board. Shared decision making must be a centerpiece of this process. The Declaration of Helsinki, which states that placebo trials are permissible when no major harm could be expected to come to trial participants as a result of delaying treatment, remains a major guideline for investigators. With the use of appropriate guidelines to exclude high-risk patients, placebo-controlled trials of osteoporosis treatments can benefit some patients and can inform investigators and the health care profession in a safe, transparent, and scientific manner.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Maine Medical Center Research Institute, Scarborough (C.J.R.); and the College of Medicine, Mayo Clinic, Rochester, MN (S.K.).


Recent large, randomized, controlled trials indicate that newer therapies for osteoporosis — denosumab,1 tibolone,2 zoledronic acid,3,4 teriparatide,5 strontium ranelate,6 and lasofoxifene7 — significantly decrease the risk of fracture as compared with placebo. At the time of these trials, standard guidelines recommended that pharmacotherapy be administered in patients with osteoporosis,8 since placebo-controlled trials had demonstrated that available drugs, such as bisphosphonates,9,10 reduced the risk of fracture by approximately 40 to 50% relative to placebo.11,12 There is general agreement that placebo-controlled trials are unethical when a therapy that decreases the risk of serious complications or death is available,13-16 which suggests to us that careful review of the ethics of using placebo controls in trials with fracture end points in patients with osteoporosis is indicated.17-21 We and others14,22,23 have identified a number arguments that could support the use of a placebo in trials. We discuss these with respect to osteoporosis trials with fracture end points.

Many believe that it is ethical to withhold an effective treatment when adverse consequences are minor or rare. However, osteoporotic hip and vertebral fractures have serious consequences, including increased risk of death, surgical procedures, and long-term impairment of physical function.24,25

The Ethics of Placebo in Studies with Fracture End Points in Osteoporosis

C. Michael Stein, M.B., Ch.B., and Wayne A. Ray, Ph.D.

This article presents one viewpoint on the issues surrounding placebo-controlled trials in osteoporosis. The other Sounding Board article in this issue presents an opposing view. At NEJM.org, in a related interactive feature, the authors of each article give their Point of View about the other article.

At NEJM.org, readers can participate in forming community opinion by choosing one of the viewpoints and, if they like, providing their reasons.
The risk of fracture in women with untreated osteoporosis is substantial, even when those at highest risk are excluded from studies. In one study, 7.2% and 1.2% of women receiving placebo had new vertebral fractures and hip fractures, respectively, as compared with 2.3% and 0.7%, respectively, in the active-treatment group.1 The common practice of excluding patients with the highest risk of fracture from placebo-controlled trials does not resolve concerns about adverse outcomes in patients receiving placebo, but rather, in our view, implicitly acknowledges that untreated osteoporosis carries a risk of clinically important consequences that available treatments can reduce.

One possible justification for contemporary osteoporosis trials is that almost all patients receive calcium and vitamin D. However, review of the available data indicates that calcium alone and calcium and vitamin D have limited efficacy, at best2; a recent meta-analysis reported a 12% reduction in the risk of fractures with calcium or the combination of calcium and vitamin D as compared with placebo.26 Indeed, the benefits of proven osteoporosis therapies have been shown relative to patients taking these supplements.10,27 Adding placebo or an active drug to a baseline drug regimen that is suboptimal does not resolve the ethical concern.

The ethics of performing placebo-controlled studies in countries or regions in which a proven effective therapy is not available are debated.28,29 In countries or regions in which standard therapies are available, the same argument may be raised for patients unable to afford these standard drugs, since some patients might receive an effective therapy in a placebo-controlled trial. Would a placebo-controlled study that would be considered unethical in patients with access to standard treatment be ethical in those without access? Such a trial could not include any patients who could afford recommended therapy, since a trial must be ethical for all its participants. In addition, ethical guidelines mandate that extreme caution be used in studies in which a patient’s vulnerability becomes an incentive for participation.30-32 Thus, in countries in which standard therapy is available, specifically enrolling patients who do not have access to such therapy into a study in which it will in fact be withheld from some would nearly always be unacceptable.

