AN OVERVIEW OF THE CLINICAL TRIAL SYSTEM IN PLACE IN INDIA

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Abstract

There is a rapid growth in clinical trials not just in India but also all over the world. Trials are now being globalized and the need for development and growth, especially scientific and technology related growth, has caused the ethical aspects of trials to take a back seat. The government itself promotes trials in India despite the fact that there is no proper way to regulate the same, poor people are forced to take part in trials as that is the only way that they can afford to get the care required for that particular problem. The worst part however is that Medical professionals themselves induce patients to take part in trials and are given substantial incentives to recruit them. Another instance in which the ethical aspect of a trial was questioned significantly in India is in a case in 2009, wherein the states of Andhra Pradesh and Gujarat launched a vaccination project against HPV, some types of which can cause cervical cancer. This trial was conducted without proper consent causing the death of these girls. Another major problem emerges from globalization of clinical trials, as once again the proper measures to regulate them are absent. India is an attractive site for offshoring of clinical trials because of its lack of stringent laws.

Keywords: Clinical Trials, Ethics, Globalization, Guidelines, Research

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Introduction

It is generally viewed that pharmaceutical companies play a key role in doing good to the society as they formulate drugs crucial for solving a number of diseases and health problems. However, there is another side to the formulation of drugs. The drugs available in the market go through the process of clinical trials. The definition of clinical trials according to the World Health Organization is as follows;

"For the purposes of registration, a clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiological procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc."[1]

Rule 122 DAA of Drugs & Cosmetics Rules, 1945[2] defines clinical trials as a "systematic study of new drug(s) in human subject(s) to generate data for discovering and/or verifying the clinical, pharmacological (including pharmacodynamics and pharmacokinetic) and/or adverse effects with the objective of determining safety and / or efficacy of the new drug"

Drug companies are attracted to India for a few reasons, including an in fact skilled workforce, patient accessibility, low expenses and friendly drug control laws. While in some ways this is uplifting news for India's economy, the expanding clinical trial industry is raising concerns as a result of an absence of direction and regulation of private trials and the uneven application of requirements for educated and informed consent and appropriate ethics review.

The government is aggressively promoting India as a location for clinical trials even before setting up the structure to regulate the conduct of these trials.[3] Clinical trials are conducted by contract research organisations which are making inroads into small towns, identifying trial sites in small private hospitals and developing databases of potential trial participants.

Ethics aspects in connection with clinical trials

The World Medical Association (WMA), in the Declaration of Helsinki (Declaration), established the first set of ethics rules for research in humans formulated by the international medical community in 1964[4].

[1] *Clinical trials*, World Health Organisation (Sep 4,2018), http://www.who.int/topics/clinical_trials/en/

[2] Drugs and Cosmetics Act, 1940, No.23, Acts of the Parliament,1940 (India)

[3] Sandhya Srinivasan, *The Clinical Trials Scenario in India,*Vol. 44, Econ Polit Wkly, 29, 29 (2009)

[4] Johan PE Karlberg & Marjorie A Speers, Reviewing Clinical Trials:A Guide for the Ethics Committee, PFIZER, accessible at

One cornerstone of human research ethics is that individuals who participate in clinical research should do so voluntarily. The voluntary aspect is important, since it is the participant's choice to participate according to his or her own preferences and wishes. To maintain the voluntary air, participants should be free to withdraw from the research at any time[5].

It is important that the subjects of clinical trials are made aware of the methods that are used for participant recruitment. This is an important aspect of ensuring that the trials have been conducted by informed consent. Undue influence and exploitation come into the picture mainly when trial participants are approached by someone who does not have the required position or authority to do so. Any sort of relationship of dependency between the participants and the recruiters can the cause of undue influence.

