Patient Protection in Clinical Trials in India: Some Concerns

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Abstract

Clinical trial participants should not be influenced by undue inducement. Clinical trial investigators should be guided by ethical principles, and patient protection should be a top priority. This does not seem to be the case in India.

Key words: Ethics, Patient Protection, Patient Recruitment, Consent

Those concerned with the ethics of clinical research have rightly highlighted the need to ensure the protection of trial participants. In a previous issue of the journal, Dr Mahaluxmiwala notes that clinical research "should be associated with altruism and trust". On the one hand, trial participants should be motivated by the good that they can do for society – not the benefits of trial participation. At the same time, those conducting a trial should be trustworthy – they should ensure that "agreeing participants are treated with dignity, their well being and rights preserved and safety protected." ¹

Unfortunately, interviews with investigators, representatives of contract research organisations (CROs) and others concerned with the clinical trials industry, and a scan of the websites of some CROs, suggest that reality is quite different. Patients enter trials not because of altruism because they feel compelled to participate, for various reasons. Physician-investigators have conflicts of interest between their duty to their patients and the incentives that they receive to recruit trial participants. CROs collect patient information through unethical practices. As a result, there is every reason to fear that participants are not assured their dignity, wellbeing, rights and safety.

Dr Mahaluxmiwala has described the importance of ethics review committees in protecting clinical trials participants. She points out that committees need to have the skills, resources and powers to do their job, ensure that the informed consent process is properly implemented, and monitor to the trial after it starts. She also notes that the public needs to be educated in order to trust the clinical trial process, with information on issues such as consent process, confidentiality, steps taken to protect participants’ rights, the protection guaranteed by ethics review, and the provision of insurance. We must consider whether the industry and the government are doing all they can to address these important concerns.

Clinical research and the pharmaceutical industry

Practices in the clinical trials industry are influenced, if not determined, by the requirements of the pharmaceutical industry. And these are: to develop a profitable drug and get it into the market as soon as is humanly possible. However, a drug is not necessarily marketed for its medical values so much as its commercial potential. The most obvious examples are sildenafil citrate and minoxidil. In such cases, the focus is on getting marketing approval for these drugs. Likewise the many "me-too" drugs on the market, minor variants of established drugs, developed by competing companies in order to grab a portion of the market. ²

Second, drug companies are naturally under pressure to get new drugs on the market as soon as possible, so that they can start making money. This means that they must complete the steps necessary for marketing approval – the clinical trials necessary to prove efficacy and safety –as soon as possible. Every day counts. Recruitment rates matter. So do the costs of clinical trials which, according to the pharmaceutical industry, represent a large chunk of the costs of developing a new drug and bringing it to the market.

We do not expect the industry to be motivated by social concerns. But we do expect that clinical research conforms to international ethical guidelines, in both letter and in spirit.

The Drugs Controller General of India (DCGI) has been upfront about why countries like India are important for the clinical trials industry: we have the human power and the medical infrastructure, trials here are much cheaper than say in the US, there is a drug naïve (untreated) population, and recruitment rates are among the highest – if not the highest – internationally.³

Implied in the DCGI’s statement is that Indians are resources – possibly not different from other natural resources such as petroleum and iron ore. This seems to be a major selling point when promoting India as a site for clinical trials – we have the people on whom you can do your research.

In fact, India’s unique selling proposition is that its people do not have access to essential medical treatment and are
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therefore far more willing to be recruited into clinical trials than are people in countries such as the United States (US). Their inability to obtain treatment is also why they are more willing to be recruited into clinical trials. So by definition, trial participants in India are in need of extra protection: their desperation for treatment should not make them overlook the risks of research.

Why patients enter trials

A survey conducted by a contract research organisation provided some interesting information.

First, the vast majority (97%) of patients entered trials because of their physicians either the trial’s principal investigator was their primary physician (76%) or they were referred by their primary care physician (21%). Few patients in India are likely to openly disregard their doctors’ advice, including advice to enter a clinical trial.

A second important finding of the survey was that a substantial percentage (26%) of trial participants was looking for better treatment, or free treatment. Indeed, investigators have suggested that patients enter trials to obtain care. In a public hospital, entry into a clinical trial is likely to provide a standard of medical care that is higher than otherwise possible, including priority for a hospital bed. Patients in the private sector faced with exorbitant medical bills are vulnerable to viewing entry into a clinical trial as a way to get free treatment. People who can afford treatment are just not likely to enter a clinical trial. Clinical trials give access to drugs and healthcare. This is likely to encourage participants to ignore the risks of a trial in order to gain the benefits of trial-related healthcare.

