EDITORIAL

Fatal trials: clinical trials are killing people

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In many quarters there is satisfaction that India is developing into the "clinical trials capital" of the globe. By all accounts the business of conducting clinical trials in India is growing at a phenomenal rate. The reasons have been discussed widely and merit only a brief mention here. Situating clinical trials in India provides the advantage of low costs (estimated as 60% lower than in developed countries), relatively high levels of technical expertise and a large population base on whom clinical trials can be conducted. The large population base has the additional advantage (as subjects of clinical trials) of being largely "treatment-naïve", or not exposed to any form of treatment, and representing a large genetic diversity as six out of the seven genetic varieties of the human race are represented in India. Clinical trials conducted here also have the advantage of being able to target populations that are at risk from diseases of poverty and underdevelopment (communicable diseases and diseases related to under-nutrition) as well as the so-called "lifestyle diseases", or diseases related to an affluent lifestyle.

Spectacular growth with lax control

There have, simultaneously, been efforts by the government in India to promote India as the preferred destination for conducting clinical trials. Before 2005 the Indian law permitted clinical trials of drugs being developed outside India with a "phase lag": the trial in India had to be conducted one phase earlier than elsewhere. This meant that, for example, if the Phase 3 of a trial was completed outside the country, trials within India had to commence from Phase 2. However, an amendment of Schedule Y of the Drugs and Cosmetics Rules, in January 2005, allows "concurrent phase" trials in the country. Thus, Phase 2 and Phase 3 trials for drugs discovered outside India can now be conducted concurrently with international trials. It is understood that further changes are on the anvil to allow Phase 0 and Phase 1 trials for all drugs developed outside India; this would be a change from the present situation where Phase 1 trials of drugs developed outside India are allowed only for drugs relevant to the subject population and phase 0 trials are not permitted.

These factors have combined to produce a growth in the clinical trials industry in the country that can only be termed as spectacular. It is estimated that one in four clinical trials in the world are now conducted in India, and the turnover for the industry is expected to touch US$ 1.52 billion by 2010 (1). The Association of Indian Contract Research Organisations (ACRO) chairman Dr S P Vasireddi is quoted as claiming: "We have now a share of 24 per cent while China has 33.3 per cent of the global business." (2) The total number of registered ongoing trials in the country exceeds 700, up from around 250 just two years earlier (3). This phenomenal growth has happened, unfortunately, in a situation where regulatory mechanisms have not kept pace. Even industry sources admit that at present levels there is a need for about 5,000 new professionals trained in good clinical practice (GCP) in the industry to augment the 600 odd who are available in the country. While ethics review is now mandatory for clinical trials, there is little review of the functioning of ethics committees by the drugs controller general of India (DCGI). There is little interaction between ethics committees in different locations, thereby allowing the practice of "ethics committee shopping": sponsors whose trial is rejected by one ethics committee approach a different centre for approval.

Spate of reports on fatalities

The state of the clinical trials industry in the country has been brought into focus by a spate of reports of fatalities among subjects of clinical trials. The death of 49 children in six clinical trials conducted at the All India Institute of Medical Sciences (AIIMS) was brought to public notice through a Right to Information action filed by a non-governmental organisation (3). While a committee set up by the ministry of health has subsequently cleared AIIMS and opined that all prevailing guidelines were adhered to, the very high number of deaths among clinical trial subjects in the premier institution of the country is a cause for concern. Since then two other deaths have been reported in clinical trials conducted by one of the premier contract research organisations of the country, GVK Bio. GVK claims to work with 15 of the top 20 pharmaceutical companies operating in the country (4).

