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A New Colonialism? — Conducting Clinical Trials in India

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In January 2005, the government of India enacted a new rule that allows foreign pharmaceutical companies and other interested parties to conduct trials of new drugs in India at the same time that trials of the same phase are

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being conducted in other countries. This new rule supersedes a directive of India's Drugs and Cosmetics Rules that required a "phase lag" between India and the rest of the world. According to the old rule, if a phase 3 study had been completed elsewhere, only a phase 2 study was permitted in India. Even under the new rule, phase 1 trials will not normally be permitted in India. The old rule was designed to protect Indians from being used as guinea pigs in the testing of unproved drugs of foreign origin; trials of domestically discovered drugs were not subject to this provision.

The change was made in response to vociferous demands from multinational drug companies and private organizations that conduct clinical research for a relaxation of the rules for drug trials — those necessary hurdles whose price tags can run to 40 percent of the cost of drug development.¹ It has become increasingly difficult to test drugs in Western countries, with their strict regulations, elaborate safety and compensation requirements, and small populations, all of which make the recruitment of research subjects slow and expensive. Consequently, many research-based companies are now outsourcing some of their trials to Third World countries such as China, Indonesia, Thailand, and India.

India is a particularly attractive site for such trials because of its genetically diverse population of more than 1 billion people who have not been exposed to many medications but have myriad diseases, ranging from tropical infections to degenerative disorders. Virtually all Indian doctors speak English, and many have acquired postgraduate qualifications abroad, primarily in Britain or the United States. Added to these attractions are cheap labor and low infrastructure costs, which can reduce expenditures for clinical trials by as much as 60 percent.² However, even from the viewpoint of foreign drug companies, there are some major drawbacks to working in India. Sponsors do not have exclusive rights to the clinical data they generate: because trial reports are in the public domain, manufacturers of generic drugs can use the data to obtain regulatory approval of their own versions of a drug.

Furthermore, the Drugs Controller General of India (DCGI) — the equivalent of the U.S. Food and Drug Administration (FDA) — is understaffed and lacks the expertise to evaluate protocols. Currently, the technical staff consists of just three pharmacists, including the controller, and not one medically qualified doctor. As a result, persistent follow-up, including personal visits to the DCGI, is required in order to push an application for a trial forward.

In addition, although the country has more than half a million practicing doctors, fewer than 200 investigators have been trained in good clinical practice. Among some 14,000 general hospitals, no more than 150 have the adequate infrastructure to conduct trials, and there are fewer than a dozen pathology laboratories that meet the criteria for compliance with good laboratory practice. Only about half of the large hospitals have institutional

review boards, and even these boards have not yet formulated standard operating procedures — and they, too, often lack the expertise with which to evaluate protocols. Information about conflicts of interest is neither sought nor voluntarily provided by investigators.

Given the sorry state of the apparatus for reviewing proposals, the greatest concern about clinical trials in India, from the vantage point of both Indians and ethicists, is illegal and unethical trials, a number of which have attracted adverse coverage in the media in recent years. In 2002, two new chemical entities, called M4 N and G4 N, that had been discovered in the United States were tested in 26 patients with oral cancer at the government-run Regional Cancer Center in Kerala. In the same year, self-styled researchers working in their own clinics formulated "vaginal pellets" of erythromycin and tried them as contraceptive agents in more than 790 poor, illiterate, rural women in West Bengal. In 2003, letrozole, an anticancer drug, was tested in more than 430 young women at a dozen private clinics to find out whether it promoted ovulation. All these trials took place without regulatory approval.

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A Private, "One-Man" Clinic in New Delhi Where Letrozole Was Tested.

These studies were conducted by Indian organizations, but in the past, Western pharmaceutical companies have conducted similarly unethical trials.³ Moreover, the sponsors of many such trials engage in practices that are currently legal yet ethically dubious. They have been known to offer financial inducements to participants — such as paying illiterate blue-collar workers more per month to participate in a trial than they earn at their jobs and enticing subjects by providing medication that is worth more than their annual salary. Widespread illiteracy makes it particularly easy to sidestep the standard methods of obtaining informed consent. Investigators frequently enroll patients in trials as if their participation were a necessary next step in their care. And no protocol we have ever seen has promised to continue to supply the studied medication free of charge after completion of the trial, if it is found to be beneficial.

There have, of course, been some ethical and successful drug trials of immediate relevance to India and other developing countries. A notable example was a study,

conducted in the early 1960s, of a new regimen for home-based treatment of tuberculosis, which was sponsored by the World Health Organization, the British Medical Research Council, and the Indian Council of Medical Research.⁴ Nevertheless, even as corporate sponsors, clinical research organizations, investigators, and hospitals demand easier access to Indian subjects for studies of new foreign drugs, opponents argue that India itself would not benefit greatly from these studies.

The first reason it would not benefit is that the much-hyped earning potential is likely to remain a distant dream. Last year, although U.S. companies spent a total of \$33 billion on new-drug research, U.S. and other Western companies combined spent only \$30 million in India. Even with relaxed rules, India makes as much in one day by exporting computer software (which offers no direct risk to anyone's health) as it can in a year by offering up its citizens as study subjects.

Second, according to the FDA, no more than 20 percent of the drugs introduced during the past decade have been breakthrough agents. The rest represent marginal improvements over existing therapies that are more expensive than the older drugs and are often aimed at extending the patent life of a therapy without offering any major new benefit for patients. Although this issue arises even in the developed world, it is of particular concern in countries like India — the poor in the Third World should not be used to establish the "safety and efficacy" of such products. Moreover, if trials are used to promote drugs that are more expensive but neither more effective nor safer than the standard treatments, the result is higher overall costs for health care and poor patients paying more for equivalent therapies.

Third, the sponsors do not guarantee that new drugs tested in India will be made available there at affordable prices. Recent examples suggest that new patented drugs will cost so much that most Indians will not be able to buy them. For example, Eli Lilly plans to price just one 10-mg tablet of tadalafil (a treatment for erectile dysfunction) at \$9 (400 rupees), which is equivalent to four days' wages for a well-paid manual worker.⁵

No one disputes that researchers should be encouraged to conduct Indian trials of new drugs for diseases that are endemic to this country, such as kala-azar (visceral leishmaniasis), leprosy, trachoma, tuberculosis, and water-borne diseases. But to our knowledge, hardly any trials involving such new drugs have taken place in India; globally, only 1 percent of the new drugs discovered in the past 25 years have been for tropical diseases. Moreover, even before such a limited form of "liberalization," or opening of the economy, occurs, adequate safeguards must be put in place to protect participants. Such safeguards might range from a procedure for the proper review of study protocols by the DCGI to the registration of trials and their results on publicly accessible Web sites to requirements for insurance and appropriate compensation of subjects in whom the drugs under study have adverse effects.

Real informed consent should be obtained from participants in the presence of an objective third party. Trials should be conducted only by investigators trained in good clinical practice at designated research hospitals. Truly independent institutional review

boards should be formed, and a system should be created to enable these boards to share information about trials they have rejected and their reasons for doing so. All projects should be carefully scrutinized for their value to the Indian people. In a population such as India's, a large proportion of the subjects in any trial will inevitably be disadvantaged persons. It is therefore of paramount importance to protect the most vulnerable — women, children, the poor, and the illiterate — by making sure that their enrollment in trials is truly voluntary and that their consent is genuinely informed. They should have access to the drug after the trial if it is found to be effective, and they should not only be treated and compensated for injury but also be compensated for any resultant loss of income. These things can be done only when the government has strengthened its regulatory system so that it is geared toward guarding the rights of patients and protecting them from exploitation.

Source Information

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