Clinical Trials in India: Searching for a humane face

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ABSTRACT

Clinical trial is a systematic study of new drugs in human subjects with the objective of determining safety and/ or efficacy of the drug. In India numerous legislations are framed to regulate this trial. Indian Council of Medical Research (ICMR) was established for rendering research and development and issued guidelines in 2000, mandatory for conducting clinical trials in India. The Drug Controller General Of India (DCGI) is the regulatory authority for approval of clinical trial .

But contrary to adherence to these regulations, Clinical trial in India is often tinted with violation and abuse. Reported cases of Deepak Yadav of Indore, Dhananjay Shrievastava of Madhya Pradesh, Sarita Kundamala of Andhra Pradesh are few among hundreds of such cases. The horrifying picture of Serious Adverse Events(SAE) including death subsequent to Drug trials came to surface following RTI application to DCGI by Dr. Anand Rai Of Indore in 2012. Out of 2031 SAE deaths only 22 compensations were paid. Overall picture is so gloomy that the Apex Court had to Intervene and in July 2012 a Division bench headed by justice K.M. lodha commented that it was "Unfortunate "that human beings were treated as "Gunieapigs" in these trials.

With burden of millions of patients suffering from various Chronic and incurable diseases, India is fast emerging as the Global hub for Drug trials. Regulatory reforms and strict ethical Safeguard are demands of the day. Introduction of Clinical trial registry, in 2007 and amendment of Drugs and Cosmetic Rules 1945 for " Informed consent" are few of the appropriate steps taken. But unless Authorities enforce strict Vigilance, human life in India will continue to be downgraded as "Gunieapigs".

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INTRODUCTION

Progress of medical science is dependent on medical research. We cannot dream of a world without medicines and vaccines available today as a result of these research activities. We get account of medical research in many ancient scripts. in the 'Book of Daniel' we get description of planned experiment of 'The Kings Meet.'[1] In India, in 'Charak Samhita' (200 B.C.) and 'Sushruta Samhita' (200 A.D.), we find account of medical research.

However, the first controlled trial on a group of sailors suffering from Scurvy was conducted by James Lind in 1747. [2]Medical researchers since then are conducting various clinical trials on human subjects for development of medical therapy.

Ethical issues and medical experiment were often interwoven. When Dr. Jean-Baptiste Denis started transfusing animal blood to human beings in 1667, there were many deaths and French Parliament officially banned all transfusions involving human beings.[3] Exposure of the devastating facts of Nazi physicians conducting unethical medical research on human subjects without their consent during Second World War and subjecting them to grave risk of death and permanent disability arose great concern in International community. This resulted in formulation of

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[1] 'Book of Daniel' chapter I, verse 12 through 15

[2] Tröhler U (1978) Quantification in British medicine and surgery 1750-1830, with special reference to its introduction into therapeutics. PhD Thesis, University of London: 346-396.

Tröhler U (1981). Towards clinical research on a numerical basis: James Lind at Haslar Hospital 1758-1783. Proc XXVII Int Congr Hist Med Barcelona 1980. Barcelona: Academia de Ciènces Mediques de Catalunya I Balears 1:414-419.

Tröhler U (2000). "To improve the evidence of medicine": The 18th century British origins of a critical approach." Edinburgh: Royal College of Physicians, 2000:59-68

[3] national guideline on blood donor motivation published by ministry of health and family welfare National aids control Organisation ,Government of Tripura page -20

'Nuremberg Code' in 1947 where voluntary consent was included as an absolute requirement for any research on human subjects.[4]

In 1964, World Medical Association declaration of Helsinki developed 'Ethical Principles for Medical Research Involving Human Subjects'.[5] International Covenant on Civil and Political Rights 1966 in article 7 declared that "No one shall be subjected to torture or to cruel, in human or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation."[6] In 1993, CIOMS brought out International Guidelines for Biomedical Research involving Human subjects. Since then, different bioethics advisory bodies formulated principles in specified area of research involving human subjects.[7]

CLINICAL TRIAL REGULATIONS : INDIAN SCENARIO

'Clinical Trial' as defined in the Drugs and Cosmetic Act 1940 means "a systematic study of new drug(s) in human subject(s) to generate data for discovering and/or verifying the clinical, pharmacological (including pharmacodynamic and pharmacokinetic) and/or adverse effects with the objective of determining safety and / or efficacy of the new drug."[8]

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[4] ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH ON HUMAN PARTICIPANTS INDIAN COUNCIL OF MEDICAL RESEARCH NEW DELHI 2006,Chapter I, Statement of General Principles on Ethical Considerations/involving Human Participants, Background

[5] Central Drugs Standard Control Organization(Dte.GHS, Ministry of Health and Family Welfare, Government of India), Good clinical practices for clinical research in India, Appendices, Appendix : Declaration of Helsinki.

