Protection of Subjects and Regulation of Clinical Trials in India

by

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Dedication

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Abstract

Access to better healthcare and payment may provide powerful incentives to participate in clinical research in developed countries. In India, however, problems may arise in obtaining consent due to language and cultural differences. While India has been a preferred destination to perform clinical trials, serious concerns exist, such as failure to obtain informed consent, a lack of attentive regulatory authorities, insufficient infrastructure, and a failure to follow International Conference on Harmonization-Good Clinical Practices (ICH-GCPs). Research projects that violated ethical norms have taken place in India during and after the release of regulatory guidelines. Hence, there is a need for regulatory agencies to enforce these guidelines to ensure subject protection.

In many developing countries, such as India, there is no agency that exclusively protects clinical trial subjects or regulates clinical trials, as there are in developed countries. This study suggests proposals such as strengthening regulatory bodies, developing a plan to address deficiencies in the current Indian model, and protecting subjects during subject recruitment.

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Introduction

The U.S. Food and Drug Administration (FDA) approves new drugs for marketing by pharmaceutical companies after reviewing clinical trial results generally containing more than 4000 patients. This is one of the greatest challenges for pharmaceutical companies in the United States because less than 5% of patients are willing to participate in clinical trials (Garg et al., 2011; Cekola, 2007). The main reason for this disinclination among American patients is because of their physician's discouragement for participation (Cekola, 2007). Many patients are also worried about treatment with placebo rather than the active product (Garg et al., 2011; Cekola, 2007). Additionally, of Americans willing to participate, many may be disqualified from a study because they already take drugs that may confound the experiment (Cekola, 2007). As result, pharmaceutical companies may move their studies to other countries with populations that are more viable and willing to participate to find a large enough pool of subjects.

Developing countries have become the preferred location to conduct clinical trials (Garg et al., 2011). Clinical trials in India often cost 40% of the price of American drug trials (Cekola, 2007). The lack of access to adequate health care in developing countries has created a desperate environment in which many individuals can only receive the treatment they need through clinical trials. In developing countries, the large populations, lower costs of technical services, spectrum of diseases, lower per-patient trial costs, and wide range of races offer pharmaceutical companies an attractive location to conduct clinical trials (Garg et al., 2011). Hence, there are great opportunities to conduct clinical trials in developing countries compared to developed countries.

India has an environment that is suitable for conducting clinical trials. In 2005, India became such a popular destination for clinical trials it acquired the nickname "Guinea pig of the world" (Nundy et al., 2005). Unlike many other favorite destinations for clinical trials, India

provides highly regarded institutions with a sophisticated technological infrastructure that can accommodate foreign studies. Additionally, these facilities are organized with responsible medical professionals who speak English and are willing to conduct clinical trials for less money than an American with similar training (Bhatt, 2011).

Additionally, India is stratified. Many medical facilities are too expensive for the poor to afford. The majority of India's population is desperate for affordable medical attention (Cekola, 2007). For many sick individuals in developing countries such as India, clinical trials are their only access to health care (Bhatt, 2011; Cekola, 2007; Glickman et al., 2009).

Regulations and guidelines on international research are important because they (a) inform researchers what is acceptable, and (b) regulations and guidelines provide a crucial point for researchers and other professionals to discuss issues in international health research (RTI International, 2004). One quarter of clinical trials conducted in developing countries fail to undergo an ethical review (Fleck, 2004). Only about one half of the large hospitals have Institutional Review Board (IRBs), and as per Indian Pharmacological Society, these few boards have not yet formulated standard operating procedures (Prakash, S. 2009). An Informed consent is a process for getting permission before conducting a clinical trial on a person. It is a way to educate the subject about the research. An informed consent must be obtained from the subject or his or her legally authorized representative prior to the onset of a clinical trial (FDA, 1981). Some unethical trials were being conducted in developing countries due to absence of adequate regulations and proper laws in these countries (Srinivasan, 2004). Due to this, there is a need to protect the subjects and regulate the trials.

Background

It is estimated that 20-30% of global clinical trial activities are conducted in developing countries (Bhatt, 2004). Seven percent of all global phase 3 trials and 3.2% of all global phase 2 trials are performed in India (Jayasheel, B. G., 2010). The availability of a large patient population, a lower cost of technical services, limited health-care services, a spectrum of diseases, and a wider range of races have made India an attractive place for conducting clinical trials (Bhatt, 2004). However, concerns exist regarding the current Indian model. For example, deficiencies exist in functioning of ethics committees, regulatory bodies, and investigators' unethical approaches to recruiting subjects (Bhatt, 2004). As a consequence, Indian participants assume a greater risk than patients in developed countries.

Each country has its own regulatory authority that is responsible for enforcing the rules and regulations for the drug development process, including the licensing, registration, manufacturing, marketing and labeling of pharmaceutical products. The Central Drugs Standard Control Organization (CDSCO) is the national regulatory body for Indian pharmaceuticals and medical devices. The Drug Controller General of India (DCGI) is part of CDSCO and regulates the pharmaceutical industry in India (Desai & Naik 2011). The functions of the DCGI include approval of trial and sending biological overseas for testing (Desai & Naik 2011). In India, the Indian Council of Medical Research (ICMR) is the highest authority for formulation and promotion of biomedical research (ICMR, 2006). The Indian Council of Medical Research (ICMR) established its "Ethical Guidelines for Biomedical Research on Human Subjects" in 2000 (ICMR, 2006). These guidelines covered general principles such as voluntariness, informed consent, privacy and confidentiality, risk minimization, community agreement, general ethical issues, non-exploitation by providing remuneration to the research participants irrespective of the

social and economic condition, and institutional arrangements such as ensuring research reports and materials connected with the research are to be made in a transparent manner (ICMR, 2006). Good Clinical Practices (GCP) guidelines were developed by the International Conference on Harmonization (ICH). In 1996, the ICH published this set of standards and technical requirements for the registration of pharmaceuticals for human use. This publication was harmonized by FDA for research efforts across the United States. Regulatory bodies at clinical research sites, serve as safeguards of ethical research conduct. Currently, ICH regions such as the United States, Japan, and European countries have stringent rules and regulations (Guideline for Good Clinical Practice, 1996).

