Clinical Trials in India: History, Current Regulations, and Future Considerations

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Project

Submitted to the School of Health Sciences

Eastern Michigan University

in partial fulfillment of the requirements

for the degree of

MASTER OF SCIENCE

in

Clinical Research Administration

June 12, 2017

Ypsilanti, Michigan

Acknowledgements

I would like to express my deepest gratitude to my research guide, Dr. Irwin Martin for his constant support, guidance, and encouragement throughout the conduct of this project. This gratitude also extends to Ms. Beth Sobo from the University Writing Center, EMU for helping me in the writing part and arranging meetings in her busy schedule. I would also like to thanks my classmates for always providing their valuable inputs.

Abstract

Clinical research has become globalized. Because of the higher cost, the strict regulations, extensive safety and compensation requirements, and a small population of developed countries, many trials are now taking place in developing countries such as India, China, etc. India has been recognized as one of the most promising hubs for clinical trials due to the high availability of treatment-naive patients, lower cost, and large numbers of qualified professionals. In 2005, India amended its patent law and since then, in order to promote clinical trials, the government has been trying to make changes in the regulatory framework. However, many multinational companies took advantage of India's favorable regulatory systems by enrolling a large number of illiterate and poor subjects without obtaining adequate informed consent and hence, many unethical trials took place. Many issues were raised by media and health activists and therefore, the Supreme Court halted the approval of clinical trials until the regulatory framework was updated. This paper discusses the history of Indian regulations, reasons for the Supreme Court halt, recent regulatory changes, and effects of new regulations on clinical trial business.

Key words: clinical research, the Supreme Court, India

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Introduction

Recently, clinical research has become globalized, and, because of this, many trials are taking place in developing countries. There are now more than twofold of the study locations outside of the US as the numbers of trials undertaken has decreased in the last 10 years in the United States and Western Europe (Silva, Amato, Guilhem, & Novaes, 2016). Due to many reasons, pharmaceutical companies in the US resort to outsourcing clinical trials to developing countries.

For pharmaceutical companies, the toughest task is to recruit sufficient numbers of patients into clinical trials. According to Bagale, Joshi, & Kadam (2011), the Food and Drug Administration requires on the average 4,000 patients into clinical trials to get marketing approval of an investigational drug. Yet in the United States, fewer than 5% of patients are willing to participate in clinical trials. Bagale et al. (2011) and Maiti,& Raghvendra (2007) also stated that 86% of clinical trials in the United States fail to enroll the desired number of participants which delays the process for about 366 days on average. Hence, clinical trials in the USA have become very expensive. In fact, one million dollars of potential revenue are lost with each day that the market release of a drug is delayed.

In addition, the recruitment of subjects in western countries is slow and expensive due to strict regulations, extensive safety and compensation obligations, and small populations (Bagale et al., 2011; Maiti, & Raghvendra, 2007). A shortage of clinical investigators also leads to clinical research outsourcing. According to Center Watch, in the United States, only 48,000 investigators were available in 2005 versus a demand of 56,000, which amounted to a shortage of 15% (Bagale et al. 2011). Thus, many pharmaceutical companies now outsource large multicenter Phase III trials to developing countries.

India has been recognized as one of the most promising research hubs. In 2005, India became completely consistent with TRIPS- Trade Related Aspects of Intellectual Property Rights (Jaysheel, 2012; Najmi et al., 2013). Since then, the government has been trying to make modifications in policy framework and regulations in order to advance clinical trials in India. These changes have urged pharmaceutical organizations to expand their clinical research programs in the country. Moreover, multinational pharmaceutical companies have outsourced their programs to India for many reasons: 1) operational costs are cut by nearly half; 2) there are large numbers of efficient, trained, English speaking professionals; 3) there is a large number of patients; 4) subjects have diverse ethnicity; 5) a broad age range of subjects is available (64% Indians are between 15-64 years); 6) there is high unmet medical need - high prevalence of acute and chronic diseases and lifestyle related disorders are on rising; 7) there are institutions and laboratories with state-of-art facilities, etc (Imran, Najmi, Rashid, Tabresh, & Shah, 2013; Kondal, Krishna, & Bansal, 2016).

Moreover, favorable regulatory system, illiteracy, poverty, a lack of information about clinical trials, and a broken healthcare system also made India an attractive place to outsource clinical trials (Kondal et al., 2016). A lack of GCP training among stakeholders and a weak regulatory system in India resulted in unethical clinical trials (Bowhmik, Chandira, & Chiramjib, 2010). It became easier for the investigators to enroll more patients without giving them proper information about clinical trials. In fact, the majority of patients who were enrolled in these trials were illiterate and poor, received unfair compensation, and gave inadequate informed consent (Kondal et al., 2016). It does not help that most people in India see their doctors as a god and so, patients do whatever doctors ask. This allowed most of the companies to take advantage of poor and illiterate people by enrolling them in clinical

trials. Moreover, due to a weak regulatory system of India, it was easier for the pharmaceutical companies to get approval of trials.

As a result of these unethical clinical trials, nongovernmental organizations (NGOs), and media activists in the country have raised many issues over the years. Meanwhile, in 2013, the Supreme Court in India expressed serious concerns over clinical trials by acknowledging the gaps in the existing regulatory framework by halting the approval of new trials until the laws and regulations were updated (Bagcchi, 2013). This prompted the CDSCO, the regulatory agency of India, to fix the loopholes relating to execution and approval of clinical trials to protect the rights and welfare of Indian citizens. The clinical trial business in India responded to this pressure by scaling down operations (Kondal et al., 2016; Ramamurthy, 2012). Companies also moved some of their business to other Asian countries, while there were many uncertainties regarding regulations, and while clinical trial approvals were halted in India.

This paper summarizes the history of clinical trial regulations in India, including why the Supreme Court put a halt on clinical trials, recent regulatory changes, effects of new regulations on clinical trial business, and what is still needs to be done to protect the rights, welfare, and safety of Indian citizens.

Clinical Trial Regulations in India Before 2013

The central government, via the Central Drug Standard Control Organization (CDSCO) under the Ministry of Health and Family Welfare, regulates drug manufacturing, sales, clinical trials and, import and export in India. To standardize clinical research in India, the CDSCO works on developing the standards and regulations for drugs, diagnosis, and devices; updating regulations by amending acts and rules; and regulating the marketing authorization of new drugs to bring safe and effective drugs in market (Jaysheel, 2010).

The history of drug regulation in India goes back to the British Rule when most medications were imports. Najmi et al. (2013) stated that in the early decade of the 20th century, large numbers of illegal foreign drug manufacturers overflowed the Indian market with spurious and adulterated medications. As a result, the government formed a drug inquiry panel whose recommendations were later on presented for discussion in legislative assembly as The Drug Bill, which then became the Drugs and Cosmetic Act of 1940 and the Drug and Cosmetics Rules of 1945 (Najmi et al., 2013). These legislations are the fundamental acts that regulate drug and cosmetic importation, manufacturing, distribution, and sale in India. They also formed the Central Drug Standard Control Organization (CDSCO) and the Office of Drugs Controller General India (DCGI) under the division of Ministry of Health and Family Welfare (Najmi et. al, 2013). The DCGI is the government official who grants permission for new drugs to be administered to human subjects in clinical trials conducted in the country.

The Drug and Cosmetic Act of 1940 has been divided into Chapters, Rules, and Schedules and is amended from time to time to oversee the safety, efficacy, and quality of the medicines. Under Chapter 2 of this Act, one statutory board and a committee have been

established, namely the Drugs Technical Advisory Board (DTAB) and the Drug Consultative Committee (DCC) (Najmi et al., 2013). The DTAB consists of the experts who advise central and state governments on technical areas of drug regulations. Any amendment to the Drug and Cosmetic Act is made after consulting the DTAB. The DCC ensures drug control measures all over India and has central and state drug control officials as it members (Najmi et al., 2013).

In India, as per The Indian Patent Act of 1970, there was a provision only for 'process' patents (Tulasi & Rao, 2008). In 1994, Indian government signed the affidavit on Trade-Related Aspects of Intellectual Properties (TRIPS) to give the least protection to the intellectual properties of the member states of the World Trade Organization (WTO) (Najmi et al., 2013). Hence, Indian companies were easily able to duplicate the patented medicines by making small changes in the production process. As a result, western companies had concerns in marketing their new drugs in Indian markets. Later in 2005, to attract multinational pharmaceutical companies, India amended its Patent Bill for pharmaceutical products and broadened its weak process patent to strengthen TRIPS competent 'product' patent system (Jaysheel, 2012; Najmi et al., 2013; Thwani, & Gharpure, 2006).

