1438

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Inappropriate Use of Placebos in Human Experiments

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Thank you for the opportunity to testify before the committee on the critical issue of inadequate protections for human subjects in clinical trials, specifically the misuse of placebos.

The best place to begin when discussing the ethics of placebo use is with the accepted national and international ethical guidelines. The most commonly cited is the World Medical Association's Declaration of Helsinki, which states unequivocally that "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] While a literal reading of the Declaration might suggest that this precludes placebos altogether, it is commonly assumed that an exemption exists for the use of placebos in situations where no therapy has yet been proved effective or the condition being treated is not serious or life-threatening, like mild pain. Indeed, we do not take exception to the use of placebos per se; at issue here is the use of placebos in situations where an effective treatment for a serious medical problem has already been identified.

Further support for precluding placebo-controlled trials in most cases where effective therapy exists comes from the Nuremberg Code, which holds that "The experiment should be so conducted as to avoid all unnecessary physical and mental

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[1] Declaration of Helsinki IV, 41st World Medical Assembly, Hong Kong, September 1989. In: Annas GJ, Grodin MA, eds. The Nazi doctors and the Nuremberg Code: human rights in human experimentation. New York: Oxford University Press, 1992;339-42.

suffering and injury."[2] Indeed, even federal regulations would seem to preclude placebo-controlled trials after an effective therapy has been identified. Active-controlled trials are to be used "when the condition treated is such that administration of placebo or no treatment would be contrary to the interest of the patient ..."[3] These regulations apply as long as federal funds are utilized, regardless of where the research occurs.

Yet the use of placebo controls in such situations is common. Rothman and Michels have identified a large number of studies using placebos after effective treatment was identified in areas as diverse as rheumatoid arthritis, antidepressants, congestive heart failure, hypertension and onchocerciasis (river blindness).

Placebos for Patients with Hypertension

There are several more recent examples. The results of the Systolic Hypertension in the Elderly (SHEP) study, a placebo-controlled trial of isolated systolic hypertension, a condition where only systolic blood pressure (the top number) is elevated, were published in 1991.[4] The study found that treatment of this condition was superior to placebo. A then ongoing placebo-controlled trial of this condition (Syst-Eur) funded in part by Bayer, the maker of the drug being studied, was not stopped; instead recruitment continued, including patients from Eastern Europe until 4,695 subjects were recruited, half of whom received placebo.[5] In 1997 the results of the study were published, again showing treatment to be superior to placebo. A trial with a very similar design has also taken place in China (Syst-China).[6]

Although it has been known for many years that treatment with at least some

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[2] Trials of war criminals before the Nuremberg Military Tribunals under Control Council Law No. 10, Vol. 2. Washington, DC: U.S. Government Printing Office, 1949.

[3] 21 CFR 314.26(b)(2)(iv) 1991.

[4] SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA 1991;265:3255-64.

[5] Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. Lancet 1997;350:757-64.

[6] Wang JG, Liu G, Wang X, et al. Long-term blood pressure control in older Chinese patients with isolated systolic hypertension: a progress report on the Syst-China trial. J Hum Hypertension 1996;10:735-42.

antihypertensive agents can reduce mortality, the Shanghai Trial of Nifedipine in the Elderly (STONE), partly funded by Bayer, compared the antihypertensive agent nifedipine to placebo for an average of 2.5 years.[7] After studying more than 1,600 Chinese hypertensives, half of whom were randomized to placebo, nifedipine was shown to reduce the number of cardiovascular events by 59%. In all of these studies, except the original SHEP study, an ethical design would have compared the proven treatment to the experimental treatment. Despite preexisting evidence of the need to treat these hypertensive patients, hundreds were unnecessarily exposed to placebos, leading to preventable strokes and cardiac events.

Placebos for Drug Users

Another area where unethical placebo-controlled trials are common is in drug use treatment research. This is facilitated by the paucity of drug treatment facilities in this country; only 15% of drug injectors are estimated to be in treatment on any given day. Some researchers use the lack of available treatment to argue that the placebo does no harm, since the subject would not have received treatment anyway. This is sometimes referred to as the "standard of care argument." We do not believe that it is ethically acceptable to use subjects' social conditions to justify research of this type.

Buprenorphine is a drug being studied for the treatment of heroin and other opiate addiction. We have identified two studies where placebos have been administered to subjects, even though methadone was demonstrated to be effective in treating opiate addiction decades ago. In one such study, funded by the U.S. Public Health Service, a total of 150 subjects were randomized to placebo or one of two doses of buprenorphine.[8] At the midpoint of the two-week trial, the subjects were permitted to request further random assignment to a different study arm. Not surprisingly, the buprenorphine-treated patients were less likely to request random reassignment, were less likely to use illicit opioids and were more satisfied with how well their withdrawal symptoms were controlled than the patients who received placebo. More recently, a study in 12 U.S. hospitals, coordinated by the U.S. government and the buprenorphine manufacturer, Reckitt and Colman, had to be terminated prematurely when buprenorphine again proved substantially superior to placebo.[9] In an ethically designed trial, buprenorphine would have been compared to methadone. Instead, the patients in these trials were unnecessarily forced to endure the extreme discomfort of heroin

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[7] Gong L, Zhang W, Zhu Y, et al. Shanghai trial of nifedipine in the elderly (STONE). J Hypertension 1996;14:1237-45.

