Journal of Clinical Densitometry, vol. 9, no. 3, 274–280, 2006

1094-6950/06/9:274–280/$32.00
DOI: 10.1016/j.jocd.2006.04.001

Original Article

Is It Ethical to Use Placebos in Osteoporosis Trials?

Sergio Ragi-Eis,[1] Cristiano A. F. Zerbini,[2] José R. Provenza,[3] Luiz H. M. Griz,[4] Luiz H. de Gregório,[5] Luis A. T. Russo,[5] Nilzio A. Silva,[6] João L. C. Borges,[7] Antonio C. A. de Souza,[8] Marize L. Castro,[9] and E. Michael Lewiecki[10]*

[1]*Osteoporosis Diagnosis and Research Center of Espírito Santo, CEDOES, Vitória-ES, Brazil;*
[2]*CEPIC, Hospital Heliópolis, São Paulo, Brazil;* [3]*Pontifícia Universidade Católica de Campinas, São Paulo, Brazil;*
[4]*Universidade de Pernambuco, Recife-PE, Brazil;* [5]*Center for Clinical Research, Rio de Janeiro, Brazil;*
[6]*Faculdade de Medicina da Universidade Federal de Goiás, Goiânia-GO, Brazil;* [7]*Catholic University of Brasília-DF, Brazil;* [8]*PUC RS, Brazil;* [9]*Universidade Federal de São Paulo, São Paulo, Brazil; and*
[10]*New Mexico Clinical Research & Osteoporosis Center, Albuquerque, NM*

Abstract

The use of placebo control groups (e.g., subjects using calcium and vitamin D) in osteoporosis trials with subjects at high risk for fracture has been systematically questioned by institutional review boards (IRBs). Regulatory agencies, on the other hand, continue to not only recommend but also require that placebo-controlled trials be presented for the registration of new drugs for osteoporosis treatment. The Declaration of Helsinki and its updates have upheld the principle that protection of research subjects' rights is of primary concern. Nevertheless, even the Declaration keeps clearly opening the possibility of using placebo-control designs if it is justified for ''compelling and scientifically sound methodological reasons.'' The use of intermediary endpoints or surrogates to establish the efficacy or safety of new medications in the management of osteoporosis is currently considered scientifically insufficient. This concept has led regulatory agencies, such as the Food and Drug Administration in the United States and the European Medicines Agency in the European Union, to require ''fragility fracture reduction'' as the primary endpoint in clinical trials for the registration of new drugs. Superiority or noninferiority trials are alternatives to placebo-controlled designs. However, factors such as sample size, cost, and statistical limitations render these models impractical for the registration of new medications for osteoporosis. We recommend collaboration among regulatory agencies, IRBs, scientists, and ethicists on the design of clinical trials for the registration of new medications for reduction of fracture risk. Delay in developing mutually acceptable models may impair scientific development in the field and possibly deprive patients of potentially beneficial treatments.

Key Words: Clinical trials; control; drug studies; ethics; fracture; osteoporosis; placebo.

Introduction

With the growth of requirements for scientific evidence for the registration of drugs by institutions such as the Food and Drug Administration (FDA) in the United States and the European Medicines Agency in the European Union, the last decades have been characterized by an increase in investments in clinical research sponsored by pharmaceutical companies (Fig. 1). This trend has initiated new debates on the ethics of placebo-controlled trials (PCTs), necessitating careful consideration by all stakeholders in the research process.

