Need for ethical oversight of clinical trials in India

J. S. Srivastava

It has been estimated that within the next five years India will host more than 20% of the global clinical trials[1]. Before 1996, USA, Europe and Japan were the major participants in conducting clinical trials following the guidelines set on the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH; http://www.ich.org/cache/compo/276-254-1.html, 1996). As a result of economic globalization, major pharmaceutical companies have started outsourcing their clinical trials to developing countries, and India is one of the preferred destinations. In a recent report from the Office of the Inspector General, Department of Health and Human Services, FDA, USA, 80% of the drugs approved for sale in 2008 had trials in foreign countries and 78% of all subjects who participated in clinical trials were enrolled outside the US (http://oig.hhs.gov/oei/reports/oei-01-08-00510.pdf, 2010). Testing of ten drugs approved in 2008 was done entirely abroad and not a single patient from the US was recruited. Although the majority of human participants in these trials were recruited from western Europe, central and South America, India has the potential to provide a hunting ground for pharma multinational companies. Certainly, India has this unique position amongst developing countries due to its vast human resource, improving economy and English-speaking clinical investigators. But there have been reports in the international media and medical journals about unethical clinical trials, that were even termed as new colonialism[2,3]. An editorial published a few years ago in *Lancet* emphasized the need for ethical oversight and strict regulation to strengthen clinical research in India and to meet the global standards set by the ICH guidelines[4]. The editorial highlighted the enforced areas and outlined the persisting weaknesses in the system. The enforcement aimed to bring India on par with international standards such as adoption of good clinical practice (GCP), patent protection as well as removing the phase lag between India and other countries. However, weaknesses persist in the implementation of ethical and regulatory guidelines.

The regulation of clinical trials in India follows a two-fold path – one through a central regulatory agency and the other through ethical oversight by the ethics committees at the local level. Ideally, these should be complementary to each other. To fulfil this commitment, Schedule Y implemented through Drugs and Cosmetics Act requires following the Indian Council of Medical Research (ICMR), New Delhi ethical guidelines to conduct clinical trials. But, ethics committees that are constituted by the institutions individually express a lot of variability in their structure and mode of functioning. The ethical oversight for initiation and conduct of clinical trials should be through prior review and monitoring by the research ethics committees. Unless a proper review has been undertaken, it is difficult to consider whether ethical norms have been followed. The ICMR issued two versions (2000 and 2006) of ethical guidelines and also conducted bioethics education programmes across the country[5]. Despite these initiatives, there is inadequate regulation of clinical research in India. One of the important factors for effective ethics implementation is the view of clinical investigators towards their institutional ethics committees. These investigators are mainly drawn from academic faculty from medical institutions. In developed countries, the requirements of ethics review and the processes to follow are well established. However, the same is not true for countries like India as the process of ethics review is relatively new and it is not implemented with the same rigour as in the West. A recently published report on the Clinical Trial Registry in India, maintained by the National Institute of Medical Statistics under ICMR, has 'revealed the lack of awareness of various regulatory processes, especially those related to ethical review of all human research. Instances where academic institutions did not have a proper EC to review clinical trials were also brought to our notice'[6]. Carrying out clinical trials in developing countries should be encouraged because at the end the benefits will reach the people of these countries as well. And if that is the case, why should they also not participate in the development of medical science and even the development of new drugs? However, problems in ethical conduct in clinical research have been encountered occasionally. One case was reported from Indore, and the role of the doctor has come under the scanner over trials sponsored by pharmaceutical companies. The state government has initiated an enquiry (ebhopal.blogspot.com/.../clinical-drug-trials-doctors-role-under.html). In another case from Bhopal, the Drugs Controller General of India has issued notice to the Contract Research Organization (CRO), based in Bangalore on clinical trial of the drug, telavancin, an antibiotic tested on patients with hospital-acquired pneumonia. CRO was working on behalf of an US-based multinational pharma and the study involved the death of three patients (www.livemint.com/2010/08/.../Drug-regulator-seeks-inquiry-i.html?). In developing countries, the prevailing circumstances are vastly different (economic and educational) and subjects are more vulnerable than in the developed world. There are three major issues in this context: understanding the value of ethics review by the investigators and institutions themselves; ethics viewed as a hindrance by the investigators resulting in unwillingness to undergo ethical review; and finally, an outline of suggested measures that are likely to be successful.