After knowing the benefits of clinical research for new therapies, the government also developed various ethical and regulatory guidelines. One of such guideline was developed by the Indian Council of Medical Research (ICMR), a regulatory agency that formulates, coordinates, and promotes biomedical research. In 2000, the ICMR published ethical guidelines for biomedical research on human subjects (ICMR guidelines, 2006). The ICMR guidelines mandate the ethics committee at the institutional level providing that the researcher should get approval from an appropriately constituted ethics committee of the

institution before submitting the proposal to the DCGI (ICMR, 2006). However, the approval of an ethics committee was not a mandatory prerequisite for permission to conduct a clinical trial.

Meanwhile in 2001, the CDSCO released guidelines on Indian Good Clinical Practice (CDSCO, 2005; ICMR guidelines, 2006). However, without the regulatory requirement for GCP compliance, most pharmaceutical organizations at the time did not follow the GCP principles which resulted in low-quality data and hence, deteriorating of country's reputation in the field. In addition, it was initially mandatory in India that a Phase II trial can be conducted only if Phase III study was proceeding elsewhere (Nundy, & Gulhati, 2005). The government took this step to protect the Indian people to make sure that Indians were not the only ones taking experimental drugs, and drug safety data are available. However, it resulted in Phase lag and, at the same time, was time-consuming for pharmaceutical companies.

To overcome all these problems, the CDSCO amended the Schedule Y of the Drug and Cosmetic Rules of 1945 in 2005, which provided a collection of clinical trial guidelines and regulations. This new amendment removed the Phase lag, described the responsibilities of sponsors and investigators, and the required notification of protocol changes (Thatte, & Bevdeka, 2008). The modifications that took place are as follows (CDSCO, 2005; Najmi et al., 2013; Ramu, Kumar, & Ramakrishnan, 2015):

- Definitions of Phase I-IV trials, which removed the Phase lag;
- Submission of clinical trial application which should include study protocol, a draft informed consent form, a list of proposed investigators, and the background information about the drug;
- Detailed the responsibilities of investigators and sponsors;

- Detailed the requirements for reporting changes in protocol.

In the meantime, India's amended "Patent Bill" of 1970 became effective in 2005. Following international standards, Indian companies started to respect intellectual property rights.

In 2006, the CDSCO introduced a fast-tracking system to decrease application review period from 16 weeks to 10 weeks (CDSCO, 2005). The DCGI created two categories for clinical trial applications (Kumar, & Kher, 2007):

- Category A: Clinical trials that are taking place in countries with competent, fully fledged regulatory systems, e.g., trials that have received approval in the USA, Japan, Canada, Europe, Australia, and Switzerland;
- Category B: Everything else.

A trial that comes under category A would be qualified for fast-track review in India, and the approval process takes less than 2 to 4 weeks. Trials in category B would approximately require 12 weeks. Almost all Phase III trials are in Category A.

In 2007, the Indian government provided another boost to the pharmaceutical industry by removing the 12% service tax on clinical trials (Najmi et al., 2013). The Indian government also started registration of clinical trials in 2007. Although it was not mandatory to register the trial at that time but, in 2009, it became compulsory to register trial on www.ctri.nic.in (Sanghavi, 2013).

Because of all these amendments, from 2005 to 2010, the clinical research industry in India witnessed enormous growth with a total of 2,282 trials approved by the CDSCO (Kondal, Krishna, & Bansal, 2016). However, there were still many loopholes in the regulations, which were reflected in the ICMR 2002 survey. This survey showed a lack of

enforcement (Moure, 2015). India's failure to implement its ethical guidelines had been observed in many human rights violations committed by researchers.

Clinical Trial Misconduct in India

The Indian clinical trial market had started flourishing after the amendment of the patent law and Schedule Y of Drug and Cosmetic Rules in 2005. Foreign pharmaceutical companies had turned to India as a drug research opportunity by taking advantage of the vast population and loose regulatory system. Many important trials in India were conducted according to the relevant standards, but inadequate supervision had led to several incidents where poor, ill, and sometimes illiterate subjects were enrolled in trials without properly giving informed consent. That is, they did not know what they were signing up for. Some of the examples of such unethical clinical trials are as follows.

In Trivandrum, the Kerala Regional cancer treatment center conducted a clinical trial for the drug Nordihydroguaiaretic acid (NDGA) for the treatment of oral cancer during 1999-2000. The sponsor of the trial was Johns Hopkins University Hospital. The drug was administered to 26 patients before the animal safety was known; moreover, patients were not informed that they were taking part in a trial and that they can deny participation. Two patients died in this trial. Due to media and NGO pressure, the government conducted an inquiry, and results were not made public (Gulhati, 2004; SOMO, 2008). The government just decided to suspend this trial for 6 months instead of penalizing the guilty. Later, Johns Hopkins University admitted that the consent form was inadequate, and the safety of the drug was not established, so they banned the investigators from serving as a principal investigator in any of their future clinical trial (SOMO, 2008).

In 1999, Otsuka's Cilostazol clinical trial was approved by DCGI for the treatment of intermittent claudication. The common serious adverse effects, such as angina and

myocardial infarction, were not mentioned to DCGI during the approval, and so the trial was approved based on incomplete information (Gulhati, 2004; SOMO, 2008).

Around the year 2000, Solvay Pharmaceutical conducted a Phase III trial of Cilansetron for the treatment of diarrhea due to irritable bowel syndrome. At that time, a foreign company should have only been allowed to conduct Phase III in India if it was previously completed in another country. DCGI had approved this trial even though only Phase II had been completed abroad (Gulhati, 2004; SOMO, 2008). Similarly, in 2000, DCGI approved clinical trial for one of Pfizer's drugs Zoniporide without completion of its Phase II abroad and completion of animal toxicity studies (Gulhati, 2004; SOMO, 2008).

In 2002, Novo Nordisk conducted a large Phase III clinical trial in 32 countries, including India, for the drug Ragaglitazar which was a treatment option for diabetes. Approximately 2,500 subjects were enrolled in the trial all over the world, including the EU and USA. However, Indian scientists questioned the ethics of this trial because the drug was not fully tested on animals. As per the Indian regulations, before Phase III trial began, the results of the animal toxicity studies for chronic diseases should have been available. In July 2002, the trial was suspended when it was found that the mice treated with the drug had developed urinary bladder tumors. Novo Nordisk refused all the allegations and said that the long-term toxicity data are only required for the filing of the marketing application. Later, in the company's follow-up program with participants, it was found that there was no relation between exposure to the drug and cancer (SOMO, 2008).

In the year 2003, Johnson & Johnson conducted a trial in Gujarat, India for the drug Risperidone which was meant to treat acute mania. During the trial, psychiatric patients were taken off their ongoing medications and informed that medicines were discontinued and no

longer available in the market. In the trial, participants received either a placebo or Risperidone, and patients who received the placebo were put at higher risk. One of the patients also explained that, even though he signed the form, he had no idea that he was taking part in a clinical trial; he signed the form because doctors required it. However, Johnson & Johnson did not admit any accusations and stated that informed consent was taken from all the patients (SOMO, 2008). Based on the patient's testimony, informed consent forms were presented and signed, but the participants were not informed properly on what they were taking part in.

According to Gulhati (2004) and SOMO (2008) in the year 2003, two leading Indian companies, namely Biocon (Insulin) and Shantha Biotechnics (Streptokinase), conducted an illegal Phase III trial in Hyderabad. The trial was for recombinant insulin and streptokinase for the treatment of clot-busting in heart attack and diabetes. Companies conducted this trial without obtaining approval from Genetic Engineering Approval Committee. Moreover, they did not inform patients about the trial, which unfortunately led to the death of eight patients. Without any independent inquiry, the death of trial subjects has been attributed to "causes other than the use of the drug" (Gulhati, 2004). In March 2004, Delhi-based NGO filed the litigation and the Supreme Court found that the trial was illegal. However, even though the Supreme Court decided that the trial was illegal, there is no public information regarding the punishment imposed on the company or on the investigators involved.