Ethical issues were addressed by the Declaration of Helsinki (Declaration), which was adopted during the 18th World Medical Assembly in 1964 *(1)*. The Declaration determined that medical research involving human subjects must conform to generally accepted scientific principles based on a thorough

Received 02/07/06; Revised 04/03/06; Accepted 04/03/06.
*Address correspondence to: Sergio Ragi-Eis MD, CCD, Osteoporosis Diagnosis and Research Center of Espírito Santo, Rua João da Silva Abreu 78 Praia do Canto, Vitória (ES) 29055.450, Brazil. E-mail: seragi@cedoes.com/br

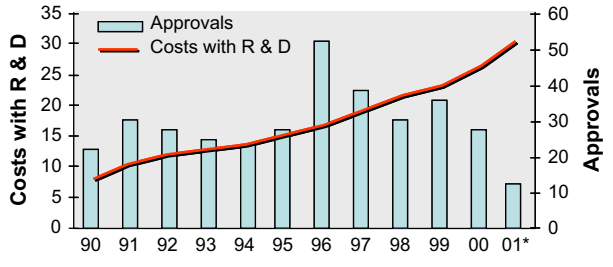

Fig. 1. The Federal Drug Administration approvals in the United States (estimated data from 2001) *(28)*.

knowledge of the medical literature, other relevant sources of information, adequate laboratory testing, and when appropriate, animal experimentation. During its development, the Declaration was revised five times. Amendments such as the following were included: ''Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.''

Several statements in the Declaration *(1)* affirm basic principles of morality and ethics in medicine, but the same statements, in certain circumstances, may create conflicts between the needs of science, society, and individuals. For example, the Declaration states: ''In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.''

Differences in social, economic, cultural, and religious perspectives may create important differences in ethical judgments when the well-being of the individuals and the interests of the society are considered. In many countries, societal interests have precedence over individual rights. In these countries, laws are written and resources, including resources for healthcare systems, are often allocated according to this premise. The approval and availability of generic versions of medications, frequently without bioequivalence and bioavailability data *(2)*, may result in cost savings for healthcare systems, while not necessarily being safe and efficacious for individuals. In some countries, individual autonomy is not the norm. In Turkey, for example, the smallest unit of society that can function as an autonomous entity is the family *(3)*. In such cultures, governmental paternalism does not have a negative connotation, as it may in the United States and some other countries. The balance, and tension, between the welfare of society and the individual are considerations in Western ethics and are well understood in medical care. The diversity of culture, religion, and value systems in many countries renders most broad ethical statements unacceptable. It is perhaps for these reasons that the notion of ''collective autonomy'' *(3,4)* or ''collective consent'' has been proposed, which requires respect and consideration of previous experience, beliefs, and traditions *(3)*. It is likely that as long as social, economic, cultural, and faith-based differences remain, we will continue to have conflicts between individual autonomy and the needs of society.

The Declaration was rightfully established to prevent the abuses of patients that occurred in the name of *research* during World War II and the years thereafter. Since that time, the rapidity and breadth of scientific communication, and the level of peer review, have undergone tremendous changes. Several attempts to modify the Declaration to be more compatible with the milieu of modern medical research have been rejected *(5,6)*. Although rules to protect patients participating in clinical trials are clearly necessary, blind adherence to all rules may sometimes obscure the true ethical issues and could ultimately impair the development of useful new drugs or procedures, to the detriment of all.

Clinical trials in osteoporosis started after the scientific recognition (in the early 1980s) that osteoporosis is a disease, not just a radiological finding. Since then, the scientific definition for this disease has been evolving. Prior to 1995, it was necessary for a bone fragility fracture to occur before osteoporosis could be diagnosed. This diagnostic approach was far from ideal. With the development of methods for bone mass measurement and other potential surrogates of bone strength, it became possible to stratify populations according to risk levels. Bone mineral density (BMD) testing allowed a diagnosis of osteoporosis to be made before a fracture occurred. Today, although BMD testing remains the best clinical tool for osteoporosis management, other qualitative parameters of the bone tissue have grown in importance. In addition, some clinical risk factors, such as smoking, the presence of prevalent fragility fracture, and glucocorticoid use are being evaluated and validated in large populations.

The first medications developed for osteoporosis received their regulatory approval after being tested in clinical trials in the 1980s and early 1990s. These trials showed changes in BMD and sometimes reported biochemical, clinical, and quality-of-life data. Drugs such as estrogens *(7)*, fluorides *(8)*, and calcitonin *(9)* were tested using the valid research models at that time with comparisons of those drugs to a placebo (no medication at all or calcium and vitamin D). With advances in scientific knowledge about osteoporosis, it became clear that surrogates of bone strength such as BMD and bone turnover markers did not always translate directly and consistently to fracture risk reduction *(10)*.