[6] page 24 'Human Rights: International perspective' by Directorate of Distance Education, Tripura University, International Covenant on Civil and Political Rights 1966 in article 7.

[7] Council for International Organizations of Medical Sciences (CIOMS), INTERNATIONAL INSTRUMENTS AND GUIDELINES,GENERAL ETHICAL PRINCIPLES,PREAMBLE,THE GUIDELINES.

[8] Drugs and Cosmetics Rules, 1945, Part X-A, rule 122-DA

"Good clinical practice is an ethical and scientific quality standard for designing, conducting and recording trials that involve the participation of human subjects."[9]

These days clinical trials are required to be conducted in compliance to the guidelines laid down by International Conference of Harmonization -- Good Clinical Practice norms. Medical research in India is regulated by the following legislative framework.

Drugs and Cosmetics Act – 1940 (Schedule Y)
Drugs And Cosmetics (II Amendment) Rules, 2005
ICMR guidelines, DBT guidelines
Medical Council of India Act - 1956, (amended in the year 2002)
Central Council for Indian Medicine Act - 1970
Guidelines for Exchange of Biological Material (MOH order, 1997)
Right to Information Act – 2005
The Constitution of India
The Biomedical Research on Human Subjects(Regulation, Control, Safeguards)Bill 2005

Apart from these legislations, the Indian Council of Medical Research (ICMR) was established for the purpose of fostering a research culture, improve and develop infrastructure and foster community support. The Drug and Cosmetic Act, The Medical Council of India (MCI) Act states that all clinical trials in India should follow ICMR guideline 2000.[10]

The Drugs Controller General of India (DCGI) is responsible for regulatory approvals of clinical trials in India. The ICMR has Central Ethics Committee on Human Research (CECHR), the committee audits the functioning of this Institutional Ethics Committee (IEC). The recently amended schedule Y of drugs and cosmetics rules order the composition of IEC as per the ICMR guidelines. The DCGI's office in collaboration with WHO and ICMR are conducting training program for members of Ethics Committees across the country. The ICMR guidelines for clinical trials make

[9] GOOD CLNICAL PRACTICES FOR CLINICAL RESEARCH IN INDIA, foreword http://cdsco.nic.in/html/GCP.htm
[10] ICMR Ethical Guidelines icmr.nic.in/ethical_guidelines.pdf

mandatory to set up Ethics Committee at institutional level for the purpose of scrutinizing and approving a clinical trial.[11]

The DCGI issued guidelines on registration of Ethics Committees and inspection of trial site and direction to the committee to keep a vigil on drugs trial. The schedule Y of the Drugs and Cosmetics rules specifies that it is the responsibility of Ethics Committee that reviews and accords approval to a trial a protocol to safeguard the rights, safety and wellbeing of all trial subjects. The Ethics Committee should exercise particular care to protect the rights, safety and wellbeing of all vulnerable participating in the study.[12]

CLINICAL TRIAL IN INDIA -- TRIAL OR CONVICTION ?

From the legislation and guidelines, it seems that India do have very standard regulations of conducting clinical trial at par with International standard. But, reality speaks otherwise.

Case report : 1

Deepak Yadav, a mentally disabled boy of 4 years from the city of Indore was undergoing treatment for his stomach problems at Chacha Nehru Bal Chikitsalaya, a government pediatric hospital in Madhya Pradesh. His condition became worse when he was repeatedly administered an anti-ulcer drug, Rabeprazole, without any knowledge or consent of his parents. The boy had been treated like a lab rat for an

[11] http://www.indialawjournal.com/volume2/issue_3/article_by_sreesudha.html

[12] http://www.downtoearth.org.in/content/drug-trials-india-killed-2031-persons

untested drug. Deepak is totally incapable of doing anything and reliant on his mother for survival by courtesy of an unethical drug trial.[13]

Case report : 2

Dhananjay Shrievastav, on pretext of being treated for tuberculosis was put on a drug, Olodaterol, on trial by one Indore-based doctor without any knowledge or consent of the patient. This resulted in serious adverse events (SAEs) including cataract in his right eye, constant headache, nausea and fatigue. Mr. Shrievastav came to know about the trial only after his name figured on the list of 1112 victims of illegal drug trials made public by the Madhya Pradesh assembly in response to a question from MLA, Bala Bachchan.[14]