The first case of a fatality in a trial conducted by GVK pertains to the death of an infant while being part of a trial on a pneumonia vaccine developed by Wyeth Pharmaceuticals, at St John's Hospital in Bangalore. The DCGI stepped in, after media reports were published, to cancel the trial. GVK maintains that the infant died of an underlying condition, a serious congenital heart disease, and was not even administered the new vaccine as it was part of the control group (5). While this may be true, it is unacceptable that the serious congenital heart disease was overlooked by the paediatric specialist while recruiting this child into the study. This

is an unpardonable lapse given that the trial was cleared to cover healthy subjects (healthy babies who were between 42 and 72 days old) only. It also points to the callous manner in which clinical trial subjects are recruited.

The other case pertains to the death of a young adult in a Hyderabad-based facility. The person who died was a subject in a bioequivalence study of the cardiac drug Felodipine. Here again GVK has denied any lapse on its part and claimed that the death occurred over a week after the drug was administered, by which time the drug would have been "washed out" of the body. What is particularly curious about this case is GVK's additional claim that the subject was a part of many other studies. The company claimed that the subject "has been participating in similar bioequivalence studies in various CROs. He has been a part of similar studies in GVK Bio in the past." (6) This raises the suspicion that the deceased was a "professional" subject of studies and trials and was recruited after being provided monetary incentives. Not only would such a practice be unethical, it would also be dangerous given the cocktail of different drugs to which such a participant would be subjected.

The cases discussed above are, in all likelihood, the tip of the proverbial iceberg. The Wyeth vaccine case is a landmark of sorts as it is the first instance of the DCGI stopping a trial for non-compliance with regulations. That all these cases came to light after media reports points to the inability of the DCGI to monitor clinical trials in any meaningful manner.

Clearly, what we have today is a gross mismatch between the rate of growth of the clinical trials industry and mechanisms to oversee and regulate them. Expanding the scope of clinical trials without transparent and explicit mechanisms for protection for trial subjects is unacceptable. Drug companies have been known to perform research in developing countries that do not conform to the Declaration of Helsinki (DoH) on "Ethical Principles for Medical Research Involving Human Subjects" and could not be conducted in the developed world. The commercial secrecy that surrounds early clinical research means that much preliminary research is unpublished, particularly when adverse effects are high and further development is abandoned (7).

Protection for subjects of clinical trials

Today, in a large number of cases, volunteers in clinical trials in India are volunteers only in name. Ethical principles are flouted regularly, informed consent is not taken properly, and participants are enrolled in situations where they have few options to refuse participation. It is believed that the ICMR was in the middle of a study on the quality of informed consent in India - but the study could not go ahead due to paucity of funds (8). If at all we are to favour the promotion of clinical trials in India, restrictions are necessary to ensure that the health of trial participants is adequately protected in case of any contingency. Also, importantly, it must be assured that trial subjects are volunteers in the true sense; they have not enrolled because of monetary or other incentives, and that they have been explicitly informed that they are to be part of a clinical trial. The DoH is clear in this regard: "The subjects must be volunteers and informed participants in the research project."

As a beginning, in order to protect clinical trial subjects, amendments must be made to the GCP guidelines requiring the following: comprehensive five-year health insurance for all participating volunteers must be purchased from a shortlist of insurance suppliers; sponsors must give viable bank guarantees as proof of their sincerity in assuming the obligation of compensation for any direct and indirect adverse consequences and trial participants must be income tax-payees.

The issue of compensation to participants for research-related injury is addressed variably across the world. In the United States, sponsors and institutions are not legally bound to provide either free medical care or compensation for research-related injuries to trial participants. Many European countries mandate the provision of "no fault" clinical trial insurance. The Association of the British Pharmaceutical Industry guidelines recommends that subjects suffering from research-related injuries be compensated. The vulnerability of clinical trial subjects in India is a strong argument in favour of mandating insurance cover and compensation in cases of injury or death.

Finally, it is time that the ministry of health took a hard look at what it seeks to gain by promoting India as a haven for clinical trials. If recent trends are to be taken note of, there is a very good case for tempering the current enthusiasm to promote clinical trials in the country with strong regulatory mechanisms.

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