

Medicine and Society

Clinical trials in India sponsored by the pharmaceutical industry: A proposal for reforms

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Suddenly, India appears to be the top destination for many multinational companies planning to conduct clinical trials and test new drugs.¹⁻³ There has been a 400% increase in the filing frequency of investigational new drugs (INDs) with the Drug Controller General of India (DCGI) during 1999-2000, as compared to the figures for the previous year.² Lower costs of conducting trials, faster patient recruitment, availability of well-trained medical and computer professionals, high-tech hospitals, fluency in English of health professionals and a high disease burden in the country are some of the reasons given for this dramatic trend.¹⁻⁴ The DCGI has been quoted as stating that 'India has a vast pool of patients, qualified doctors and good hospitals that make it an attractive site'.⁴ In parallel, there is a clear increase in the number of contract research organizations (CROs) that undertake trials and other services for pharmaceutical companies.¹ Transnational companies such as Quintiles Transnational and Covance have begun trials in India.¹ Pharmaceutical companies are also collaborating with western universities in conducting trials. For instance, Max India has signed a deal with an affiliate of Harvard Medical School to conduct trials in India and other developing countries.¹ For the first time, clinical trials have found a mention in the union budget,⁵ and the finance minister has extended the scope of weighted average deduction to clinical trials.⁵

In this milieu, there is an urgent need to re-examine issues related to industry sponsorship of clinical trials in India, given the recent allegations of unethical trials and human experimentation.^{4,6,7} In response to the concern that India has now become an attractive testing ground for experimental drugs and vaccines,^{1,4,6} the Indian government has begun to examine the role and conduct of clinical trials and has proposed certain changes. On 16 May 2001, the Ministry of Health and Family Welfare proposed new rules to rationalize the system of approval of new drugs, and conduct of clinical trials and post-marketing surveillance.⁸ Drug companies are now required to provide the DCGI with trial protocols and names of investigators who will be involved in the trials.⁸ A system for random auditing of clinical trial centres in India has been proposed which will cover private hospitals and research centres.⁹ It has also been proposed that all institutions in India that conduct biomedical research adhere to the revised Indian Council of Medical Research (ICMR) guidelines on ethics for biomedical research.¹⁰ There are indications that the Indian government will not approve trials of unproven treatments when conducted exclusively on Indian patients.⁶

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These issues are not unique to India. Leading western biomedical journals have facilitated an extended debate about sponsorship of clinical research by the pharmaceutical industry.¹¹⁻¹³ There is a growing sense of unease in the research community about the risks and dangers of such sponsorship. Recently, the *New England Journal of Medicine*¹⁴ and the *Journal of the American Medical Association*¹⁵ (*JAMA*) carried editorials entitled 'Sponsorship, authorship and accountability', released simultaneously by members of the International Committee of Medical Journal Editors (ICMJE)—the Vancouver group (www.icmje.org). This document explores the problems involved with industry-sponsored trials and outlines the new policies that are being adopted by journals, including a revision of the *Uniform requirements for manuscripts submitted to biomedical journals*. This document deserves to be widely read and debated in India, particularly by physicians and researchers who are involved in trials sponsored by the industry.

One major difference with industry-sponsored research is that trials are often conducted to promote the approval of a new drug or device rather than test a scientific hypothesis or answer a research question.^{14,15} Sponsors attempt to influence the design, conduct, analyses and interpretation of the trials supported by them.^{11,13} Physicians and researchers, therefore, may not have complete control over issues such as ethical concerns, design issues, sample size, analysis and publication.^{11,13} Even when physicians can participate in the design and analyses, they often tend to be left out of the process during the publication phase.¹³ Additionally, there have been reports of sponsors trying to and even succeeding in suppressing the publication of results unfavourable to their goals.^{16,17} Given that patients may participate in trials for altruistic reasons, the authors of the editorial state, '...the use of clinical trials primarily for marketing, in our view, makes a mockery of clinical investigation and is a misuse of a powerful tool'.^{14,15}