Medical professionals are given substantial incentives to recruit their own patients into these trials thus creating a major conflict of interest that threatens the well-being of patients[6]. Another point to be noted is that clinical trials are generally accompanied by monetary compensation for participating, the. Reason behind this is to make up for any time lost or inconvenience incurred. This compensation however should not be so high and attractive that it becomes an incentive to take risks higher that would be in normal cases.

The decision of whether to participate in clinical trials should involve voluntary and informed weighing of the risks and benefits of agreeing to take part in the trial. There should be an informed consent discussion between the investigator and the participant and the same should be in the form of a written consent document and should include detailed explanations of important issues. Schedule Y of the Drugs and Cosmetics Rules (Government of India 2005) clearly stated that informed consent form (ICF) must include the compensation procedure as an essential part in the document.

Another and separate compensation is provided to in cases where there is any kind of injury or temporary/permanent disability. In cases of death of the participant, their dependents are entitled to monetary compensation. The Indian council of Medical Research guidelines[7] as well as Indian GCP

https://www.pfizer.com/files/research/research_clinical_trials/ethics_committee_guide.pdf (Sep. 2, 2018, 10:15 PM)

[5] Johan PE Karlberg and Marjorie A Speers, Reviewing Clinical Trials: A Guide for the Ethics Committee, 70 (2010)

[6] Sandhya Srinivasan, The Clinical Trials Scenario in India,Vol. 44, Econ Polit Wkly, 29, 29 (2009)

[7] Indian Council for Medical Research, Ethical Guidelines for Biomedical Research on Human Participants, ICMR. 2006, accessible at http://www.icmr.nic.in/ethical_guidelines.pdf (Oct 29, 2018)

guidelines[8] provide provisions for the same. The Drug Controller General of India has stated that the clause mentioning hat any trial injury or death and medical care will be compensated by the sponsor must be included in the informed consent form. There are several instances that show that there have been numerous ethical violations when it comes to conducting trials and while there are a number of legal provisions for the purpose of protecting trial participants, they have not always been effective in doing so.

In November 1999, 12 people who went to the government-run Regional Cancer Centre in Thiruvananthapuram were given an experiment drug without following the established treatment for the condition. Moreover, they were not even informed that the drug was experimental and that they were being given trial drugs and the established treatment was not followed. Later it was found that the trial had not been approved by the Drugs Controller of India (approval was obtained retroactively). Further, the sponsor institution, the Johns Hopkins University in the United States, had not given ethical clearance to the study, but managed to release the money for research anyway[9].

In 2002, the multinational company Novo conducted multi-centre phase III clinical trials of a diabetes drug even before getting the results from the animal studies. The study found that the drug, caused urinary bladder tumors in rats and this information should have been known before the drug went for even phase one trials, let alone phase two and three. The trials were conducted on 650 people from North America, 200 from Latin America, 100 from Australia / New Zealand, 800 from the European Union, and 200 from non EU Europe and 550 from Asia -- including 130 people from India. Half of these people received the experimental drug[10].

Another instance in which the ethical aspect of a trial was questioned significantly in India is in a case in 2009, wherein the states of Andhra Pradesh and Gujarat launched a vaccination project against HPV, some types of which can cause cervical cancer. The trial, included girls aged 10-14 years who would receive the vaccination. The project had two components: a Phase 4 clinical trial of the HPV vaccination and observational research on the delivery of the vaccine. The project was designed and executed by PATH (Program for Appropriate Technology in Health), an US-based NGO, in collaboration

[8] Central Drugs Standard Control Organisation, Ministry of Health and Family Welfare, Government of India, Good Clinical Practice-CDSCO, accessible at http://www.cdsco.nic.in/html/GCP1.html (Oct 28, 2018)

[9] P. Sree Sudha, How ethical are clinical trials in India?, India Law Journal, accessible at http://www.indialawjournal.org/archives/volume2/issue_3/article_by_sreesudha.html (Sep 2, 2018, 6.50 PM)

[10] *Id.*

with the Indian Council for Medical Research (ICMR) and the State Governments of Andhra Pradesh and Gujarat. Pharmaceutical company Merck developed and provided the vaccine Gardasil and GlaxoSmithKline developed and provided the vaccine Cervarix. The project was funded by the Bill and Melinda Gates Foundation. In April 2010, the Ministry of Health and Family Welfare suspended the program following the deaths of seven tribal girls and strong opposition by women's groups, health activists, and some doctors who questioned its rationale, ethics, and informed consent procedures[11].