Developing countries must protect their citizens that participate as subjects in clinical trials. Most developing countries lack a strong organization that exclusively protects clinical trials' subjects and regulates clinical trials. The purpose of this paper is to explore unethical clinical practices, their impact on human subjects and summarize ways in which regulatory agencies can protect the subjects and regulate the clinical trials in India. This paper also focuses on measures that can be taken to overcome the problem.

Methods

This paper contains a brief review of the protection of subjects and regulation of clinical trials in developed countries such as US and developing countries such as India. This review contrasted the procedures and processes in developed and developing countries using the US and India as examples. The sources for the study included a combination of papers which include published research articles, textbooks, and international guidelines, ethical and regulatory policies. The literature was searched for topics concerning laws and regulations regarding conduct of clinical trials in US and India and examples of unethical trials that took place in India. The databases for health sciences pubmed, cinahl and googlescholar were used for literature search. This paper aimed to collect information from several publications with regard to unethical trials that took place in India. Keywords such as protection of subjects, developing countries, developed countries, regulations, unethical trials, etc., were used and all such retrieved information from search results were carefully scrutinized and applicable information for this project was collected. All such findings from literature review and publicly available clinical trials data were summarized.

Results

The literature review discovered the regulatory and ethical principles and bodies in developed countries (see Table 1) and India (see Table 2).

Table 1. Laws and Regulations Concerning Conduct of Clinical Trials in Developed Countries

Laws and Regulations	**Important Points**
Good Clinical Practice (GCP)	A worldwide ethical and scientific quality standard for creating, recording and verifying assessments that includes the participation of human subjects. GCP standards ensure that rights, security and well-being of clinical trial subjects are properly secured (European Commission, 1997). *The Principles of ICH GCP: Before a clinical study is initiated, expected threats and distractions should be weighed against the advantages for the individual subject, topic, and community. A clinical trial should be performed in compliance with the protocol was established by IRB/IEC approval* (European Community, 1997).
Independent Data Monitoring Committee (IDMC)	A separate data-monitoring panel that may be established by the sponsor to assess the improvement of a trial, protection information, and crucial efficacy endpoints, and to suggest to the sponsor whether to proceed, change or quit a trial (European Commission, 1997).
Institutional Review Board/ Independent Ethics Committee (IRB/IEC)	Protects human rights and well-being of all clinical trial subjects. The IRB/IEC should contain a reasonable number of members who jointly have the credentials and experience to evaluate and assess the technology, medical factors, and values of the suggested clinical trial (European Commission,

Responsibilities	1997).
Public Health Service Act of 1944	This act was passed, and protected a wide variety of health issues, including the regulation of biological products and control of communicable illnesses (FDA, 2012).
Regulations for Human Subject Protections	In 1981, the FDA and the Division of Health and Individual Services modified regulations for human subject protections, based on the 1979 Belmont Review, which had been from the Nationwide Percentage for the Security of Individual Topics of Biomedical and Behavior Analysis (FDA, 2012).

Table 2: Laws and Regulations Governing the Conduct of Clinical Trials in India.

The Pharmacy Act of 1948	This act regulates the pharmacy profession in India. The act controls the registration of pharmacists, education regulations, and cancellation of registrations.
Good Clinical Practice Guidelines (GCP)	Good Clinical Practice is an international quality standard for the design, monitoring, auditing, and recording and reporting of clinical trials. In 1996, Indian GCP guidelines were issued by the ICMR with WHO, ICH, USFDA and European GCP guidelines (Gupta & Kohli, 2006).
Central Drug Standards Control Organization (CDSCO) and Drug Controller General of India (DCGI)	The national drug authority is the Central Drug Standards Control Organization (CDSCO) in New Delhi, which is controlled by the Drug Controller General of India (DCGI). This system is responsible for medical devices, clinical trials, and quality standards, and it also registers all imported drugs, new drugs, and biological drugs. The main regulatory bodies in India include CDSCO and DCGI. The Federal CDSCO is responsible for the safety, efficacy, and quality of drugs supplied to the public. The DCGI is an important body in the pharmaceutical industry for the approval of clinical trials, test licenses, drug testing, bioequivalence studies, registration for importing and exporting NOCs, biological sample, drugs, licensing of blood banks, r-DNA products, vaccines and medical devices, amendments in drugs and cosmetic acts. To conduct a

	clinical trial in India, the regulatory authority of India (i.e., DCGI) must give permission and also companies where the trials must be conducted (Desai and Naik 2011).
Schedule Y of the Drugs and Cosmetic Act	This act was enacted in 1945, and improved in 2005 (Desai and Naik, 2011). To conduct a trial, an applicant should submit the study's details, such as the protocol of the clinical trial, with a consent form, chemical and pharmaceutical data, generic and chemical names, dosage form, composition, animal pharmacology and toxicity data, and also Phases I, II, III, and IV data to the DCGI.
Expert Committee (EC)	DCGI composed independent Expert Committees to frame guidelines for clinical trials. These committees used to examine the reports of serious adverse events also it will decide the cause of death. These committees will work under the provisions as mentioned in Appendix XI1 of Schedule Y of Drugs & Cosmetics (D&C) Rules (Shankar, 2013).

