Why did the DCGI of India cease clinical trials on NCEs in India, and what changes were implemented prior to starting them again?

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Abstract

India has been one of the most favorable destinations for clinical trials. A huge population, low cost, and lenient clinical trial regulations have been some of the reasons for choosing India as a destination for clinical studies. In the last decade, ethical concerns related to clinical trials conducted by foreign sponsors led to a ban of clinical studies in India for several months. Oversight by the United States Food and Drug Administration (USFDA) and Central Drugs Standard Control Organization (CDSCO) did not seem to be enough to ensure patient safety. Both social and economic conditions limited the FDA's capability to monitor the clinical trials conducted at foreign sites. The FDA has brought timely changes to the strategies of monitoring foreign clinical sites, but these changes were not good enough to control the ethical violations at Indian clinical sites. The Supreme Court of India ordered the cessation of clinical trials until the Drugs Controller General of India (DCGI) had made amendments to the clinical trial regulations in order to protect the rights of trial participants and ensure their safety. Schedule Y is one of the regulations defined as part of the Drugs and Cosmetics Act, 1940. Schedule Y consists of requirements and guidelines for permissions to import or manufacture a new drug for sale or for clinical trials in India. Amendments that were suggested are related to serious adverse event reporting and compensation, conduct of clinical trials and ethics committee registration, and functioning, informed consent process. These amendments to Schedule Y were passed into law on February 19, 2015. Though these amendments are aimed at patient safety, it would increase the cost and the time for the companies to conduct various clinical trials. The government of India should take appropriate steps to create a right balance between the safety of clinical trials and the speed at which the clinical trials shall be approved.

Introduction

Outsourcing has become a core component of many pharmaceutical and medical device-manufacturing companies. Outsourcing of clinical trials to developing countries such as India and China has many advantages. Some of these advantages include cost savings and reduction in the timeline of a trial. Because of the increased outsourcing, the FDA has to spend more time and human resources working with the local regulatory bodies, as the FDA is a United States organization. Crossing the borders means additional cost and work. Also, with the increase in clinical trials in foreign sites, there would be an increase in the number of international visits to audit the sites to ensure patient safety. The strategy of outsourcing clinical trials to developing countries raises a question about ethics followed, safety of subjects, and reliability of the data, because those sites may lack proper oversight of the study activities. Strict guidelines to be followed while conducting research and establishing ethical review boards at regional levels are still on the horizon (Glickman, Hutchinson, Peterson, Cairns, Harrington, & Cliff, 2005).

Clinical Research in the US: Expensive and Time-consuming

Pharmaceutical industries in the US invest as much as five times more than the average manufacturing company in research and development relative to their sales (Congressional Budget Office, 2006). The US represents the largest pharmaceuticals market in the world. It accounted for approximately $190.4 billion in 2005 compared to $57.5 billion in Japan (U.S. retail pharmacy drug sales, 2006). In 2005, the average cost of developing a drug was estimated at $1.3 billion (DiMasi & Grabowski, 2007). Big pharmaceutical companies like Abbott, Pfizer, and Johnson and Johnson spend more than US $5 billion per drug development (Harper, 2013).

Developing a new drug is definitely a costly affair and is also time-consuming. For every drug that will eventually reach the market, 10,000 compounds are screened at the discovery stage. Around 250 compounds make it to next stage, preclinical development. According to Daniel Klein, "FDA control over drugs and devices has often overlooked costs that almost certainly exceed benefits." The FDA's review process has also caused an increase in the cost of drug development (Madden, 2007).

To bring a drug into a market, a company conducts an average of 60 separate trials with 140 different medical procedures on a large number of patients (Centre Watch, 2011). In the US, a company spends an average of $1500 to retain a single test subject (Brescia, 2002). These high costs of drug development are one of the reasons for outsourcing clinical trials.

Outsourcing Clinical Trials

In order to reduce the high costs associated with drug development, big pharmaceutical industries have begun to explore various cost-saving strategies so that they can use their manpower and financial resources on core skills such as drug manufacturing and research. One of these strategies is to outsource clinical trials to developing countries. According to the Department of Health and Human Services, 271 clinical trials were conducted outside the US in 1990. This number went up to 6485 in 2008, which is an increase of 2000%. In 2008, the top 20 US-based pharmaceutical companies conducted one third of their clinical studies exclusively in foreign sites. In the same year, out of 106 applications submitted for marketing approval of drugs, 15 applications were supported by domestic data, and the remaining 91 applications were supported by foreign data. The FDA approved 10 drugs that were tested entirely in foreign sites (OIS, 2010). Outsourcing to third world countries saves lot of money for the manufacturer. In 2005, GlaxoSmithKline shifted 30% of its clinical trials business to populous and low cost