Regulatory authorities require the demonstration of efficacy and safety of a new drug in well-controlled trials,33 with preference given in general to placebo control because this is almost always the most scientifically rigorous and economical design. However, as effective treatments are identified and the consequences of untreated disease defined over time, previously accepted study designs may become unethical, despite their scientific efficiency. For example, once placebo-controlled studies showed that treatment of mild hypertension decreased the risk of cardiovascular events, long-term, placebo-controlled clinical trials of patients with established hypertension were no longer considered ethical.34

Ethical guidelines for research emphasize minimizing risks and protecting the individual patient, rather than obtaining benefits for society at the cost of serious preventable harm to some.15,16,32 Many volunteers participate in studies that have associated risks and that do not provide personal benefit but do provide societal benefit. However, patients are generally not asked to forgo proven effective therapy and to deliberately place themselves at risk of a serious or irreversible event that is the study end point.

Institutional review boards (IRBs) and other committees provide important ethical oversight, but their approval does not necessarily make a study ethical.35 IRB members are seldom as expert in a clinical area as the investigators performing the study; thus IRB members may be swayed by precedent and the researchers’ assertions that a particular placebo-controlled trial is ethical. However, some IRBs may be beginning to question the ethics of placebo-controlled studies of fracture in patients with osteoporosis.1-2

Although written informed consent is almost always necessary for a clinical trial to be ethical, it is not sufficient.16 A study must be deemed ethical before enrollment is offered to potential participants. Thus, the ability to obtain consent does not automatically make a trial ethical.16

Could a trial that requested fully informed patients to forgo the proven benefits of long-term treatment for the benefit of society ever be ethical? Although such a study would have some parallels with investigations involving altruistic volunteers, it would raise many difficult questions. If this approach were ever appropriate, it would only be in extremely unusual circumstances that we do not believe are present for
osteoporosis studies. Such trials would require extraordinary measures to ensure that patients fully understood the risks to which they would be exposed and to ascertain that patients were not unduly influenced by their physicians or the sponsors of the trial.

Several alternative designs have been considered for placebo-controlled studies of fracture in patients with osteoporosis. These include trials of patients with osteopenia, for whom therapy is not currently indicated; add-on study designs, in which a placebo or new drug is added to the best available therapy; and trials with “informed refusal,” in which patients have either refused currently available therapies, cannot tolerate them, or did not benefit from them.

These alternative designs all have inherent limitations. It may not be valid to extrapolate findings in patients with osteopenia to those with osteoporosis. Add-on trials may have limited clinical relevance. Informed-refusal trials often involve investigators who have an inherent conflict of interest, because the same clinician who advises the patient about currently approved and available therapy may recruit them for a trial that requires refusal of such therapy. Resolving such a conflict could include the use of clinicians not directly involved with the study and without a conflict of interest; such a person would determine the reasons for refusal of standard therapies and obtain informed consent from the patient that demonstrates explicit understanding of the risks of withholding standard therapies. Oversight from third parties about the quality of the informed consent in a sample of study patients would also be needed. Informed-refusal trials may face greater logistic difficulties than other trials in recruiting patients and maintaining adherence, because the participant pool consists of patients who already have been unable or unwilling to take recommended therapies.

Thus, these alternative-design placebo-controlled trials often will not be feasible. Studies comparing a new drug with an active control generally will be required, even though such trials are more complex and expensive, usually require larger sample sizes, and have more methodologic complexities than placebo-controlled trials. However, these challenges should not be considered an ethical justification for administering placebo to some patients, which would result in potentially preventable fractures. Furthermore, trials involving active comparison drugs would also provide comparative effectiveness and safety information that is key to rational therapy.

In summary, because several drugs that materially decrease the risk of fractures in patients with osteoporosis are currently available, we believe that placebo-controlled studies with fracture end points in patients with osteoporosis will nearly always be unethical. Such trials cannot be justified by regulatory preferences for placebo-controlled studies, the approval of local IRBs, or informed consent from the participants. Study sponsors and investigators, regulatory authorities, and medical journals must work to ensure that trials with fracture end points in patients with osteoporosis are ethical.

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From the Department of Medicine, Divisions of Clinical Pharmacology and Rheumatology (C.M.S.), and the Department of Preventive Medicine, Division of Pharmacoepidemiology (W.A.R.), Vanderbilt University School of Medicine, Nashville.

11. Stevenson M, Jones ML, De Nigris E, Brewer N, Davis S,

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