Furthermore, these surrogates sometimes obscured other risks, depending on the model used *(11)*. This led to scientific organizations and regulatory agencies requiring demonstration of the ability of new drugs to reduce fracture risk, the ultimate consequence of osteoporosis, as proof of efficacy. Now, fracture risk reduction must be demonstrated to obtain approval and registration for the treatment of osteoporosis *(12)*.

In recent years, researchers have confirmed the effectiveness of calcium and vitamin D (i.e., the placebo in most osteoporosis studies) to not only improve intermediary parameters of bone strength (e.g., BMD), but also to reduce fracture risk *(13)*. These findings are important because they allowed

placebo-controlled fracture studies to continue with the knowledge that the placebo-treated patients were likely receiving benefit in terms of fracture risk reduction. Studies that include placebo groups, nevertheless, are covered by the Declaration *(1)* in its 29th article (Fig. 2), as well as in the notes from the last revision, which are reproduced as follows. As a consequence, the ethics of PCTs with fractures as a primary endpoint are questioned, leading to contradictory opinions about the use of placebo groups for the approval of new drugs or new indications for older ones.

In this article, we discuss the rationale as well as positive and negative aspects of PCTs in osteoporosis.

Rationale of PCTs and Alternatives to This Model

The objective of clinical trials is to determine whether the investigated treatment is effective and safe for the proposed use. The effectiveness can be demonstrated in several ways. The most common way is to conduct a PCT in which the subjects are randomized to receive the new treatment or placebo. Then, the results obtained in both groups are compared to determine whether the new treatment is more effective than the placebo, and furthermore, whether it has an acceptable safety profile that is proportional to the benefit.

As an alternative to this model, trials can be designed to determine whether a new drug is more effective than an existing treatment with a similar safety profile. This is called a *superiority* trail. A third option is to design a trail to determine whether the new drug has approximately the same level of effectiveness as an existing option. This approach, called a *noninferiority* trial (or *equivalency* trial, according to the criteria used for statistical comparison), is different from the previous two, and not applicable in all situations. Trials that compare drugs are intuitively attractive because all patients receive active treatments, thereby avoiding placebo-related ethical issues. However, many new treatments are not intended to have superior efficacy when compared with the existing ones. Some are developed for other potential advantages, such as improved toxicity profiles, more favorable methods of administration, more convenient dosing, more comfortable and desirable formulations, extra-skeletal effects, or other secondary benefits. For these reasons, non-inferiority trials are often inadequate to support conclusions that the new medication is effective and safe. Moreover, the required sample size in each of the studies previously mentioned is different (Table 1). The number of individuals needed to be involved in equivalence or noninferiority studies for fracture reduction would be from 25,000 to 75,000 subjects to achieve statistical significance and to guarantee the applicability of the results.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.*

***Note of clarification on paragraph 29 of the WMA Declaration of Helsinki**

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or ther apeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

Fig. 2. Paragraph 29 of the WMA Declaration of Helsinki and related notes and clarifications.

The FDA and the majority of drug regulatory agencies in the world still maintain clear requirements and recommendations that PCTs with fractures as a primary endpoint be conducted to register new drugs for the treatment of osteoporosis. The justification for continuing to use PCTs includes the following: *(1)* the informed consent clearly states that the placebo will be used in the study and that effective treatments are available; *(2)* subjects are not exposed to permanent risks and limitations or death; and *(3)* the comparison of a new intervention with another one, without the use of a placebo group, may not lead to a clear interpretation of the data *(14)*.