countries like India and Poland, which saved the company around $150 million that year (Drug Industry Daily, 2005). India represents one of the most favorable destinations for outsourcing clinical trials. India has a huge population, of which a significant portion are "drug-naïve," and has the diseases that many potential new drugs aim to target. With the low cost of health care and a lenient regulatory environment, it is one of the most favorable destinations for outsourcing a clinical study (The dark underbelly, 2012). Sick are abundant and numerous diseases are prevalent, which makes subject recruitment easier. "Ski where snow is," Neman Medical International advertised; "Conduct clinical trials where the patients are." According to the CIA World Fact book, an average American's income is 16 times more than an average Indian's income. Patient-to-physician ratio is quite high in India. In America, for every 384 patients there is one doctor, whereas in India there are 1667 patients for one doctor (WHO). The average American patient consumes nearly $7,000 in medical care each year, while the average Indian's annual health care tally is only $39 (Glickman, 2005). The charges for a case report in a second class medical center in the US is ten times the cost at a superior medical center in India. It costs about $2,000 to track the progress of a single Indian patient in a clinical trial, GlaxoSmithKline CEO Jean-Pierre Garnier wrote in the May 2008 Harvard Business Review, before retiring that month. It costs 10 times more in the US to develop a new drug than it does in India (Glickman, 2005). India has made a name for itself in the international pharmaceutical field as an ideal destination for worldwide companies to conduct clinical trials, which is a test for both the government and the private sector to create a balance between ethics and trade.

Clinical Trials Conducted by U.S.-based Sponsors in India

From 2009 till 2014, US-based sponsors registered a total of 1442 studies conducted in India. Out of 1442, 41 studies were sponsored by the NIH and the rest by pharmaceutical

companies and others like universities, individuals and organizations (Clinicaltrials.gov). All clinical trials conducted in India need prior permission from the DCGI. Schedule Y of the Drug and Cosmetics Rules, 1945, regulates current clinical trials in India. Schedule Y defines the requirements and guidelines for import and/or manufacture of new drugs for sale or for clinical trials. During the amendment of Drugs and Cosmetics Rules, 2005, the Schedule Y was extensively revised to bring the Indian regulations on par with internationally accepted definitions and procedures. For example, rules governing the informed consent process and ethical committees are not well established in India, as they are in the U.S. Therefore, the new amendments included rules for ethics committee registration and functioning. India has regulatory bodies like the Central Drugs Standard Control Organization, the Indian Council of Medical Research, the Ministry of Health and Family Welfare, and the Department of Ayurveda, Yoga, Naturopathy, Unani, Sidha and Homeopathy (Regulation and Guidelines).

Usually, the US-based sponsors approach contract research organizations to conduct their clinical trials. These CROs contact principal investigators to actually conduct the study. The PI has to submit the study protocol to the Ethical Committee of the institution (IRB) for approval before recruiting patients. There was a great increase in the number of clinical trials conducted in India, but the ethical and regulatory practices couldn't keep up with the increase. For example, according to a WHO Bulletin report, in India less than 40 ECs are properly constituted and functioning (Chatterjee, 2008). It took until January 2013 for the Indian government to realize the need for regulatory reform. There are many advantages to conducting clinical trials in India, like less strict laws and regulations, cheap labor, and low infrastructure costs, which could save 60% of clinical trials cost (Nundy et al., 2005). But with the improper functioning of the Ethical Committee and non-stringent regulations, questions about the safety

of patients and ethics followed. Many incidents have been reported where ethics and safety of patients were compromised. Six cases of questionably ethical clinical trials are as follows:

Case 1: Clinical trials on Bhopal Gas Victims at Bhopal Memorial Hospital and Research Center, Maharashtra.