Case report : 3

Sarita Kundumula, a poor tribal girl of 13 years was put to a medical research to test the feasibility of vaccinating large number of young women against Human Papiloma Virus, a sexually transmitted virus, which could cause cervical cancer. The teenager was involved in this study carried out in a remote part of Andhra Pradesh without any knowledge or consent of her parents. Her parents came to know about the study after she collapsed and expired, few days after receiving the injection.[15]

Case report : 4

Twenty five people with oral cancer who were treated in a government-run Regional Cancer Center in Thiruvananthapuram in November 1999 were put on experimental drug, M4N or G4N, though there were established drugs for treatment of their condition. They were neither informed about the experimentation nor shown any reason for denial of an established treatment. The trial was not approved by DGCI at the time of conducting it.[16]

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[13] http://swasthsamarpan-ctva.org/case-study-of-deepak-yadav

[14] http://swasthsamarpan-ctva.org/case-study-of-dhananjay-shrivastava

[15] http://www.independent.co.uk/news/world/asia/without-consent-how-drugs-companies-exploit-indian-guinea-pigs-6261919.html

[16] http://www.indialawjournal.com/volume2/issue_3/article_by_sreesudha.html

These few reports expose only the tip of an iceberg, viz, violation to the regulations mandatory for conducting a drug trial. Although, each cases represented different types of violation of regulations, one thing was common to each of these cases -- no 'Informed Consent'[17] was obtained in any of these cases.

Insufficiency in implementation of control mechanism and laxity in regulation has prompted many US and European pharmaceutical companies and research organizations to look to India as a better venue for drug trial as there are stringent regulations for conducting Clinical Trials in those countries. India has other advantages for being chosen for Clinical Trial.

* In India, trial is relatively cheap. The average cost of phase I/II/III trials in US is over US $20/50/100 millions respectively. Whereas in India, cost of same will be almost half.[18]

* The population is quite large with varieties of illness and genetic diversity.

* Poverty and illiteracy prompted to larger participation as people believe that participation would offer them better healthcare which otherwise they could not have afforded.

* Regulatory changes -- particularly schedule Y of the Drugs and Cosmetics Act 1940 amended in 2005, now permits concomitant phase II and III trials. Previously, for a phase III trial to be carried out in India, that phase had required already to be completed elsewhere.[19]

* India has a good number of doctors and research workers who are English-speaking and the Indian hospitals store their data in English. It is easier to conduct a clinical trial even in a government hospital in India.

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[17] DRUGS AND COSMETICS (IIND AMENDMENT) RULES, 2005/ SCHEDULE Y/ REQUIREMENTS AND GUIDELINES FOR PERMISSION TO IMPORT AND / OR MANUFACTURE OF NEW DRUGS FOR SALE OR TO UNDERTAKE CLINICAL TRIALS/ CLINICAL TRIAL/ Informed Consent

[18] http://legalservicesindia.com/article/article/clinical-trial-regulation-in-india-678-1.html

[19] http://www.scidev.net/en/health/clinical-ethics/news/fines-expose-failings-in-policing-of-indian-drug-trials.html

* There is well-developed IT.

At least 80 Indian hospitals are presently engaged in conducting clinical trials which is projected to go up to 14,000. India is expected to be conducting over 15% of total Global Clinical Trials.[20]

As per study report of Indian Society for Clinical Research (ISCR), Boston Consulting Group (BCG), Indian Trial market is estimated to be US $498 million and total trial registered in India is 2059.[21]

India is thus emerging as a global hub for clinical trial which is wide open to abuses.

An intervention by the Supreme Court is India in July 2012 exposed the unethical practices of clinical researchers and pharmaceutical companies. A division bench headed by Supreme Court justice R. M. Lodha commented that it was "unfortunate" that humans are being treated as "guinea pig" for testing drugs and vaccines produced by multinational corporations.[22]

The scenario of Serious Adverse Events (SAE) including death which had taken place in India during January 2008 to January 2012 following Clinical Trial, has come to light when Dr. Anand Rai of Indore filed RTI application to DCGI. Public information officer (PIO) in his reply stated "The Serious Adverse Events (SAEs) of death may occur during clinical trial due to various reasons. These could be disease related deaths like cancer etc or administration to critical or terminally ill patients or side-effects or unrelated causes. As per available data, the number of Serious Adverse Events of deaths in clinical trials reported during the last four years viz. 2008, 2009, 2010 and 2011 were 288, 637, 668 and 438 respectively. The data of respective trial sites (trial site code and hospital name) and their respective states is not maintained by this Directorate."

