The drug approval process in this country is a rigorous one. There has long been interest in trying to help safe and effective drugs through this process efficiently, and in recent years, the Food and Drug Administration (FDA) has focused increased attention on the development phase, principally to assure that drug developers carry out appropriately designed studies of adequate size. According to Robert Temple, MD, director of one of the FDA’s five offices of Drug Evaluation, one of the most critical issues is the use of the control group in randomized clinical trials. In February, Temple visited the campus of Jefferson Medical College in Philadelphia, where he gave a lecture on active and placebo-controlled trials in clinical research.

“We try to reach agreement with the companies ahead of time on what an adequate study design will be,” Temple said in an interview following his presentation. “We have meetings by the hundreds. When a marketing application comes in, we work very hard to reach conclusions about the data needed for approval.” If his staff determines that a trial design is unsafe or will not meet the stated objectives, they can “hold” (stop) the study, but that is unusual. Usually, because everyone wants the studies to “do the job,” the FDA and the company can reach agreement on what is considered adequate.

Temple is also Associate Director for Medical Policy at the FDA’s Center for Drug Evaluation and Research. In this position, he acts as the agency’s “point man” on a number of challenging and sometimes controversial issues, such as the use of placebo controls in clinical trials. The double-blind placebo-controlled trial is often considered the “gold standard” of clinical research, the design best able to assess the toxicity and efficacy of an experimental drug. However, in recent years, some have argued that the use of placebos in trials is unethical if there already exists an effective therapy for the disease being studied. In support of this view, they often cite the following sentence from The World Medical Association’s Declaration of Helsinki: “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.” They argue that these words, read literally, bar the use of placebo when there is an existing effective therapy.

Temple disagrees. He says that when the sentence was added in 1975, it wasn’t directed at placebo controls at all, but was intended as a reminder to investigators that the needs of the patients were paramount. Indeed, the statement could not have been meant to be taken literally, because then it would have said that any study would be forbidden when effective treatment already exists; the patients getting the experimental drug would plainly not be getting the “best proven” treatment. Interestingly, however, in 2000, the World Medical Association modified the Declaration to say that use of placebo was in fact unethical whenever there was an effective treatment; but they then modified this statement in 2001 to say that such trials could be carried out if people were not harmed by being on placebo.

The FDA’s position is expressed in an article by Temple and Ellenberg (Ann Intern Med 2000; 133:455–463) and the FDA’s guidance document, Guidance Choice of Control Group and Related Issues in Clinical Trials, developed by the International Conference on Harmonisation (ICH E-10). This guidance document states that it is ethical to invite people to participate in a placebo-controlled trial, even when there is existing effective treatment, if death, irreversible morbidity, or other serious harm will not occur to the patients receiving the placebo.

Assuming careful, informed consent and appropriate review by an institutional review board (IRB), Temple says there is no reason not to accept a patient’s decision about whether to participate. “People make decisions everyday about whether to use antidepressants, antiobiotics, analgesics, and the like. They can judge whether a period of non-treatment is acceptable to them.” Temple cites specific non-life-threatening illnesses, such as outpatient depression, obsessive-compulsive disorder, panic disorder, anxiety, allergic rhinitis, dental pain, and angina, as examples of cases in which there is known effective therapy but where placebo controls are appropriate. On the other hand, it would be unacceptable to conduct a placebo-controlled trial in heart failure if the trial lasted more than a short time, because several treatments (angiotensin-converting enzyme inhibitors, beta blockers) improve survival.

It is important not to avoid placebo controls where it is not ethically necessary to do so (i.e., because patients will be harmed) because the alternative design, active-control equivalence or non-inferiority trials, which compare new treatment with old treatment, are not informative (can’t prove efficacy) in many contexts, according to Temple. For example, an active-controlled trial might show no difference in effect between the standard drug and the drug being tested. “This is uninformative,” he says, “unless you know that the active control drug worked in that study. People don’t realize that many apparently good studies of depression, anxiety, allergic rhinitis, etc. lack ‘assay sensitivity,’ the ability to tell an active [drug] from an inactive drug. We see this, for example, with antidepressants, where about half of apparently well-done trials of drugs we know work cannot tell drug from placebo. Obviously, if such a trial compared two drugs and found no difference, it wouldn’t tell you anything.”

Such issues of trial design are important considerations for members of P&T committees, who need to know how to assess the value of clinical studies in making formulary decisions. For example, of the many trials that compare two antidepressants, which ones are capable of concluding that the test product is effective? According to Temple, only those that also have a placebo group to show assay sensitivity. “If somebody said, ‘well, I know that the cheap one is just as good as the more expensive one because there was no difference,’ and the trial lacked a placebo, they’d be making a mistake. They would not know anything from that trial. You have to be conscious of these things. Not all comparative trials make useful comparisons.”

Antidepressant and other drug studies often use three arms—new drug, active control, and placebo. If the control drug is better than placebo, the trial did have assay sensitivity. Then if the test drug was not better than placebo, it is probably ineffective. If neither drug beat placebo, however, then the study lacked assay sensitivity and the drug might work, and more studies would be required.

Although the question of the ethics of placebos in medical research has made for a lively debate at conferences and in scientific journals, Temple does not think it will go on much longer. “There will be a few people still raising the issue, but it’ll go back to where we were before,” he predicted. “The ethical argument against placebo-controlled trials where no harm comes to the placebo-treated patients is not logical. It just doesn’t make sense.”