According to a letter written by the Hospital's director Brigadier KK Madur to the deputy drug controller of India, D.R Ramakrishna on February 22, 2011, unethical trials were conducted on 279 patients, of whom 215 were gas victims. More than 10 clinical trials were conducted in Bhopal Memorial Hospital in 2010-2011. A few drugs being tested were Fondaparinux, in the Cardiology department; Tigecycline, in gastro surgery department; and Televancin, in the anesthesiology department. Fourteen patients died while on the clinical trial. Out of those 14, 10 were Bhopal gas victims (Sharma, 2011). These clinical trials were sponsored by Theravance, Sanofi, and Wyeth pharmaceutical companies. Theravance conducted "Attain" clinical trials. Tigecycline clinical trials were conducted by Wyeth pharmaceuticals (acquired by Pfizer in 2009). (Clinicaltrials.gov) The informed consent process wasn't documented at all. Even the director of the hospital had no clue how the informed consent was taken from the victims (Sharma, 2011). The hospital made a profit of 623,820 INR in the Attain study and 1,936,158 INR in studies conducted by Wyeth (acquired by Pfizer). In both cases the studies were conducted by a CRO named Quintiles. Pfizer claims that it conducted only two studies in BMHRC, whereas the hospital claims that it paid for four studies. The discussion about clinical trials during the Ethical Committee's review process was brief and superficial. The investigators were part of the Ethical Committee's board that approved their own clinical trials. Medical experts questioned the sponsors about the ethics of testing the drugs on gas victims when long-term effects to Methyl Isocyanate exposure are not

known. None of the 14 deaths related to clinical trials were investigated properly, and patients were not given any compensation (Lakhani, 2011).

Case 2: Clinical trials conducted in Majaraja Yashwantrao Hospital, Indore, and Maharashtra.

Dr. Anand Rai, a former resident at Maharaja Yashwantrao Memorial Medical College, wrote to National Human Rights Commission (NHRC) about the deaths associated with clinical trials being conducted in the hospital. The clinical studies were conducted in the department of psychiatry in contravention with Schedule Y of the Drugs and Cosmetics Act, which has explicit guidelines for clinical trials involving the mentally ill, and the Indian Council of Medical Research's (ICMR) Ethical Guidelines for Biomedical Research on Human Participants (Jayaraman, 2012).

Case 3: Clinical trials on Risperidone (Risperdal) in seven cities in India.

These clinical trials were sponsored by Johnson & Johnson pharmaceutical company. It is placebo-controlled trial of Risperidone for acute mania. Many of the lead investigators conducting these trials told the media reporters that the trial design was methodologically unnecessary because an effective treatment for the same problem already exists and there isn't a need to compare with a placebo (Srinivasan, 2006). Patients recruited in the US for the same clinical study had a mean YMRS score of 29, whereas in India, the mean YMRS score of the patients recruited for the study was 37.9. The YMRS score was used to measure the efficacy of the clinical study. This clinical study violated the Declaration of Helsinki 2000, according to which a placebo-controlled study was unnecessary when an effective treatment already exists. The informed consent process was conducted according to Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, in the 1989 version of the

Declaration of Helsinki (World Medical Association, 1989). The Declaration of Helsinki was revised according to the present-day needs. How could FDA accept the data from a study that followed the 1989 version of DOH instead of a current one? (Drug trials outsourced to India, 2006).

Case 4: Clinical trials of a vaccine for Human Papilloma Virus that causes cervical cancer.

These clinical trials were conducted as a five-year project to advance the prevention of cervical cancer caused by the Human Papilloma Virus. The trials were conducted in tribal, semi-urban and -rural areas of two states of India, Andhra Pradesh, and Gujarat. The study was funded by the Bill and Melinda Gates foundation, and the vaccine was provided by Merck Sharpe and Dohme. These clinical trials were called "Demonstration Projects" and were conducted by the state government's Ministries of Health and Family Welfare, along with a non-government and international non-profit organization, PATH (Program for Appropriate Technology in Health). The program started on July 2009. The clinical study got approvals from all the necessary institutions in India. Girls aged 10-16 were recruited for the study. Seven deaths were reported in the study. It was found that concerned school staff, like teachers, wardens, and principals, signed 2763 consent documents. Nearly 2000 consent forms had parents' thumb impressions because the parents were illiterate. Sixty-nine consent forms didn't contain any witness signatures, and in four consent forms, the signature and the respective names didn't match. It was found that Deputy District Medical and Health Officer Mr. P. Mohan Rao asked the project officers of the Integrated Tribal Development Authority to issue orders to the school principals and hostel wardens. The orders were to sign the informed consent forms on behalf of the girls who stay in the hostel, as it would be difficult

to wait to contact the parents. On April 15, 2010, the Indian government enquiring about the irregularities in the conduct of the clinical trials formed a committee. When the HPV vaccine was tested in US, 29,323 women participated in that study. During these studies, 37 died, 255 cases of serious systemic adverse reactions were reported, and 463 cases of new medical conditions were reposted that were considered potentially indicative of systemic autoimmune disorders. The question raised here is, "Why was such a study conducted in a place where proper and necessary training isn't provided to staff involved in the conduct of study?" (Bhowmik, 2012).