According to the Council for International Organizations of Medical Sciences, a World Health Organization institution, placebo use in clinical trials can be ethical as a comparator in the following circumstances: (1) when there is no established effective intervention; (2) when withholding effective intervention would expose to, at most, temporary discomfort or delay in relief of symptoms; (3) when the use of an established effective treatment as a comparator would not yield scientifically reliable results and a placebo would not add any risk of serious or irreversible harm; in mild conditions (i.e., baldness, smoking cessation, overweight, headache, allergic reactions, mild elevation of cholesterol/blood pressure, and so forth); (4) if the use of the active comparator is unreliable because there is no proven efficacy or scientific proof; the treatment response in condition may vary or spontaneous improvement is high; the treatment response is modest (i.e., almost the same as the placebo); or the study yields no reliable scientific result and thus it is unethical.

Clinical trials with a placebo should include safety measures based on rigid principles. Article 17 in the Declaration states: ''Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results'' *(1)*. Thus, specific criteria could be used, based on intermediary surrogates, to detect unacceptable risks for each particular subject to determine the adoption of safety procedures (e.g., introducing an approved medication, moving the subject from one arm of the study to the other, or in some situations discontinuing the participation of the subject).

Methodological designs and regulatory requirements should not overshadow ethical principles, but rejecting all

Table 1
Sample Scenarios with and without Placebo Control Group (Modified from Reference 14)

Study 1:	New treatment: expected response (fracture reduction) 50% Existing treatment: expected response (fracture reduction) 50% 12,500 vs 12,500 patients are needed to prove equivalency or noninferiority (12,500 subjects exposed to the new agent)
Study 2:	New treatment: expected response (fracture reduction) 50% Placebo group: expected response (fracture reduction) 25% 3500 vs 3500 patients are needed to prove efficacy and safety (3500 subjects exposed to the new agent)

Note: Which design seems to me more ethical, taking the context of this article into consideration?

osteoporosis PCTs may create a conflict with certain realities *(15)*. The publication of the National Osteoporosis Risk Assessment study data *(16)* and data collected and published by the International Osteoporosis Foundation *(17)* has made it clear that in the *real world* of clinical practice, the majority of individuals who could benefit from osteoporosis treatment do not receive any treatment. As a consequence, it may be stated that for these patients, participation in a placebo arm of a controlled study (i.e., receiving calcium and vitamin D) is far better than receiving no treatment by participating in the trial. In addition, patients who take part in clinical trials, once they are sufficiently informed about the availability of effective and approved drugs for treating osteoporosis, may do so for both altruistic reasons and to receive high-quality medical care.

The clinical utility and societal benefit of PCTs is illustrated by the Women's Health Initiative (WHI) study *(18)* comparing postmenopausal women using hormone therapy with women using a placebo. This study was prematurely terminated when an increased risk of cerebrovascular disease, venous thromboembolism, and breast cancer was found in the treated group. As a consequence, despite decades of using estrogen therapy for primary prevention of cardiovascular disease and other disorders, based on the evidence of numerous observational studies, clinicians have dramatically changed their use of estrogens in postmenopausal women.

Recently, strong criticisms have been directed to the FDA regarding safety issues with the drug rofecoxib *(19)*. The majority of the trials done with this medication, including the registration trials, were conducted by comparing rofecoxib with other active drugs, such as ibuprofen and naproxen. In these studies, an increase of cardiovascular risk was not detected. Nevertheless, when a PCT was used to evaluate its safety, cardiovascular adverse events were identified. Some experts have stated that if PCTs had been required for its approval, the risks would have been revealed earlier and perhaps some deaths could have been avoided *(20)*.

The Question of the "Best Available Treatment"

There are substantial differences of opinion among medical specialists as to which drug should be considered the "best available treatment" for the majority of patients with osteoporosis. Calcium and vitamin D have been used in osteoporosis phase 3 trials for years. In the majority of these studies, the patients included in placebo arms (i.e., treated with calcium and vitamin D only) maintained or gained small amounts of BMD during the trial period. This phenomenon has been associated with a decreased fracture risk compared with groups with no treatment *(21–23)* (Fig. 3).