The drug Letrozole was approved all over the world for the treatment of breast cancer in post-menopausal women but was never authorized for any other indication in India. In 2003, Sun Pharmaceutical conducted a clinical trial of Letrozole for the treatment of inducing ovulation. The USFDA and British Authority had already labeled Letrozole as embryotoxic,

fetotoxic, and teratogenic at minuscule doses. At more than nine centers across India, approximately 300 women were enrolled in this trial without their prior knowledge or consent (SOMO, 2008). The trial was conducted without any permission from the DCGI, and animal testing was also not done for a new indication. Moreover, it was conducted by an investigator who just had a diploma in gynecology (Gulhati, 2004). A doctor with just a diploma in gynecology, which is obtained after MBBS (Bachelor of Medicine and Bachelor of Surgery), is not an expert to understand women's reproductive diseases, and hence, is notcompetent to understand the use and effects of an unapproved drug in women.

Controversies in Indore

From 2004 to 2010, the city of Indore in the state of Madhya Pradesh was in the limelight for negative reasons. During this time, 3,300 patients, including 1,833 children, were taking part in 73 clinical trials at the Maharaja Yashwantrao Public Hospital (Chamberlain, 2015; Lakhani, 2011). The trials were for vaccinations and the treatment of leg pain, asthma, heart failure, epilepsy, depression, schizophrenia, and many other diseases. The trials were sponsored by multinational pharmaceutical companies. But many of these trials were conducted unethically without obtaining informed consent and following regulations in the country.

In 2009, many people in the Maharaja Yashwantrao Public hospital were unknowingly enrolled in the clinical trial for Tonapofylline, a drug developed by Biogen Idec. Most of the patients were poor and illiterate and were informed that some charity was going to pay for their expensive treatments. Some of the patients in this trial suffered cardiac arrest and seizures. The exact number of patients who had cardiac arrest and seizures are not

available. Later in the same year, the trial was halted by the company due to the number of seizures recorded in the UK (Roberts, 2012).

According to Roberts (2012), another case of the Maharaja Yashwantrao Public Hospital involved a three-day-old baby, who was given a testing vaccine. The family signed a form written in English, which they did not understand and were informed that polio vaccine was being administered to the baby so, they had no idea that the doctor was giving her an experimental vaccine. According to hospital records, she had seizures and bronchitis attacks after receiving the vaccine and later on suffered from breathing and eating problems. The family was told that these problems were not due to the vaccine even though they probably were.

In another asthmatic trial at Maharaja Yashwantrao Public Hospital, an inhaler was used. As a side effect patients started to lose their sight and developed cataracts. Doctors in the hospital removed the cataracts, but those who took part in the trial were unaware of the side effects in the first place (Bhan, 2012; Chamberlain, 2015).

Dr. Anand Rai of the Maharaja Yashwantrao Public hospital was the whistle-blower who exposed hospital's unethical trials since 2004. Dr. Rai had just started his career in medicine when in 2005 he noticed the suspicious actions of his senior doctors (Chamberlain, 2015). He determined that some patients were visiting the hospital regularly and were given special attention. He later on realized that these patients were enrolled in clinical trials, but that most of them did not know that they were taking part in clinical trials. Doctors had told them that the drugs being given to them were new from foreign countries and were not available in the market, so they had to take it from the hospital. The patients were also told

that a charity foundation was funding their treatment cost (Bhan, 2012; Chamberlain, 2015; Presse, 2013; Roberts, 2012).

Dr. Rai saw thumbprints on consent forms that were written in English. The doctors of this hospital chose poor, illiterate, and ill patients who were in need of medicine. They violated all the basic ethical principles because they did not inform the patients about the trials and did not report adverse events or death cases. From all these trials, a total of 81 patients, including 18 children, suffered from serious adverse events while 35 patients died (Chamberlain, 2015; Roberts, 2012; Yee, 2012). However, autopsies were not done on the patients who died from these clinical trials so, the link between their death and the drugs that were given to them remains unknown (Chamberlain, 2015).

In response to this tragedy, health activists in Indore registered official complaints with the state and national human rights commissions and the DCGI (Yee, 2012). For their involvement in improper procedures, twelve doctors were fined by the state government for only Rs 5,000 or US$100 (Presse, 2013; Yee, 2012). The government also did not disclose the investigation report hence, the data on adverse events or death cases are not available. Understandably, the activists who filed the complaints were not satisfied with the small penalty. This fine was much less in comparisons to what the doctors have received from pharmaceutical companies to conduct the clinical trials. For example, six doctors who worked in the same hospital received $1.2 million from pharmaceutical companies to conduct the trials in question (Yee, 2012).

Table 1 summarizes the controversial events that occurred in Indore due to unethical clinical trials.

Table 1: Summary of controversies in Indore due to unethical clinical trials

Event	Details
72 clinical trials were conducted in Indore from 2004 to 2010	3,300 patients, 1,833 of whom were children, took part in these clinical trials
The Maharaja Yashwantrao Public Hospital enrolled unknowing patients to different clinical trials	Some of the patients who tested the drug Tonapofylline suffered from cardiac arrest and seizures. An experimental vaccine that was used on a 3-day-old baby caused her to suffer from seizures and bronchitis. An experimental inhaler caused patients to develop cataracts and lose their sight.
Dr. Anand Rai exposed the hospital's misconducts.	He started noticing the suspicious behaviors of his senior doctors in 2005. He also saw thumbprints on consent forms that were written in English which was odd because most patients were poor and illiterate.
Clinical trials resulted in serious adverse effects and deaths	81 patients, 18 of whom were children, suffered from serious adverse effects. 35 patients died.
Health activists filed official complaints	12 doctors were fined RS5000 (US$100) even though pharmaceutical companies paid them as much as US$1.2 million for 6 doctors. The investigation report was not disclosed.

Controversies in Bhopal

Beginning in 2004, Bhopal Memorial Hospital conducted clinical trials on victims of the gas disaster of 1984 (Buncombe & Lakhani, 2011; Lakhani, 2011; Roberts, 2012) which violated the international ethical principles. Moreover, these clinical trials put the vulnerable patients at risk because they were already ill and suffering from different problems (e.g., vision, respiratory, and digestive problems) due to the gas tragedy.

Approximately 14 patients died during the eight different trials of Pfizer, AstraZeneca, Sanofi and others. (Lakhani, 2011; Roberts, 2012). These trials included one comparative study of two antibiotics to treat hospital-acquired pneumonia (Theravance trial), a second study of another antibiotic (Pfizer trial), and the other study was a cardiac trial (GlaxoSmithKline trial) (Lakhani, 2011). None of the victims were aware that they were participating in clinical trials. They were given Rs200. every time they come for a visit, but the subject's families were not given any compensation for any trial related injury or death to the subject (Vermal, 2011). Aside from not providing compensation to the families of the victims, the companies behind these trials also did not report the deaths of the patients within the specified time limit (Lakhani, 2011).

Even though the hospital was dedicated to treating the gas disaster survivors free of charge, it was involved in conducting unethical clinical trials on the victims. The execution of the trials exposed the hospital and its illegal practices, and activists criticized the hospital by saying that that the gas disaster survivors were used as guinea pigs (Lakhani, 2011; Roberts, 2012). The hospital made more than Rs.10 million from drug companies for carrying out the trials (Lakhani, 2011).The hospital's ethics committee members who approved the trials were, therefore, questioned for their involvement. It was found that most

of the trustees were serving as an ethics committee member. Meanwhile, one of the committee members was a sub-investigator in a trial while another was reviewing the trial for a family member (Lakhani, 2011). These are serious conflicts of interest.

The questionable decision by the hospital trustees and drug controllers to endorse the hospital as a clinical trial site proves the inadequate protection that was provided to the gas victims. Moreover, medical professionals have scrutinized the scientific validity of drug testing on gas victims because the long-term effects of exposure to Methyl Isocyanate (MIC) are not well known. None of the trials specifically required gas victims as participants, but the hospital still used them to earn money. The pharmaceutical companies consistently defended this decision by saying that it was up to doctors to determine if patients met the inclusion criteria. In addition, no strict action was taken by the government against hospital ethics committee or the investigators. They only issued warning letters to the pharmaceutical companies involved (Lakhani, 2011), the content or extent of which remains unknown.

Table 2 summarizes the controversial events that occurred in Bhopal due to unethical clinical trials.