Third, some patients enter trials for the money. The Indian Council of Medical Research (ICMR) guidelines limit payments to reimbursement of expenses and compensation of work days lost. But clearly some people view this money as sufficient incentive to join a trial. The payments in bioequivalence trials are high enough to be called “undue inducement.” The recent death of a “volunteer” because he had participated in more than one bioequivalence trial, for the money, is evidence enough that these payments encourage people to risk their health for the money. In fact the CRO concerned actually stated that it was not responsible for the death of the “volunteer” because he had participated in multiple trials. It is not clear whether the CRO overlooked this fact or whether it knew but chose to permit his participation despite the known risks.

Recruitment practices in the CRO industry

Interviews with investigators and CROs (3) suggest that the methods used to recruit patients into clinical trials are unethical. However, these methods do not seem to provoke comment, within the industry and with regulatory bodies.

Trial investigators are paid substantial incentives to recruit participants. When these investigators are also a patient’s physician, there is a direct conflict of interest between the investigator incentives to recruit and the investigator’s duty to keep the patient’s best interests in mind. Paragraph 26 of the World Medical Association Declaration of Helsinki states: “When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.” It is well established that the patient-physician relationship is generally one of dependence; this is all the more true in India, where economic and other inequalities exacerbate this dependence – and in India a large number of potential clinical trial subjects come from lower socioeconomic groups. For this reason, it is clear that, in India in particular, a patient’s physician should not be the person who seeks informed consent for trial participation. Is this done? It seems that the general public – which includes the media – is not entitled to copies of patient information sheets and informed consent forms. But members of ethics committees have indicated that conflicts of interest are not routinely disclosed.

Can physician-investigators ensure that the patient’s interests are top priority? How do they ensure that patients don’t listen to them only because of the unequal relationship? Do they ensure that the recruiter is not the treating physician? Do they disclose that they are paid to recruit? In such a situation, it is quite possible that physicians do not ensure that such patients overlook the risks of a trial to participate in trials.

Another equally worrisome practice is to develop databases of potential trial participants from health camps, patient education programmes and community outreach through social workers and NGOs. This violates the trust implicit between the camp organiser or NGO and the patient and misleads the patient to think that the programme is in the patient’s interests. Those who attend screening camps are also more likely to seek care through these camps, and a clinical trial may be seen as an opportunity to get treatment for a new drug that is otherwise not affordable to them.

It has also been reported that CRO representatives in hospitals can get access to patient databases. This gives a third party – who has no medical standing — access to a patient’s confidential records, for that party’s personal benefit. This is an extraordinary practice and a violation of the Code of Medical Ethics.

At a meeting of CROs some time ago, it was heartening to hear a CRO representative publicly express reservations about the use of camps to recruit patients. But the impression is that, as a rule, CROs are not worried about the ethics of such practices. A systematic survey of CROs will give a better picture of the industry. However, few people within this industry are willing to speak openly and provide detailed information. This lack of transparency is a reason for the
Public to be suspicious of the industry’s intentions.

Conclusion

Of course, clinical research should require that all trial protocols be reviewed by a qualified and registered ethics committee, that the trial itself is monitored to ensure that the various ethical requirements are followed – participants are chosen appropriately, informed completely of all the risks and benefits and other components of consent, and consent obtained. The law on clinical research should be followed: trials done only after establishing their need, that all prior research is carried out, the results available, that the ethics committee is convinced that the trial is necessary, risks minimised, protection in the form of insurance, compensation, etc. The question is whether it is enough to follow legal requirements and document them.

There is a danger of focusing on paperwork that documents the accuracy and completeness of clinical trial data. This does not address issues such as the context of clinical research in poor countries without access to healthcare. There are also the consequent pressures on potential trial participants, the use of recruitment incentives and conflicts of interest that they pose. Such issues make it especially important for patients to be protected – a challenging proposition given that the government sees clinical trials as a potentially lucrative industry.

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From the World of Clinical Trials

The study focuses on a crucial aspect of the attitudes of the relatives, who are asked to consent on behalf of unconscious relatives in ICU, towards drug trials. The authors performed a prospective questionnaire survey of the next-of-kin to 50 unconscious adult patients, admitted to ICU. Of the 42 relatives surveyed, majority were positive/positive with some scepticism towards performing drug trials in unconscious ICU patients, or would most likely accept trial-participation by their relative. The majority felt that they should decide if their relative was to participate in a drug trial, and that deferred consent would be acceptable if there was a limited time frame for initiation of treatment. Factors considered important for trial participation were: 1) adherence to legislation, 2) treatment benefit for the study patient and for future patients, 3) no patient-risk or -discomfort and 4) development of new drugs. The authors concluded that relatives of unconscious ICU patients expressed positive attitudes to drug trials in the ICU and the inclusion of their relative in drug trials.