

When Patients Become Guinea Pigs – A fictitious case of ethics dumping based on real events

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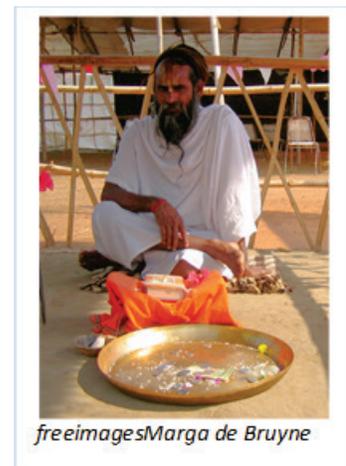
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Disclaimer: *This case has been developed as an academic exercise to create an unethical case study based on a number of trials reported in India over a period of time. No individual trial has been described.*



Abstract Between 2006 and 2008, a multinational double-blind placebo-controlled phase III clinical trial to study the safety and efficacy of a drug in patients with a chronic disease was sponsored by a large multinational company, and initiated at fifteen sites in India, along with sites in other low- and middle-income countries. An Indian physician with a private practice was chosen as the investigator for one of the sites in India. He conducted the clinical trial in patients with ailments under the guise of providing free treatment with costly imported medicines. The patients were not informed about the clinical trial and were not aware that they were research subjects. The patients were happy to receive the “free imported medicines” which they believed were good medicines as they came from abroad.



The investigator in return received per-patient recruitment fees or incentives for quick recruitment from the pharmaceutical company through the local contract research organization. The recruitment incentives were large and were not reported to the ethics committees. Following complaints from social workers, issues were raised in the Panchayat / Council and a list of more than five hundred uninformed subjects who had been included in several clinical trials was

reported by a local TV channel. One man who discovered through these news reports that he had been part of the clinical trial without his knowledge had suffered from side effects of the test drug. However, he had not been aware of the trial, nor had he been provided with any information, or any treatment or compensation, even though insurance cover was available through the trial. Many similar cases have been reported, which show how poor Indian people are inducted into unethical clinical trials without their consent, and how Indians are used as guinea pigs in these clinical trials. Contributing considerably to this exploitation is the practice of pharmaceutical corporations to outsource research and ethics responsibilities to local contract research organizations without any oversight. Such clinical trials on poor, unaware and unsuspecting patients violate all applicable national and international guidelines, rules and regulations, and are a clear case of “ethics dumping”.

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Area of Risk of Exploitation

India is a large country and a majority of the population are extremely poor, uneducated and often unaware of their rights. They frequently see doctors as near-demigods, for whom they have a lot of respect and trust. Many health care facilities are extremely crowded, and there is very limited time for any doctor-patient interaction or discussion. Therefore, when the treating physician becomes a clinical trial investigator, the patients effectively have no choice but to follow the advice given. In this situation, if contract researchers receive considerable payments for research participant recruitment and only have to deal with inadequate ethics approval structures, the risk of exploitation is high.

The Case

Between 2006 and 2008, a multinational pharmaceutical company conducted a phase III clinical trial to study the safety and efficacy of an experimental drug in chronic disease patients in India. The inclusion criteria specified the following:

- adults of both sexes from 40 to 99 years of age
- current or ex-smokers with a smoking history of more than ten years
- patients with a diagnosis of the said disease

The study was conducted at fifteen sites in India along with sites in other low- and middle-income countries (LMICs). Since the study required a large sample size, a contract research organization (CRO) was engaged by the pharmaceutical company to coordinate and manage the study at all participating sites in India. Out of a total of 1,000 patients to be recruited globally for this trial, 100 were to be recruited from India (about 7 to 8 from each site).

At this time, India was moving towards becoming a “global hub for clinical trials” (Srinivas 2005) for a number of reasons. India has a large population suffering from a range of diseases, including a double burden of communicable as well as non-communicable diseases. India also has a large number of medical institutions, research centres and qualified practitioners and researchers to carry out research and clinical trials, along with a sizeable English-speaking workforce. Since the cost of accessing the medical infrastructure is much lower in India than in high-income countries, it is cheaper to carry out a clinical trial in India. As a result, a large number of CROs have been set up in India, focusing on clinical trial management. More than 300 small and large CROs are estimated to have come into existence within a very short time to serve the requirements of pharmaceutical companies (De Ron 2006, Srinivasan & Nikarge 2009, Bhan 2012, Yee 2012).

The primary objective of this drug trial was to assess the long-term efficacy and safety of a once-daily treatment, compared with placebo, in patients with the said disease. The study was coordinated by a local CRO. The principal investigator of the 15 Indian study sites was the senior project manager of the CRO, who did not have a medical degree but had qualifications and experience in clinical trial management. In India, the investigator should be qualified by education, training and experience to assume responsibility for the proper conduct of the study and should have medical qualifications prescribed by the Medical Council of India (CDSCO nd, MCI 2002).

