Parliamentary Committee indicts Clinical Trial Industry

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THE Seventy-Second Report of the Parliamentary Standing Committee on Health marks a strong indictment of the way in which clinical trials are being conducted in India. Before discussing the report, it is important to understand the underlying reasons for the present state of affairs.

Open Invitation for Foreign Companies to Conduct Clinical Trials in India

The story dates back to 2005 when the Indian government revised a very crucial section of the Drugs and Cosmetics Act, which governs the use of medicines, vaccines and other products that are used to improve human health. The amendments in 2005 pertained to the section on clinical trials, ie, research done to prove that a product is safe and effective. All medical products, before being allowed to be marketed, need to pass through different phases of clinical trials.

The 2005 amendments made it easier for drug companies to do research that involved Indian participants. The government's rationale for easing conditions under which research could be done by foreign companies were that it would bring in foreign investment (the abiding mantra of neo-liberal policies!), that it would help Indian science by drawing more research activities into the country, and it would help Indian patients by promoting early introduction of new drugs. Within a year, the number of clinical trials being conducted jumped to over 500 per year , from less than 100 per year in the pre-2005 era. What followed was a virtual free for all – unscrupulous trial sponsors and contract research organisations (CROs) milked the system and patients suffered. The regulatory systems did not have the capacity to deal with the sudden rise in the number of trials. The resulting confusion could well have been termed a 'comedy of errors', except for the fact that the consequences were tragic, and in several instances, fatal.

Shift of Clinical Trial Locations to Developing Countries

Traditionally the United States has been the major centre for conducting clinical trials. A vast majority of clinical trials used to be conducted in the United States and Western Europe. While even today a majority of trials are conducted in these two regions, the situation has started changing quite rapidly in recent years. Given that most pharmaceutical companies that develop new medical products are based in the US and Western Europe, it was logical that trials to validate these products would be conducted in these regions.

The shift of clinical trials to other countries has been driven by several factors. One major factor that has contributed to the globalisation of clinical trials is the rise of contract research organisations and the accompanying outsourcing of clinical trials. Unlike a few decades earlier, drug companies often prefer not to directly conduct trials but outsource them to CROs. The CRO industry has grown phenomenally – its turnover grew from $1 billion in 1995, to $7 billion in 2005, and to an estimated $21.4 billion in 2010. CROs prefer non-traditional sites to conduct clinical trials because they are cheaper in countries such as India as compared to the developed world. What is left unsaid is that the cost of human lives is also cheaper. Most European countries have regulations that mandate compulsory insurance for human trial subjects that includes 'no fault liability' – ie, insurance coverage that covers the possibility that the research may result in adverse effects on subjects even if the trials were properly designed and executed. In India, we are just starting to discuss the issue of compensation for trial subjects who suffer adverse effects. Also left unsaid is that CROs prefer countries such as India because regulatory capacity is weak and laws and rules are yet not commensurate with requirements. There is clear evidence that trials are moving to places outside the US and Western Europe. This is clear from data from the European Medicines Agency (EMA) regarding number of trial participants involved in Phase III trials (the largest final

phase of trials before regulatory approval) for which data was submitted for regulatory approval of different drugs in the EU. In 2005, 79.8% of trial subjects lived in the EU or the US, but by 2011 this had declined to 62.7%. The largest increase was in Asia – from 2.0% to 12.8%.

Exploiting the Vulnerability of Poor Patients

There is another very important reason why it is easy to enroll 'volunteers' for clinical trials in a country like India. Theoretically all trial participants are volunteers, and choose to participate after they are clearly explained about the risks involved. It is important to recognise that all trials are experiments, and hence carry a theoretical risk. That is why there is a huge premium put on the 'informed consent' process of clinical trials. In countries such as India the entire process of procuring informed consent from trial participants has been converted into a sham in a very large number of cases. First, a bulk of trial participants are drawn from underprivileged sections, many of who do not have the capacity to understand the consequences of participating in a clinical trial. Second, and perhaps most importantly, trial subjects are vulnerable because they are at the mercy of a non-functioning health system. They are vulnerable to pressure from their treating physicians – who could also be the investigator in a clinical trial – because participation in a trial can often be the only way in which a poor patient is able to afford treatment for a chronic or life threatening conditions. CROs exploit the vulnerability of patients to recruit trial patients and the tag of a 'volunteer' means very little.