In a meta-analysis of 15 studies *(24)* in postmenopausal women who were randomized to receive calcium supplementation or only the usual dietary intake, calcium supplementation reduced the bone loss in the lumbar spine, hip, and total body. The risks of vertebral and nonvertebral fractures were also reduced. In a 3-year intervention study in a community of elderly people, a reduction of 16% in the incidence of fractures was found among men and women that had received calcium and vitamin D supplementation *(25)*. Daily treatment, with 500 mg of calcium and 700 IU of vitamin D for elderly individuals with an average age of 71, significantly reduced the total number of vertebral fractures *(21)*. Currently, calcium and vitamin D supplementation is considered to be the standard treatment for patients with osteoporosis, even though few patients are currently receiving appropriate supplementation. In two recent studies published in the United Kingdom, calcium and vitamin D supplementation *(26,27)* did not reduce fracture risk compared with no supplementation in postmenopausal women treated for a mean time of 2 years. Unfortunately, in these studies, adherence to therapy

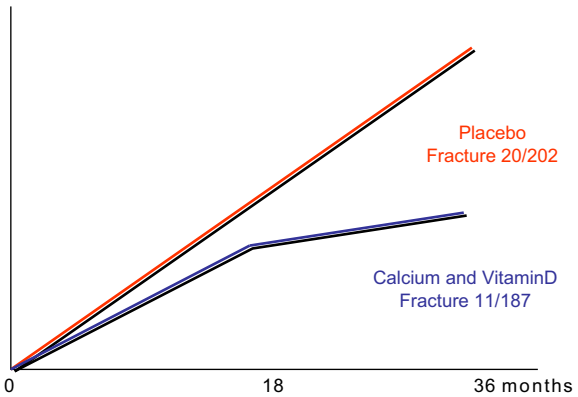

Fig. 3. Modified from reference 21 showing the cumulative fracture reduction, with the use of calcium and vitamin D, when compared with a placebo group.

was poor. Adherence declined to approximately 50-60% after 2 years and might have been as low as 45% when nonresponders to the study questionnaire were included. These studies have the same limitation of most previous studies, in that serum 25-hydroxyvitamin D (25-OH-D) was measured in only a small subset of the entire sample. Thus, the vitamin D status of the trial population at baseline remains largely unknown. Another confounding variable may be fall risk. All participants were educated on measures to limit the risk of falling. This advice was apparently successful, because the fracture rates were significantly lower than those expected for all the participants, including those receiving no supplementation, in both studies. These studies illustrate that this kind of supplementation may sometimes be associated with adverse events and seem to be more beneficial when used in individuals with baseline deficiency or insufficiency of calcium and vitamin D. It is now recognized that in patients with postmenopausal osteoporosis, the prevalence of insufficiency and deficiency of vitamin D is substantial *(29)*. Almost all individuals hospitalized with nontraumatic fractures are vitamin D insufficient as assessed by their serum 25-OH-D levels *(30)*. The benefits of calcium and vitamin D supplementation were recently reaffirmed in the WHI study, which showed a significant increase in hip BMD in the entire study population, and a reduction in hip fracture risk in women who were adherent to therapy, women age 60 and older, and women taking estrogen *(31)*.

A meta-analysis *(32)* of fracture studies with calcitonin, raloxifene, and hormone replacement therapy (Table 2), all comparing treatment with drug plus calcium and vitamin D to treatment with calcium and vitamin D only, showed decreases in vertebral fracture risk that were similar to those obtained by calcium and vitamin D users when compared with ''true placebo'' groups (i.e., subjects taking no medication or supplements at all). Since the populations, ages, fracture prevalence, and BMD at baseline in the trials were different, no comparison of efficacy can be made based on these data. In addition, some drugs were not tested or did not include enough subjects to prove their efficacy for reducing the risk of nonvertebral fractures. Considering the scientific evidence at this point, it is very difficult to identify the best available treatment.