Case 5: Cancer Clinical trials in Thiruvananthapuram, Kerala, India.

The clinical trials were conducted at the Regional Cancer Centre in Thiruvananthapuram during April 1999 and November 2000 by researcher Dr. Ru Chih C. Huang from Johns Hopkins University. Compounds M4N and G4N, derivatives of plant products, were tested on oral cancer patients. These were the first clinical trials of compounds M4N and G4N. Twenty-seven patients were recruited for the study. On March 18, Dr. V. N. Bhattathiri, Associate Professor of Radiotherapy, registered a complaint at the Kerala Human Rights Commission, claiming that the hospital conducted unethical clinical trials in oral cancer patients on behalf of a western pharmaceutical company. This led to an investigation of the case. In July 2001, Johns Hopkins authorities announced that the clinical trials conducted at RCC in India were not authorized by any department of the university, and neither of the trials had an IRB approval. The study was approved by Drugs Controller-General (India) in February 2001, after the experiment had concluded. It was found that not all of the 27 patients were monitored after the administration of the injections, and there was no proper follow-up. The Indian government ordered an inquiry through a one-man commission, Dr.

Parvesh Parikh of the Tata Memorial Hospital in Mumbai. He concluded saying that all the patients were fine and had no side effects. But the truth he revealed to the Frontline was that he examined only 10 patients and was made to conclude that everyone was fine, to keep up the reputation of the hospital. It was also found that the patients weren't told about the clinical trial and were just asked to sign a paper to get an injection that was part of the treatment. Dr. Huang was barred from being a principal investigator of any research conducted in human subjects (Mudur, 2011).

Case 6: Clinical trials of Zoniporide by Pfizer.

Phase III clinical trials of Zoniporide, a drug used in perioperative cardiac events, were approved to be conducted in India. The DCGI approved the Phase III trials before even the completion of the Phase II trials and mandatory carcinogenic and reproductive studies on animals (Gulhati, 2004). It violated the Schedule Y regulations of prohibition of clinical trials on drugs that did not undergo animal testing and Phase trial.

These are only examples of clinical trials in India sponsored by US-based sponsors which do not meet ethical standards. There are many such incidents of similar clinical trials conducted by other countries and also by native Indian pharmaceutical companies and private organizations. The most common ethical concern, which relates to the conduct of clinical research in India, is the informed consent process. In the words of Arun Bal, president of the Association for Consumer's Action on Safety and Health, "In India there is no law to safeguard the interests of volunteers involved in clinical trials. Though the Indian Council of Medical Research laid down the guidelines for conducting the trials, there is no mechanism in place to ensure that they are being implemented" (Economic Times, 2004). Why are the trial participants not being informed about the clinical study in which they were being involved?

Why are the patients being blindfolded? Why are the officials not bothered about patients' interest and safety? To find answers to these questions we need to understand other deficits in Indian Clinical Research.

Deficits in Indian Clinical Research

1. Insufficient number and improper working of Ethical Committees:

In February 1980, the first Ethical Committee was set up in India. Guidelines were issued by the Indian Council for Medical Research (ICMR). These guidelines included recommendations for membership criteria and ethical standards for review. After 20 years, in 2000, ICMR released a guidance document for research in medical, epidemiology, and public health. These guidelines were revised in 2006; the document was called "Ethical Guidelines for Biomedical Research on Human Participants" (Ethical Guidelines, 2006). There are about 200 ethical committees established in India. With the increase in clinical trials, there should be many more ethical committees to make the process easy and faster. Despite the guidelines issued by ICMR, many of these Ethical Committees do not function adequately (Rashmi Kadam, 2012). According to a survey conducted by the Indian Council of Medical Research (ICMR; Kumar, 2003), some of the problems associated with the working of ECs in India are the following:

- Lack of clarity about the appointment procedures and qualification of EC Members. Absence of legal experts on the Ethics Committee board, which is mandatory according to Schedule Y.
- Many times the head of the institution takes charge as chairperson of the ECs. This questions the EC's independent working nature.
- Lack of Standard Operating Procedures.

- No proper record-keeping.
- No proper documentation of the meeting held, like the details and minutes of meeting and issues discussed. Lack of proper space to accommodate for meetings and record keeping.
- Lack of proper administrative support.
- Inadequate remuneration offered to members serving on EC boards. These issues culminate into reluctance of trained individuals to serve as members of the EC.
- Lack of formal training of board members on clinical research and bioethics committees.
- Very few ECs review the Informed Consent document thoroughly and conduct follow-up monitoring of the study.
- Until 2012, there wasn't any central registration system to maintain the proper functioning of Ethical Committees in India.

