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CLINICAL TRIAL PRACTICES IN INDIA: A THREAT TO MILLIONS LIFE

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Abstract

Global clinical researchers have identified India as a potential place of subjects where research can be conducted even without rigid compliance with regulatory norms. This has led to many controversies about the efficacy of clinical trial in India. It also put question mark on the practice and working of authorities involved with under Indian regulatory mechanism. This research paper aims at understanding the root cause of non-compliance of the clinical trial phases. It will also analyze the gaps of ground realties and functional requirement. An evaluation shall also be done to understand is it the demand of patient or requirement new disease is responsible for such events. This paper also explores the remedies thereto. The researcher has notices that there are numerous government-funded medical and pharmaceutical institutions with state-of-the-art facilities are the major reason for India being the targeted destination for clinical trial. However, to rule out any misuse independent institutional review boards should be formed, and a system should be created to enable these boards to share information about trials they have rejected and their reasons for doing so.

Key Words: Clinical Trial , Professional Obligation of Doctors, Informed Consent, patients' right and Institutions of Clinical Trial

1.0. Introduction

The new advances in science and medicine are a cause for celebrations and apprehension both. Undoubtedly every technology encompasses merits and demerits hence there is a need to ensure careful risk assessment.[1] Recent news with regard to clinical trial[2] practices in India has raised alarm throughout the country and almost every segment of the society is worried; and the conduct of officials and doctors involved with the process has been questioned. Moreover, it is reasonable to put a question mark; how come a certificate is issued without completion of clinical trial.[3] Whether the doctors and staff of the hospitals are exempted from the professional ethics. Although the mandates of conducting clinical trials are obligatory in nature even we had witnessed several instances of compromising the steps and ignoring the completion of all phases required thereto. We all knew that search for new drugs; new formulations and new therapeutic products need an ever-increasing demand for subjects on which the 'frontiers of science' can experiment. But the requirement of new subjects does not grant any exemption to either agency who are engaged with the different phases of clinical trial.

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[1] S. P. Srivastava, *Unsolicited Commercial E-mail: A Need for Legislation in India*, VI (3) NYAYA DEEP (2005).

[2] Clinical trials are the set of practices required to certify a new drug molecule as safe and efficacious for the market.

[3] Clinical Trial Certificate without actual Trial, Times of India, New Delhi, 09 May 2012, at 1.

Clinical trials form an integral part of the drug discovery process worldwide. Global clinical researchers have identified India as a potential place of subjects where research can be conducted even without rigid compliance with regulatory norms. This has led to many controversies about the efficacy of clinical trial in India. It also put question mark on the practice and working of authorities involved with under Indian regulatory mechanism. This research paper aims at understanding the root cause of non-compliance of the clinical trial phases. It will also analyze the gaps of ground realties and functional requirement. An evaluation shall also be done to understand is it the demand of patient or requirement new disease is responsible for such events. This paper also explore the remedies thereto.

2.0. Historical Background of Clinical Trail Practice

Several cases of research abuse were revealed after World War II, many of which involved non capable[4] or impaired subjects.[5] These cases became the stimulus for several codes, declarations and reports on the ethics of research on human subjects. The first International code of Ethics for Research involving human subjects 'The Nuremberg Code' had evolved against the cruelties committed by Nazi Research Physicians. The code provides standards for carrying out human experimentations, emphasizing the subject's voluntary consent. A literal interpretation of the Nuremberg Code would preclude all research involving persons unable to consent; however, several later codes and declarations allow such research under certain conditions.[6]

World medical association took a step further to reassure society by adopting the 'Declaration of Helsinki' in 1964, which laid down the ethical guidelines for research involving human subjects.[7] At the 29th World Medical Association Conference (1975), the Helsinki Declaration was greatly revised and the word 'informed consent' was put in the declaration. The Declaration of Lisbon on the Rights of the Patient was approved at the 34th World Medical Association Conference and the scope of informed consent was enlarged to include all patients.