We discussed earlier that it was believed that by changing the regulatory norms in favour of less restrictions on clinical trials by foreign companies, Indian patients and Indian science will benefit. Neither has happened. Indian patients rarely benefit as trials conducted by foreign companies are used to generate data that allows them to get marketing approval in their home countries. These drugs are patented and sold in the global market at exorbitant prices, well out of the reach of virtually all Indian patients, and definitely not available to poor patients who form the bulk of trial participants in India. Nor has Indian science benefited. CROs today recruit both patients to participate in trials and doctors or scientists who conduct the trials. The latter are not involved in designing the trial, or in using the data to further their own research. The data generated flows back to the parent company and Indian scientists are used as mere conduits to generate and transmit data.

The horror story of the Indian clinical trial industry has now started unfolding and the evidence has been so compelling that the Supreme Court, in early 2013, stepped in to put severe restrictions on approvals to clinical trials. The Supreme Court, in an interim order that responded to a Public Interest Litigation (PIL) by Swashya Adhikar Manch and others, directed that the Drug Controller General of India (DCGI) would have to consult the health industry before allowing any clinical trial in the country. There are extensive reports of ethical violations and of multiplying severe adverse effects involving trial subjects.

The Gory History of Clinical Trials

The gross and repeated rights violation of trial subjects in India are grim reminder that when private capital stands to benefit, and when public scrutiny is muted, rights violations are the norm rather than an aberration. The history of trials on human subjects, has in the past, thrown up several such instances. Two of the worst instances of such violation relate to the Auschwitz trials in Nazi Germany and decades of violations of human rights among the prison population and among people of African origin in the United States, who were coerced into participating in clinical trials.

A particularly horrendous tale in the US (among several others) unfolded with revelations in 1972 surrounding the 'Tuskegee Study of Untreated Syphilis in the Negro Male', which was begun in the 1930's and lasted 40 years. In it, several hundred mostly illiterate men with syphilis in rural Alabama were left untreated, even after a cure was discovered, so that researchers could study the disease.

In the late 1970s, other horror stories emerged. In 1979, the Philadelphia Inquirer reported that inmates in Holmesburg (Philadelphia Detention centre) had been used as guinea pigs to test whether mind-altering drugs were useful as Army weapons. In 1981, the paper reported that inmates had been dosed with dioxin to test the herbicide's effects on human health. The centre was later to gain further notoriety as it became known that for twenty years, tests involving toothpaste, deodorant, shampoo, skin creams, detergents, liquid diets, eye drops, foot powders and hair dye were conducted on the prison inmates, all

accompanied by constant biopsies and frequently painful procedures. Finally in 1978, public opinion forced Congress to adopt legislation that severely restricted the use of prison populations for clinical trials. It has been conjectured that the move of clinical trials to developing countries found its early impetus in this change in the US law.

The HPV Trial in India

The story of the HPV trials in India, sponsored by a US based NGO called Program for Appropriate Technology in Health (PATH), appears to be a throwback to the dark ages of the Auschwitz, Tuskegee and Holmesburg trials. Instead of concentration camp, jail inmates, or African Americans, here the trial subjects were thousands of young pre-adolescent girls, many of them living in hostels, in rural areas of Andhra Pradesh and Gujarat. PATH was given approval for a trial that they called a 'demonstration project'. PATH's so called demonstration project was funded by the Bill and Melinda Gates Foundation and the vaccines were provided free of cost by the two giant vaccine manufacturers – Merck and Glaxo Smith Kline (GSK). The trial involved vaccinating girls with a vaccine that would protect them against the Human Papilloma Virus (HPV). It is believed that infection by the HPV virus predisposes to the development of cancer of cervix (the last portion of the uterus). While only a fraction of patients infected by the HPV virus develop cervical cancer, almost all cervical cancer patients are found to harbour the virus. The two vaccines developed by GSK (Cervarix) and Merck (Gardasil), are available in many countries (including the United States where it has been extensively used since 2006) and is also approved for marketing in India. However the issue we pick up here is not the efficacy and safety of the vaccine (regarding which there are several questions, which we are not elaborating here) but of the way in which the trial was designed and executed.