[8] Johnson RE, Eissenberg T, Stitzer ML, Strain EC, Liebson IA, Bigelow GE. A placebo controlled clinical trial of buprenorphine as a treatment for opioid dependence. Drug Alcohol Dependence 1995;40:17-25.

[9] Cloud J. A way out for junkies? Time, January 19, 1998, p. 59.

withdrawal.

The Role of Active-controlled Trials

These examples indicate that the problem of the use of placebos when an effective treatment for the condition exists is not only a problem of the violation of accepted ethical guidelines. These trials often do not provide the information that is most useful clinically. A drug treatment professional, for example, is not interested in whether a new treatment is better than nothing. To optimize therapy for a patient, the physician needs to know how the new treatment compares to the older, known effective treatment. These treatments need not be exactly equal in efficacy to be useful; depending on side effect profile, patient characteristics and even cost, the physician may even select the somewhat less effective medication. But trials that compare new treatments to placebo, with predictable results, do not aid physicians in making these decisions.

Active-controlled trials, in contrast, benefit many parties. Experimental subjects benefit by being assured that everyone will receive at least arguably effective treatment. Doctors benefit by learning how competing therapies compare with one another in a controlled trial. Once the medication is approved, patients benefit because doctors can make more informed clinical choices based on the results of these studies. Payers benefit because they can use such data to favor a cheaper, yet equally effective, drug.

As medical knowledge advances, there are increasingly few conditions for which no proven therapy exists. For example, in 1990 and 1991, the last years for which the FDA collected such data, only 27% of the 49 new drugs approved by the FDA represented "important therapeutic gains," including all AIDS drugs. The market is thus being inundated with large numbers of medications that are not substantial advances on their predecessors. Indeed, some involve only minor chemical modifications on a proven medication and are thus known as "me-too" drugs. This makes the role of active-controlled trials all the more important for the future.

The Role of the FDA

If the active-controlled trial for conditions for which known therapy exists is preferable both ethically and clinically, why does the placebo-controlled trial continue to flourish? One reason is that the placebo-controlled trial has become a kind of religion in science, and studies with other designs, no matter how preferable from an ethical, clinical or public health perspective, are subject to criticism for their failure to live up to this "gold standard." While not the only source of the problem, it is clear that FDA policy is seen as a critical driving force behind the use of placebos, both because the agency often requires them for new drug approval, and because the FDA sets a standard for clinical trials that is adopted internationally, even in studies where drug approval is not an issue. Both critics and supporters of the placebo-controlled trial

orthodoxy point to a series of articles by Robert Temple of the FDA as evidence that the FDA heavily favors placebo-controlled trials over active-controlled ones.[10,11,12]

It is ironic, therefore, that neither FDA laws nor regulations actually require placebo-controlled trials for drug approval. Rather, the regulations require "adequate and well-controlled studies," and list five types of acceptable studies: 1. randomized, placebo-controlled trials; 2. dose-response studies; 3. active-controlled studies; 4. no treatment concurrent controlled studies; and 5. historical controls.[13] So new drugs can be approved in the absence of placebo-controlled studies. Indeed, in some divisions of the FDA, active-controlled trials are commonly used as the basis for drug approval. The field of oncology has for years eschewed placebo controls in trials of treatments of cancers for which effective therapy exists. In the past several years, the FDA has approved a number of antibiotics based entirely on equivalency studies, a type of active-controlled trial: trovafloxacin, cefdinir and sparfloxacin. The cardiac drug reteplase was also approved based on active-controlled testing. Yet, because these are exceptions rather than the "rule," the impression persists that the FDA has a strong preference for placebo-controlled studies.

Placebos for HIV-positive Pregnant Women in Developing Countries

We first became involved in this issue when we learned of a series of 15 unethical studies being conducted in Africa and Asia among HIV-positive pregnant women. Despite a well-conducted, placebo-controlled study in which the drug AZT was proved dramatically more effective than placebo,[14] these 15 studies involving more than 17,000 women gave at least some women placebos or other medications not proved effective. The object was to identify a less costly method of administering AZT so that it could be accessible in developing countries where the approximately $800 per course

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[10] Temple R. Problems in interpreting active control equivalence trials. Accountability in Research 1996;4:267-75.

[11] Temple R. Government viewpoint of clinical trials. Drug Info J 1982;16:10-7.

[12] Temple RJ. Special study designs: early escape, enrichment, studies in non-responders. Commun Statist - Theory Meth 1994;23:499-531.