3.0. Regulatory Framework of Clinical Trial in India

Clinical trials in India are regulated by Schedule Y of the Drugs and Cosmetics Rules. The Rules are enforced by the office of the DCGI who is also responsible for monitoring all clinical trials submitted to that office for approval. For new drugs being developed in India

[4] A person lacks capacity in relation to a matter if at the material time he is unable to make a decision for himself because of an impairment of, or disturbance in, the functioning of the mind or brain. The incapacity could be caused by mental illness, learning disability, brain damage, dementia or any other cause.

[5] Roelke, V. Historical perspectives on human subjects research during the 20th century, and some implications for present day issues in bioethics. In: Roelke V, Maio G (Ed.). Twentieth century ethics of human subject research. Historical perspectives on values, practices, and regulations. Stuttgart: Franz Steiner Verlag; 2004. p. 11-8.

[6] The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Ethical principles and guidelines for the protection of human subjects of research (known as The Belmont Report). Washington, DC: US Office for Protection from Research Risks (OPRR), National Institutes of Health (NIH),publichealth Service (PHS), Human Health Service (HHS); 1979.
See,< http://lrsitbrd.nic.in/ethical guidelines.html > (accessed on 12 october2011).

clinical trials have to be conducted in India from phase 1.[8] For marketing approval of drugs already approved in other countries, a phase 3 clinical trial is required on about 100 patients in three or more centres, in order to establish the drug's impact on the Indian ethnic population. In January 2005, the government of India enacted a new rule that allows foreign pharmaceutical companies and other interested parties to conduct trials of new drugs in India at the same time that trials of the same phase are being conducted in other countries.

This new rule supersedes a directive of India's drug and cosmetics rules that required that required a "phase lag" between India and the rest of the world. According to the old rule, if a phase 3 study had been completed elsewhere, only a phase 2 study was permitted in India. Even under the new rule, phase 1 trials will not normally be permitted in India. The old rule was designed to protect Indians from being used as guinea pigs in the testing of unproved drugs of foreign origin; trials of domestically discovered drugs were not subject to this provision. The change was made in response to a lot demands from multinational drug companies and private organizations that conduct clinical research for a relaxation of the rules for drug trials those necessary hurdles whose tags can run to 40percent of the cost of drug development. It has become increasingly difficult to test drugs in Western countries, with their strict regulations, elaborate safety and compensation requirements, and small populations, all of which make the recruitment of research subjects slow and expensive. Consequently, many research-based companies are now outsourcing some of their trials to Third World countries such as China, Indonesia, Thailand, and India.

3.1. Patients' Rights and Safety

Every human being of adult years and sound mind has a right to determine what shall be done with his own body; and a surgeon who performs an operation without his patient's consent commits an assault, for which he is liable in damages."[9] This right finally developed as concept of informed consent.

3.2. Informed Consent

The concept of "informed consent" was developed on the premise of two distinct components. Firstly, every individual has an inherent right to determine what happens to his or her body. Secondly, it is a doctor's inherent duty to provide a person with enough information so as to ensure that the patient's ultimate decision is based on an appreciable knowledge of his/her condition. Before using any person as subject of clinical trial the team of trial has to ensure the available options for treatment, known risks, prognoses, etc. Importantly this means that the patient does not have a duty to inquire about risks or options, the duty rests with the treating doctor.[10]

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[8] Phase I trials collect information on the drug, including its safety an adverse reactions. They are usually conducted on a small number of healthy volunteers. Phase II trials evaluate the effectiveness and safety of a drug on patients. Phase III trials are conducted on larger numbers of people to confirm the evidence from earlier phase trials towards obtaining marketing approval of the drug. Phase IV trials are conducted after a drug obtains marketing approval. They are conducted for various purposes including monitoring for drug interactions and testing for new uses of the drug.

[9] *Schloendorff v. Society of New York Hospital,* 211 NY 125 (1914).

[10] *"Informed Consent."* Cutter, Mary Ann G. University of Colorado Dept. of Philosophy. Available at: http://www.du.edu/-craschke/consent.html.