2. The second major problem in Indian clinical research is informed consent process:

The basic idea of informed consent process is to tell the trial participant about the study in which they would participate, risks and benefits, procedures involved, possible side effects, and results from previous similar studies which the subject needs to know. It is up to the patient to decide whether to participate in the trial. It is a voluntary decision from the patient. No one can influence the patient to participate in the study (CFR TITLE 21 PART 50).

But the very purpose of informed consent is clearly not understood by many medical officials in India. In most of the cases, patients were not aware of their participation in clinical trials. The officials misused their trust in doctors for best treatment. Many times subjects participating in the trials are illiterate, and while 22 different languages exist in India, the informed consent forms are not available in those languages. Patients have no idea of their

rights and responsibilities as a clinical trial participant (Pranati, 2010).

3. Lack of proper training on clinical research ethics, rules, and regulations:

Staff involved in conducting clinical research should be given formal training on bioethics, the informed consent process, and other clinical research rules and regulations, especially Schedule Y, which constitutes requirements and guidelines for permission to undertake clinical trials. In a vaccine clinical trial conducted in Andhra Pradesh and Gujarat, the teachers and hostel wardens signed the Informed Consent (IC) forms on behalf on the girls. Lack of knowledge about the informed consent and training on clinical research ethics led authorities to misuse their power, leading to ethical violations (Bargaje, 2011).

4. Above all, corruption and desire for money:

There is a wide economic disparity between the U.S. and India. As we discussed earlier, an average American's income is 16 times more than an average Indian's income. A doctor with MD specialization in India earns about RS 8-10 lakhs (US $12k-16k) per annum (Abrar, 2010). In the U.S., the average salary of a physician is about $250,000 (Conover, 2013). An average American patient's healthcare costs nearly $7,000 per year, whereas in India it is $39 per person. In many cases in India, recruitment fees are paid to doctors, nurses, and other staff involved, as a reward for referral of patients. A recruitment fee is often integrated with the clinical trial budget and is usually paid as administrative costs. As a result, some physicians ignored exclusion criteria while referring patients to research for conditions they did not suffer from (Andrews, 2000).

It is now clear that greed and lack of formal training are the two main reasons for the ethical violations of informed consent process. The majority of people recruited into clinical trials at Indian Government hospitals are poor and illiterate. Their innocence and desire for

good health care is taken advantage of. Above all, there is no evidence of proper periodic monitoring of the clinical trial sites. If clinical trial oversight had been strict enough, then the atrocities would have come to light at the beginning of the clinical trial or at least within a short period of time after the trial started.

FDA's and Central Drugs Standard Control Organization's (CDSCO) Strategies in Oversight of Clinical Sites in India

The oversight of clinical trials in India by US sponsors is a combined responsibility of FDA and CDSCO. The same rules and regulations should be imposed, irrespective of the location of clinical sites. If the site is on foreign land, then the clinical trial process should also abide by the local regulatory bodies. The FDA and CDSCO have made a great effort to deal with shortcomings/discrepancies in monitoring of clinical trials activities.

In 2010, the FDA documented some challenges that it was facing in inspecting/ monitoring clinical trials that are being conducted at foreign sites (Levinson, 2010). Of all those, below are the important ones:

1. The FDA is unaware of many early phase clinical trials; there is no prior approval needed to conduct early phase clinical trials in foreign countries. The FDA allows sponsors to submit these clinical trial data conducted without IND approval in support of their Investigational New Drug/New Drug Application (IND/NDA).
2. Logistical challenges, which include rules for travel time, visas, and budget constraints.
3. Nonstandard format of clinical trial data: Submitting data in different forms made the review process for FDA a very difficult task. Often tracking the data, particularly site locations and subject enrollment, was a tedious job.

The FDA has put effort into addressing the above-mentioned challenges. As part of those efforts, it release guidelines for clinical trial monitoring, "Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring" (HHS, 2013). Centralized monitoring is emphasized for the present-day clinical trial process oversight. The implementation of electronic case report forms and computerization of various documentation in the field of health care has sped the clinical trial process to an extent and also reduced hours of paperwork for the review process (Guidance for Industry, 2013). Also, efforts have been made to standardize the format in which the sponsors need to submit the data (Guidance for Clinical Trial Sponsors, 2006). Indian Contract Research Organizations are also stressing the advantages of a risk-based monitoring approach. The DCGI has yet to bring standard rules implementing the risk-based monitoring approach.