ISSUES RELEVANT TO INDIA

Having conducted clinical trials (JMC) and having done research consultancy for private hospitals (MP), we would like to offer our perspective on this issue and raise a few concerns relevant to this debate. Since the relationship between sponsors and individual researchers is confidential, our observations are largely based on personal, anecdotal experience. It is hard to find published literature from India on this issue because of the rather closed nature of the process and the difficulty in obtaining information from pharmaceutical companies or institutions. It is our hope that this article will stimulate a debate and that readers will respond to it by contributing their personal experiences, positive or negative, with industry-sponsored trials.

In India, pharmaceutical companies are, in recent years, legally

required to perform clinical trials to obtain approval from the DCGI for manufacturing or marketing new drugs.^{8,18} The approval for permission to conduct clinical trials for new drugs in India is also granted by the DCGI, under the Drugs and Cosmetics Act, 1940, and the Rules, 1945 made thereunder.¹⁸ For example, though sildenafil citrate (Viagra) has been tested in clinical trials abroad (and is already in use), four drug companies in India were given permission by the DCGI to conduct clinical trials in order to market the drug in India.¹⁹ To meet such regulatory requirements, companies may approach academic institutions, private hospitals and private physicians to conduct trials on their behalf. The companies may sometimes view and treat these institutions as CROs rather than academic collaborators. They may offer financial inducements and gifts (such as equipment) to the hospitals for participating in these trials. For individual physicians, the inducements may include honoraria, speaker's fees, gifts, supplies of drug samples and national/international trips for attending conferences and meetings.²⁰ Such inducements are widely used by drug companies in India²⁰ and other countries¹¹ for drug promotion and marketing. Some physicians may find the process of testing out a new drug intellectually and scientifically challenging, while others may conduct trials merely to receive funding.

What are the problems concerning industry-sponsored trials in India? Drug companies usually approach reputed physicians with large, successful practices and encourage them to enrol participants for the trials according to protocols set out by them. The physicians may be expected to passively adhere to these protocols without allowing for their input into the design. While these physicians may be excellent clinicians, they may lack the research expertise necessary for conducting clinical trials properly. Furthermore, they may not always fully comprehend the ethical issues involved in any trial, and may find themselves involved in research that may be poorly designed and, therefore, unethical. Since trials may be done for regulatory purposes, the sample sizes may be small, as seen by one of us (MP). Such trials simply could not have adequate statistical power (sample size) to pick up the effects of the treatment they were designed to identify. In other words, these studies were hopelessly underpowered and could be considered unethical because such studies would not be able to answer the research hypothesis conclusively. Multicentre trials, in particular, are prone to this problem. The sponsor may recruit many centres or physicians and compile the data together at the end of the trial. Each centre, however, is asked to enrol only a limited number of patients. This strategy ensures that no one centre has adequate statistical power to test any hypothesis and is thus prevented from independently publishing the data.

Institutions that agree to conduct these trials may have little control over the data, which are usually 'owned' by the drug companies and, once the drug is approved, these companies may choose not to publish the data at all. In fact, companies may view trials as activities done for purely regulatory and promotional needs.²¹ A retired medical director of Pfizer India has been quoted as saying that: 'drug companies should not use clinical trials as a promotional activity but accept it as a research or scientific activity'.²¹ Drug companies have been reported to suppress findings that are not favourable to their products.^{16,17} There are instances of companies analysing and publishing data without involving the original investigators.¹⁶ The scandal involving the drug synthroid is an apt example.¹⁶ Synthroid, a synthetic brand name of thyroxine, is manufactured by Boots Laboratories (now called Knoll Pharmaceutical Company). In 1987, Boots had contracted with researchers at the University of California, San