At the time of the suspension, about 23,000 girls had already been vaccinated. The Indian Government set up an inquiry committee to look into the "alleged irregularities in the conduct of studies using HPV vaccine" by PATH in India[12]. An inquiry committee was constituted to look into the allegations. The report supported the contentions and agreed to the claims that, there had been a number of violations that infringed the rights of the participants. The committee report, however failed to hold anybody liable and also did not make any recommendations as to whether those involved in designing, conducting, launching and permitting should be made liable. All those involved in the trials were not held accountable despite the fact there were clear violations.[13]

After taking into consideration the degree of procedural and ethical lapses in the trials, the 72nd Parliamentary Standing Committee on Health and Family Welfare (MoHFW) carried out an enquiry and presented a report on the same — "Alleged Irregularities in the Conduct of Studies using Human Papilloma Virus (HPV) Vaccine." This report (henceforth referred to as the 72nd Report), is proof of the many allegations made regarding the violations in the vaccine trials. The report acknowledges the unethical nature of the trials conducted by PATH in India in the year 2009 and clearly states that the "démonstrations Project" as it was repeatedly referred to by PATH, was a clinical trial, irrespective of what PATH called it. The report takes note of the observations of the MoHFW's enquiry committee that, "The demonstration project is a study of a pharmaceutical product carried out on humans and since the primary objectives include the study of serious

[11] G. Mudur, "Human papilloma virus vaccine project stirs controversy in India," BMJ 340 (2010); G.Mudur, "Row erupts over study of HPV vaccine in 23,000 girls in India," BMJ 344(2012)

[12] Enquiry Committee, "Alleged irregularities in the conduct of studies using human papilloma virus (HPV) vaccine by PATH in India," Final Report of the Enquiry Committee appointed by the Govt. of India, Vide notification No.V.25011/160/2010-HR (February 15, 2011)

[13] Final Report of the Committee appointed by the Government of India (vide notification No. V 25011/160/2010 –HR dated April 15, 2010) to enquire into "Alleged irregularities in the conduct of studies using Human Papilloma Virus (HPV) vaccine by PATH in India". New Delhi: Government of India (Sep 1, 2018)

adverse events, it is clear that clinical trial rules and guidelines should apply." The report further states that by carrying out the clinical trial in the disguise of an "observation/demonstration project," PATH has violated the laws and regulations laid down for clinical trials by the Government of India[14].

The 72nd Report also recognizes that the project design was flawed and hence disapproves of the same due the failure to report certain events. There was also an absence of independent systems or detailed monetizing of the same. The 72nd Report also observes that there were numerous violations in regard to consent and the legal requirements for it. This conclusion was drawn from the "incomplete and inaccurate" consent form and the failure to give all relevant information to the participants as well as the parents or guardians in regard to the vaccination. On top of this, there was direction by the state (Andhra Pradesh) to hostel wardens to sign the consent forms on behalf of the parents/guardians. Another major issue was that no insurance cover was given for the girls.

The report also that …The study was initiated by PATH on its own … without any reference from the National Technical Advisory Group on Immunization (NTAGI), the official body of the GOI on vaccines… and in is unclear as to whether or not the state expenses were funded by PATH or came from their own resources. There was a gap in the report however as to failed to talk about the funding from the Bill and Melinda Gates Foundation and other sources, or of the money spent by the ICMR and state governments. Hence, the actions of PATH are a clear violation of human rights the trial participants.