Value of ethics review

India is a country of more than 1 billion people and the government is facing grave challenges in meeting healthcare sector requirement despite launching the National Health Policy and undertaking the National Rural Health Mission. In a recent report from UNDP, published in *London Economic Times*, it has been mentioned that eight Indian states account for more poor people than 26 of the poorest African nations combined. In such a situation of conducting clinical trials on populations living under such extreme conditions, it is not difficult to imagine their vulnerability. Clinical research involves two sections of the society – one the active participation by

researchers and the relatively dependent participation by the research subjects. There is a need is to ensure that the active group does not become too enthusiastic to put research subjects at risk during the planning, conduct, analysis of data and result interpretation of a clinical study. Clinical investigators may be interested to conduct and complete the research projects quickly, and obtain research grants for promoting their careers. Those could result in distorted judgements while designing, conducting and analysing research. An independent review of such projects by experts would minimize the impact of potentially conflicting interests[7]. This type of review is also important for social accountability and obtaining the support of communities. Clinical research should be undertaken with no risk or minimal harm posed to the subjects who are a part of the society. Independent reviews are expected to mitigate the possibilities of one section of the society taking advantage over another. These points highlight the need for ethical review of scientific projects. There are some examples from India where studies have been undertaken with no proper ethical review before initiating a research study. An example is the 'erythromycin study' in women for evaluating the antibiotic as a contraceptive and finally using it as a sterilizing agent[8]. Similar concerns were raised in earlier studies with new anticancer and anti-diabetic drugs, where the investigators conducted trials with questionable ethical review[9,10]. These examples should serve as eye-openers to our regulators, before it is too late.

Ethics as a hindrance

There may be several highly qualified and experienced clinical investigators in developing countries like India. However, in our country doctors are treated like 'Gods' by the patients. Thus the doctors feel that they have a right to decide what is good or bad for their patients and deliver accordingly. In this backdrop, it is difficult for them to imagine a situation where they have to appear before ethics committees for approval of their research protocol or monitoring of their projects. Therefore, occasionally they view ethics as a hindrance to their research ideas taking final shape. Other reasons could be a delay in the review process, fear of disclosing their intellectual pursuits, lack of trained bioethicists/subject experts in review committees, inability to differentiate between ethical and unethical research, fear of disapproval and encroachment on their academic freedom. These factors result in general unwillingness to undergo ethical review that could mainly be linked to the lack of appreciation about the significance of such reviews. Usually physician-researchers consider themselves as self-claimed protectors of a subject's interests. Most of them feel that obtaining an informed consent is sufficient for undertaking research on patients or healthy volunteers. It is generally believed that doctors always work for the benefit of patients, whether in research or patient care. Further, there is growing concern on unintended consequences of regulations on clinical trials[11]. However, rising bureaucracy is affecting the conduct of clinical trials as well. Several processes take undue time resulting in delays in the completion of trials and ultimately delays in therapeutic modalities that should reach the patients early. These may also have a bearing on other non-commercial researches which could mirror increasing bureaucracy as GCP guidelines are not legally binding on the regulatory authorities to most non-commercial research. Lastly, maximum regulation does not mean increased protection for human subjects, and it is better to have lesser regulation for research involving minimal risk for the participants[12].