Nuremberg Code is the first attempt to legalise the informed consent[11] and preserved it as a patient's right it had created difficulty by imposing complete restriction with regard mentally impaired patients. The voluntary consent of the human subject is absolutely essential. his means that the person involved should have legal capacity to give consent; should be situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion, and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decisionn. It is a common practice in clinical trials done in India to obtain consent from relatives if patients are incapable of giving consent. This is ethically questionable and needs to be debated in a larger context. In the western world, no clinical trials can proceed and receive ethical approval with the consent of relatives alone.[12] Moreover, there are many cases where the relatives in lure of money or due to poverty have compromised with the interest of the patients.

4.0. Control Mechanism and Supervision of clinical trial practices

4.1.Drugs Controller General of India

All trials of experimental drugs (not approved for a particular indication) are required to be approved by the Indian regulators – the Drugs Controller General of India.

4.2. Ethics Committee

All trials are also reviewed and approved by an Ethics Committee. The Ethics Committee is required to be composed of individuals that represent a cross section of society, doctors, scientists and non-scientists. The members of the ethics committee needs to approve the conduct of a trial after careful consideration and after establishing that the trial is ethically and scientifically justified. On an ongoing basis, ethics committees are required to monitor the conduct of trials to ensure that they are being conducted in an ethical and law-abiding manner. Patients have the right to approach their doctor and/ or a designated member ofthe ethics committee with questions about the trial. Discussions or exchange of talks is supposed to be held in the language the patients are most comfortable in. Patients are entitled to get a copy of the signed informed consent form.

5.0. Issues of Concern

Before we need to focus on the manner and procedure of clinical trials practices in India and on the basis of incidents of recent past we need to identify matter of concern. A Rebobank India report submits that India is the most sought and preferred place for conducting the clinical trial for its cast is comparatively low in India.[13] Clinical trials are time consuming, expensive, and often burdensome on patients. Clinical trials can fail for many reasons. Failures can arise from a lack of efficacy, issues with safety, or a lack of funding to complete a trial, as well as other factors such as failing to maintain good manufacturing protocols, failing to follow FDA guidance, or problems with patient recruitment, enrollment, and retention[14]. Flawed evaluation of clinical trial quality allows flawed trials to thrive (get

[11] https://research.unc.edu/human-research-ethics/resources/ccm3_019064/.
[12] Department of Health, UK 12 key points on consent: the law in England. London: 2001
[13] *See,* Arvind Pandey, "Clinical Trial Registry in India: Raising the Veil, *Indian Journal of Cancer*, July-September 2008, vol 45 issues 3
[14] *See*, David B. Fogel, "Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: A review", *Contemp Clin Trials Commun*. 2018 Sep; 11: 156–164.

funded, obtain IRB approval, get published, serve as the basis of regulatory approval, and set policy). A reasonable evaluation of clinical trial quality must recognize that any one of a large number of potential biases could by itself completely invalidate the trial results.[15] It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.[16] However, It was found that due to due to vested interest many a times negative results are not brought to the notice of general public and physicians.[17] In the Vioxx controversy[18] it was reported that unethical clinical trials are being conducted in India without proper clearance from relevant authorities. Even in some cases it has been approved ignoring that there is no proper toxicities studies have been conducted.

In clinical Trials for us special concern is the Trials of Phase- I, in general terms, are first-time trials in the country on human subjects of new drugs[19] especially of investigational new drugs[20]. Since this involves testing on humans of new drugs that is to say drugs inadequately tested before on humans, and in the context of investigational new drugs, not tested at all on humans before. However, the multinational companies are using the loopholes in the law and many trials have been conducted ignoring formalities. Deficiencies in the functioning of the ethics committees has aggravated the problem and corporate housed have used an unethical approach for bringing illiterate and vulnerable Indian people to clinical trials. It has been noticed that number of multinational companies is coming India to conduct clinical trials on human subjects to avoid the complex technical requirement of US system.[21]

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[15] *See*, Vance W. Berger & Sunny Y. Alperson, "A General Framework for the Evaluation of Clinical Trial Quality", Rev Recent Clin Trials. 2009 May; 4(2): 79–88.