Francisco to study whether synthroid was more effective than other generic thyroxine preparations available in the market. The study concluded that it was no better. Boots waged a major campaign to discredit the study and do everything it could to prevent the trial results from being published. A *JAMA* editorial on this issue warned that 'scientists should never sign any agreement that gives their sponsors veto power over publication'.¹⁶

How do Indian medical journals address issues such as sponsorship of research, sources of funding, role of a sponsor and conflict of interest? We did a survey of 15 journals and abstracted data from the 'Guidelines to contributors' sections of these journals. We accessed the journal websites (all accessed on 24 and 25 September 2001) and recent issues of the journals to collect this information (references available from the authors on request). The journals surveyed were the *National Medical Journal of India*, *Indian Journal of Medical Research*, *Journal of the Association of Physicians of India*, *Indian Pediatrics*, *Indian Journal of Pediatrics*, *Indian Journal of Cancer*, *Indian Journal of Cardiology*, *Indian Journal of Surgery*, *Indian Journal of Dermatology*, *Indian Journal of Gastroenterology*, *Indian Journal of Ophthalmology*, *Indian Journal of Pharmacology*, *Journal of the Indian Medical Association*, *Indian Heart Journal* and *Neurology India*. As shown in Table I, 8 journals (53%) required disclosure about funding support but only 3 (20%) required disclosure about personal or financial conflict of interest. None of the journals required information about the role of the sponsor, the degree and type of involvement of the sponsor, information regarding the authors' access to data and control over the decision to publish the results. The survey also revealed that not all journals required the entire manuscript to conform to the ICMJE guidelines; 5 journals required only the references to conform to the ICMJE style. Five journals did not provide a citation for the ICMJE guidelines and some journals cited guidelines published in 1979, 1982 and 1988.

Dr M. S. Valiathan, formerly Vice-Chancellor of the Manipal Academy of Higher Education, has succinctly articulated the challenges of industry-sponsorship of trials in the Indian context: '...clinical trials are necessary insofar as they promote the interests of healthcare. The problem is a mismatch between the interests of the group which developed the product and those evaluating it in human subjects. Firms in India and abroad who spend millions on developing products would want to maximize profits; ethics in business is a controversial subject. On the other hand, the evaluating institutions need money and must also

TABLE I. Sponsorship and conflict of interest: Data from the 'Guidelines to contributors' section of 15 Indian medical journals

Information required from the authors by the journal	Frequency (%)
Entire manuscript to conform to ICMJE (Vancouver) guidelines	9 (60)
Only the references to conform to ICMJE guidelines	5 (33)
Disclosure about source of funding	8 (53)
Disclosure of financial or personal conflict of interest	3 (20)
Information about the type and degree of involvement of the sponsor or funding agency	0
Authors to sign a statement indicating that they accept full responsibility for the paper	4 (27)
Authors to sign a statement indicating that they accept full responsibility for the conduct of the study, had access to the data, and controlled the decision to publish	0

protect the interests of patients and subjects. Medical investigators who are approached to take up clinical trials therefore face serious ethical dilemmas... In the last few years, this issue has become pressing because medical investigators have themselves promoted firms. It is now mandatory for authors of papers for top journals to indicate any direct or indirect links they may have with the firms/industry where the product/process being reported on were developed.²²

RECOMMENDATIONS

What can be done about these problems in India? To begin with, we need to be aware of the problems that arise with industry-sponsored research. We need to learn from the experiences of researchers and institutions that have encountered such problems. Unless researchers publish their dilemmas and experiences, their experiences will not be available to help others. The ICMJE document should be read and debated in every institution involved in such research. We offer the following suggestions:

1. When approached by an industrial sponsor, researchers and Institutional Review Boards (IRBs) should debate the advantages and disadvantages of accepting such an offer or contract. If the hospital does not have an IRB, one should first be constituted before accepting any offer. While working for a private hospital, one of us (MP) received offers to become involved with sponsored research. When the IRB of the institution debated the issue, it, as an institution, decided against accepting such offers. In general, when IRBs decide against accepting offers, individual physicians involved in the proposal should be given an adequate explanation as to why the offer is being declined so as to avoid resentment. Otherwise, the IRB may be perceived as a body that blocks research.
2. During the review process for a proposed study, if the proposal is accepted, the IRB or the hospital should refuse to sign any contract or agreement which denies the institution the right to design, analyse and publish their data independently of the sponsor. That is, the offer should come with no strings attached.
3. There is wide agreement that patients need to be in a state of personal equipoise to justify participation in any clinical trial.²³ Equipoise refers to a state of genuine uncertainty about the relative advantage of one therapy over another in a trial. In the informed consent process, patients should be informed that the trial is being done to meet regulatory and marketing needs rather than to answer a scientific question. This information may influence a patient's equipoise and is vital to allow her/him to make a fully informed decision about participating in a trial.
4. Data are required regarding the number of clinical trials conducted in India, their sources of funding, information regarding conflict of interest and information about the exact role of sponsors in these trials. Such data, as shown in a recent survey, can be very revealing.²⁴ A survey of 268 trials published by the *Annals of Internal Medicine*, *BMJ*, *JAMA*, the *Lancet* and the *New England Journal of Medicine* showed that '... just over a third were supported wholly or in part by industry, and only 9% failed to give the source of funding. In the trials supported by industry, a third did not provide any information on the authors' relations with industry. The type and degree of involvement of the funding source was disclosed in only 8% of cases and all these disclosures were in the *Annals of Internal Medicine*'.²⁴ In the absence of a registry or database of trials,

such data are hard to come by in India. We recommend that premier research agencies such as the ICMR or major teaching medical institutions in India initiate an effort to register all controlled clinical trials in India, and make the data available on the World Wide Web. Such initiatives have already been undertaken elsewhere: the Current Controlled Trials website (www.controlled-trials.com) has been developed by Current Controlled Trials Ltd, part of the Current Science Group of Companies, and includes a searchable, international database of ongoing controlled trials. This database currently includes over 10 000 trials.

5. There is now some evidence suggesting a substantial underreporting of clinical trials in the medical literature.²⁵ As articulated by Chalmers, 'Failure to publish an adequate account of a well-designed clinical trial is a form of scientific misconduct that can lead those caring for patients to make inappropriate treatment decisions'.²⁵ Recent ethical guidelines from India also emphasize that 'Reporting of research and its results is the right as well as duty of every researcher and institution that conducted the study'.²⁶ We need information about how many trials are conducted in India and how many are actually published. This is particularly relevant if public funds are used to conduct trials. Concerns have been raised about the relevance of research done in India and the accountability of individuals and institutions regarding funds spent for research.²⁷ This process would be greatly facilitated if there was a registry of all trials done in India, which routinely collected information such as the number of trials done, source and amount of funding, publication status and conflict of interest.
6. Our survey of a sample of journals clearly demonstrates the need for editors of medical journals in India to revise their submission guidelines to cover current developments in publication ethics and explicitly demand information regarding sponsorship, conflict of interest and control of data. As suggested by the new ICMJE guidelines, authors should be routinely required to disclose information about their role and that of the sponsor of the trial.
7. Medical journals in India could initiate a debate in India and invite papers and editorials on this issue. The Indian Association of Medical Journal Editors could greatly facilitate this debate and push for reforms. This body should set standards for biomedical journals in India, educate authors on research and publication ethics, organize courses on scientific writing, conduct surveys on the relevance, impact and nature of research done in the country, and periodically review and update submission guidelines and editorial policies for Indian journals.

The leading Indian journals have a unique opportunity to elevate the standards of both the reporting as well as conduct of clinical research in the country. The *National Medical Journal of India* will be revising its editorial policies and submission guidelines in view of the new ICMJE guidelines (Editor, personal communication). We have a long way to go and need to start somewhere.

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