence explicitly spells out, with regard to the use of placebo controls, researchers' obligation to safeguard subjects' health stated more generally in Paragraph 4.

The guidelines in Paragraph 33 implicitly assume that placebo controls are necessarily inferior to existing treatments. Although the identification of placebos with no treatment is frequently made by researchers, it is erroneous. For starters, the outcomes of a placebo-controlled arm are not necessarily placebo effects. Subjects in a placebo-controlled arm can improve for a host of reasons that have nothing to do with placebo effects. For example, the natural history of the disease being studied, regression to the means, the "washing out" of previous treatments, and other biases and statistical artifacts can generate positive outcomes independent of the placebogenic effects of the control. Conversely, placebo effects in the control arm can produce dramatic results that not only surpass the results of a no-treatment arm but also can even outperform existing treatments. Jonathan Kimmelman has argued, for instance, that given the adverse profiles of some novel neurological therapies, an experimental subject is often better off being in the placebo arm.[1]

Consider the results from trials investigating the efficacy of vertebroplasty in comparison to sham vertebroplasty conducted by David Kallmes et al. (2009) and confirmed by Cristina Firanescu et al. (2018).[2,3] Introduced in the late 1990s, vertebroplasty quickly became the standard treatment for compression vertebral fractures. The procedure involves the injection of an organic cement at the site of the fracture to provide structural support and to prevent further breakage. When compared to conservative treatments, that is, long-term use of analgesics, vertebroplasty proves to be superbly

effective.[4] Kallmes noticed that technicians occasionally injected the cement in the incorrect vertebra and patients reported comparable improvements. His team conducted a study in which half the subjects received verum vertebroplasty while the other half received a sham equivalence, which consisted of an identical procedure other than the actual injection of the cement. The experiment was single-blinded since the technicians would know whether a subject was receiving the verum or the sham. The results showed that patients in the sham arm experienced comparable improvements as those in the verum arm in terms of both pain and mobility immediately after the intervention and a month later. Indeed, since sham vertebroplasty involves no actual penetration of the skin and the injection of a foreign substance, the odds of adverse effects are lower than verum vertebroplasty.

Suppose a researcher conducts a controlled trial on a new form of vertebroplasty. According to Paragraph 33 of *the Declaration*, the use of a placebo control is permissible only if there is no proven treatment. In this case, the use of verum vertebroplasty appears to be indicated. But since there is clear evidence that sham vertebroplasty is equally effective, the use of placebo vertebroplasty ought to be justifiable on the ground that it does not expose subjects to any unnecessary harm. Indeed, if sham vertebroplasty is more effective than the verum, not only are researchers permitted to use the sham as a control, but also they might have an ethical obligation to prefer the sham over the verum.

The need for a separate paragraph in *the Declaration* to specify the use of placebo controls partly stems from a mistaken belief that placebo interventions are necessarily inferior to existing treatments or to no treatments. Countless recent studies have demonstrated that placebo interventions can be superior to non-placebo treatments. *The Declaration's* broader commitment to minimize harm to human subjects adequately covers the use of placebo controls, regardless of whether the control is a placebo or an active treatment. In that respect, Paragraph 33 can simply be rewritten as

> The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s) which can be existing treatments or effective placebo interventions.

The need to revise Paragraph 33 is more than a matter of ensuring the conceptual accuracy of *the Declaration*; for example, placebos are not equivalent to no treatments. As the possibility of placebo therapies grows, we ought to undo some of the stigma attached to placebo effects. All too often, we think of receiving a placebo as "getting nothing" and that placebo responses are the results of one being gullible or tricked. The mechanisms for placebo effects are as physiologically real as any allopathic treatments. To ensure that placebos can play a contributive role in clinical medicine, it is imperative that we refrain from perpetuating the negative association with placebos. Revising the placebo guidelines in the *Declaration of Helsinki* will go a long way to undo placebos' unwarranted connotation.

Notes

1. Kimmelman J. Better to be in the placebo arm for trials of neurological therapies? *Cell Transplantation* 2018;**27**(4):677–81.
2. Kallmes DF, Comstock BA, Heagerty PJ, Turner JA, Wilson DJ, Diamond TH, et al. A randomized trial of vertebroplasty for osteoporotic spinal fractures. *New England Journal of Medicine* 2009;**361**(6):569–79.
3. Firanescu CE, de Vries J, Lodder P, Venmans A, Schoemaker MC, Smeet AJ, et al. Vertebroplasty versus sham procedure for painful acute osteoporotic vertebral compression fractures (VERTOS IV): Randomised sham controlled clinical trial. *BMJ* 2018;**361**:k1551.
4. Hochmuth K, Proschek D, Schwarz W, Mack M, Kurth AA, Vogl TJ. Percutaneous vertebroplasty in the therapy of osteoporotic vertebral compression fractures: A critical review. *European Radiology* 2006;**16**(5):998.

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