[16] https://jamanetwork.com/journals/jama/fullarticle/1760318

[17] *See,* Young Hoon Youn & Ilhak Lee, "Conflict of Interest in Medical Practice and Research", he Korean journal of gastroenterology, 2012 60(3):149-54.

[18] Daniel H. Solomon, "Poison Pills: The untold story of the Vioxx drug scandal" The Journal of Clinical Investigation, 2009 2009;119(3):427-427. Some consider the voluntary removal of Vioxx from the market in September 2004 by its manufacturer, Merck, after studies revealed that it was linked to an increase in dangerous cardiovascular events such as strokes and heart attack, a huge loss of a valuable drug. Others consider the removal of this COX inhibitor to be the final step in a drug regulatory debacle. And still others consider the removal of Vioxx evidence of a pharmaceutical industry gone mad, where profits and marketing hype rule the day. Each of these points of view may have some merit and are the topic of Tom Nesi's book *Poison pills: the untold story of the Vioxx drug scandal*.

[19] A new drug means; i. a drug, including active pharmaceutical ingredient or phytopharmaceutical drug, which has not been used in the country to any significant extent has not been approved as safe and efficacious by Central Licencing Authority (CLA) i.e. DCG(I) with respect to its claims; or ii. a drug approved by the CLA for certain claims and proposed to be marketed with modified or new claims including indication, route of administration, dosage and dosage form; or iii. a fixed dose combination of two or more drugs, approved by CLA separately for certain claims and proposed to be combined for the first time in a fixed ratio, or where the ratio of ingredients in an approved combination is proposed to be changed with certain claims including indication, route of administration, dosage and dosage form; or iv. a modified or sustained release form of a drug or novel drug delivery system of any drug approved by the Central Licencing Authority; or v. a vaccine, r-DNA derived product, living modified organism, monoclonal antibody, stem cell derived product, gene therapeutic product or xenografts, intended to be used as drug;

[20] An "investigational new drug (IND)" means a new chemical or biological entity or substance that has not been approved for marketing as a drug in any country.

[21] *See,* http://www.indialawjournal.com/volume2/issue_3/article_by_sreesudha.html.

Moreover, it has been identified as direct threat to right to life. A Hyderabad based women's organization[22] has initiated a proceeding against the ICMR and alleged that a contraceptive drug was administered to women for which serious liver complaints and other physical disorders was known but was concealed in literature. On top of it remains a matter of concern, for India is one of the developing countries with population in millions; out of which half of them are below the poverty line who are illiterate and cannot afford to take medical facilities in times of need hence they are so readily available for clinical trials irrespective of its harm that can be caused to them. They are not competent enough to understand the process of clinical trials and compliances of the informed consent. In some cases people are not even informed about the trial being conducted on them and half of them are least bothered about its impact.

On Aug 17th, 2008 it was reported by the Delhi edition of Times of India that 49 babies died during clinical trials at the premier All India Institute of Medical Sciences (AIIMS) during the last two-and-a-half years. The AIIMS Paediatrics department conducted 42 sets of trials on 4,142 babies- 2,728 of them below the age of one- since Jan 1, 2006. Forty-nine babies died during the trials.[23]

Sometimes the clinical trial has been performed and authorities didn't find it relevant to inform to the subjects. In November 1999, 25 people with oral cancer who went to the government-run Regional Cancer Centre in Thiruvananthapuram were given an experimental drug; but were not told that they were taking part in an experiment. Only later it came to knowledge of everybody when the trial had not been approved by the Drugs Controller of India.[24]

Moreover, in 2002, the multinational company Novo Nordisk conducted multi-centre phase III clinical trials of a diabetes drug before receiving the results of animal studies. The study report found that the drug, Ragaglitazar, caused urinary bladder tumors in rats -- and this should have been known before the drug went for phase I trials, let alone phase II and phase III.[25]