Table 2: Summary of controversies in Bhopal due to unethical clinical trials

Event	Details
The Bhopal Memorial Hospital conducted clinical trials on victims of the 1984 gas disaster since 2004.	Using victims of the gas disaster violates international ethical principles. Patients were already suffering from different problems, e.g. vision, respiratory and digestive problems.
14 patients died during 8 clinical trials conducted by Pfizer, AstraZeneca, Sanofi, etc.	Trials included: o Two antibiotics from Theravance for hospital-acquired pneumonia; o One antibiotic from Pfizer; o One cardiac study by GlaxoSmithKline. Patients did not know they were participating in clinical trials They were given RS200 for every hospital visit, but families were not compensated for injuries/deaths caused by the trials. Companies did not report deaths within given time limit.
There is a conflict of interest amongst trustees and members of the ethics committee.	The hospital made more than RS10 million from drug companies. Trustees of the hospital were serving in the ethics committee. One member of the committee was also a sub-investigator.
Government did not take any strict action	Warning letters were issued to the pharmaceutical companies but no actions were taken against any involved physicians

Cervical Cancer Screening Trial

Since 1998, three separate randomized clinical trials of cervical screening in Mumbai, Osmanabad, and Tamil Nadu, has been done with Indian women. US National Cancer Institute funded the Mumbai trial, while Bill and Melinda Gates Foundation funded the other two trials (Bagcchi, 2014; Nagrajan, 2014). The aim of these trials was to compare the death rate from cervical cancer between those who were screened for the disease and those who were not screened (Bagcchi, 2014; Nagrajan, 2014). The trials also aimed to find a cheap screening treatment for cervical cancer that can potentially be introduced into public health programs (Nagarajan, 2014; Suba, 2014). The screening treatments used were Visual Inspection with Acetic acid (VIA), Pap smear, and HPV screening with Quagid hybrid capture 2 (Nagarajan, 2014; Suba, 2014).

A total of 224,929 women were screened during the trials, while 138,624 women were not. Based on the reports, a total of 254 women died in the three clinical trials in the unscreened treatment groups (Bagcchi, 2014; Nagrajan, 2014; Suba, 2014). As a result, a complaint was filed to the United States Office for Human Research Protection, and it was found that women were not given adequate information about the experiment they were participating in (Nagarajan, 2014). Indian women of lower socioeconomic status were enrolled in trials, and the decision of whether to put women in controlled group or screening group was based on their socio-demographic status (Nagarajan, 2014; Suba, 2014) which was the main ethical concern of these studies: was it justifiable to deprive women of lower socioeconomic background from screening when it was easily available? After all, looking for a cheap screening method does not require the trials to have unscreened control group.

Like most of the previous clinical trials, the women involved in these studies were not given complete information and, they did not know if they were placed in the unscreened group. It is unethical to not screen women for cervical cancer when the screening procedures are available. During the last 15 years, if at any time the women were informed during the consent process that a cervical cancer screening could bring down their risk of death from cancer, they may not have taken part in the trial and may have gone for screening on their own. As per the ethical principles, one should be given all the information on risk benefit, alternatives, and procedures, yet participants were not informed of the randomization process that might place them in the unscreened group in these trials. In May 2011, Dr. Suba, a pathologist from San Francisco, filed a complaint in the US and urged involved institutions to give compensation to the families of women who died, as well as to provide urgent screening and treatment to the women in the unscreened group (Nagarajan, 2014; Suba, 2014).

Table 3 summarizes the controversial events that occurred during the cervical cancer screening trials.

Table 3: Summary of controversies with the cervical cancer screening clinical trials

Event	Details
3 separate randomized clinical trials for cervical screening was performed in Mumbai, Osmanabad, and Tamil Nadu since 1998	One trial was funded by the U.S. National Cancer Institute. The other two was funded by the Bill and Melinda Gates Foundation. The studies wanted to compare the death rate between screened patients and unscreened patients. The studies also wanted to find a cheap screening treatment for cervical cancer. Screening treatments included VIA, Pap smear, and HPV screened using hybrid capture 2.
224,929 women were screened and 138,624 were not	254 women from the unscreened groups died.
A complaint was filed to the U.S. Office for Human Research Protection.	Women were not given adequate information regarding the experiments. Socio-demographic bias affected the assignment of groups.
Dr. Suba filed a complaint in the U.S. in May 2011	The pathologist urged companies to: o give compensation to the families of the women who died; o provide screening to women in the unscreened groups.

HPV Vaccine Trial

In 2009, a research project was launched for the vaccination against the human papillomavirus (HPV- which can cause cervical cancer) by the states of Andhra Pradesh and Gujarat. The aim of the research was to calculate the cost and feasibility of introducing the HPV vaccine into the country's universal vaccination program (Bagla, 2013; Nair, 2015; 72nd Parliament Standing Committee Report, 2013). According to some reports, the trial was misinterpreted as "a post-licensure observational study" when, in fact, it was a large safety trial (Tandon, 2011). The project was designed and conducted by PATH (Program for Appropriate Technology in Health) and funded by the Bill & Melinda Gates Foundation (Bagla, 2013; Case Summary-ECCHR, 2014; Tandon, 2011).

During the project, vaccination was given to adolescent girls aged 10 to 14 in the states of Andhra Pradesh and Gujarat. The vaccines were provided by GlaxoSmithKline (Cervarix) and Merck (Gardasil). Several reports of ethical standards violations were reported by human rights organizations during the course of the trial. As a result, the Indian government ceased the project in April, 2010. However, vaccines had already been given to 24,000 girls by the time the order was issued to cease the trial (Bagla, 2014; Buncombe, & Lakhani, 2011; Case Summary-ECCHR, 2014; Chamberlein, 2015). Most of the participants were tribal girls (Chamberlein, 2015).

There were several ethical issues and violations committed during the trial, which the Committee has acknowledged (Mudur, 2012; Terwindt, 2014). Firstly, informed consent or assent was not obtained from parents of the girls. These girls were given the vaccine based mostly on the consent of a hostel warden (Buncombe, & Lakhani, 2011). An official order issued by the state of Andhra Pradesh, which was dated June 2, 2009, stated that all the hostel

wardens and Ashram schools must sign the consent forms on behalf of the girls' parents. Furthermore, several girls involved in the Gardasil trial suffered adverse events such as dizziness, fatigue, weight loss, and menstrual problems, none of which was reported (Chamberlein, 2015).

However, according to PATH and ICMR, the deaths of three girls were unrelated to the clinical trial. Meanwhile, another girl died from pyrexia which was very unlikely related to the vaccine, and a fifth died from a suspected cerebral hemorrhage (Bagla, 2013). Some experts say that it is impossible to determine the cause of death in the absence of autopsies (Bagla, 2013; Mudur, 2012), but the deaths of these five girls were not reported promptly (Bagla, 2013; Sharav, 2011). After the trial, many women activists visited schools in Gujarat and Andhra Pradesh to learn more about the trial procedures. They discovered that the girls were not informed of the nature or purpose of the vaccine. The girls did not know where the cervix is located and this had not been explained to them. The girls believed the vaccination was being administered by the government. Many girls felt it was compulsory to be vaccinated. They were not informed of any possible side-effects of the vaccine (PIL filed by Mehta, 2013; Terwindt, 2014).

Table 4 summarizes the controversial events that occurred during the HPV vaccine trial.

Table 4: Summary of the controversies with the HPV vaccine clinical trial

Events	Details
HPV vaccine research project was launched in Andhra Pradesh and Gujarat in 2009	The project wanted to calculate the cost and feasibility of including HPV vaccines to the country's vaccine program. The project was conducted by Path and was funded by the Bill and Melinda Gates Foundation.
24,000 adolescent girls between 10 and 14 years old were given the vaccine	GlaxoSmithKline provided the vaccine. Most of the girls who participated were tribal.
Human rights organizations reported unethical conduct during the project.	Informed consent was not obtained from the parents of the girls. Girls thought it was compulsory to participate in the trials. Girls suffered from adverse effects o e.g. dizziness, fatigue, weight loss, menstrual problems; o Adverse effects were not reported; Five girls died o One girl died from pyrexia, which is unlikely caused by the vaccine; o One girl died from cerebral hemorrhage; o Deaths were not reported right away.

The Supreme Court Intervention

The HPV vaccine trial brought major changes in India. After the death of seven girls, health activists and media representatives asked the ICMR to respond to all the unethical trials conducted in the country. Public concerns were at the highest level because of the number of deaths in clinical trials.

In April 2010, the director general of the ICMR confessed to the Indian Parliamentary Standing Committee on Health and Family Welfare that the guidelines imposed by the DCGI had not been followed during the HPV trial (Nair, 2015). Still, the government did not take any strict actions. Finally, therefore, a Public Interest Litigation (PIL) petition was filed in the Supreme Court by the women's health activists who had brought the case to the consideration of the Indian Parliament. A Public Interest Litigation (PIL) is a right given to the socially responsible citizen or NGO to support a public cause by seeking judicial decision for redress of public injury, and it can be filed in any High Court or directly in the Supreme Court. The petition filed by the women's health activists was about the unethical advertisement of the vaccine in the private and the public sectors, violation of informed consent rules, and the demand to investigate the deaths and adverse events after the immunization (Nair, 2015; Terwindt, 2014). A petition was filed against the DCGI, the ICMR, the states of Gujarat and Andhra Pradesh, PATH International, and the vaccine manufacturers Merck and GlaxoSmithKline (Nair, 2015).