There were gross ethical violations in which trial participants were recruited. In Andhra Pradesh, consent was not taken either from the girls or from their parents or guardians. Hostel wardens signed up to give consent for hundreds of girls in their charge. The district health systems were in no position to monitor the health of the trial subjects or to follow up on possible adverse effects. The story broke when four deaths were reported among trial subjects in Khammam. Till this day the cause of death and its possible link with the vaccine has not been established or disproved for the simple reason that there were no systems in place to follow up trial participants.

When the issue was raised by several health and women's organisations and was also raised in parliament, the ministry of health and family welfare promised to conduct an enquiry. The enquiry report agreed with the contention that there had been several violations of rights and of regulatory procedures, but remained silent as regards apportioning of blame and recommendation of punishment for those involved in allowing and in conducting such a trial.

PATH tried to hide behind its façade of being a non-commercial NGO and a self proclaimed philanthropy. It repeatedly tried to obfuscate the issue by claiming that it had conducted a 'demonstration project' and not a clinical trial, and hence rules governing clinical trials did not apply to their project. This is a blatant lie as clearly any experiment conducted on human subjects (especially one where a medical product was administered), irrespective of the nomenclature, is a clinical trial. The DCGI provided approval for the trail when the trail design was flawed as it did not have proper protocols in place to record informed consent, or systems in place to effectively monitor the vaccinated children. The ICMR, the apex body in the country that develops guidelines on clinical trial ethics, was complicit participant and collaborator. In fact the Project Advisory Group (PAG), set up for the project, included representatives from ICMR, PATH, AIIMS, governments of Gujarat and Andhra Pradesh, and the World Health Organisation (WHO).

Scathing Criticism of the Indian Regulatory System

Given this context, the recent report of the Parliamentary Standing Committee on Health, comes as a timely corrective. The report has been scathing in its criticism of all those who were involved – PATH, DCGI, ICMR, and the inquiry committee. In its report the Standing Committee has remarked:*"It is apparent the PATH has exploited with impunity the loopholes in our system as also the absence of a nodal point or a single window for maintaining a data bank of foreign entities entering the Country for setting up their offices". It further goes on to say: "Coming to the instant case, it is established that PATH by carrying out the clinical trials for HPV vaccines in Andhra Pradesh and Gujarat under the pretext of*

observation/demonstration project has violated all laws and regulations laid down for clinical trials by the Government. While doing so, its sole aim has been to promote the commercial interests of HPV vaccine manufacturers who would have reaped windfall profits had PATH been successful in getting the HPV vaccine included in the UIP of the Country. This is a serious breach of trust by any entity as the project involved life and safety of girl children and adolescents who were mostly unaware of the implications of vaccination. The violation is also a serious breach of medical ethics. This act of PATH is a clear cut violation of the human rights of these girl children and adolescents. It also deems it an established case of child abuse. The Committee, therefore, recommends action by the Government against PATH. The Committee also desires that the National Human Rights Commission and National Commission for Protection of Children Rights may take up this matter from the point of view of the violation of human rights and child abuse".

It is hoped that the government and concerned agencies will act on the parliamentary committee report expeditiously. At stake is not just the immediate case of the HPV trials but the entire perversity that now permeates the clinical trials industry in the country. Clinical trials are necessary if safe and effective medicines are to be developed. But by allowing the conversion of the clinical trials industry into the worst kind of profit making enterprise, we are doing gross disservice to both experimental science and health care.