A small private doctor’s outpatient facility was selected to conduct this trial. It was not attached to any research or teaching institution or hospital, and did not have an ethics committee of its own. As a result, ethics approval for the study was sought from an independent ethics committee from a nearby city. Committees such as this one are autonomous, with no organization to supervise or oversee their functioning, and they are not bound to make their decisions public. This has led to the mushrooming of for-profit independent ethics committees, and “ethics committee shopping” has become common (Pandya 2011, Thatte & Bavdekar 2008).

The CRO swiftly completed the paperwork requirements, including the identification of sites and investigators, registration with the drug regulator, registration of the trial on the national trial portal and ethics committee approvals for all sites through independent ethics committees, and the clinical trial began. The actual site investigators had only a small role to play, as these activities were handled by members of the CRO team.

Case Analysis

The ethical issues in this case are considerable as the following shows.

No Informed Consent

The investigator conducted the clinical trial at his clinic under the guise of providing free treatment to the patients with costly imported medicines. No questions were raised as this was

taken to be a noble deed, and it was easy to convince the poor patients visiting the clinic that this expensive imported drug could cure their diseases. These patients had no idea that they were being inducted into a clinical trial. Informed consent was not obtained, and they were not informed about possible adverse effects. The patients unwittingly participated in the study in the hope that they would get medicines of high international standard imported to India at no cost.

Financial Incentives for Recruitment

The investigator was paid incentives from the sponsor for conducting the trial, which violates Medical Council of India guidelines on professional conduct. According to the council's regulations,

“The physician, engaged in the practice of medicine shall give priority to the interests of patients. The personal financial interests of a physician should not conflict with the medical interests of patients”, and “A physician shall not give, solicit, or receive nor shall he offer to give solicit or receive, any gift, gratuity, commission or bonus in consideration of or return for the referring, recommending or procuring of any patient for medical, surgical or other treatment” (MCI 2002).

Payments to patients as well as physicians or ethics committees can play an important role in how they take decisions. Incentives in the form of per patient recruitment fees can encourage investigators to overlook the study design and inclusion or exclusion criteria in order to complete recruitment at the earliest opportunity. In this case a group of social workers submitted a complaint to the National Human Rights Commission of India. The complaint gave details of money received for conducting the clinical trials.

Exclusion Criteria Violated

Criteria for the selection of subjects specifically excluded patients with a number of pre-existing health diseases or conditions.

However, the investigator violated the exclusion criteria of the trial by including patients with some of these diseases.

Risks and Insurance Handled Inappropriately

The investigator obtained insurance cover but never informed the participants regarding any possible risks or discomfort. Some participants in the trial suffered from headaches, fatigue, nausea and more. There was no follow-up or assessment of the adverse outcomes to see whether they could be related to the trial drug. The lack of information meant that the patients who suffered injuries could not demand treatment or compensation, as they were not made aware that they were part of a trial.

Following a complaint by social workers, questions were raised in the Panchayat / Council, and heated debates and reports on local TV channels led to some investigations by the authorities. In response to a question from an elected people's representative regarding the patients in such trials, a list of more than 500 names was discussed in public forums.

It was through a local news channel that one of the participants discovered that he was an uninformed guinea-pig for a big international drug manufacturing firm, and that a drug trial had been conducted on him without his knowledge. He suffered from probable serious side effects. But like the other participants, he was unaware that he was enrolled in a trial. He believed that the physician was helping him by providing free treatment using costly high-quality medicines. Since he did not know that he was enrolled in a trial, he had not complained about his side effects. Following the news reports, he got in touch with local social workers and made a complaint to the Medical Council of India, the Drug Controller General of India (the country's drugs regulator) and the National Human Rights Commission for having been made a trial subject without informed consent, and for having received no compensation for the serious side effects he was suffering.

Post-study Obligations

The *Ethical Guidelines for Biomedical Research on Human Participants* of the Indian Council of Medical Research require post-trial access to successful medications for trial participants:

Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review (ICMR 2006:30).

The guidelines of the Central Drugs Standard Control Organization (CDSCO) incorporate Schedule Y of the Drugs and Cosmetics Rules (Government of India) and provide as follows:

Subsequent to the completion of the study or dropping out of the subject(s), the investigator should ensure that medical care and relevant follow-up procedures are maintained as needed by the medical condition of the subject and the study and the interventions made (CDSCO nd: sec. 332).

The *Declaration of Helsinki* states:

In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must be disclosed to participants during the informed consent process (WMA 2013:34).

However, it would not have been possible for those research participants who were unaware that they were part of a trial, to have received or requested post-study access to the drug, even though it was available in principle. This illustrates how violations of one aspect of ethical conduct impacts on others.

