Science versus ethics

New ethical guidelines regarding the use of placebos in clinical trials have sharpened the conflict between public health and patients' rights

The ultimate ethical standard among the medical profession is the Hippocratic Oath. The oath states: 'I will follow that system of regimen which, according to my ability and judgment, I consider for the benefit of my patients, and abstain from whatever is deleterious and mischievous'. It demands that the physician use every means possible to cure the patient's ailment—but does this apply in a clinical trial, which is understood to be experi-

medical community, with cries of 'medical imperialism'.

This issue has heated up following the World Medical Association's revision in October 2000 of its guidelines, known as the Declaration of Helsinki. First issued in 1964 as the successor to the Nuremberg Code, which was created in response to Nazi doctors' abuses during World War II, the Declaration is generally recognised as a universal foundation of human research

Due to the accepted ethical standard that one must treat a patient with a life-threatening disease, or not expose her or her offspring to undue risk, trial 076 would have been forbidden in the USA and Europe. But its sponsors, the Centers for Disease Control in Atlanta, GA, and the National Institutes of Health in Rockville, MD, maintained that it should be permitted in developing countries, since women in these regions generally have no access to anti-HIV medicines. Hence, their thinking was that a 50:50 chance of treatment would be better than no treatment at all, and they argued that the treatment being tested was precisely for use in developing nations where health-care is minimal. According to an opposing view, 'residents of impoverished, post-colonial countries [...] must be protected from potential exploitation in research. Otherwise the abominable state of health care in these countries can be used to justify studies that could never pass ethical muster in the sponsoring country,' maintained Peter Lurie from Public Citizen Health Research Group in Washington, DC.

While the EU and Japan strongly support the revised Declaration, the US Food and Drug Administration, the agency responsible

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mental, not treatment? In a clinical trial, tension exists at the outset between gaining knowledge that can be used in the longer term to benefit the public health, and the basic right of the patient to receive treatment.

For the scientific profession, the ultimate standard is to produce results that withstand scrutiny. For physicians and researchers, the 'gold standard' in testing new drugs is a double-blind, placebo-controlled study in which some of the patients receive no treatment at all. These standards present an ethical dilemma as drug-approval agencies tend to lean toward the need for clear scientific data, which is best gained when a drug is tested against a control, or placebo.

Furthermore, it becomes harder to convince patients in First World countries to participate in drug trials when there may be a 30–50% chance of receiving only a sugar pill instead of a helpful medication. Placebo-controlled trials are also, by necessity, larger than other types of trials, and hence more expensive.

As a consequence, drug companies are looking increasingly to Third World countries to conduct placebo-controlled trials, and therefore raising much dissent in the

ethics, although it does not have the force of law. The new version prohibits the use of placebos when an approved treatment exists, stating that the 'benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods [...] every patient [...] should be assured of the best proven diagnostic and therapeutic method.'

The most recent revision was the result of an AIDS drug trial, known as 076, conducted in Thailand and Africa in the mid-1990s, in which pregnant women

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were given either a placebo or AZT to determine whether a low-dose treatment could prevent transmission of the disease to their infants. The alternative would have been a non-inferiority trial, in which a drug candidate is tested against an approved medication; the problem is that such trials may produce more equivocal results than a placebo-controlled study.

for approving new drugs in the USA, has not yet taken a clear stand. In March 2001, the FDA issued a White Paper in which it stated that 'the FDA has not taken action to incorporate those revision into its regulations.' Furthermore, in this Guidance for Industry, it notes 'that the action of the World Medical Association did not change FDA regulations.' Paradoxically,

the document also states that the FDA 'will accept a foreign clinical study [...] only if the study conforms to the ethical principles contained in the Declaration of Helsinki, here referring to the previous version from 1989, or to laws of the

But, it is the regulatory agency that decides whether to accept the results of a placebo-controlled study or to demand a non-inferiority study from the drug's sponsor. And one of the most ardent advocates of placebos is Robert Temple,

trials, one ought not to undertake placebo-controlled trials,' Leroy Walters, PhD, Director of the Kennedy Institute of Ethics at Georgetown University in Washington, DC, said. 'The next step should be an active control equivalence trial,' he added. Indeed, when the Harvard School of Public Health conducted a randomised, double-blind equivalence trial of AZT in overseas patients, they reproduced the results of the previous placebo-controlled trial. 'In this case, all patients benefited by being in the study,' Walters said, although he admits that sometimes, some scientific information may be sacrificed in equivalence trials in the name of ethical research.

