MEDICAL RESEARCH

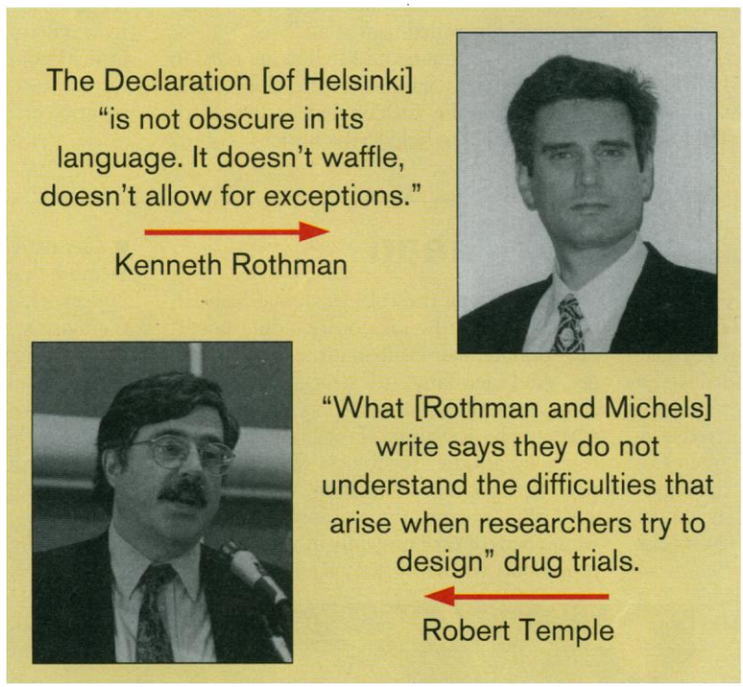
Use of Placebo Controls in Clinical Trials Disputed

When it comes to clinical trials, few issues are simple. And many are controversial (*Science*, 10 June 1994, p. 1534). The most recent example is a debate in this week's *New England Journal of Medicine* (*NEJM*). At issue: Is it ethical to compare a potential new disease treatment with inactive placebo controls if an accepted treatment for the disorder already exists? As a collection of a dozen letters in the 5 January issue of *NEJM* shows, there is little agreement on the answer. Many scientists say no and blame the government for requiring such controls, while some federal officials say that the present system isn't perfect but that the suggested alternatives are worse.

The controversy was touched off by an article in the 11 August issue of *NEJM* in which epidemiologists Kenneth Rothman of Boston University and Karen Michels of the Harvard School of Public Health maintained that clinical trials today "commonly" violate provisions in the Declaration of Helsinki, the 1964 World Medical Association proclamation on biomedical research ethics, which holds that use of a placebo control in a clinical trial is unethical if a proven therapy already exists. As a result, patients may suffer unnecessarily and may even risk death. Furthermore, the authors attribute the problem mainly to the regulatory policies of the U.S. Food and Drug Administration (FDA).

The Rothman and Michels article touched a nerve, prompting a raucous debate on placebo controls at a 1 November meeting in Boston on Public Responsibility in Medicine and Research and a flurry of letters to *NEJM*. These ranged from being highly supportive of the Rothman-Michels position to being brutally critical, but all agree that the use of placebo controls is one of the thorniest issues faced by clinical researchers today. Indeed, in one letter to *NEJM*, William Denny, professor of medicine at the University of Arizona and chair of its Human Subjects Review Committee, writes that "the ethics of placebo use is the issue most frequently debated by the [university's] Institutional Review Board."

At the heart of the debate is the Helsinki document. Rothman, who is editor of the journal *Epidemiology*, cites two places where the declaration militates against the use of placebo controls where effective therapies already exist. In particular, the declaration declares that "every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method." The Declaration "is not obscure in its language. It doesn't waffle, doesn't allow for exceptions. It's straightforward, and it is easy to interpret," Rothman says. In their article, he and Michels provide several examples of clinical trials that they think violate its prescriptions, although they point out that the full extent of the problem is impossible to calculate because many clinical trials are performed to gain regulatory approval for drugs and are therefore never published.



Some of *NEJM*'s correspondents agree that there is a problem. Arizona's Denny writes, for example, that the routine inclusion of a placebo control group in many protocols seen by his institution's Institutional Review Board (IRB) "is neither scientifically necessary nor ethically sound." And he, too, puts the problem at the FDA's feet, adding that, when challenged, the investigators who write these proposals "invariably contend that the FDA requires the use of a placebo control."

For their part, FDA officials take issue with the idea that they are requiring unethical placebo controls. Placebo controls are often necessary to get a true measure of a drug's effectiveness, says Robert Temple, director of one of the FDA's two drug evaluation offices. "What [Rothman and Michels] write," he maintains, "says they do not understand the difficulties that arise when researchers try to design" drug trials comparing a possible new treatment against only the best accepted treatment (known as an active control clinical trial). Indeed, says Temple, "Rothman and Michels have not contributed one word of usefulness to being able to conclude that a drug is effective without a placebo control."

One major problem is that even active drugs cannot be shown to work in every trial. "There's a lot of very well worked-out examples with antidepressants, for instance," says Temple. As a result, these drugs are often tested on moderately depressed patients—those who are not suicidal—against both an active drug and a placebo. "When you have a trial like that you can learn two things," he says. "You can tell your drug is better than a placebo, and you can also tell whether the study is a useful study." If a drug of known effectiveness does not seem to work, it would mean that the study itself is flawed. It might, for example, be too small, or include the wrong population, or the results might be confounded by the huge placebo effects often seen with anti-depressants and other psychoactive drugs.