Corrective measures

In 1997, the Medical Council of India recommended including bioethics in the medical curriculum and again in 2002 advised medical professionals to abide by the ICMR ethical guidelines for conducting biomedical research. The development of national ethical guidelines is definitely a positive step in this direction. However, there is also a need for proper implementation of these guidelines. The ICMR has made efforts in this direction through the bioethics education programme. Measures to educate health professionals involved in research, through workshops and symposia on research ethics for human participant protection, were the major steps. Although research institutions are required to constitute their own ethics committees and review research proposals according to guidelines, most institutions do not have such committees and even if these exist they are not according to the guidelines. It is required that duly constituted ethics committees also undertake educational aspects and researchers be informed about earlier instances of putting subjects at unnecessary risk or harm. Helping researchers in identifying and resolving ethical issues encountered in clinical research would actually strengthen the effort. Gradually they will be able to perceive the difference between ethical and unethical research. The investigators and ethics committee members may also be invited to attend such sessions so that they perceive that research involving human subjects must be undertaken only to prove or disprove a sound scientific hypothesis as the primary criterion[13]. Secondly, there should be no other possible way of conducting such research, and results thus obtained should be capable of producing benefits that would reach, directly or indirectly, the subjects and the society. Further criteria for ethical research should include provisions for a fair subject selection, favourable risk–benefit ratio, independent review, properly informed consent process, and continued respect for the enrolled participants. The Forum for Ethics Review Committees in India, the Forum for Ethics Review Committees in the Asia-Pacific (FERCAP) region and ICMR are making efforts to accredit the ethics committees. WHO and Fogarty International Centre have also joined various national agencies like DST, ICMR and DBT to organize ethics workshops, as developed countries have a moral responsibility to conduct ethical research in developing countries. One example is the University of Toronto collaboration with ICMR, funded by Fogarty International Centre. Several identified individuals were trained for a Master's course in bioethics under this programme[14]. There are examples of other Fogarty programmes running at Monash University, Harvard University and Erasmus Mundus programme in Europe, in addition to several online courses on research ethics. However, it has been a great challenge to devise programmes to train research professionals in our country in view of the mushrooming of several clinical research courses all over the country. In March this year, a draft on

National Health Research Policy was put on the web to initiate public debate with the intention to outline priorities and formulate steps in the right direction. It contains a proposal for a Bill on Research on Human Subjects and establishment of National Biomedical Research Authority, along with strategies to harmonize the various guidelines developed for health research. To support these initiatives, the Indian government could formulate legal measures similar to the US Department of Justice that had already started investigating cases of corrupt practices like payments, etc. offered to doctors conducting clinical trials (http://www.timesofindia.indiatimes.com/.../US-probes-pharmacos...bribing-doctors/.../6334175, 19 August 2010). The investigations were triggered by a report that 40–65% of clinical trials for FDA-regulated products were conducted outside the US, which brought concern about the reliability of the data (http://oig.hhs.gov/oei/reports/oei-01-08-00510.pdf, 2010).

Conclusion

India is certainly prepared to undertake clinical trials both on domestic products and sponsored clinical trials from abroad. The clinical research industry in India touched US$ 320 million in 2009, starting from US$ 140 million in 2006. An estimate shows that clinical research in India is expected to be US$ 630 million by 2012 (http://www.researchandmarkets.com/reports/1212074/, 2010). Currently there are more than 150 CROs operating in the country, but only 20 of them are ICH–GCP compliant; more are coming up in view of the business potential. However, in order to avoid exploitation, the emphasis should be on linking science to benefit the society and educating the professionals on finer aspects of clinical research. There is a need to understand the significance of an ethical review by researchers in view of outsourcing of clinical trials to developing countries. The proposed National Health Research Policy by the Indian government may bring in the desired changes and encourage health research by giving well-defined directions. Finally, it can be concluded that educational efforts with a focus on ethical and regulatory requirements would definitely improve not only the quality of clinical trials, but clinical research in our country.

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J. S. Srivastava is in the Division of Clinical and Experimental Medicine, Central Drug Research Institute, Lucknow 226 001, India.
e-mail: js_srivastava@cdri.res.in

Malaria recession and the way forward

Vas Dev

Malarial threat is receding with reported decline in malaria cases not only locally, but also globally. Worldwide map of the distribution of cases is shrinking and subject experts are now contemplating malaria eradication in many parts of the globe that were earlier intractable. In the next decade there will be a huge challenge that would present an unprecedented opportunity for research and investment on new potent antimalarials, scaling up interventions, and developing stronger health systems ensuring equitable healthcare access and all-round economic development.

India shares the success stories related to malaria research, including the Nobel Prize-winning discovery that malaria is transmitted by mosquitoes by Ronald Ross in Secunderabad on 20 August 1897 and control operations during 1960s under the National Malaria Eradication Programme (NMEP)[1]. With the advent of DDT post-independence, the malaria eradication programme in India became popular the world over for its well-organized action towards freedom from the disease.

But the euphoria of success did not last long, when focal disease outbreaks with 6.47 million cases were reported in 1976, the highest ever resurgence. Among several constraints that led to resurgence, drug-resistance in malaria parasite and insecticide resistance in mosquito vectors continued to hinder the equitable development in many parts of the country. To