The Methodological Problem

Alternatives to PCTs have been sought in recent years, but so far, none have been found. Not all therapies are appropriate for all patients. The results of each therapy are different

Table 2
Meta-Analysis of Clinical Trials for the Treatment of Osteoporosis *(26)*

Intervention	No. of trials/patients	Relative risk of vertebral fractures (95% CI)	Relative risk *p* value
Vertebral fractures			
Calcium	5 (576)	0.77 (0.54−1.09)	0.14
Calcium and Vitamin D	8 (1130)	0.63 (0.45−0.88)	<0.01
Alendronate (5−40 mg)	8 (9360)	0.52 (0.43−0.65)	<0.01
Etidronate (400 mg)	9 (1076)	0.63 (0.44−0.92)	0.02
Risedronate	5 (2604)	0.64 (0.54−0.77)	0.01
Calcitonin[a]	1 (1108)	0.79 (0.62−1.00)	0.05
Raloxifene	1 (6828)	0.60 (0.50−0.70)	0.01
HRT	5 (3117)	0.66 (0.41, 1.07)	0.12
Fluoride (4 yr)	5 (646)	0.67 (0.38, 1.19)	0.17
Nonvertebral fractures			
Calcium	2 (222)	0.86 (0.43, 1.72)	0.66
Calcium and vitamin D	6 (6187)	0.77 (0.57, 1.04)	0.09
Etidronate	7 (867)	0.99 (0.69, 1.42)	0.97
Alendronate (5 mg)	8 (8603)	0.87 (0.73, 1.02)	0.09
Alendronate (10−40 mg)	6 (3723)	0.51 (0.38, 0.69)	<0.01
Raloxifene	2 (6961)	0.91 (0.79, 1.06)	0.24
Calcitonin[b]	1 (1245)	0.80 (0.59, 1.09)	0.16
Risedronate	7 (12,958)	0.73 (0.61, 0.87)	<0.01
HRT	6 (3986)	0.87 (0.71, 1.08)	0.1
Fluoride	5 (950)	1.46 (0.92, 2.32)	0.11

Abbr: CI, confidence interval; HRT, hormone replacement therapy.

[a]Due to the potential for publication bias, the estimate for the larger Randomized Control Trial (RCT), the Prevent Recurrence of Osteoporotic Fractures Study (PROOF) trial is presented. The pooled estimate for calcitonin from the PROOF trial and the three smaller studies combined is 0.46 (95% CI, 0.25−0.87; $p = 0.02$; n = 1404).

[b]Due to the potential for publication bias, we are presenting the estimate for the larger RCT estimate from the PROOF trial. The pooled estimate for calcitonin from the PROOF trial and the three smaller studies combined is 0.52 (95% CI, 0.22−1.23; $p = 0.14$; n = 1,481).

according to the type of fracture. Additional data are necessary to evaluate the onset of pharmacological action, efficacy in elderly people, in non-Caucasians, on the hip, and extraskeletal effects. To enhance patient treatment, new agents that evaluate these aspects should be studied with ethical and safety limits always being respected. The PCT is the only model that allows adequate evaluation of the true efficacy and safety of pharmacological agents. Despite the clinical benefit of placebo-controlled fracture trials, a rigid requirement for the use of a placebo, in which subjects are exposed to unnecessary risks, is not appropriate.

Considering the previous information, the following question must be asked. Is it more appropriate to: (1) involve a large number of subjects in experiments comparing a new drug to the best available treatment, recognizing that these studies have a limited capacity to evaluate the efficacy for fracture risk reduction or the true safety? or (2) involve a smaller number of subjects in PCTs, in which the safety and anti-fracture efficacy of new drugs can be determined with appropriate safety and escape mechanisms as required by regulatory agencies and the World Medical Association?

