

In focus

Clinical trials without ethical review under the spotlight

A recent series of unethical, and in some cases illegal, clinical trials in India is fuelling concern over the incidence of clinical trials conducted without ethical approval in other countries where legislation may be either inadequate or not implemented.

In a series of articles last year, Dr Chandra Gulhati, editor of an independent pharmaceuticals journal, the *Monthly Index of Medical Specialities in India*, shed light on the illegal trials and illegal promotion of the anti-cancer drug, Letrozole, as a fertility drug in India.

More than 400 women, who had been trying in vain to conceive, were enrolled without their knowledge or consent to take part in clinical trials across India to see if the drug induced ovulation.

The drug was a copy of a patented Novartis product, Letrozole by Mumbai-based generics firm, Sun Pharmaceuticals. The women were under the impression they were receiving expensive fertility treatment.

Letrozole has been approved globally for the treatment of breast cancer in postmenopausal women, but it is not approved for any other use in any country, including India.

Since then, India has seen a huge public outcry over the regulatory authorities' failure to crack down on a recent series of illegal and legal, but unethical clinical trials.

A Delhi-based nongovernmental organization is filing a complaint about the Letrozole case to India's Supreme Court and last month, the Indian Government pledged to push through tougher, more effective legislation to tackle the problem this year.

Dr Gulhati contends that although the company and doctors who carried out the tests broke the law no one has been put under criminal investigation by the Indian authorities.

The Letrozole trials are a shocking example of a widespread global phenomenon. A recent survey of more than 200 health researchers concluded that a quarter of clinical trials conducted in developing countries do not undergo

ethical review. The survey was commissioned by the former US National Bioethics Advisory Commission and published in February's edition of the *Journal of Medical Ethics* (2004;30:68-72).

John Williams, director of the ethics section of the World Medical Association in Paris, said drug approval agencies in developed countries such as the US Food and Drug Administration and EMEA (European Agency for the Evaluation of Medicinal Products) require ethics committee approval of trials for the sale and distribution of any drug.

"These are strong incentives to seek such approval," Professor Williams said, adding that editors of major journals also require such approval for studies submitted for publication.

"There are efforts under way to strengthen ethical review throughout the world through SIDCER and its regional committees," Professor Williams said, referring to the Strategic Initiative for Developing Capacity in Ethical Review, an international project to develop the ethical review of biomedical research globally.

WHO has been involved in this project and in October 2002 opened its own ethics unit, whose goals include harmonizing ethical review standards for clinical trials and ensuring such studies are effectively regulated in WHO's 192 Member States.

"This is a problem for many countries, not only developing countries," said Dr Marie-Charlotte Bouësseau from WHO's department of Ethics, Trade, Human Rights and Health Law.

Most, but not all developing countries have ethical review committees in the form of research institutes or other scientific panels. "WHO has already been working with many countries in Latin America and Asia to make their ethical review committees work more effectively and recently started working with several African countries too," said Bouësseau.

"We need to provide training to ensure that these panels are independent and able to review clinical trials without prejudice," she said.

The Letrozole case illustrates this problem well. Dr Gulhati said pharmaceuticals in India often have a "cosy relationship" with regulators and bribe researchers, hired to conduct purportedly independent clinical trials, with expensive gifts like cars, paid speaking engagements, over-paid consultancy work and free overseas holidays. He said there was no independent safety monitoring of clinical trials and that participants sometimes do not even know they are participating in tests.

"Neither the regulatory authorities nor the Ethics Committees seek conflict of interest information from investigators," Dr Gulhati said, adding: "Most of the clinical trials here are conducted without any arrangement for compensation in case of study-related injury, disability or even death."

These initiatives come at a time when pharmaceuticals and biotechnology companies try to save time and money by conducting clinical trials in developing countries, where there are plenty of willing subjects and often more relaxed regulatory regimes.

Dr Eugene Braunwald of Harvard Medical School, who is chairman of a clinical trials group of doctors, told the *New York Times* recently that half as many US patients are enrolling in clinical trials compared to five years ago.

The trend of outsourcing clinical trials to developing countries has sparked concerns about unscrupulous biotech and drugs firms exploiting the healthy, in the hope of earning some cash, and the sick, who hope to get free treatment.

A key question for regulators is whether US drug manufacturers should apply FDA standards when they conduct trials abroad. This will be less of an issue once developing countries tighten laws and make their ethical review panels truly independent. ■

Fiona Fleck, *Geneva*

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