Indian GCP guidelines are not completely in line with ICH-GCP. There are significant differences in some of the areas (Bhatt, 2010). Indian guidelines mandate that the sponsor and investigator sign a copy of the standard operating procedures (SOPs) and be aware of and comply with SOPs. However, ICH-GCP expects the investigator to comply with the protocol and leaves the task of monitoring compliance with SOPs to monitors and auditors. Another example is that Indian GCP requires that an investigator sign and forward the study's data (e.g., case report forms, results and interpretations), analyses, and reports from his or her center to the

sponsor and ethics committee. However, ICH-GCP mandates that when the trial is completed, the investigator must provide the IEC with a summary of the trial's outcome (Bhatt, 2010).

According to Indian GCP, the IEC has the power to order the discontinuation of a trial if it finds that the goal of the trial has been achieved midway or unequivocal results were obtained. However ICH-GCP mandates that this is the responsibility of the independent data monitoring committee (IDMC). Additionally, the monitor is supposed to inform the sponsor and the IEC of any unwarranted deviation from protocol or any transgression from GCP principles. However, ICH-GCP states that the monitor must verify that the documents provided by the investigator are legible. India is considering adopting ICH-GCP guidelines, but it has not yet adopted a complete set of guidelines as described by ICH-GCP (Bhatt, 2010).

The Central Drug Standards Control Organization (CDSCO) built an expert committee in consultation with clinical experts and formulated GCP guideline for generation of clinical data on drugs, based on its recommendation these guidelines will be updated in a timely manner. The DCGI also checks the regulatory status of the drug in other countries, such as the names of the countries where the drug was approved or where the investigational new drug program was filed. It typically takes between 10 and 12 weeks for approval, as compared to an average of 30 days with the U. S. Food and Drug Administration (USFDA) and 60 to 90 days in Europe (Desai and Naik 2011). Once approval is given, the sponsor must send the safety reports and annual report of that particular year with all of the details of the study in India. Once the study is completed, a detailed report to be submitted to the DCGI. The DCGI also ensures that trials are conducted as per the protocol and ethical guidelines (Sarda et al., 2012).

Indian Penal Code 1860, Sections 52, 80, 81, 83, 88, 90, 91, 92 304-A, 337, and 338 contain the laws for medical malpractice to protect patients from treatment adversities (Med

India, n.d.). This section enables hospitals to be held responsible for treatments; this section also applies to physicians. Additionally, the physicians and hospitals can be penalized for any irresponsibility and carelessness. In 2011, the Ministry of Health and Family Welfare proposed amendments to the Drugs and Cosmetic Rules, 1945, to ensure payment of compensation to the study subject for clinical trial related injuries or death. After more than a year, the final amendments were notified and effective in 2013, resulting in the Clinical Trials Compensation Law (Desai & Naik, 2011).

The Law states

a. *Clinical trial subjects are entitled to free medical management as long as required and financial compensation for clinical trial related injury or death.*
b. *The sponsor or its representative, whosoever so is conducting the clinical trial in India, is compelled to bear the expenses of the subject's medical management and provide financial compensation. With respect to compensation, the sponsor, whether a pharmaceutical company or an institution, is also required to give an official declaration to the DCGI, stating that they will provide compensation in the case of clinical trial related injury or death.*
c. *The Sponsor, Investigator and Ethics Committee have to submit their report with an analysis on the cause of the adverse event to the Experts Committee (in case of death or injury, the DCGI appoints such Committee) and the DCGI within a stipulated time. The Experts Committee would be set up by DCGI and would investigate the cause of death or injury (if required by DCGI), and recommend financial compensation.*

d. *The DCGI is authorized to decide the cause of the serious adverse event as well as pass an order on payment of compensation, if applicable, taking into account recommendations of the Experts Committee.*

e. *The time frame for determination of the cause of the serious adverse event and order of financial compensation is three months from the date of report of the serious adverse event by the investigator.*

f. *The sponsor or sponsor representative is given a time frame of 30 days from receipt of the order of the DCGI to provide compensation to the subject.*

g. *Failure of the sponsor or sponsor representative to provide free medical management and/or financial compensation, as ordered, may lead to the Failure of the sponsor or sponsor representative to provide free medical management and/or financial compensation, as ordered, may lead to the suspension or cancellation of the existing and further scheduled clinical trials in India.*

h. *The Informed Consent Form was modified to include relevant details for the purpose of determination of compensation such as occupation, annual income and qualification of the subject. It is obligatory to hand over a copy of the informed consent sheet and duly completed informed consent form to the subject or his or her attendant* (Desai, 2013)**.**

Examples of unethical practices in India

Clinical trials in India require DCGI and Ethics committees' approval and can be performed only at certified center by qualified investigators. In Practice, DCGI and Ethics review committee are approving without duly reviewing protocol and adverse events. Table 3 summarizes the 7 major cases that were available publicly out of 10 cases where DCGI gave permission for phase 3 trials without phase 2 trials, trials conducted without DCGI and ethical review committee approval, subjects involved in unethical trials without their knowledge or informed consent.

Table 3: Examples of Unethical practices in India.

Trail Name	**Description**
Letrozole Trials	Novartis anti cancer drug Letrozole is to be used only in post menopausal women and not intended nor permitted to use for reproductive health in women. As per Indian law Phase 3 studies can be conducted only after phase 2 studies, however DCGI gave permission to clinical trial sponsor company Sun Pharma to conduct phase 3 studies prior to phase 2. These trails were also conducted in private hospital by three doctors on only 55 subjects. On April 10, 2007 DCGI approved usage Letrozole improving fertility (Sinha, 2012). On October 12, 2011 Indian Ministry of Health and Family Welfare banned the drug based on its findings as per section 26A of the Drug and Cosmetics Act, 1940(23 of 1940) (CDSCO, 2011).