The responses of institutional review boards (IRBs) and regulatory agencies to this question will have a major impact on the development of new drugs to reduce fracture risk. If fracture studies cannot be conducted, then regulatory agencies may consider returning to the use of intermediary endpoints (i.e., surrogates), such as BMD, as a final proof of efficacy for new anti-osteoporosis medications *(33)*. According to another statement in the Declaration: ''Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.'' This suggests that it may not be possible to return to old models using surrogates for fracture as endpoints to avoid PCTs. Finally, it must be asked whether it is ethically appropriate to impede the development of new drugs by requiring study designs that increase costs of the studies and, as a matter of consequence, result in very high cost products that are unaffordable for many patients who may benefit from the use of these drugs.

In summary, the design of clinical trials for the registration of new pharmacological agents to reduce fracture risk must provide for the protection of the rights and safety of participating subjects. With appropriate informed consent, we believe that subjects have the right to participate in PCTs. The *placebo* given in most fracture trials is calcium and vitamin D, which has been shown in some studies to increase BMD, suppress bone turnover, and reduce fracture risk. Therefore, many osteoporosis treatment studies that are now classified as *placebo-controlled* are in fact comparing a control group receiving therapeutically active agents with another group receiving the same agents plus the study drug. We recommend that stakeholders (i.e., regulatory agencies, IRBs, clinical researchers, ethicists, and advocates of patients' rights) collaborate on the design of clinical trials for the registration of new medications for reduction of fracture risk. Delay in developing mutually acceptable models may impair scientific development in the field and possibly deprive patients of potentially beneficial treatments.

In the authors' view, the use of a placebo (e.g., calcium and vitamin D supplementation) as a comparator in a clinical trial is ethical and reasonable to demonstrate efficacy in reducing fracture risk for new drugs of a new class of therapeutic agents, provided that standards for obtaining informed consent are followed and study subjects are fully aware of the potential risks and benefits of participation in the study. The duration of the study should be no longer than necessary to obtain essential efficacy and safety data. Surrogate markers of bone strength, such as BMD and bone turnover markers, should be used appropriately, but at the present time can not be considered a substitute for fracture data with new drugs of a new class. The PCTs may not be ethical when the *best proven treatment* is clearly and scientifically defined and available for potential study subjects. We, as a society, as clinical researchers and as compassionate individuals, must continue to consider the three essential pillars of clinical research: (1) safety for the research subjects, (2) scientific relevance, and (3) feasibility.

Acknowledgments

Author, José Roberto Provenza, has received research grants from Merck-Sharp & Dohme, Sankyo, Ache. Author, E. Michael Lewiecki, has received research grants from Amgen, Merck, Eli Lilly, Novartis, Sanofi-Aventis, Amgen, Pfizer, Wyeth-Ayerst, Roche, GSK, and Procter & Gamble.

References

1. World Medical Association (http://www.wma.net/e/policy/b3.htm).
2. Epstein S, Cryer B, Ragi S, et al. 2003 Disintegration/dissolution profiles of copies of Fosamax (alendronate). Curr Med Res and Opinion 19(8):781−789.
3. Oguz NY. 2003 Research ethics committees in developing countries and informed consent: with special reference to Turkey. J Lab Clin Med 141:292−296.
4. Wang V, Marsh F. 1992 Ethical principles and cultural integrity in health care delivery: Asian ethnocultural perspectives in genetic services. J Genet Couns 1:81−92.
5. Levine RJ. 1999 The need to revise the Declaration of Helsinki. N Eng J Med 341:531−534.
6. Levine RJ. 2003 Placebo controls in clinical trials of new therapies for osteoporosis. J Bone Miner Res 18(6):1154−1159.
7. Lindsay R. 1991 Estrogens, bone mass and osteoporotic fracture. Am J Med 25;91(5B):10S−13S.
8. Riggs BL, Hodgson SF, O'Fallon WM, et al. 1990 Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. N Engl J Med 22;322(12):802−809.
9. Rico H. 1985 Calcitonin and treatment of osteoporosis. J Med 16(4):493−495.
10. Kleerekoper M. 1996 Fluoride and the skeleton. Crit Rev Clin Lab Sci 33(2):139−161.
11. Nelson HD, Humphrey LL, Nygren P, Teutsch SM, Allan JD. 2002 Postmenopausal hormone replacement therapy: scientific review. JAMA 288(7):872−881.