Indian Government Efforts Towards Better Patient Safety

Many efforts are being made by the Indian regulatory agencies to ensure the safety of trial participants. The Supreme Court of India passed a ruling in January 2013 to stop the clinical trials on NCEs until necessary reforms are made to the regulations of clinical trials. A committee called Apex was set up to further investigate in the discrepancies of the clinical trials and to suggest necessary steps to strengthen the clinical trial regulation policy in India, in turn stressing patient safety in India. (CDSCO, 2013)The regulatory agency overseeing and approving clinical trials is the CDSCO, "Central Drugs Standard Control Organization" (Central Drugs Standard Control Organization, 2014). The Apex Committee suggested amendments to the Drugs and Cosmetic rules for safety of the clinical trial participants. The three amendments suggested were:

a. First amendment: Rule 122 DAB

In the case of an injury occurring to a clinical trial subject, free medical management should be provided as long as required, and he or she shall also be entitled to financial compensation as per order of the Licensing Authority. In case the clinical trial results in the death of the subject, financial compensation, as per the order of the Licensing authority, has to be compensated to the nominee (s) of the deceased subject. The preceding subsections of the rule explain the circumstances that are considered as a "direct nexus" to an immediate cause to the injury/death, consequences of non-payment of compensation, and so on.

b. Second amendment: Rule 122 DAC

This amendment specifies the requirements for the clinical trial approval by the DCGI. Further, the rule increases the power of the DCGI to impose any additional conditions to be fulfilled in case of grant of permission in respect to any specific trial, as it is deemed fit.

c. Third amendment: Rule 122 DD

This amendment specifies the mandatory registration of the Ethics Committee and specifies that no Ethics Committee shall review and accord its approval to a clinical trial protocol without prior registration with the Licensing Authority as defined in clause (b) of rule 21 and describes the procedure of such registration. CDSCO has mandated Ethics Committee registration and has laid down the requirements for its registration and functioning. CDSCO imposed a rule that the Independent ECs, unlike the Institutional ECs, can review only Bioavailability and Bioequivalence studies and not any other type Clinical studies. Also the ECs' responsibility doesn't end with clinical trial approval but should be involved in the periodic on-site monitoring process. It is now mandatory for the Ethics Committee to submit periodic reports to CDSCO.

According to the latest proceedings of the Apex committee held on December 24, 2014, a complete amendment is placed for public opinion (CDSCO, 2015). It is to be proposed in the 2015 Budget Session of parliament in India.

The summary of the main changes suggested:

Introduction of a New Chapter in Schedule Y: "CHAPTER IA CLINICAL TRIALS"

This chapter includes revised regulations about:

a. No clinical trials without prior permission.
b. Compensation and medical treatment for injury and death.
c. Deferment of clinical data requirements to DCGI.
d. Registration, functions, and responsibilities of ethic committee.
e. Inspections by drugs control officer.
f. Disclosure of name, address, etc. of persons involved in clinical trials.
g. Maintenance of record and furnishing information.
h. Penalty for conducting clinical trial of any drug or investigational new drug or any notified category of medical device or investigational medical device without permission, and penalty for repeat offense.
i. Penalty for contravention of any provision of this Chapter 1.
j. Power of central government to make rules.

No clinical trial without prior permission.

No one can conduct any kind of clinical trials without prior approval of the DCGI. Approval from the Ethical Committee must be granted before anyone can initiate the

clinical study. The fee for the approval process may be notified by central government.

Compensation and medical treatment for injury and death.

If the injury or death of a person is proved to be related to the clinical trial, then the sponsor shall provide appropriate medical treatment and compensation to the patient or patient's legal heir.

Registration, functions, and responsibilities of ethic committee.

All Ethics Committees should be registered with the DCGI. Clinical trial protocol and other related documents related to the clinical trial should be approved before the initiation of the clinical study. The Ethics Committee shall be responsible for overseeing the conduct of the clinical trial, safeguarding the rights, safety, and well-being of all trial participants enrolled in the clinical trial. The Ethics Committee shall make periodic reviews of the trial, based on the study of progress reports furnished by the investigators and monitor internal audit reports furnished by the sponsor, or by visiting the study sites in such manner as may be prescribed. The Ethics Committee shall have power to revoke its approval granted to a clinical trial protocol and other related documents, for reasons to be recorded in writing and communicated to the Investigator and to the DCGI. The DCGI can cancel the registration of the Ethics Committee if the EC is not able to discharge its functions and responsibilities. On the suspension or cancellation of the registration of the Ethics Committee, the DCGI shall review the approval granted by the Ethics Committee for continuance of the clinical trial. If the registration of the Ethics Committee is cancelled, then every member of such committee shall be disqualified to be a member of any other Ethics Committee for a period of two years.