On January 7, 2013, the petition was admitted to consideration by the Court. The Sama Resource Group for Women and Health, the Karnataka-based Drug Action Forum, and the Delhi Science Forum had also filed a second petition on the HPV vaccination project (Nair, 2015; Terwindt, 2014). These petitions were actually a timely follow-up to two other

PIL petitions filed by Dr. Anand Rai and Swasthya Adhikar Manch (Health Right Forum) on other clinical trials in India. The petitions by Dr. Rai and Swasthya Adhikar Manch had already requested the Court to ask the Indian Government to improve protection of trial subjects by enhancing the quality of conduct (Nair, 2015; Terwindt, 2014; The Times of India, 2012).

Although the petition was focused on a particular group of trials, it generally alleged that "more than 150,000 people were involved in at least 1,600 clinical trials and that during 2006-2011 at least 2,163 people have reportedly died in India while, or after, participating in such trials" (Moure, 2015). Conversely, according to an affidavit filed by the Health Ministry in the Supreme Court in response to a petition by healthcare NGOs, only 80 deaths were reported between January 2005 to June 2012 from clinical trials (Biswas, 2013). The Ministry of Health and Family Welfare also agreed that the death of 2,664 subjects occurred between 2005 and 2012 during clinical trials of 475 new drugs and, 11,972 subjects suffered serious adverse events (Biswas, 2013). Because of the fact different sources reported different numbers, there were many controversies about the number of deaths and injuries in clinical trials. For example, the DCGI reported that there were 2,031 deaths during clinical trials between 2008 and 2011. The DCGI was not aware whether companies paid any compensation to the victims of these trials (Jain, 2013). Meanwhile, according to Narayan (2013), as per the government report approximately 2,800 subjects have died during clinical trials since 2005 and out of these, only 89 of the deaths occurred due to the effect of the new drugs under investigations, while rest of the deaths were due to advancing ages, terminal illnesses etc. However, it is impossible to agree on the death causality as in most of the cases

autopsies were not done and only a few deaths were actually reported. In addition, only 70 subjects received compensation ranging from Rs. 180,000 to Rs. 420,000.

Table 5 shows the number of deaths and injuries reported by various sources.

Table 5: Numbers of deaths and injuries reported by various sources

Sources	Year	Number of subjects died	Number of Injuries	Location	No. of subjects who received Compensation
Swasthya Adhikar Manch (Biswas, 2013)	2005-2012	89	NA	All over India	82 subjects received compensation
Ministry of Health and Family Welfare (Biswas, 2013)	2005-2012	2644	11952	All over India	Information not available
DCGI (Jain, 2013)	2008-2011	2031	NA	All over India	Information not available
DCGI (Jain, 2013)	2010	668	NA	All over India	Information not available
Narayan (2013)	2005-2012	2800	89	All over India	70
Bhatnagar (2013)	2004	14	NA	Bhopal, India	0
Bhatnagar (2013)	2005-2010	32	NA	Indore, India	0

In January 2013, the Court called uncontrolled clinical trials of drugs on humans by pharmaceutical companies as “havoc” in the country, noticing that the government had slipped into “deep slumbers” in addressing this “menace” (The Hindu, 2013). The Court criticized the failure of the Ministry of Health and Family Welfare and the Central Drugs Standard Control Organization (CDSCO) for not taking any strict actions on previous issues and asked for urgent action (Krishnan, 2013; Terwindt, 2014). Furthermore, on September 30, 2013, the Court suspended the approval of clinical trials by the Drug Controller General of India and said that no clinical trial ought to be conducted for investigational medications

until a mechanism is set up to monitor them (Nair, 2015; Terwindt, 2014). Because of the Supreme Court's action, the number of clinical trials dropped significantly. Data from the clinical trial registry showed that the number of applications fell from 480 in 2012 to 207 in 2013 (Nair, 2015).

Recent Regulatory Changes in India

The Supreme Court decision prompted the CDSCO and Ministry of Health and Family Welfare to tighten the mechanism of clinical trials by enacting strict laws and regulations. Therefore, three new Rules were introduced in Schedule Y, namely Rule 122DAB, Rule 122DAC, and Rule 122DD (Burt et al., 2015; Kondal et al., 2016).

The particular concerns about the skills and capacity of CDSCO, including lack of coordination between state-level offices, violations in approval of new drugs, unethical clinical trial conduct, and a lack of transparency in the new drug approval process in the country, were raised by the 59th Parliamentary Report on the operation of the CDSCO by the Department Related Standing Committee on Health and Family Welfare (Kondal et al., 2016; 59th Parliamentary Report, 2012). In response to the recommendations given by 59th Parliamentary Report, the Ministry of Health and Family Welfare established an expert panel under the leadership of Professor Ranjit Roy Choudhry to develop policies and guidelines for the approval of new medicines, clinical trials, and banning of drugs (Kondal et al., 2016; MHFW, 2013). The recommendations of this committee were partly accepted by MHFW. Table 6 summarizes the recommendations given by the committee report and the actions taken by MHFW on the recommendations given by 59th Parliamentary Report. The actions taken by MHFW was given in the 66th Parliamentary report of April 2013. As a result, various regulatory amendments for clinical trials were introduced by the CDSCO giving the highest importance to the protection of trial subjects. The amendments introduced by the CDSCO are discussed in the following sections.

Table 6 Summary of issues identified by 59th Parliamentary Report and actions taken by MHFW (Source: Chaudhury, & Mehta, 2016; Kondal, Krishna, & Bansal, 2016; MHFW, 2013)

Section No.	Issues identified by Prof. Ranjit Roy expert committee	Actions taken by MHFW
1	Shortage of CDSCO staff and infrastructure	• Established 3 new sub-zonal offices in Bangalore, Jammu, and Chandigarh; converted two sub-zonal offices into zonal offices in Hyderabad and Ahmedabad. • Increases the number of posts of drug inspectors and deputy drugs controllers • Upgrades of six central drug laboratories with stae-of-art facilities • Introduces pharmacovigilance program of India
2	Requirement for strengthening of regulatory approval mechanisms	• 12 different committees for reviewing clinical trial applications are replaced by Subject Expert Committee (SEC) with members randomly selected from experts across the country • Technical Review Committee (TRC) is also set up to review the recommendations of SEC. They can approve, reject, or sent back to SEC with modification
3	Lack of coordination among regulatory authorities	• CDSCO website will upload information on approvals, file tracking systems etc • e-Governance system is proposed to link all the sub-zonal, zonal, central laboratories, and state drug controllers
4	Need of accreditation of ethics committees, investigators, and clinical trial sites	• Ethics committee are required to obtain registration from Licensing Authority before they review any protocol • Registered ethics committee members undergo large-scale training given by two organizations in India • The Quality Council of India has set up the National Accreditations programs. This will first review the SOPs and develop the standards for quality assurance. • Ethics committees will be reviewed in the first Phase followed by clinical trial sites and investigators
5	Compensation in the case of death/ injury	• Compensation formula is derived

Table 6 continue...		
6	Need to form a different department to conduct post-marketing surveillance of drugs, rationale use of medicines, and adverse drug reaction monitoring	• No such provision has been provided by the CDSCO
7	Need to demonstrate the necessity of clinical trials	• CDSCO passes an order that requires the consideration of ethnicity of local population while approving trials • During the approval of clinical trial, it is required to consider risk/benefit assessment, new drug vs. existing treatment, and unmet medical need in the country
8	Lack of confidence building measures for investigators and sponsors	• Within 6 months application will be reviewed • CDSCO has cleared the entire backlog • To make the application process easy, steps are being taken to ensure the use of information technology at every stage of clinical trial process
9	No need to pay compensation for death or injury due to unrelated causes	• Expert committee has been set up by CDSCO to determine the causality but still, rule has not been amended

Addressing Serious Adverse Events

The comprehensive data regarding compensation for any SAEs given during the past clinical trials are not available, primarily because SAEs were underreported and companies have not disclosed any compensation provided. Therefore, D&C Rules 1945 have been modified to provide the methodology for examining SAEs and the procedures for compensation payment. Rule 122 DAB in Schedule Y lays down the procedure for addressing SAEs and remittance for injury or death of participants related to clinical trials (DCGI, 2013; Kondal et al., 2016). With this amendment, within twenty-four hours of SAE occurrence, investigators are required to report to DCGI, the sponsor, and the Ethics Committees (CDSCO, 2013). However, a clause is also provided that "in the case, the investigator fails to report any SAE within required time frame, he/she shall have to furnish the reason for the delay to the satisfaction of the licensing authority along with a report of SAE" (CDSCO, 2013). Sponsors and CROs are also required to examine and send SAE reports within fourteen calendar days to the head of the institutions where the event took place, the institutional ethics committees, and the DCGI. The DCGI has final authority to decide the causality of SAE. Once the order is received from CDSCO about the causality of SAE, the sponsor is liable to pay compensation within thirty days (MHFW, 2015).