Streptokinase Trials	Without prior approval from DCGI and Genetic Engineering Committee, Bangalore based Biocon and Hyderabad based Shanta conducted phase III trials of genetically engineered drugs (insulin for diabetes by Biocon and streptokinase for heart attacks by Shantha) (Srinivasan, 2004). As a result of the trials eight people died. Based on this event, Aadar Destitute and Old People's Home (a Delhi based social organization) has filed Public Interest litigation in the Supreme Court of India and Court against the above two companies (Basu, 2004).
Risperidone Trials	In 2003 Johnson and Johnson conducted Risperidone trials in Gujarat, India to treat acute mania. A subject explained that he signed a form as advised by his doctor, but he did not know he was participating in a clinical trial. Violated norms: Not all subjects were informed they were participating in a trial. Informed consent was not properly obtained from all participants (Parth et al., 2013).

NDGA Trials	In collaboration with Indian doctors, the Johns Hopkins University tested NDGA in Indian patients before its safety was established in animal tests. Between the time periods November 1999 to April 2000 this drug was injected into 26 oral cancer patients. A Radiobiologist, Dr. V. Narayan Bhattathiri, at the clinical trial center accused his colleagues of violating ethics by conducting clinical trials without informed consent for drugs which are not approved and using patients as guinea pigs. He reported the issue to Human Rights Commission. Indian health ministry appointed a committee and submitted its finding to the government. The Johns Hopkins University committee then agreed that safety testing of the NDGA drug in animals was inadequate and it also confirmed Dr Bhatathiri's accusations were valid regarding informed consent (Mudur, 2011).
Zoniporide Trials	In 2000, Pfizer conducted Zoniporide trials to treat perioperative cardiac events. Although Phase II trials were not completed in the United States, the DCGI gave it's the approval for Phase III trials in India. This implied the following violations: Schedule Y of the Indian Drug and Cosmetic Act: Before 2005, the act prohibited Phase II clinical trials outside the country. Phase III trials of drugs were allowed only if the drug had already been tested (Parth et al., 2013).

Cilostazol Trails	Cilostazol is an oral phosphodiesterase type 3 inhibitor with antiplatelet and vasodilating activity. This drug helps in reduction of intermittent claudicating symptom in patients with peripheral vascular disorder (Rao, 2013). DCGI gave clearance for this drug to Otsuka America Pharmaceutical, Inc with insufficient information on its adverse effects such as diarrhea, headache, hypoglycemia, hypotension, and palpitations (Kumar & Chandy, 2006).

Salbutamol Ipratrpium Inhaler	Ethics Committee of governments Mahatma Gandhi Memorial Medical College's had given approval for Salbutamol Ipratrpium Inhaler drug trial on September 12, 2005 to Mumbai-based company Cipla and trials were conducted by contract research organization — LAMBDA. Anwar Bi complained to DCGI, Medical Council of India and the National Rights Commission (NHRC) as her husband Abdul Rasheed died on April 21, 2010 due to drug trials. According to Anwar Bi Rasheed went to Manorama Raje TB hospital for treatment where TB specialist Salil Bhargava took Rasheed to his private clinic Gyanpushp Research Centre for Chest and Allergy Diseases and tested an unknown medicine on him as part of drug trial without patient consent. He treated Rasheed for chronic obstructive pulmonary disease from 2005-2010 with a new drug Salbutamol Ipratrpium Inhaler. This matter was raised in the State Assembly, following which the Medical Education Department had sent a list of patients on October 29, 2010, to three Members of Legislative Assembly, including Leader of Opposition Ajay Singh, Paras Saklecha and Pratap Grewal. The list, which was prepared on the directives of Assembly Speaker Ishwardas Rohani, contained names of patients, including Rasheed's, on whom the drug trial was carried out since the last five years (The Hindu, 2012).

According to the data available from the Drugs Controller General of India (DCGI) for the year 2011 there were 159 deaths in clinical trials. The below (see Table 4) shows the list of pharmaceutical companies named in clinical trial death list.

Table 4: Death during Trials in India (Dey, 2012).

Deaths During Trials in 2011 as per DCGI	
Deaths	**Company**
57	Novartis
32	Quintiles Technologies
20	Bayer
20	Pfizer
19	Bristol Mayer Squibb India
10	MSD Pharmaceutical
1	Dr Reddy's Laboratories

Supreme Court asked the Center to investigate 'unauthorized' clinical trials in a judgement on a Public Intrest Litigation (PIL). The Supreme Court of India issued a notice to Government of India. According to this appeal, GlaxoSmithKline had conducted unauthorized trails of a vaccine for cervical cancer on 24000 tribal girls in Andhra Pradesh and Gujarat states. The PIL also alleged that the vaccine has an adverse reaction on the girls health followed by companies' failure in providing treatment, which lead to death of seven girls. The Supreme Court also directed Christian Medical College, Vellore to scrutinize the medical records of the girls and submit a report to the court (Manjesh, 2013).

The Government of India is planning to amend the Drugs & Cosmetics Act to add 10 years of imprisonment and cancellation of license for violating norms of clinical trials on humans. This act would ensure that those who do not follow the norms set by the Drug Controller General of India (DCGI) for conducting clinical trials on humans will be punished (Dey, 2009).

A probe by Government of India against drug trials in 2010 found six tribal children died after administration of Human Papilloma Virus (HPV) vaccines as part of clinical trials. The Government of India took disciplinary action against medical professionals who had allegedly been conducting these trials. Following this incident, the government ordered suspension of clinical trials on April 7, 2010. Thirteen thousand seven hundred and ninety one (13,791) and 9,637 girls were vaccinated in Andhra Pradesh and Gujarat states, respectively. A three-member committee was then appointed by the ministry to probe issues of ethics (Patro, 2012).