Rothman, Michels, and their supporters concede that it is hard to show every time that even well-accepted treatments are better than nothing. But they have another solution to the problem—larger, more informative trials to assess treatments more accurately and to create a better standard against which to measure the efficacy of a new drug. "If they did studies with enough people in enough variety of circumstances, they could figure out exactly how effective the drug was in the first place and could use that to show how effective the drug would be in future studies," say Rothman.

Temple also maintains that IRBs and patient consent forms, which tell patients exactly what they might be getting into, can assure the ethical nature of drug trials. But Denny, for one, questions whether IRBs prevent clinical trials from taking place. In his *NEJM* letter, he says that when the

University of Arizona review board rejects what it considers unethical protocols, the most likely result is that "the sponsor (and the FDA) would simply complete the project elsewhere."

As for patient consent forms, Rothman and Michels and their supporters argue that those can be problematic at best. The informed consent agreement is an "escape clause," says Rothman, that puts the burden "on the patient for ethical studies." And Ian Chalmers, head of the Oxford, U.K., Cochrane Center, part of a multinational collaboration to prepare, maintain, and disseminate systematic reviews of randomized clinical trials, calls informed consent a "fiction," pointing out that patients in placebo-controlled trials are rarely if ever told clearly that there already exists an accepted treatment for their condition, and the risks of not getting it are not accentuated. If they were, he says, "they wouldn't go into the trials."

By no means all bioethicists, however, agree with Rothman and Michels. Take Robert Levine of Yale University School of Medicine. At the meeting on Public Responsibility in Medicine and Research where the issue was so intensely debated, he suggested that the Declaration of Helsinki may be the wrong standard for assessing the ethics of clinical trials. It was meant to be a guide to physicians concerned about treating their patients, he says, adding that "what Helsinki calls clinical research is what most other people call compassionate use of a new drug; it's not a controlled trial at all."

While Rothman and Michels are right in calling for more careful justification of placebo controls, Levine concludes, clinical trials should not be held to the standards of the "flawed" Declaration of Helsinki. Those, he suggests, are too rigid because they don't allow patients to choose to accept small risks or temporary discomfort on placebos so that new drugs can be tested.

Whether or not the controversy touched off by the Rothman and Michels article will have any effect on the way clinical trials are carried out is not yet clear. But Benjamin Freedman, a bioethicist at Montreal's McGill University, says the time has come to re-examine the placebo issue once and for all. "The problems had been apparent for some time," says Freedman, "but now the issue is openly joined. We're now going to have to face up squarely to what our ethical commitments oblige us to do with respect to ethical research and the current practice on placebos."

–Gary Taubes

HIGH-ENERGY PHYSICS

CERN's LHC Gets the Go-Ahead

After 6 months of uncertainty, European physicists got the final go-ahead last month to build the world's most powerful particle accelerator. The member countries of CERN, the European high-energy physics center near Geneva, approved a plan to build the Large Hadron Collider (LHC) in an existing 27-kilometer tunnel built for the Large Electron-Positron Collider. The plan, which had been worked out over the past few weeks (*Science*, 16 December 1994, p. 1799), was endorsed by the CERN council on 16 December (just after the final 1994 issue of *Science* went to press).

For CERN's physicists, that's the good news. The bad news is that the plan is the result of compromises that will inflict some pain on CERN's operations. At the insistence of cash-strapped Germany, host countries France and Switzerland will have to pay extra. Even so, CERN itself must make severe cuts in its budget to support the SFr2.6 billion ($2 billion) project, and the LHC may take 5 years longer to complete than originally planned. "It will not be easy, but it will be possible," says council chair Hubert Curien, France's former science minister. The CERN staff, he adds, is stoical about the coming cuts. "They know the future of CERN must be ensured, and that could not be guaranteed without economies."

When CERN's management first asked the council to approve the LHC last June, it planned to fund the project from CERN's normal budget, plus contributions from nonmember countries such as the United States and Japan. But while all 19 member countries agreed that the collider should be built, they balked at the idea of including uncertain nonmember contributions in the budget. And Germany, still struggling with the costs of reunification and supporting its own particle physics center, DESY, in Hamburg, threw up another roadblock. With the support of the United Kingdom, Germany argued that because France and Switzerland would benefit economically from having the project on their soil, they should cough up additional payments—originally totaling SFr250 million—beyond what they would normally pay as CERN members.

CERN

Double duty. As shown in this mock-up, the LHC will be squeezed into the same tunnel as the Large Electron-Positron Collider.

After 6 months of hard bargaining, Germany has not gotten everything it asked for, but it has gained significantly:

- France and Switzerland will have to contribute an additional SFr65 million and SFr60 million, respectively, to the LHC budget.
- Germany's subscription—which should be more than its current 22.5% of the CERN budget because reunification has increased Germany's gross national product—will be held at this level until the end of 1998.
- The total CERN budget will not rise to compensate for inflation in the next 3 years, and after that it will be increased by 1% per year, half the expected rate of inflation.
- These measures will force CERN to cut its own costs by SFr650 million over the project's lifetime.

Although the original plan had the accelerator fully operational by 2003, these budget restrictions mean that the LHC will have to be built in two phases. Some of its 14-meter superconducting magnets will be installed by 2004, allowing the accelerator to operate at an energy of 10 tera-electron volts. This energy will enable physicists to seek the elusive top quark and study heavy-ion physics. The remaining magnets will be in place by 2008, boosting the power to 14 TeV and making possible the search for the Higgs boson, the postulated origin of mass.

This schedule could be accelerated, however, if the United States and Japan chip in. And that may happen. University of Heidelberg physicist Volker Soergel, one of Germany's council representatives, says that several countries, including the United States and Japan, "made clear statements of their intention to collaborate" at the council meetings in both June and December. If they do, Curien says, "contributions from outside will not be used to reduce members' subscriptions; they will be used to reduce the delays."

–Daniel Clery