Unfortunately, not every investigator and clinical trial site has Internet or fax facilities to report SAE data to the CDSCO, which makes it almost impossible for all investigators in the country to report SAEs within twenty-four hours investigators.

Remittance to trial participants in the Event of a Clinical Trial Related Injury/Death

The clause of remittance in the case of trial-related injury or death is stipulated in Rule 122 DAB in Schedule Y. The DCGI has developed a draft formula for remittance

(CDSCO, 2013; CDSCO, 2015; MHFW, 2015). These guidelines have conveyed objectivity in the procedure remittance and have likewise added validity to clinical trials conducted in India. As per this rule, in the event of an injury, free medical treatment will be provided to the subject for as long as required or until the time that it is determined that the injury is not due to the clinical trial (Kondal et al., 2016).

Events that will be acknowledged as clinical trial-related injury or death are: 1) adverse effects of investigational drug, 2) malpractice or inattention by sponsor/investigator, 3) protocol violation, 4) use of placebo, 5) failure of the investigational drug to give the desired therapeutic effect, 6) adverse effects due to concomitant medications, and 7) injury to fetus (DCGI, 2013; MHFW, 2013). However, arguments are progressing regarding the use of placebo, compensation for AEs due to concomitant medication, compensation due to failure of IP, and compensation in the event of death or injury unrelated to the clinical trial.

According to this writer, in a research, no one can predict whether the investigational drug will have a therapeutic effect or not. But in the case of the injury or death not being related to the investigational product, it is indeed not a sponsor's responsibility to provide compensation. Moreover, there is no differentiation between compensation paid to healthy volunteers and to patients. There is also a concern that people may participate in a risky trial under undue influence to get free medical care in case of injury.

Amendments of the Informed Consent Process

Participation in a clinical trial must be voluntary for all subjects. As per the basic ethical principles, informed consent has three components: voluntariness, informed, and competent. In this writer's opinion, it is mandatory to give all the information to the

participants including, but not limited to the information about a drug, risks and benefits of the trial, trial protocol, difference between trial and treatment, randomization, and placebo.

In the majority of the past trials that were done unethically in India, informed consent was the issue. To overcome this, on November 19, 2013, the DCGI issued the order and made the Audio Visual (AV) recording of the informed consent process compulsory for all clinical trials (DCGI, 2013). As per this rule, while conducting clinical trials in India, investigators shall be required to maintain an audio-video (AV) recording of the informed consent process of each participant, i.e., the procedure of providing information to the subject and his/her understanding on such consent (DCGI, 2013).

According to many sources, AV recording makes informed consent tedious, but it acts as a hindrance for investigators to disobey the regulations, and it enhances the quality of the informed consent process (Kondal et al., 2016). However, when considering the subject's privacy, AV recording is an obstacle. Moreover, women may not give permission on an AV recording in the conservative society of India. Moreover, when there is a case of sexual disease or psychiatric trial, it is not advisable to do AV recording of the informed consent process so as to protect the subject's identity. AV recording may also increase the cost and time needed to complete the process. However, this provision has been further revised, and currently, the AV recording of informed consent process is compulsory only for the vulnerable subjects in clinical trials of new chemical entities (MHFW, 2015). But the government has not given specific definitions of vulnerable subjects. In India, the majority of the population is vulnerable hence, clarification is needed.

Approval for Conduct of Clinical Trial

Rule 122 DAC of Schedule Y describes the conditions for conducting clinical trials by the CDSCO. In the past, the New Drug Advisory Committee, Medical Device Advisory Committee or Investigational New Drug Committee reviewed clinical trial applications. Their recommendations then were reviewed by the Technical Review Committee (TRC), and then finally approved by the Apex Committee (Kondal et al., 2016). Recently, these NDACs have been renamed as Subject Expert Committee (CDSCO, 2014). The members are selected randomly from a group of experts from across the country.

According to recent changes, applications for clinical trials are reviewed in a three-tier system. First, applications are reviewed by the SEC, and then their recommendations are assessed by the TRC. Finally, the CDSCO confers approval of clinical trials based on the assessment of the TRC (CDSCO, 2014). Now it is mandatory to obtain prior approval from the respective ethics committee, to register the trial with the CTRI, and to submit an annual study report to the DCGI (MHFW, 2013).

Clinical Trial Inspection Plan

The instruction has been issued by the CDSCO headquarters to CDSCO officers and drug inspectors to conduct annual inspection of clinical trial sites to assure their compliance with study protocol, GCPs, Ethics Committee approval of a trial and protocol, and other regulatory requirements (CDSCO, 2010). In the case of any non-compliance found during the inspection, CDSCO can now stop the clinical trial and suspend the investigator, sponsor, and CRO from undertaking any future clinical trial. The sponsor, CRO, investigators or any other stakeholders against whom action has been initiated by the CDSCO can appeal to the

government of India within 90 days. The government of India may confirm, reverse or modify such actions after a hearing (MHFW, 2015).

Registration of Ethics Committees

Rule 122 DD in Schedule Y details the process of Ethics Committee registration. As per this rule, registration of Ethics Committee is valid for only three years. In the event of non-compliance, the DCGI can cancel the EC registration. After study completion, Ethics Committee is required to maintain all the study records for five years (MHFW, 2013). This step may reduce the biased review of clinical trials.

Other Major Amendments

Based on recommendations given by Prof. Ranjit Roy Chaudhury Expert Committee, the CDSCO signed several other rules on July 3, 2014 to further strengthen the regulatory framework, (CDCSO, 2013). These amendments are as follows (CDSCO, 2013; CDSCO, 2014):

- It is mandatory for the Ethics Committee, investigators, and clinical trial sites to get accreditation. The EC must get accreditation concerning to its composition, SOPs, decision-making process etc. The principal investigator must get accreditation based on experience in GCP, and rules and regulations. Clinical trial sites need to be accredited with regard to its infrastructure, site-specific SOPs, and documented procedures.
- Investigators can undertake only three clinical trials simultaneously.

  The author of this paper believes that, this rule may have bilateral repercussions. It may enhance the quality of research but at the same time, will decrease the number of clinical trials in the country.

- Sponsors are required to market the drug in India after the completion of the trial. To meet this requirement, the sponsor has to provide an commitment that they will market drug in India after the completion of trial in the clinical trial application form to the CDSCO.
- The CDSCO has established a separate department to conduct post-marketing surveillance of drugs, rational use of medicines, drug utilization studies, and adverse drug reaction monitoring.
- As per the new rule, only bioavailability and bioequivalence studies can be reviewed by an independent ethics committee, while academic and industry-sponsored clinical trials must be reviewed and approved by institutional ethics committees and not by the independent ethics committee.
- When providing NDAs, the CDSCO will now see that adequate proportions of Indian subjects are included in Phase III clinical trials.
- As per the new order issued on July 3, 2014, the CDSCO can now approve waivers for clinical trials in the case of national emergency, epidemics, and orphan drugs.
- The CDSCO has decided to enhance its manpower and capacity building. The CDSCO decided to upgrade existing offices and to set up new offices and Central Drug Testing Laboratories (Kondal et al., 2016). The CDSCO has established 3 new sub-zonal offices in Bangalore, Jammu, and Chandigarh, and converted two sub-zonal offices into zonal offices in Hyderabad and Ahmadabad. The CDSCO has decided to create more posts, and has already enhanced its manpower with 15 assistant Drug Controller and 148 drug inspectors (Chaudhury, & Mehta, 2016**)**.