In response to queries of health activists under Right to Information Act (2005), State Government exposed drugs and herbal treatments that were tested on mentally challenged patients and children. Following a legal investigation, the Government fined 12 doctors 5000

($99) each under State Nursing Homes Act. However private doctors were exempted from fines as they are not covered under this Act (Reporter, 2012a).

Some pharmaceutical companies that have conducted clinical trials in India have granted meager compensations, sometimes as low as ₹ 50,000 ($820), to the legal heirs of the victims. In 2010, compensation was given to 22 cases of death by firms, mostly foreign, such as Merck, Quintiles, Lilly, Bayer, Amgen, Bristol Myers Squibb, Sanofi, Pfizer and Wyeth. In 2011, ₹ 35.21 lakh ($57721) was offered as compensated for 16 cases for drug trial deaths by Pharmaceutical companies such as ICON, VEEDA, Pfizer, Sanofi, Fresenius and Sun Pharma. Total compensation of ₹ 70.33 lakh ($115295) paid for all cases (The Hindu, 2013). Independent Expert Committee (formed by DCGI) prepared a formula to pay compensation in case of adverse event of death. Compensation was calculated based on 3 factors, age, risk and base amount.

$$\text{Compensation} = B*F*R/99.37$$

In the above formula B represents base amount (i.e., 8 lacs), F represents factor (depending on the age of the subject), and R represents risk factor (depending on severity of disease) (Kavitarana, 2013).

Discussion

Based on the above findings, there is a need to develop a new plan that addresses deficiencies in current Indian Model. The results Risperidone and NDGA trials of the Parth el al. (2013) and Mudur (2011) shows that due to illiteracy, patients signed informed consents without understanding the procedures, benefits or risks involved in clinical trials. Not all subjects were informed they were participating in a trial. Clinical trial investigators should explain the informed consent to subjects, the nature and purpose of the study, the duration of research, the risk factors and the freedom to withdraw from the trial at any time. There are instances where patients have signed the informed consent however not aware that they have an option to withdraw the clinical trial at any point of time (Berne Declaration, 2013). The company should obtain proper informed consent from an eligible adult participant. Additionally, there should be reasonable distribution of the problems and advantages of research and equal attention for all subjects in a trial, and risk of harm should be minimal**.** Researchers should develop techniques to ensure that participants can better understand the information provided in the consent process and should describe the procedures in the protocols. While taking the informed consent from the subject, family members should provide consent also for mentally retarded subjects. In the absence of a family member's permission, an individual's voluntary informed consent should suffice. The researcher should use the same procedure while taking the informed consent process for women and men. The government should provide awareness programs for people regarding the pros and cons of clinical trials and ensure that ethical clinical practices are in place. Since the literacy rate in developing countries such as India is comparatively low, it has to advantage of latest technology and implement recording of audio and video of informed consent process of each trial subject. Poverty, low literacy, and pressure from sponsors for early completion of

patient enrollment leads to unethical subject recruitment. Therefore, a need exists to enroll only participants who have basic education qualifications, so that can increase the awareness of informed consent in the subjects. Therefore, the GCP should stress the implementation and documentation of the informed consent process. Good Clinical Practice should be considered as the universal ethical and scientific quality standard to conduct a clinical trial. The GCP should emphasize following strict adherence to the study at the sites to protect the subjects during subject recruitment. Recruitment policies to be made available in English as well as the regional languages to improvise the patient's awareness. Developing countries should follow the system of protections that is at least equal to that of developed countries**.** Continuous monitoring of the safety of the research studies should require more qualified human resources. Decision-making choices must be clear and all of the information and decisions should be available for review by public. Failures of the trials should be advertised to public, as safety and transparency of clinical trials is the most important concern in India**.** Reports by The Hindu (2012) illustrates that ethical committees are not effectively working, so it needs to improve in below areas. Ethical committees should be entrusted with review of the proposed clinical research protocols prior to the start of the study. They should also extend their responsibility to monitor approved projects regularly for the compliance of ethics until the studies are completed. An ethics manual should be followed by ethics committees across both high resource and low resource regions. It should tie international standards, such as Council for International Organization of Medical Sciences (CIOMS) and the Declaration of Helsinki. In this way, an ethics manual should be used as a deep background reference in a clinical trial design and ethics committee operations. The role of ethics committees should include review of the proposed study and regular monitoring for the compliance of the ethics of the approved studies until the same are completed. This ongoing

review should be in accordance with international guidelines and standard operating procedures of the WHO. There is a need to develop a national Central Ethical Monitoring Cell for monitoring clinical trials sponsored by developed countries and local IRBs. All local IRBs should be required to be registered under the Central Ethical Monitoring Cell. When assigning a site for a clinical trial, caution should be followed by the Central Ethical Monitoring Cell and it should not be under the control of sponsors or CROs. Reviewing and approving protocol, standard of care, and liabilities of IRBs should be clearly declared in ethical guidelines. Reports by Kumar & Chandy (2006) shows that DCGI gave clearance for this drug to Otsuka America Pharmaceutical, Inc with insufficient information on its adverse effects such as diarrhea, headache, hypoglycemia, hypotension, and palpitations. So DCGI should give the permission only after scrutinizing the activity of the drug. The DCGI should help strengthen the pharmaceutical industry in India by updating its laws and regulations in a timely manner based on their findings after each clinical trial submissions. For instance, DCGI finds a new process is required for a specific trial based on their findings; it has to amend regulations accordingly. The Indian regulatory system should start adapting the demands of quality and accountability of global trials. Regulatory bodies should make sure that clinical trials are started only after getting written permission from DCGI and an IEC. The results of Sinha (2012) and Parth et al., (2013) shows that DCGI gave permission to clinical trials sponsor company to conduct phase 3 studies prior to phase 2 trials. DCGI should give permission for phase 3 trials only after phase 2 trials. It has been recommended that whenever clinical trials sponsored by the developed countries insure their participants from international insurance companies, pharmaceutical companies should prefer insurance to subjects from local insurance companies which will give an opportunity for clinical trial participants to visit their offices and settle issues if any. One of the major concerns