Inspection by Drugs Control Officer

The Drugs Control Officer or any other officer authorized by the DCGI shall have the power to enter with or without prior notice into any premises related to clinical trial to inspect the facilities, record, data, documents, books, drugs including investigational new drugs, notified category of medical devices and cosmetics. The officer empowered shall have the power to seek clarifications, information, and record regarding clinical trial.

Disclosure of name, address, etc. of persons involved in clinical trials.

When required, every person, sponsor, clinical research organization or any other organization or investigator conducting a clinical trial, shall disclose the names, addresses and other particulars of the persons involved in conducting clinical trials and participants in the clinical trial to the Drugs Control Officer or any other officer authorized by the DCGI.

Maintenance of record and furnishing information.

Every person, sponsor, clinical research organization, or investigator conducting a clinical trial shall keep and maintain data, record, registers, and other documents and shall furnish information as required by the DCGI or any officer authorized.

Penalty for conducting clinical trial without permission and penalty for repeat offense.

Whoever conducts clinical trials or experiments with a new drug, in contravention of the rules, shall be punished with imprisonment for up to three years or a fine which may extend to five lakh rupees or both. Repeated offenders shall ne punished with five years of imprisonment and a minimum fine of fifteen lakh rupees.

Penalty for violation of conditions of permission.

Whoever conducts clinical trials with any new drug or investigational new drug or notified category of new medical device and investigational new medical device or new cosmetics in contravention of the conditions of permission issued by DCGI: (a) which causes adverse affects on the body of participants shall be punishable with imprisonment for a term which may extend to one year or fine which may extend to three lakh rupees or both; (b) which does not cause any adverse affect on the body of participant shall be liable for a penalty, which shall not be less than fifty thousand rupees but which may extend to two lakh rupees, to be imposed by the DCGI.

Power of Central Government to make rules.

The Central Government may, after consultation with the Drugs Technical Advisory Board or the Medical Devices Technical Advisory Board, by notification, make rules for (a) the form and manner for conducting clinical trial under section, (b) the norms and procedure for approval of any clinical trial by the Ethics Committee, (c) the manner in which the Central Licensing Authority shall review the approval granted by the Ethics Committee for continuance of clinical trial, (d) the norms and procedures for deciding whether injury or death of a trial participant has been caused due to clinical trial, (e) the norms and procedures for providing medical treatment to the trial participants, (f) the norms and procedures for registration of Ethics Committees, (g) additional functions and responsibilities of the Ethics Committee, and (h) the norms and procedures for conducting inspections relating to conduct of clinical trials, provided that consultation with the Board may be dispensed with if the Central Government is of opinion that circumstances have arisen which render it necessary to make rules without such

consultation.

Along with these amendments, the Government of India passed a rule about the informed consent process. Central Government, in consultation with the Drugs Technical Advisory Board (DTAB) and the Central Drug Standard Control Organization, passed an order in November 2013 that audio-video (AV) recording of the informed consent process of individual participants by an investigator including procedure of providing information to the subject and his understanding on such consent should be maintained by the investigator for record while conducting clinical trials in India. (CDSCO, 2014)

On the whole, the Indian Government has made a great effort to improve the patient safety on streamlining and revising the clinical trial regulations by instituting a structured accreditation process accrediting investigators, trial sites and ethics committees, making ethics committees function effectively, and ensuring diligent adherence to guidelines concerning informed consent from trial subjects. (CDSCO, 2015) These are the three most necessary changes that are required based on the ethical violations that usually occur in Indian clinical trials.

Conclusion

The objective of this project was to understand the reasons behind the DCGI's decision to cease clinical trails in India and to discuss the amendments made to Indian clinical trial regulations, which subsequently led to lifting the ban on clinical trials in India.