For the Discovery trial, it would mean that a non-inferiority trial would leave no child untreated. Indeed, FDA notes that another surfactant, Infasurf, won approval by demonstrating superiority over a third surfactant, 'when placebo trials in the USA were no longer possible.' Discovery, however, noted that such a trial 'presented a clinical efficacy hurdle that the sponsor deems too high for this drug,' because the company could not assume that its drug would prove to be superior on clinical endpoints. Some bioethicists, like Ruth Macklin from the Albert Einstein School of Medicine in New York, NY, see nothing redeemable in the Discovery trial design, whereas they might have allowed the AIDS trial to move forward. 'This looks like a clear-

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country in which the research is conducted—whichever provides greater protection of human subjects.' In January 2001, the FDA held an internal meeting entitled, 'Use of placebo-controls in life-threatening diseases: Is the developing world the answer?' The subject of the discussion was a placebo-controlled study designed by Discovery Labs, a drug company in Doylestown, PA, to be conducted in Latin America, to test a new surfactant to treat premature infants with respiratory distress syndrome (RDS), a life-threatening condition.

According to Robert Capetola, president and CEO of Discovery Labs, previous non-inferiority trials of other drugs had yielded ambiguous results, although they had ultimately been approved, so it was now necessary to test its drug, Surfaxin, against a placebo. 'We had in mind several types of trials and conducted about nine months of discussion with the FDA,' said Capetola. Indeed, FDA documents state that 'a non-inferiority surfactant RDS European trial versus [another surfactant] is also planned by the sponsor.'

Furthermore, as an incentive for the countries that Discovery was targeting for the placebo-controlled trials, the company proposed to build neonatal units in underserved areas and provide its drug for slightly above the production cost for 10 years, explained Capetola. One such unit has already been built, he added. Capetola believes that the proposed placebo-controlled trial in Latin America was ethical because relatively few infants born with immature lungs are treated in that region. 'Effectively, in these nations, 80–90% of those needing the drug do not receive any treatment,' he said, adding that representatives from a number of developing countries had asked Discovery to build neonatal units and conduct trials in their countries.

Director of Medical Policy at the FDA's Center for Drug Evaluation and Research. Anticipating the Declaration's imminent revision, Temple published a two-part article in September 2000 in the *Annals of Internal Medicine*, laying the groundwork for a scientific defence of placebo use in most trials. Temple—and most scientists—believe that placebo-controlled trials yield the strongest efficacy data in drug testing, and, therefore, in all but the most life-threatening situations, such a design is imperative. He did not respond to requests to comment on the proposed Discovery trial, but has said that 'the revised Declaration is too rigid, and does not distinguish between the use of placebos in conditions such as headache or migraine, hair loss, allergies, insomnia, heartburn, or other non-life-threatening

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conditions that do not place patients who have given their informed consent at a risk of damage or death.' In summary, for the FDA, public health needs in medical research in non-life-threatening situations must supersede the individual's rights to treatment in a trial, Temple maintains.

In contrast, the World Medical Association holds that the rights of individual patients must always come before the needs of science, and, if not, there is a risk of research abuses like those in the AIDS trials and Nazi Germany, Delon Human, head of the WMA, has said. In other words, ethics and protection of the individual patient must triumph over the needs of science and public health. 'When a clear-cut result is reached in one or more placebo-controlled superiority

cut case of exploitation,' she said.

In the end, in April 2001, the FDA decided against Discovery's use of placebos in the overseas trial, but did not comment on the decision, or whether it would make this hard and fast policy or judge each trial on its own merits. So, with the FDA's defence of the use of placebos in most circumstances, and the increase of overseas trials conducted by US drug companies, the dispute promises to continue. In June 2001, the new Office for Human Research Protections (OHRP) was created at the US Department of Health and Human Services, replacing the Office for Protection from Research Risks under the auspices of the NIH. In January 2001, OHRP's first director, Greg Koski, established a new office to oversee ethical problems

caused by conducting trials in developing nations. It may be just a matter of time before the USA decides to uphold the revised Declaration of Helsinki or challenge it.

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Of silicon and submarines

Whether it be in the world's smallest pharmaceutical plants, computer factories or dockyards, engineers need look no further than biology for future solutions

The application of nanotechnology to biological concepts is a particularly interesting subject; on the one hand it

self-assembling biological molecules are providing scientists with important insights into how to create their own

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allows biologists to analyse the physical properties of biological molecules using nano techniques (Moore, 2001), while on the other it exploits these very molecules as miniature machines. After all, the most successful nanomachines ever created are those operating inside every cell. The properties and construction of complex

nanomachines, or better still, modify existing ones to take on new tasks.

'The fastest way to utilise nanotechnology is to build on the machines existing in nature,' noted Carlo Montemagno, in describing the principle of his work at Cornell University in Ithaca, NY. His pet machine is the F_1F_0 ATPase, a far more

efficient machine than any human engineer could expect to make. It should be possible to use this to make 'nano-pumps', intracellular concentrating machines that selectively pump molecules into a cellular compartment and sequester them, according to Montemagno. This may seem far-fetched, but obviously not to the National Science Foundation, which provides the funding. Already Montemagno is working on an *in vitro* sorting system, the goal being to produce human cell lines that express and assemble the pump motors—engineered variants of the bacillus ATPase—into the sorting compartment (Figure 1). Moreover, he plans to construct an artificial minimal cell to produce the

Fig. 1. A sorting device based on the the bacterial F_1F_0 ATPase could pump compounds into a harvesting compartment in a eukaryotic cell.