for participants when dealing with foreign insurance companies is communicating with them and this can be addressed by opting local insurance companies. A collaborative partnership between researchers and sponsors of developed countries should build policies for developing countries to minimize the exploitation. India should follow and adopt stringent regulations. This would result in a reduction in exploitation of subjects. Clinical trial sites in India should improve the information infrastructure by developing databases to maintain details of potential trial participants, providing sophisticated laboratories, and continuing medical education as a common approach to improving clinical practice. Current policies should be reviewed and amended to address present day challenges by considering the aforementioned models. Those models should be included in the current model and embedded into law to ensure that no clinical company or organization is exempt from following ethical standards. Due to the lack of resources, ethics review committees find difficulty in complying with U.S regulations. Therefore, companies that sponsor the research in developing countries should provide financial support for operating and managing the trial. India should have the capacity to conduct clinical trials independently and have their own ethical and scientific reviews. India should adopt new techniques, such as targeted education, case-based learning, and interactive and multimodality teaching techniques for conducting any clinical trials. A thorough review and proper assessment of governing bodies in India is required to get international acclaim in the field of clinical trials. Companies should increase spending on clinical trials so that ethical issues can be dealt with easily. Proper training should be given to the investigators in India regarding ethical and scientific considerations, as well as in the design and process of clinical trials. There was no right to information act to demand documented evidence and instructions of clinical trials procedures and consequences from pharmaceutical companies before participating in clinical trials

(Mohapatra & Kachhwaha, 2013), which may leads to unethical clinical trials. To avoid this, there is an urgent need to implement right to information act. Banned drugs in any other country should not be used for clinical trials in developing countries. Sponsors, media, health care providers and the public should arrange open communication to overcome real and perceived barriers to clinical study participation. The role of lawyers before the commencement of any clinical trial occurs when there is a precautionary approach taken by the pharmaceutical company of obtaining legal opinions from their in-house lawyers and legal practitioners. Acquiring such legal opinion is not available for patients participating in clinical trials.

There is a need to strengthen the regulatory bodies in India and the following are suggestions for strengthening the drug regulatory mechanism in India. Regulations could include educating the population, providing public health initiatives, producing public service announcements, following the company's GCP ethics policies, strengthening oversight boards, and establishing international agreements between countries, like the World Health Organization. To monitor the clinical trials in the pharmaceutical industry, regulatory bodies should be strengthened by setting up new offices in new locations, creating new central drugs laboratories, equipping them with state-of-the-art technology to enable them to carry out sophisticated analysis of drugs, upgradation of the existing 6 central drugs testing laboratories, skill development of the regulatory officials, increasing transparency in decision-making of CDSCO. Awareness must be created among all stakeholders of the guidelines set down for clinical trials by the Central Drugs Standard Control Organization. The CDSCO should make the guidelines available to the public on its websites in order to ensure fair practices. The CDSCO and the State Drug Control Administration should be adequately staffed to supervise clinical trials across the country. Since the CDSCO has a small technical staff, they face challenges in reviewing and

increasingly mounds of data that are submitted for clinical trials and drug approval. The CDSCO should gain knowledge on the pharmaceutical company's role in the health care sector, which would help protect the wellness of the people and address larger public health problems. The CDSCO should implement an e-governance program, which would enable the pharmaceutical companies or clinical trial sites to file, track, and review the clinical trial application online. Understanding drug efficiency and adverse drug reactions would help in offering better treatment for patients. Regulatory bodies in India should be ready to meet the challenges worldwide by staffing qualified and academically sound resources to discuss necessary strategies. The national regulatory authority should become more pro-industry, vigilant, and efficient, which would translate to a more USFDA-like regulatory system. The Indian government should work closely with international bodies to update the regulatory guidelines. Established regulatory bodies in various countries should redefine their guidelines and laws, as global pharmaceutical companies are becoming more competitive and aggressive. New updated regulatory bodies should be introduced, as needed, by the government. It needs to frame a more systematic regulatory process of drugs before initiating the study. The regulatory bodies recognize the need to frame guidelines and regulatory approval processes as per with international standards. The Ministry of Health and Family Welfare should monitor clinical trials in accordance with the procedure prescribed in Schedule'Y'of the Drugs and Cosmetics Act, 1940. Currently, in India Ministry of Health and Family Welfare is responsible only for four departments 1. Department of health and family welfare, 2. Department of AYUSH, 3. Department of Health Research and 4. Department of AIDS control.

Conclusion

India can protect its people from unethical clinical trials if a few simple suggestions are implemented. Unless laws are fairly implemented, the current unethical and illegal trials will pave the way for private practitioners to make money, which may leave many Indian patients diseased, deformed, or dead. India is considering ICH-GCP guidelines; however, it has not yet adapted a complete set of guidelines as described by ICH-GCP.

The research suggests that ICH should monitor and recommend the concerned governments to start implementing the ICH-GCP guidelines. Informed consent should be made mandatory to protect human subjects from any harm that may be posed during the research. The Indian government should implement a right to information act to demand documented evidence and instructions of clinical trial procedures and consequences from pharmaceutical companies before participating in clinical trials. Indian government should amend clinical trial laws by adding new rules that will oblige pharmaceutical companies that sponsor trials to pay compensation in cases where volunteers suffer trial-related death or injury and also trial sponsors will need to pay in cases of trial-related injuries and deaths. Current policies should be reviewed and amended to address present day challenges. India should adopt new techniques, such as targeted education, case-based learning, and interactive and multimodality teaching techniques for conducting any clinical trials. Ethical committees should be entrusted with review of the proposed clinical research protocols prior to the start of the study.