Another major problem faced in India is that the government has been promoting the country as a location for trials despite the fact that there is no adequate regulatory method existing. A bit on clinical research has been sick in the parliament foe a very long period of time and no move has been made by the parliament to approve the same. There is an urgent need to protect trial participants who are vulnerable to exploitation by the drug companies, the contract research organisations and investigators[15].

Clinical Trials Practice in India

For the purpose of taking a quick look at the already existing legal framework in India the

[14] Department-related Parliamentary Standing Committee on Health and Family Welfare, Department of Health and Family Welfare, Seventy second report on alleged irregularities in the conduct of studies using Human Papilloma Virus (HPV) vaccine by PATH in India, New Delhi: Rajya Sabha Secretariat; 2013 Aug 30, http://164.100.47.5/newcommittee/reports/EnglishCommittees/Committee%20on%20Health%20and%20Family%20Welfare/72.pdf (Sep 1, 2018)

[15] Sandhya Srinivasan, Clinical Trial Industry: No Accountability?, Vol. 46, No. 35, Econ Polit Wkly, 19, 19 (2011)

paper looks at the number of laws governing clinical research in India. The major provisions for this purpose are contained in —

- Drugs and Cosmetics Act - 1940
- Medical Council of India Act - 1956, (amended in the year2002)
- Central Council for Indian Medicine Act - 1970
- Guidelines for Exchange of Biological Material (MOH order, 1997)
- Right to Information Act, 2005
- The Biomedical Research on Human Subjects (regulation, control and safeguards) Bill - 2005

Despite there being a number of legislation the most important one concerning clinical trials is The Indian Council of Medical Research (ICMR), 1947. This council was set up with the object to cultivate research culture in India and also help the growth of medical infrastructure. The Drugs and Cosmetics Act, states that all clinical trials in India should follow the ICMR guidelines of 2000. Every doctor is governed by the act and any doctor doing wrong in a trial can be prosecuted and the hospital can be closed[16].

The Drugs and Cosmetics Act is a strong act and has the power to take punitive measures in case of certain violations. The Drugs Controller General of India (DCGI) is responsible for regulatory approvals of clinical trials in India. The DCGI's office depends on external experts and other government agencies for advice. Separate authorisation is needed for the purpose of export of blood samples to foreign laboratories. The Indian Council of Medical Research has a central ethics committee known as the Central Ethics Committee on Human Research (CECHR). This committee audits the functioning of this Institutional Ethics Committee (IEC). Schedule Y of the Drugs and Cosmetic Rules lay down the provisions for the composition of the IEC.

Issues with globalisation of trials:

Clinical trials are now being globalised just like any others industry. Government sponsors in wealthy countries move trials to less wealthy countries[17]. Especially in India Global clinical research is exploding. Yet, it is certainly not the West that is introducing clinical research to India. Two ancient scripts, Charaka Samhita (a textbook of medicine) and Sushruta Samhita (a textbook of surgery), compiled as early as 200 B.C. and 200 A. D. respectively, show India's age-old proficiency

[16] Drugs and Cosmetics Act, 1940, No.23, Acts of the Parliament, 1992 (India)

[17] Seth W. Glickman, John G. McHutchison, Eric D. Peterson, Charles B. Cairns, Robert A. Harrington, Robert M. Califf, and Kevin A. Schulman, Ethical and Scientific Implications of the Globalisation of Clinical Research, The New England Journal of Medicine, https://www.nejm.org/doi/full/10.1056/NEJMsb0803929 (Sep 2, 2018, 5:00 PM)

in medical research. However, a lot has changed in the clinical research scenario since then. Today, clinical trials are conducted through a regulated approach following certain guidelines laid down by the International Conference on Harmonisation (ICH). Globalisation of international clinical trials creates new questions regarding ethics in conduct of clinical trials in human subjects and conducting research on marginalised or oppressed populations[18].