In Table 7, a comparison of new amendments with old regulations is given, along with the probable impact of these new regulations on conduct of clinical trials

Table 7: Key issues before and after amendments of Schedule Y and its probable impact

Subject of amendments	Key issues before amendments	Before amendments	After amendments	Probable impact
Reporting of SAE	• Only the sponsor reports an SAE to the DCGI which may lead to misinformation, manipulation, or underreporting of incidents • SAE was not reported to IEC within 24h that can modify or stop the trial immediately • Not required to inform Head of the institution about SAE	Sponsor reports to DCGI Investigator reports to IEC within 7 days No requirements for investigator to report to DCGI No requirement to report SAE to head of the institution	Within 24h of occurrence Investigators require to report all SAEs to DCGI, sponsor and ethics committee Investigators needs to give reason for not reporting in 24h Within 14 calendar days, sponsor should report SAEs to the head of the institution where the clinical trial is happening	It may not be possible for all the investigators to report SAE within 24h, as there is no availability of electronic data transfer Will improve validity of clinical trials as IEC and DCGI will become aware of SAEs and can take some action
Remittance to trial participants	• no regulatory requirement related to compensation • poor and illiterate subjects were targeted by offering a small amount	No provisions for remittance to trial subjects	CDSCO has drafted the formula to calculate compensation	Do not consider age, risk factors, and differentiation of healthy volunteer and patients Under requirement to provide free medical care for injury/illness, there is no clarification of causality Influence participants to take part in risky trial

Table 7 continue...				
Informed Consent process	• Informed consent was not obtained adequately in most of the trials • Fingerprints were taken on the form without informing the subjects about trial	Paper-based informed consent form	AV recording of IC was mandatory for all participants but recently, rule is gain amended and now required for vulnerable subjects	Privacy and confidentiality issues Increase cost and time
Clinical trial approval	• Ethics Committees were biased, were not monitoring clinical trials	Approval from IEC was not mandatory IEC can approve both clinical trials for new drug and BA/BE studies	New drug study has to be approved by institutional EC and not by the independent EC Independent ethics committee can approve only BA/BE study.	Eliminate the likelihood of a biased review from an independent Ethics Committee, and improve current standards
Inspection plan	• There was no inspection plan	No arrangement for inspection plan before	Clinical trial inspection plan introduce to inspect investigators, clinical trial sites	Can assure data validity and find violation of regulations and ethical principles CDSCO never reveal inspection results and lacks the transparency
Registration of ethics committee and accreditation of clinical trial sites	• CDSCO did not know the composition, qualifications, SOPs, and working standards of ethics committee • Many clinical trial sites were lacking basic infrastructures and involved in malpractices	Registration was not mandatory No specific standards or regulatory requirements for ECs, investigators, and clinical trial sites to conduct clinical trial	Registration of ethics committee is mandatory CDSCO drafted proposal for accreditation of ethics committee, investigators, and clinical trial sites	All stakeholders will now work toward maintaining the highest standards and hence protecting the safety, rights, and welfare of trial participants

Impact of Recent Regulatory Amendments

Because of the latest regulatory changes, the rate of clinical trials approval has been affected. The increased numbers of regulatory submissions— such as the sponsor's affidavit to give medical management and remittance in the event of trial-related injury, to market medicine in India after trial completion, changes in the IC procedure, annual reporting of the study, and SAE reporting mechanisms—have resulted in prolonged approval timelines (Bhatta, 2014; Kondal et al., 2016).

In early 2013- 2014, after the establishment of three new rules, there was an enormous decline in the number of clinical trial approvals (Figure 1). As shown in Figure 2, the decline was also observed in the number of registered trials in India on ClinicalTrials.gov (Kondal et al., 2016). Because of these amendments, as shown in Figure 3, only six clinical trials were approved between January and March 2013 (CDSCO, 2015). These data show that either the government is taking too long to review the applications or industry is hesitant to conduct trials in India.

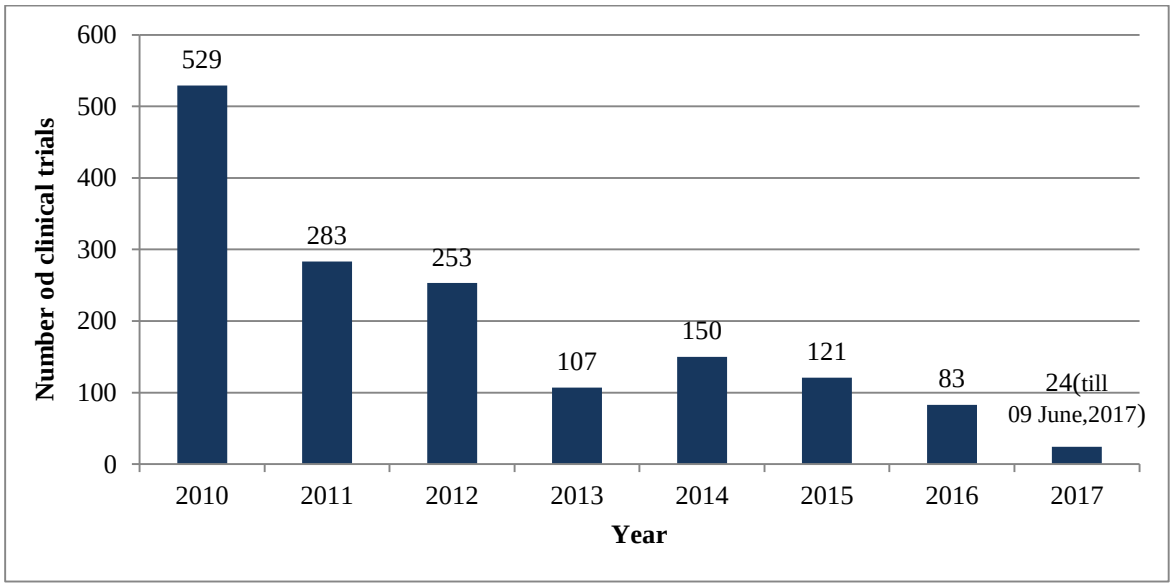

Figure 1: Numbers of CDSCO approved clinical trials in India between 2010 to May 2017 (Source: http://www.cdsco.nic.in/forms/list.aspx?lid=2093&Id=11)

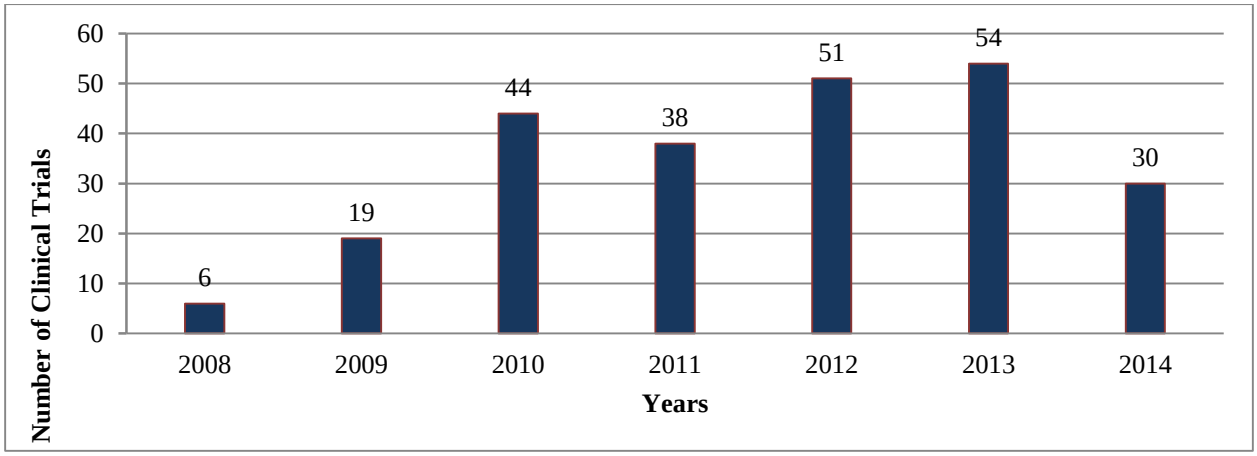

Figure 2: Numbers of registered clinical trials in India on ClinicalTrials.gov between 2008 and 2014

(Source: https://www.clinicaltrials.gov)