References

Basu, I. (2004). India's Clinical Trials and Tribulations. Asia Times Online, Retrieved Feb 14, 2013, from http://www.atimes.com/atimes/South_Asia/FG23Df03.html.

Berne Declaration. (2013, September). Study on Clinical Trials Conducted by Swiss Pharmaceutical Companies in India. Exploratory study on Clinical Trials Conducted by Swiss Pharmaceutical Companies in India: Issues, Concerns and Challenges. Retrieved February 2, 2013, from http://www.evb.ch/cm_data/1309_INDIA_Final_Report.pdf.

Bhatt, A. (2004). Clinical trials in India: Pangs of globalization. Indian Journal of Pharmacology, 36 (4), 207–208.

Bhatt, A. (2010). *Differences bw Indian GCP and ICH-GCP*. Retrieved September 16, 2013, from http://www.docstoc.com/docs/54989649/Differences-bw-Indian-GCP-and-ICH-GCP

Bhatt, A. (2011). Quality of clinical trials: A moving target. *Perspectives in Clinical Research*, 2(4), 124-128.

CDSCO (2011). Gazette Notification. The Gazette of India. Retrieved Feb 24, 2013, from http://www.cdsco.nic.in/writereaddata/Letrozole.pdf.

Cekola, J. (2007). Outsourcing Drug Investigations to India: A Comment on U.S., Indian, and International Regulation of Clinical Trials in Cross-Border Pharmaceutical Research. *Northwestern Journal of International Law & Business , 28*, 125-145.

Chatterjee, P. (2008). Clinical trials in India: Ethical concerns. *World Health Organization*, 86, 577-656.

Desai, S., Naik, S., (2011, January). Clinical trial regulations in India: Inundation of global clinical trials. Clinical Research. *Modern Pharmaceuticals*, 4(12), 60-62.

Desai, N. (2013). Rules for compensation in clinical trials related injury, death notified. Association of Corporate Counsel. Retrieved February10, 2014, from http://www.lexology.com/library/detail.aspx?g=6b820914-b4a4-441b-90dc-d4456cf06dc7.

Dey, S. (2009, April 15). Unethical clinical trials may invite painful penalty. *The Economic Times*. Retrieved August 19, 2013, from http://articles.economictimes.indiatimes.com/2009-04-15/news/284510551clinical-trials-drug- controller-general-pneumonia-vaccine

Dey, S. (2012, July 24). Pharma majors named in clinical trial death list. *Business Standard*. Retrieved Oct 23, 2013, from http://www.business-standard.com/article/companies/pharma-majors-named-in-clinical-trial-death-list-112072400005_1.html

European Community. (1997). Good Clinical Practice. Retrieved August 20, 2013, from http://ec.europa.eu/health/files/eudralex/vol-10/3cc1aen_en.pdf

FDA. (1981). Protection of Human Subjects; Informed Consent. Retrieved Feb 20, 2014, from http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm113818.htm

Fleck, F. (2004). Public Policy: Clinical Trials without Ethical Review. *The Body*. Retrieved Dec 12, 2013, from http://www.thebody.com/content/art12291.html.

Garg, T., Singh, O., & Arora, S. (2011). Opportunities and growth of conduct clinical trials in India. International Journal of Pharmaceutical Sciences Review and Research, 8, 152–160.

Gaur, A. (2012). 13 Clinical trial deaths in state private hospitals in 4 years. *The Times of India* .Retrieved February 8, 2013, from http://articles.timesofindia.indiatimes.com/2012-08-20/indore/33287177_1_sae-and-deaths-clinical-trial-deaths-trial-sites.

Glickman, W. S., McHutchison, G. J., Peterson, D.E., Cairns, B. C., Harrington, A. R., Califf, M. R., Schulman, A. K.(2009, February 19). Ethical and scientific Implications of the globalization of clinical research. *The New England Journal of Medicine*, 360:816-823.

Guideline For Good Clinical Practice. (1996, June 10). Guideline for Good Clinical Practice. *ICH HARMONISED TRIPARTITE GUIDELINE. Retrieved February 26, 2014, from http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf.*

Gulhati, C. M., (2004, January). Needed: closer scrutiny of clinical trials. *Indian Journal of Medical Ethics, Vol 1 No 1*. p. 4-5, ISSN 0975 - 5691. Retrieved February 1, 2014, from *http://www.issuesinmedicalethics.org/index.php/ijme/article/view/768/1837*

Gupta, M. & Kohli, K. (2006). Current Regulatory and Ethical Requirements for conducting Clinical Research in India .*Journal, Indian Academy of Clinical Medicine*. 7(3), 189-192.

Kavitarana. (2013). Compensation formula by DCGI for cases of clinical trial related SAEs of death. Retrieved February 12, 2014, from *Auriga Research* website: http://www.aurigaresearch.com/2013/09/compensation-formula-by-dcgi-for-cases-of-clinical-trial-related-saes-of-death/

The Hindu. (2012, January 16). Women alleges her husband died after drug trial. The Hindu. Retrieved on Feb 27, 2013, from http://www.thehindu.com/todays-paper/tp-miscellaneous/tp-others/woman-alleges-her-husband-died-after-drug-trial/article2804648.ece.

The Hindu. (2013, January 4). Govt set to notify rules for clinical trials. *The Hindu*. Retrieved on Nov 1, 2013, from http://www.thehindu.com/news/national/govt-set-to-notify-rules-for-clinical-trials/article4273210.ece.