[13] 21 CFR 314.126(b)(2) (1991)

[14] Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. New Engl J Med 1994;331:1173-80.

cost of AZT was out of reach. We suggested that instead of comparing the less expensive AZT treatment regimens to placebo, they could be compared to the already-proven regimen, or one resembling it. But the CDC and the NIH, which were sponsoring or conducting most of the studies, demurred and the known, effective regimen was withheld, with the loss of hundreds of infant lives. Ironically, the NIH also sponsored one active-controlled trial, but this only happened when the director of Harvard University's Institutional Review Board stood up to repeated pressure from the NIH Study Section to instead conduct a placebo-controlled trial by writing to the NIH: "The conduct of a placebo-controlled trial for AZT in pregnant women in Thailand would be unethical and unacceptable, since an active-controlled trial is feasible."[15] In contrast, the CDC conducted its own placebo-controlled trial in Thailand, and even continued it after AZT became so available in Thailand that Thai researchers canceled their own placebo-controlled trial.[16] (Incidentally, the CDC research in Thailand, as well as a companion CDC-sponsored placebo-controlled trial in Cote d'Ivoire, were conducted without the Assurances required for such international research until we criticized the studies.) [17]

The results of CDC's placebo-controlled trial in Thailand were made public in February of this year. Not surprisingly, the less expensive AZT regimen was also dramatically more effective than placebo.[18] Almost two dozen infants were unnecessarily infected with HIV during the trial, public health action was delayed four years while public health officials awaited the results of the trials as 500,000 infants per year were infected internationally, and, because the two AZT regimens were never compared, we still don't know whether the two regimens are equally effective. Interestingly, the CDC investigators in Cote d'Ivoire seem to have little question that the alternative AZT regimen would prove more effective than placebo. In their protocol, the investigators state that "This [AZT] study is proposed in the belief that short-course oral therapy may be as effective or nearly as effective as the [more expensive AZT] regimen."[19] This "belief" should have led to an active-controlled study, not a

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[15] Brennan T. Letter to Gilbert Meier, Division of Research Ethics, NIH, December 28, 1994.

[16] Phanupak P. Ethical issues in studies in Thailand of the vertical transmission of HIV. New Engl J Med 1998;338:834-5.

[17] Shalala DE. Letter to Sidney M. Wolfe, Director, Public Citizen's Health Research Group, July 15, 1997.

[18] Centers for Disease Control and Prevention. Administration of zidovudine during late pregnancy and delivery to prevent perinatal HIV transmission--Thailand, 1996-1998. MMWR 1998;47:151-4.

[19] CDC/Thailand study protocol, January 15, 1996

placebo-controlled trial.

Criticisms of Active-controlled Trials

Before suggesting a solution to this problem, we would like to briefly address two common criticisms of active-controlled trials raised by the FDA and others. The first is that incentives for optimally conducting research are reduced in active-controlled trials, because any sloppiness in conducting the trial will obscure true differences between the therapies being compared. But in an active-controlled equivalency study, the kind we advocated in the AZT studies, the researcher has to prove that the two therapies are approximately the same (the "alternative" and "null" hypotheses are reversed); any sloppiness will lead to a conclusion that the therapies are not equivalent, the opposite of what the researcher is attempting to demonstrate. Second, it is alleged that active-controlled studies do not have established statistical techniques and lead to larger sample sizes than placebo-controlled studies. But appropriate statistical techniques do exist (indeed, the FDA has an entire group of statisticians devoted exclusively to equivalency studies) and the required sample sizes are often quite similar to those needed for placebo-controlled studies. For example, in the AZT studies we calculated that an equivalency study would require 620 subjects, compared to 500 for a placebo-controlled study, not a substantial difference in the world of sample size calculations.

Patients are being ill-served by the rigid adherence to the placebo-controlled dogma. Subjects are being placed at risk needlessly and doctors are denied the information they need to make decisions that are in the best interests of their patients. Furthermore, medications are coming on the market simply on the basis of their being proved better than nothing, regardless of their effectiveness relative to established therapies. As "me-too" drugs continue to flood the market, Americans need to know how these medications compare to one another, not simply if they are superior to placebo, a much weaker standard.

Legislation to Reduce the Number of Placebo-controlled Trials

Because the FDA so heavily favors placebo-controlled trials, even though existing regulations permit FDA approval based on active-controlled trials, manufacturers, acting in their own self-interest, will continue to sponsor inappropriate studies with placebos. There is little question that most drug companies would rather demonstrate that their drug is better than nothing than take the chance that it may be no better--possibly worse--than the existing treatment. And once a drug is approved using the weaker "better than nothing" standard, there is little the FDA can do to require companies to conduct comparative studies. So active-controlled studies languish as the poor cousins of the clinical trials family, despite their obvious benefits. Some

countries have required pharmaceutical manufacturers to go beyond the mere demonstration of drug safety and efficacy. Norway and Iceland have required data on comparative safety and efficacy. What is needed now is legislative action by the Congress to require active-controlled studies when a known effective therapy exists. In the absence of such action, the FDA will continue its role as one of the major enforcers of the placebo-controlled orthodoxy and subjects, patients, doctors and insurers will continue to pay the price.