5.1. Why India is preferred Over Other Countries?

It could be an issue of debate and many positive and negative reasons could be advanced for preference to India and Indian subjects. A number of factors favour India as a clinical research hub. Firstly, there are numerous government-funded medical and pharmaceutical institutions with state-of-the-art facilities, which can serve as ideal centers for multi-centered clinical trials. Secondly, India boasts of well-trained and qualified manpower, well versed in English. More importantly, there is vast clinical material, which can be utilised. In terms of the cost efficiency, India is a better bet as the cost to conduct a trial here is lower by 50 to 75 percent than in United States or European Union.[26]

According to a McKinsey report, the global clinical trial outsourcing opportunity in India in the pharmaceutical industry is estimated to be around $2 billion by 2010 and there will be

[22]See, https://sites.google.com/site/saheliorgsite/health/harzardous-contraceptives---targetting.
[23] See, http://www.rtiindia.org/forum/6212-49-babies-died-during-clinical-trials-aiims-last-30-months.html. Jayaraman killugudi, "AIIMS clinical trial deaths, a blow to medi-ethics", Bangalore, August, 2008.
[24] See, http://infochangeindia.org/health/features/some-questionable-drug-trials.html.
[25] See, http://www.indialawjournal.com/volume2/issue_3.html.
[26] Clinical trials cost approximately $300 to $350 million abroad whereas it cost about Rs 100 crore in India.

requirement of 50,000 clinical research professionals. In the field of clinical research, there is an imbalance between demand and supply with the scales tipping in favour of demand.

In addition, although the country has more than half a million practicing doctors, fewer Than 200 investigators have been trained in good clinical practice. Among some 14,000 general hospitals, no more than 150 have the adequate infrastructure to conduct trials, and there are fewer than a dozen pathology laboratories that meet the criteria for compliance with good laboratory practice. Only about half of the large hospitals have institutional review boards, and even these boards have not yet formulated standard operating procedures and they too often lack the expertise to protocols. Information about conflicts of interest is neither sought nor voluntarily provided by investigators.

Moreover, Drugs Controller General of India (DCGI) is understaffed and lacks the expertise to evaluate protocols. Currently, the technical staffs consists of just three pharmacists, including the controller, don't have qualified doctors. As a result, persistent follow-up, including personal visits to the DCGI, is required in order to push an application for a trial forward.

No one disputes that researchers should not be encouraged to conduct clinical trials of new drugs for diseases that are endemic to this country. But hardly any trials involving such new drugs have taken place in India. Globally, only 1 percent of the new drugs discovered in the past 25 years have been for tropical diseases.

6.0. Conclusion

It is well accepted that clinical research is an indispensable part of the drug discovery process to ensure the safety and efficacy of any new drug. However, in a country like India's, a large proportion of the subjects in any trial are illiterate, vulnerable and disadvantaged persons. Therefore, it is of paramount importance to protect the vulnerable women, children, the poor, and the illiterate by ensuring that their enrollment in trials is truly voluntary and that their consent is genuinely informed. Efficacy of the New Drugs and Clinical Trial Rules, 2019 (NDs & CTs Rules, 2019) which is applicable only for New Drugs and Investigational New drugs for human use depends on effective monitoring of approval of conducting of clinical trials as well as comparison of temporal findings. They should have access to the drug after the trial if it is found to be effective and they should not only be treated and compensated for injury but also be compensated for any resultant loss of income. These things can be done only when the government has strengthened its regulatory system so that a well monitored system geared towards proper protection of the rights of patients and prevention of their exploitation.

Real informed consent should be obtained from participants in the presence of an objective third-party. Trials should be conducted only by investigator strained in good clinical practice at designated hospitals. Truly independent institutional review boards should be formed, and a system should be created to enable these boards to share information about trials they have rejected and their reasons for doing so. All projects should be carefully scrutinized for their value to the Indian people.