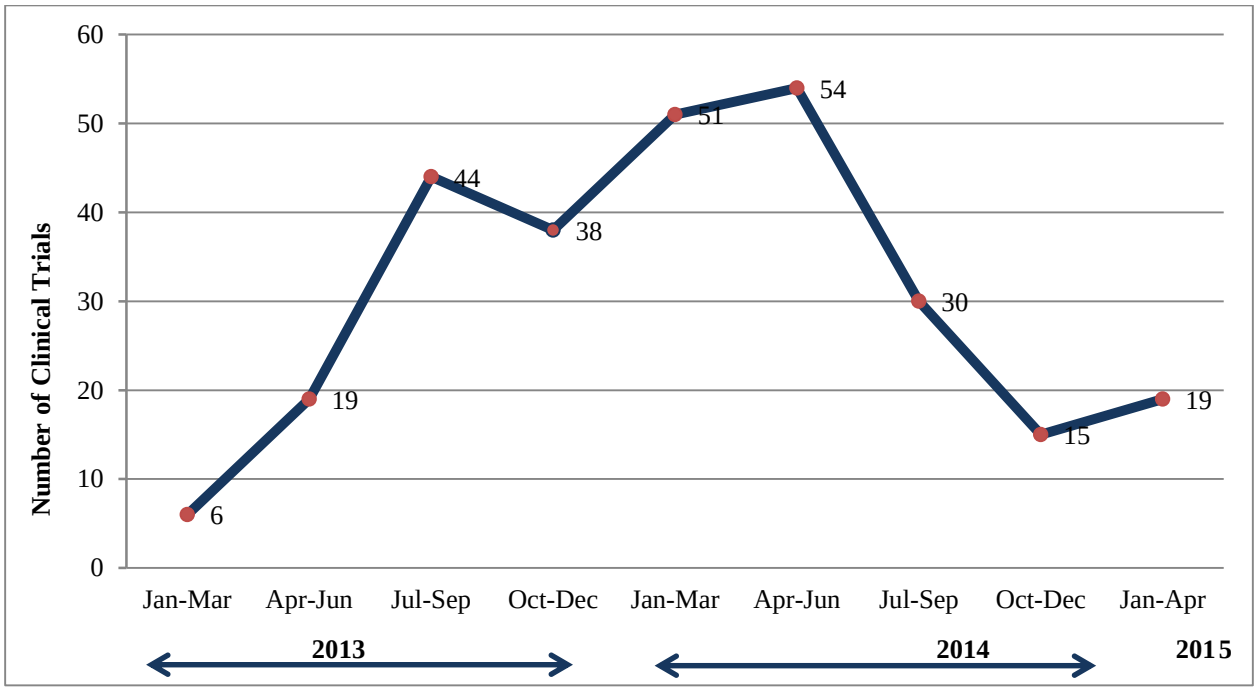

Figure 3: Numbers of clinical trial approvals in India, from January 2013 to April 2015, divided into 3 month periods

(Source: Source: http://www.cdsco.nic.in/forms/list.aspx?lid=2093&Id=11)

Clinical researchers required time to adapt to the new rules and regulations. From July 2013 to June 2014, the numbers of clinical trial approvals slowly increased. During this period, a total of 187 clinical trials were approved (CDSCO-CT approval, 2013; CDSCO-CT approval 2014). Several new orders were issued on July 3, 2014, which again forced regulators and clinical researchers to halt the clinical trial approval process. Because of such uncertainty, several multinational companies have considered shifting their business from India to other countries, such as China, Thailand, and Malaysia (Koreith & Anderson, 2013). Evidence of this shift can be seen between July and December 2014, when only 30 clinical trials were approved (CDSCO-CT approval, 2014).

This decline was continued in 2016, with only 83 clinical trials approval (CDSCO-CT approval, 2016), and through June 9, 2017 only 24 clinical trials approval (CDSCO-CT approval, 2017). The reason for this is the frequent amendments in regulations, most troubling is a requirement for sponsors to compensate trial participants in the case of adverse events or death, regardless of whether the event was caused by the study drug or preexisting disease. These frequent changes in regulations led to the increased confusion among clinical research stakeholders (Koreith & Anderson, 2013).

What Is Still Needed To Be Done In India?

For any government, transparency is required to maintain public trust. Transparency implies openness, accountability, and communication, which makes it easy for others to know what actions are taken. In India, transparency regarding clinical trial regulations is still missing. Reports of serious adverse events associated with clinical trials and specific drugs, as well as those regarding GCP inspections conducted at clinical trial sites, investigators, sponsors, and/or ethics committees are not available. Data about the number of inspections conducted by the CDSCO and their findings are not available. If the CDSCO provide everything publicly, it will become easier for citizens of India to know what deficiencies still exist and which physicians are banned from conducting clinical trials. The conduct of clinical trials in India must achieve this level of transparency.

In many developing countries and the developed world such as the USA, Europe, Canada, it is very easy to access warning letters issued by their regulatory agencies. These letters provide detailed information on the types of violation that have been made, the dates of inspections, the person who did the inspection, the details of the deficiencies that have been found, and further actions that are required to be taken. Moreover, on the US FDA website, the response from the sponsor, investigators, CROs, and/or ethics committees are also available, including the actions they are going to take to resolve the deficiencies found in the warning letter (www.fda.gov). This type of transparency is necessary to build public trust. Such transparency also forces all the clinical trial stakeholders to be more responsible for avoiding any negative disclosures that can affect public disclosure.

In India, most of the trials are large multinational Phase III clinical trials. Therefore, it may not be possible for the sponsor's home country's regulatory agency to inspect every

clinical trial site. Regulatory agencies select the key trial site that has the maximum number of patients for inspection. The USFDA conducts audit of the foreign clinical trial sites only during the following cases: 1) when only foreign data are submitted in an application, 2) lack of enough U.S. data in the application, 3) when there are conflicting results with the US and foreign data that are pertinent to decision-making, and 4) when there is a serious issue to resolve, e.g., fraud, scientific misconduct, or significant human subject protection violations (Ayalew, 2013; FDA guidance on acceptance of foreign clinical studies, 2013). For example, the USFDA Bioresearch Monitoring Programs, aimed at advancing and strengthening the FDA's oversight and protection of clinical trial participants as well as, the data integrity of all FDA-regulated clinical trials (i.e. human drugs and biological drug, devices, foods, and veterinary medicine), conducts many clinical trial inspections. In the year 2015, BIMO has conducted 1,113 inspections in the US as compared to 359 inspections in foreign countries, nonetheless, all the data are available on the FDA website (BIMO metrics FY 2015, FDA).

Therefore, India really needs to take actions in becoming more transparent regarding clinical research to protect the safety, rights, and welfare of the Indian citizens. Currently, no one really knows what kinds of violations are prevalent among Indian clinical trial stakeholders. The process of inspections is also unclear because the guidance followed by inspectors is not available in detail. By providing everything on the government website it will be easy for anyone to conduct secondary research on the available data. It will also be easy for the government because they will not have to waste their resources on providing RTI (Right To Information) requests.

Recommendations

- The CDSCO should immediately hire drug inspectors, and train them as per the international regulatory and ethical principles. Drug inspectors are the key persons in assuring data accountability and validation, as well as in protecting the right, safety, and welfare of the trial participants.
- The government should start partnerships with developed countries' regulatory agencies to strengthen the regulatory systems and to train the drug inspectors as per the international standards.
- There is a severe shortage of regulatory specialists in India. The DCGI does not release guidance documents like the FDA and EMEA to provide current understanding of the regulations. The DCGI should release detailed guidance documents.
- Currently, there is no law for penalties in case of an unethical clinical trial. There should be a provision to pay penalties by investigators and sponsors in case of GCP violations.
- List of accredited investigators, CROs, and clinical trials sites should be available on the CDSCO website.
- Pre-IND meetings and End of Phase IIa meetings should be started to save time in the long run. These meetings are useful in obtaining regulatory insight, avoiding unnecessary research study, deciding end points, and assessing special protocol, etc.
- Like the US FDA, the DCGI should involve patient advocacy group representatives during the meetings to understand their point of view.

- The government should start clinical trial awareness programs all over India to avoid subject exploitation.

Conclusion

After 2005, Indian pharmaceutical market was flooded with clinical trials, and the Indian government did everything to attract global pharmaceutical companies to conduct their trials in India. Investigators and pharmaceutical companies took advantage of the weak regulatory system, and because of this, many subjects were exploited and died by taking part in clinical trials between 2005 to 2010. Later on, many NGOs have filed for Public Interest Litigations which led the Supreme Court to put a halt on clinical trials in 2013 until the government was able to reform the regulations. This was the turning point in India in terms of changes in the regulatory environment. After 2013, many laws and regulations were changed in India, which leads to the reduced numbers of clinical trials in the country. Current changes are good in terms of public safety, but still there are many loopholes that need to be fixed.

India has a potential to become a favorable destination in the world for pharmaceutical companies because of its large patient population, low cost, and skilled professionals. But at the same time, India still needs to do a lot to match the international standards. The current government is making many good changes, and I hope will bring transparency in the field of clinical research.

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