Because of its huge population, low medical costs, and ability to conduct trials at a low cost, India (Nundy et al., 2005) has become an ideal destination for international pharmaceutical companies to conduct clinical trials. As the number of clinical trials increased, many incidents were reported where the ethics and safety of patients were compromised, some

of which are discussed above. In most of the cases, informed consent was not taken from the patients. Patients were not informed about the procedures, risks, and side effects of the drug trial in which they were about to get registered as a participant. The rampant corruption in India sometimes allowed the companies to compromise on ethics and violate them. As a result, questions were raised about the functioning of ethical committees, the non-stringent regulations, and the safety of the patients and the ethics. These violations were noticed by the Supreme Court of India, which asked the DGCI to cease the clinical trials. Later a bench of Justice R. M. Lodha and Justice Shiva Kirti Singh asked for a review of 157 new chemical entities that were cleared for clinical trials till December 31, 2012. The government of India formed the Apex Committee headed by Prof. Ranjit Roy Chaudary to investigate the discrepancies of the clinical trials in India and to suggest necessary changes to the current regulations (Sachan, 2013). The investigation of this expert committee uncovered rampant violations with regard to breach of ethical codes and the manner in which the safety of the patients was compromised. The committee also recommended a few amendments to ensure that these violations were fixed and to ensure the safety of clinical trial participants. Taking these recommendations into account, the DCGI and CDSCO drafted a bill, Drugs and Cosmetics (Amendment) Bill, 2015. The new amendments mainly concentrate on the approval process of clinical trials, registration and proper functioning of Ethical Committees, qualifications of Ethical Committee Board Members, monitoring process of clinical sites by Drug Control Officer, penalties for any wrongdoings, and power of Central Government to make rules. The new amendments are placed for public opinion and were introduced in the budgetary session in February 2015. They were approved to be made into law on February 19, 2015. One of the noticeable changes with the new amendments are the fact that the SAE report of a clinical trial

has to be forwarded to the Licensing Authority within ten calendar days instead of fourteen calendar days. The SAE report can now be sent to the Expert Committee, which wasn't the case earlier. The investigator now has to send any unexpected SAE report within 24 hours to both the Sponsor and the Ethical Committees. The new amendments clearly mention the payment/compensation given by the sponsor to the subject in case of injury/death. The previous law did not talk about the payment or the compensation given by Sponsor to the subject in case of injury/death. Under the new amendments, investigators now have the responsibility to inform the subject or his/her nominee of their rights to claim compensation in case of clinical trial related injury or death. According to the new amendments, the investigator now has to maintain audio-video recordings of the informed consent process.

With these recent reforms to clinical trial regulation in India, the concerns over ethical discrepancies can be alleviated to a great extent. Apart from these reforms, the DCGI should take initiatives to encourage training on clinical research process and to involve trained or skilled staff in the clinical trial process. DCGI should also introduce more programs to train clinical research coordinators, clinical research associates, and drug safety inspectors. Awareness programs should be conducted for the general public, especially in the rural areas of India. Initiatives should be taken to increase the number of regulatory boards, to monitor visits and to audit clinical trial sites. With the use of electronic case report forms, we can now speed up the monitoring process and review. The Indian Government should take necessary steps to introduce these forms into the health care system. There is a need to create and implement strict regulations around documentation, recording the procedures and increasing the transparency of the trials.

Even though the new amendments may curb the ethical discrepancies to a large extent, it

is expected to have an adverse affect on the revenue generated by the clinical trial industry. These amendments would increase the time for the approval process. According to Vinay Goyal, a neurologist at the All India Institute of Medical Sciences, who has supervised trials at the institute, it would take three months to a year for a trial to be approved, making the approval process more cumbersome, as the number of nodal points for the approval process has increased. These lengthy approval processes would discourage the companies from conducting clinical trials in India. Some of the Indian pharmaceutical companies, such as Biocon, Alembic, Zydus Cadila, Torrent, and Lupin, have moved trials out of the country. At Biocon, the research and development (R&D) spent was 134% higher in the second quarter of 2015 than the same period in 2014. The company's chairman, Kiran Mazumdar-Shaw, said at an analyst briefing that the high R&D spent is a result of ongoing global clinical trials that require large investments. Indian CROs, such as Veeda Clinical Research and Lambda Therapeutics, have also moved out to other Asian countries, including Malaysia and Thailand. An official at Veeda says the high degree of uncertainty in India has discouraged clinical trials (Sachan, 2013). Because of these increased costs, the Indian clinical trial industry's market that is expected to soar to $1 billion (£630 million) by 2016 may not reach the milestone.

The new amendments are a step in the right direction to make the clinical trials safer in India. However, it would increase the cost and the time for the companies to conduct various clinical trials. The government of India should take appropriate steps to create a right balance between the safety of clinical trials and the speed at which the clinical trials shall be approved. The success of the clinical trial industry in India depends upon creating such a balance and providing the right environment for conducting clinical trials.

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