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[20] Shiv Raman Dugal,Chairman,BoD,Institute of Clinical Research,New Delhi'India:Clinical research hot-spot'/www.biospectrumindia.ciol.com sept 08 2010

[21] DRUGS AND COSMETICS (IIND AMENDMENT) RULES, 2005/ SCHEDULE Y/ REQUIREMENTS AND GUIDELINES FOR PERMISSION TO IMPORT AND / OR MANUFACTURE OF NEW DRUGS FOR SALE OR TO UNDERTAKE CLINICAL TRIALS/ Application for permission/ (iv) (b)

[22] http://www.thehindu.com/news/national/article3645151.ece

Regarding compensation paid he stated, "As per available data there were total 22 cases of deaths
related to clinical trials in the year 2010. As per information made available by the Sponsor/CRO, compensation have since been paid in all 22 cases of deaths related to clinical trial which occurred in 2010."

During hearing, it also became apparent that the office of DCGI had no information of any action taken against Ethics Committee, pharmaceutical companies and contract research organizations so far. [23]
In fact, under Drugs and Cosmetics Act, there is no provision of punishment for sponsor company or ethics committee found guilty of unethical practices.

NEED OF THE DAY

India with a burden of millions of patients suffering from diabetes, bronchial asthma, epilepsy, hypertension, cardiac problems, cancer, HIV and Alzheimer's disease is looking forward for newer and better therapy for which clinical trial is a dire necessity. The issue of unethical conduct in clinical trials has brought to focus the need for regulatory reform and strict ethical safeguards. Changes for improvement are in the process.

Clinical Trial Registry: ICMR has launched Clinical Trial Registry in July 2007. The purpose of this clinical trial registry is to encourage registration of all clinical trials conducted in India before the enrolment of the first participant. Working together with Indian Journal of Medical Research, the clinical registry brought together the editors of 12 Indian Biomedical Journals who agreed not to publish the result of any trial started after June 2008 if it has not been previously registered. In June 2009, the Govt. of India decreed that all trials have to be registered under Clinical Trial Registry - India.[24]

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[23] CENTRALINFORMATIONCOMMISSION/DecisionNo.CIC/SG/A/2012/001478/19426/Appeal No. CIC/SG/A/2012/001478

[24] http://ctri.nic.in/Clinicaltrials/login.php

Recently, the Ministry of Health and Family Welfare has published draft rules for amendment to the Drugs and Cosmetics Rules 1945 along with draft guidelines for deciding Financial Compensation in cases of drug trial-related death. The Drugs and Cosmetics Rules (4th amendment) primarily aim at regulating the ethics committees by adding section 122 -DD and schedule Y - 1 to the original rules, the draft proposes to make registration of EC mandatory and lays down guidelines in details with requirements for registration process.

The Draft guidelines for financial compensation published by Central Drug Standard Control Organization (CDSCO) seek to determine the quantum of financial compensation to be paid in case of clinical trial-related injury or death. As per existing guidelines financial compensation is not mandated by law and is merely mentioned as a good clinical practice (GCP) in para 2.4.7 of the Indian Council of Medical Research's GCP guidelines for Clinical Trials in India. The guideline proposes two categories of victims -- those who were healthy at the time of participation in a drug trial and those who were suffering from a disease prior to participation. Compensation calculation will accordingly be different. The Govt. of India has sought public feedback on both draft rules.[25]

Drug and Technical Advisory Board, constituted by Ministry of Health recommended amendments to Drugs and Cosmetics Rule 1945 in regards of obtaining 'informed consent.' At present, a written consent is all that required, but person undergoing clinical trial often do not understand what they are signing. It is proposed that drug trial investigator will have to do video recording of trial subject while giving their 'informed consent.' This will ensure investigators explain details of the trial in a proper manner to the subject.[26]

If all these recommendations are implemented, India, which has already stepped to Global Trial may reap the benefit of new drugs developed by multinationals at an affordable price as a part of a global movement. It is to be seen how seriously implementing agencies stick to the ethical norms.

[25] http://techcorplegal.com/Startup_Business/Blog/drug_trials_in_india.html
[26] http://pharmabiz.com/NewsDetails.aspx?aid=71024&sid=1

CONCLUSION

As an emerging economy, India needs to promote a strong culture of research and development in health sector. There is also a need to develop competent clinical research organizations capable of carrying out Clinical Trials in compliance with International Conference of Harmonization -- Good Clinical Practice guidelines. There is a need for infrastructure development and a proper administrative and monitoring mechanism to get things going properly. Attention is to be paid to ensure stringent quality checks. Transparency should be ensured by the investigators and institutions. There is need for standardized training of the members of ethics committees with an accreditation process of the ethics committees. Media participation and government's effort for legal awareness on this issue is a demand of the time. If these are not being followed, then it will be only a matter of time before these heinous practice will be prevalent in our society and with full force. Above all, human life should be given its utmost value and no compromise in whatsoever condition should be done to downgrade it as a "guinea pig."