Since 2002, the number of active Food and Drug Administration (FDA) – regulated investigators based outside the United States has grown by 15% annually, as compared to the number of United States based investigators, which has declined by 5.5%[19]. This shows that clinical research is going through globalization similar to that by other industries.

On use of the Clinical Trails government registry in the United States to examine recruitment in industry-sponsored phase 3 clinical trials as of November 2007 for the 20 largest U.S based pharmaceutical companies; it was found that approximately one third of the trials (157 of 509) are being conducted solely outside the United States and that a majority of study sites (13,521 of 24,206) are outside the United States. Many of these trials are being conducted in developing countries, including the rapidly evolving countries of Eastern Europe and the Russian Federation[20].

The globalisation of clinical research is a relatively new concept when compared to globalisation of other industries. This makes us think why the sudden globalisation and that too on such a large scale. One reason for this may be that pharmaceutical companies can substantially reduce their costs by carrying out these trials in developing countries like India due to which they are shifting trials (especially phase 2 and 3) to such countries. It was reported by a pharmaceutical executive that a first-rate academic medical center in India charges approximately $1,500 to $2,000 per case report. This cost is less than one-tenth the cost at a second-tier centre in the United States[21].

While there are certain benefits to conducting trials in developing countries. Some of these are helping create good relationships among clinical investigators globally and also answering any queries about the safety and

[18] P. Sree Sudha, How ethical are clinical trials in India?, India Law Journal, (Sep 2, 2018, 6.50 PM), http://www.indialawjournal.org/archives/volume2/issue_3/article_by_sreesudha.html

[19] Getz KA, Global clinical trials activity in the details. Applied Clinical Trials, http://appliedclinicaltrialsonline.findpharma.com/appliedclinicaltrials/article/articleDetail.jsp?id=453243 (Sep 9, 2018, 9:00 PM)

[20] Seth W. Glickman, John G. McHutchison, Eric D. Peterson, Charles B. Cairns, Robert A. Harrington, Robert M. Califf, and Kevin A. Schulman, Ethical and Scientific Implications of the Globalisation of Clinical Research, The New England Journal of Medicine, https://www.nejm.org/doi/full/10.1056/NEJMsb0803929 (Sep 2, 2018, 5:00 PM)

[21] Jean-Pierre Garnier, Rebuilding the R&D engine in big pharma, 86 Harv Bus Rew, 68, 70 (2008)

efficiency of drugs that are useful all over the world. However, globalisation of trials raises some ethical and scientific questions. Some of these are that local regulatory bodies are more often that not structured to monitor the quality and safety of trials and drugs in their local markets; due to which they may not have the required information on certain aspects of research conducted especially if such research is outs the country. A huge issue is that there are a number of ethical oversights in researches that involve human trials in countries that are still developing. There are wide disparities in the areas like education, health care, economy, social standing etc. that jeopardises the rights of the participants[22].

There may be instances where the financial compensation for the trial participants may be more than they annual wages itself and these people may not have any other way to get the medical care required. Hence, their only choice becomes to take part in the corresponding trial. As a result of the poor standards in the health care of developing countries, they may sometimes even allow study designs and trials that will not be allowed in wealthier nations[23].

Another concern is that the transparency of research in developing nations. The International Committee of Medical Journal Editors has issued some guidelines for the purpose of investigators with regard to participation in study design, access to data, and control over the publication of results[24]. Protecting the publication right of investigators is crucial for the transparency and ethicality of the research. This is an issue in India (being a developing country) as the investigators tend to be less aware of these guidelines and hence, less likes to be able to have proper access to trial date and to publish the same.

Despite all these issues it still becomes important for developing to take part in clinical trials for the purpose of advancement of health. Given the increasing commonness of conditions such as cardiovascular disease, it is necessary to test drugs and devices on a global scale. Multiple advances are required to solve the issues caused by globalisation of clinical research. In general, the goal is to encourage innovation and access while at the same time making sure that clinical research is conducted in numbers in proportion to the potential uses of the products after approval.