Conclusion and Recommendations

Lower costs for conducting trials on unsuspecting, treatment-naive patients in a large population with a spectrum of diseases, combined with poor review by ethics committees, lack of public awareness, and the possibility of medical staff receiving cash for recruitment, make these sites highly attractive for investigators to conduct clinical trials without putting in much effort, as the trials are managed by CROs.

In this particular trial, there were violations of all the national and international research ethics guidelines and regulations, as well as of human rights:

- The principal investigator of the multicentre study was unqualified.
- The study was carried out without appropriate informed consent.
- Patients were recruited into the trial even though they fitted the exclusion criteria.
- Large financial incentives were given to investigators for early recruitment.
- The side effects were not managed.
- Risks and insurance were not managed properly.
- There was no post-trial access or care.

In India at present, formal training opportunities in research ethics are almost non-existent. Ethics is not taught as part of the curriculum in most medical schools offering graduate and postgraduate courses. Therefore researchers as well as ethics committee members are generally inadequately trained, if at all, and do not understand their roles and responsibilities well. An ethical review may in practice only be a scientific review of the study protocol and may not help to improve the safety and welfare of participants. There is a need to create better avenues for training in research ethics, so that cases like this one no longer occur. Particularly important are practical training and certificate programmes in good clinical practice, training in ethical guidelines, and training in conducting clinical trials ethically. There is also an ongoing professional responsibility on medical researchers and ethics committee members to keep up to date regarding the latest guidelines and regulations.

The role of an ethics committee is of paramount importance, and therefore the members should be trained, aware of their roles and responsibilities, abreast with current knowledge, independent, and accountable for their decisions. Where research involves vulnerable groups, there should be additional safeguards in place. The ethics committee should not just give once-off approval, but also review progress of the study appropriately in order to ensure the continuing safety of vulnerable research participants. This is especially applicable to approvals given for off-site studies. In this case the trial was carried out in a small private setting which did not have an ethics committee of its own, and clearance was obtained from an independent ethics committee. This committee did not play any role in protecting the rights, welfare and safety of research participants through follow-up. A well-functioning ethics committee would also keep a close watch on the incentives and payments made to the investigators as part of managing possible conflicts of interest.

The public are largely unaware of the potential for exploitation in medical research and do not always understand the complexities of a clinical trial. People can easily be recruited into trials

when they are not aware of their rights, but in this case, the investigators recruited patients without even informing them about the trial. Hence even educated and literate people would not have had a chance to consider the risks and benefits of the trial and would have been rendered equally vulnerable, and exploited. The pretext of providing free imported drugs is highly attractive, especially to poor and possibly illiterate patients, who believe that foreign products mean good quality.

It is important to educate the public at large and create awareness. This will empower people to understand their rights and protect them from exploitation. In this case, social workers played an important role by raising the issue with the relevant authorities. An alert civil society, well-informed health professionals, social activists and the media can assist patient groups and help prevent such occurrences. In addition, the research team needs to devote quality time to engagement with research participants. In settings where poor and illiterate participants are involved in research, informed consent is likely to take longer and require many iterations.

Realizing that a lot of money is involved in developing a new drug, companies may try to cut costs and develop new drugs or other products in a way that brings them to market at the earliest opportunity. Most high-income countries have very stringent requirements for research participant safety and follow-up, and strict regulatory and monitoring frameworks. Therefore the costs as well as the administrative efforts of conducting a trial are much greater in high-income countries (see Glickman et al 2009, Lang & Siribaddana 2012, Nundy & Gulhati 2005, Ajmera & Gupta 2013, Birtwistle & Fairnington 2013). By contrast, in LMICs neither the patients nor the investigators nor the ethics committees are as aware of the requirements. Close monitoring and penalties or warnings are not in place. As well as generally having a high burden of disease, LMICs provide an easy and cost-effective environment for the conduct of international clinical trials.

CROs focus on clinical trial management and regulatory documentation such as ethics committee approval, clinical trial registration, insurance, documentation of consent and other requirements. Their aim is to reduce the time taken to complete the clinical trial. One could argue that the focus is mostly on completing paperwork rather than on the solid implementation of the ethical and procedural requirements to ensure that all the rights of trial participants are protected.

In a country such as India, where there is a huge possibility of vulnerable individuals and groups being exploited, it is the duty of everyone involved in the process of a trial or study to try to prevent exploitation and ethics dumping.

If all stakeholders involved in clinical research were more vigilant – including those who regulate research, sponsors and their agencies or CROs, institutions and ethics committees – and if investigators followed the principles of research ethics, then exploitation could be avoided, and the population safeguarded. Better products tested more reliably could benefit the entire population of the country.

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