ICMR. (2006). Ethical guidelines for biomedical research on human participants. *Indian Council of Medical Research.* Retrieved Dec 14, 2013, from http://icmr.nic.in/ethical_guidelines.pdf

Jayasheel, B. G. (2004). Carrying out Clinical Trials in India. *Regulatory Feature.* Retrieved September 25, 2013, from http://www.acunovalife.com/pdf/whitepapers/RAJ_Pharma%20June%202010_Jayasheel%20final.pdf

Korieth, K. (2010, August). Spike in Warning Letters Sends Tremors Through Industry. Center Watch, *A Center Watch Publication,* 17:1-24.

Kumar, S. P & Chandy, S (2006, October). "Role of active surveillance in improving hospital adverse drug event monitoring." *Indian Journal of Pharmacology* 38.5. *Academic One File*.

Manjesh, S. (2013, January 07). Supreme Court asks Centre to investigate 'unauthorised' clinical trials. *New Delhi Television.* Retrieved Oct 24, 2013, from http://www.ndtv.com/article/india/supreme-court-asks-centre-to-investigate unauthorised-clinical-trials-314093

Mohapatra, A., & Kachhwaha, R. (2013, September 26). Live Law. Retrieved Oct 25, 2013, from http://www.livelaw.in/clinical-trials-in-india-the-chances-and-challenges/

Mudur, G. (2011, November 24). Johns Hopkins admits scientist used Indian patients as guinea pigs. BMJ 2001; 323(7323):1204.

Naik, D. S. (2011, January). Clinical trial regulations in India Inundation of global clinical trials. Retrieved August 15, 2013, from Modern Pharmaceuticals: http://www.siroclinpharm.com/siro_pdf/articles/MPH_Jan11_Clinical_Research.pdf

Nuffield Council on Bioethics. (1999). *The Ethics of Clinical Research in Developing Countries*. Retrieved November 12, 2013, from http://www.nuffieldbioethics.org/sites/default/files/files/Clinical%20research%20in%20developing%20countries%20Discussion%20Paper.pdf

Nundy, S., Chir, M., & Gulhati, M. C. (2005, April 21). A new colonialism? — Conducting clinical trials in India. *The New England Journal of Medicine*, 352:1633-1636.

OHRP. (1993). IRB Guidebook. Office for Human Research Protections (OHRP). Retrieved July 15, 2013, from http://www.hhs.gov/ohrp/archive/irb/irb_guidebook.htm

Parishwad, R. (2013, January 25). Indian Supreme court's anger over unregulated clinical trials. *Royal Society of Chemistry*. Retrieved Feb 4, 2013, from *http://www.rsc.org/chemistryworld/2013/01/india-supreme-court-unethical-clinical-trials.*

Parth, G., Ronak, G., Shakti, S., Jimit, S., Kabara, M., Khinchi, P. M. (2013). Clinical Trials in India. Innovare Journal of Medical Sciences. *Innovare Academic Sciences*, 19-32.

Patro, B. B. (2012, May 7). India initiates probe against drug trials. *Zee News*. Retrieved Oct 25, 2013, from http://zeenews.india.com/exclusive/india-initiates-probe-against-drug-trials_3515.html

Prakash, S. (2009). Evolution of regulatory system in India. Indian Journal of Pharmacology, 41(5):207.

Rao, G. (2013). DIRC Newsletter. Member of International Society of Drug Bulletins (ISDB). Retrieved Feb 21, 2014, from http://www.karnatakadruginfo.com/webadmin/uploads/newsletter/_April_June%202013.pdf

Reporter. (2012a). 12 M.P doctors fined for conducting clinical trials. *The Hindu.* Retrieved Dec 2, 2013, from http://www.thehindu.com/todays-paper/tp-national/12-mp-doctors-fined-for-conducting-drug-trials/article2767136.ece.

Reporter. (2012b). Strengthen regulatory bodies to monitor clinical trials: expert. *The Hindu.* Retrieved Feb 1, 2013, from http://www.thehindu.com/sci-tech/health/strengthen-regulatory-bodies-to-monitor-clinical-trials-expert/article4038730.ece.

RTI International. (2005). Strategies for Protecting Human Research Subjects Globally. *Summary Report of Conference*. Retrieved Oct 23, 2013, from http://www.rti.org/pubs/protecting_research_subjects.pdf

Sarda, R. R., Ladkat, N. B., Khodade, R. B., Chaudhari, P. M., & Kasture, P. V. (2012). The Indian pharmaceutical industry; Evolution of regulatory system and present scenario. *International Research Journal of Pharmacy*, 3(6), 49–55.

Sinha, K. (2012, May 9). House Panel to govt: Punish those guilty of approving Letrozole. The Times of India. Retrieved Feb 20, 2014, from http://timesofindia.indiatimes.com/india/House-panel-to-govt-Punish-those-guilty-of-approving-Letrozole/articleshow/13059757.cms?referral=PM.

Shankar, R. (2013). DCGI sets up 3 independent expert panels to probe deaths occurred during trials. Retrieved Feb 10, 2014, from *PHARMABIZ.com* website: http://www.pharmabiz.com/NewsDetails.aspx?aid=74417&sid=1

Srinivasan, S., (2004, September 8). Indian Guinea Pigs for Sale: Outsourcing Clinical Trials. *Indian Resource Centre.* Building Global Links for Justice. Retrieved Jan *13, 2014, from http://www.indiaresource.org/issues/globalization/2004/indianguineapigs.html*U.S. Food and Drug Administration. (2012). *Significant dates in U.S. food and drug law history*. Retrieved Oct 23, 2013, from http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm128305.htm