[22] The ethics of clinical research in developing countries. London: Nuffield Council on Bioethics, 1999. http://www.nuffieldbioethics.org/fileLibrary/pdf/clinicaldiscuss1.pdf (Aug 29, 2018, 7:00 AM)

[23] Jayaraman KS, *Indian regulations fail to monitor growing stem cell use in clinics*, Nature https://www.nature.com/articles/434259a (Sep 5, 9:00 PM)

[24] International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication. http://www.icmje.org/ (Sep 10, 12:00 PM)

It is also important to create a strong framework to ensure morality in any research that takes place. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use has issued certain Guidelines for Good Clinical Practice (ICH-GCP guidelines). These guidelines are useful in respect to technical standards and ethical oversight.

However, certain guidelines, such as the one indicating that sponsors should ensure that trials are "adequately monitored," are subject to interpretation and are only as effective as to the degree in which they are implemented. The solution is not simple; different types of trials require different monitoring procedures. A rigid set of rules will not be enough and may even impair the quality of the research;[25] instead, an extensive improvement in the quality of clinical research is required, so that trial processes meet the research goals and needs of the society.

Conclusion

Despite the fact that there so many provisions for the purpose of regulating clinical trials there is a huge gap in the law and this paper explores how this problem can be solved. The Ministry of Health & Family Welfare had constituted an Expert Committee under the Chairmanship of Prof. Ranjit Roy Chaudhury to formulate policy and guidelines for approval of new drugs, clinical trials and banning of drugs[26]. The committee made several recommendations that helped narrow this gap and the same were adopted. However this does not seem to be sufficient.

The government proposed to regulate all biomedical and health research activities by bringing them under a law to ensure ethical research in all institutions with proper care, and a compensation policy for human participants[27]. For this purpose the Biomedical and Health Research Regulation Bill was proposed in 2013. However the bill was never passed and is hanging in the parliament till date. The objectives of the bill was to provide ways to protect ethical values in accordance with both local cultural values and international standards. It is important that a separate legislation be passed wide the large and rapid growth in clinical trials not just in India. However, all over the world. The protection of participants in clinical trials

[25] Yusuf S, Bosch J, Devereaux PJ, et al, Sensible guidelines for the conduct of large randomized trials, Clin Trials,38,38-39 (2008); Eisenstein EL, Collins R, Cracknell BS, et al, Sensible approaches for reducing clinical trial costs, Clin Trials, 75,75-84 (2008)

[26] Report of the Prof. Ranjit Roy Chaudhury Expert Committee to Formulate Policy and Guidelines for Approval of New Drugs, Clinical Trials and Banning of Drugs, (July 2013)

[27] Aarti Dhar, Bill to make biomedical, health research ethical, The Hindu, June 2, 2016, https://www.thehindu.com/todays-paper/tp-national/bill-to-make-biomedical-health-research-ethical/article5143738.ece

requires regulation, including in trials that are outsourced and off-shored.

Informed consent and proper monitoring are the most important aspect of ethical trials. These two points must be taken into foremost consideration while addressing the problem of protection of participants. The more that the ethical aspects of trials are recognised especially legally, the more easy it becomes to protect it through litigations. For this purpose, the proceeding in the case of the HPV vaccination project can be used as an example.

Globalisation of trials becomes another aspect of concern. Ethical and scientific integrity is the only way to solve this problem. The World Health organisation may be able to commission a comprehensive review for this purpose. An effort to make more efficient regulations by employing faster and simpler working methods governing clinical trials can ensure more ethical conduct. Furthermore, improving research efficient can reduce the cost differences among different countries hand help ensure that trials are conducted wherever the drug under trial will be sold once approved. Greater use of centralised review boards, standard terms for research contracts, and the development of streamlined best practices in order to decrease unneeded work for investigators and medical institutions are required.