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Placebo-Controlled Trials of New Drugs: Ethical Considerations

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Much controversy exists regarding the ethics of placebo-controlled trials in which an experimental therapy will compete with an already established treatment (or treatments). In such cases, argue critics, patients in the control arm of the study should receive an accepted therapy rather than a placebo. By using an active and effective drug, the control patients would not be placed at risk for deterioration of their disease, and the study would generate more meaningful results for physicians. The key question, it is said, is not whether a new therapy is better than nothing but whether it is better than the current standard of care (1,2).

In response, say proponents of placebo-controlled trials, critical information cannot always be obtained by giving control patients an existing therapy. For some effective therapies, the drug may perform no better than placebo in a particular trial even though other trials demonstrate the drug's superiority to placebo. If an experimental agent confers the same benefit as such an existing therapy in a comparative trial, we cannot be certain that the new agent is any better than placebo. We might have one of the trials in which the existing therapy (and therefore the new agent) does no better than placebo, perhaps because of inadequate sample size, perhaps because the outcome measure can vary widely from one patient group to another (3–5). In addition, some new therapies are useful even if they are less effective than existing therapies. Some patients might choose a less effective drug if substantial cost savings or a reduction in side effects would be realized (6). Without a placebo control, however, one cannot always tell whether a new drug that is not as effective as existing therapy is still

sufficiently more effective than placebo to justify its use. Finally, not all established therapies have been shown to be superior to placebo. If newer drugs are compared with the unproven existing therapies, then patients may continue to receive drugs that are harmful without being helpful.

Moreover, say proponents of placebo controls, patients can be protected from harm by “escape” criteria, which call for withdrawal from the trial if the patient shows evidence of inadequately controlled disease (5). Other changes in study design can also be used to minimize the risk to patients from exposure to placebos (7).

Yet for all of the controversy over placebo-controlled studies, the amount of agreement may be greater than the amount of disagreement. For many studies, people on both sides of the issue would agree that a placebo control is either necessary or unacceptable. It is only in a fairly limited area of concern in which commenters part ways.

Thus, for example, opponents of placebo-controlled trials recognize that placebo controls are justified for “first-generation” drugs—drugs designed to fill a gap in the therapeutic armamentarium. Relatedly, placebo controls are often justified when there is not adequate evidence to support the efficacy of existing therapy.

Just as opponents of placebo controls accept some uses of placebos, proponents of placebo controls support some limits on placebo-controlled trials. Basic principles of medical ethics tell us that clinical studies can go forward only if the expected benefits sufficiently outweigh the expected risks. Accordingly, acknowledge the proponents of placebo-controlled tri-

als, placebo controls are not appropriate when patients' health would be placed at significant risk (8–10). A placebo-controlled study for a new hair-thickening agent could be justified; a placebo-controlled study for patients with moderate or severe hypertension would not be acceptable (11). Similarly, if an illness causes problems when it goes untreated for a long period of time, a 52-week study with a placebo control is much more difficult to justify than a 6-week study (12).

When David S.H. Bell (13) explains why placebo controls are unacceptable for new drugs to treat type 2 diabetes, he makes arguments that would resonate with proponents as well as opponents of placebo controls. As he observes, patients in a placebo arm of a study could go 6 months without effective therapy and thereby suffer significant and irreversible harm.

Still, the very fact that Bell has written his letter points to a serious concern with placebo-controlled trials. Apparently, many are conducted even though they cannot be justified in terms of widely shared views about the ethical appropriateness of such trials (2).

There are probably multiple reasons for the overuse of placebo controls. Pharmaceutical companies may believe it is in their interest to compare new drugs with placebo rather than existing therapy, even when better information for patients and physicians would be provided by an active control. There also appears to be some misunderstanding of the U.S. Food and Drug Administration's (FDA's) position on the need for placebo controls and/or some overly aggressive requiring of placebo-controlled studies by the FDA. Whether the FDA is truly at fault is not always obvious. One article, for example, criticized the FDA for demanding a placebo-controlled trial of a new anti-anginal drug, despite a study demonstrating that the drug was comparable to propranolol as an anti-anginal agent (2). According to the FDA, however, the problem with the study was not necessarily its failure to use a placebo arm. Rather, the study design was defective because it left open the possibility that neither the new drug nor pro-

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Abbreviations: FDA, U.S. Food and Drug Administration; IRB, institutional review board.

pranolol was more effective than placebo in that particular trial (8).

Where do we go from here? Undoubtedly, study sponsors and investigators need to improve their understanding of the extent to which placebo controls have a role in clinical trials. Some studies with a placebo control should have an active control instead; other studies with only an active control also need an arm with a placebo control.

In addition, institutional review boards (IRBs) need to demand more of study investigators who submit proposals for trials of new drugs. If a placebo arm is included for a drug that will compete with an established treatment, the study protocol must supply a persuasive justification for using a placebo control (2). Similarly, if a placebo arm is not included, there must be assurances that the study is designed to avoid the possibility that the new and active drugs show equal effectiveness but that neither drug would be more effective than placebo in that study. IRBs, in other words, must approach studies of new drugs more skeptically and approve studies only when they have enough information to make an independent judgment about the desirability or undesirability of a placebo control.

In providing the information necessary to justify a placebo control, the study's investigators would have to explain why adequate results could not be obtained by comparing the study drug with an existing therapy in a well-designed study with ample subjects, or why adequate results could not be obtained by using the study drug plus existing therapy in one arm and the existing therapy plus placebo in the other arm. Similarly, when a placebo arm is justified, study investigators would need to explain why the study does not also include a third arm with existing therapy.

In some cases, investigators will observe that costs are a consideration in us-

ing placebo controls, that a placebo-controlled study can often be completed with fewer subjects and in a shorter period of time (14). Costs are not irrelevant—more expensive studies may mean fewer desirable studies—but arguments about costs cannot be accepted automatically. If an IRB is to make judgments on cost grounds, the board would need specific information about the costs of the proposed and alternative studies. Indeed, as a general matter, common arguments in favor of placebo controls are not adequate to justify a particular use of a placebo control. Rather, the arguments would have to be based on the specifics of the study in question.

In deciding whether study investigators have persuasive justification for including or excluding a placebo control, IRBs should rely on one of the federal government's basic requirements for medical research, a requirement that is too often overlooked. According to regulations for the "Protection of Human Subjects," not only must studies have a favorable benefit-to-risk ratio, but they must be designed so as to have the most favorable benefit-to-risk ratio possible. In the language of the regulations, an IRB shall not approve a study unless it is satisfied that the "[r]isks to subjects are minimized" (15). In other words, it is not sufficient to demonstrate relatively low risk; it is also necessary to demonstrate that risks have been made as low as possible given the potential benefits at stake. Thus, if the same benefits as the proposed study can be obtained from a different study and the different study would pose less risk to the subjects, the IRB must reject the proposed study. Likewise, if two studies pose the same risks but one study offers greater benefit, the study with less benefit should not be approved. With this requirement as a guide, IRBs can further refine their inquiry and better distinguish acceptable studies from those that are unacceptable.

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