12. Guidelines for the preclinical and clinical evaluation of agents used in the prevention of treatment of postmenopausal osteoporosis (http://www.fda.gov/ohrms/dockets/dockets/98p0311/Tab0026.pdf).
13. Chapuy MC, Arlot ME, Duboeuf F, et al. 1992 Vitamin D3 and calcium to prevent hip fractures in the elderly women. N Engl J Med 3;327(23):1637−1642.
14. Emanuel EJ, Miller FG. 2001 The ethics of placebo-controlled trials—a middle ground. N Engl J Med 20;345(12):915−919.
15. Freedman B, Glass KC, Weijer C. 1996 Placebo orthodoxy in clinical research. II: ethical, legal, and regulatory myths. J Law Med Ethics 24(3):252−259.
16. Siris ES, Miller PD, Barrett-Connor E, et al. 2001 Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women: results from the National Osteoporosis Risk Assessment. JAMA 12;286(22):2815−2822.
17. International Osteoporosis Foundation (http://www.osteofound.org).
18. Rossouw JE, Anderson GL, Prentice RL, et al. 2002 Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002. 17;288(3):321−333.
19. Gorelick KJ, Marcus DM, Cohen FJ, Jenny-Avital ER. 2005 What ails the FDA? N Engl J Med 352:2553−2555.
20. Grocott R, Metcalfe S. 2005 Going against the flow: the impact of PHARMAC not funding COX-2 inhibitors for chronic arthritis. N Z Med J 2005. 7;118(1223):U1690.
21. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. 1997 Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med 4; 337(10):670−676.
22. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. 2005 Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA 293:2257−2264.
23. Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. 2005 Estimates of optimal vitamin D status. Osteoporos Int 16(7):713−716.
24. Papadimitropoulos E, Wells G, Shea B, et al., the Osteoporosis Methodology Group, The Osteoporosis Research Advisory Group. 2002 Meta-analyses of therapies for postmenopausal osteoporosis. VIII: Meta-analysis of the efficacy of vitamin D treatment in preventing osteoporosis in postmenopausal women. [Review]. Endocr Rev 23(4):560−569.
25. Larsen ER, Mosekilde L, Foldspang A. 2004 Vitamin D and calcium supplementation prevents osteoporotic fractures in elderly community dwelling residents: a pragmatic population-based 3-year intervention study. J Bone Miner Res 19(3):370−378.
26. Grant AM, Avenell A, Campbell MK, et al., the RECORD Trial Group. 2005 Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people: a randomised placebo-controlled trial. Lancet 365(9471):1621−1629.
27. Porthouse J, Cockayne S, King C, et al. 2005 Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care. BMJ 30;330(7498):1003.
28. LLC and PhRMA, Washington Analysis.
29. Lips P, Chandler J, Lippuner K, et al. High prevalence of vitamin D inadequacy among community dwelling post-menopausal women with osteoporosis. Abstract presented at ASBMR, Nashville, TN, September 23−27, 2005.
30. Gallacher SJ, McQuillian C, Harkness M, et al. 2005 Prevalence of vitamin D inadequacy in Scottish adults with non-vertebral fragility fractures. Curr Med Res Opinion 21(9):1355−1361.
31. Jackson RD, LaCroix AZ, Gass M, et al., the Women's Health Initiative Investigators. 2006 Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med 16;354(7):669−683.
32. Cranney A, Guyatt G, Griffith L, Wells G, Tugwell P, Rosen C, and The Osteoporosis Methodology Group, The Osteoporosis Research Advisory Group, 2002 Meta-analyses of therapies for postmenopausal osteoporosis. IX: Summary of meta-analyses of therapies for postmenopausal osteoporosis. Endocr Rev 23(4):570−578.
33. Heaney RP. 2003 Ethical issues in the design of osteoporosis clinical trials: the state of the question. J Bone Min Res 18(6): 1117−1120.