EDITORIAL

Forewarned is Forearmed! Unethical Drug Trials in the Developing Countries

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INTRODUCTION

The journey of developing and marketing a new drug although profitable is a time consuming, expensive and laborious task. Clinical trials are mandatory for development of a new drug, device or method of treatment; without which safety and efficacy in humans, and optimal dosing cannot be established and overall adverse effects cannot be known.

Thousands of such trials are conducted on tens of thousands of humans (healthy volunteers as well as patients) every year. In developed countries these trials are scrutinized and inspected by state owned boards (e.g. Food and Drug Administration in USA). In developing countries however, the situation is different.

The standard scientific method for developing a new drug is that it is first tested in vitro followed by exhaustive animal testing (usually on mice and rabbits). Once found to be safe and effective, human testing is ensued which comprises of Phase-I i.e. testing the drug on few healthy volunteers (usually paid for the purpose). Then Phase-II of clinical trial follows where the same drug is tested in a small group of relevant disease patients and once safety and efficacy of the drug is established large scale and Phase-III trials are done on patients; from different races / populations to have a wider profile. Even after a drug is established and marketed for a particular disease, bioavailability trials are conducted (Phase-IV) in different populations as this may differ from race to race. Ethical issues related to human clinical trials have always been controversial; in the developed world they are watched by organizations such as the FDA while in developing countries there is a lack of such conglomerations.

A drug is marketed on an average 8-10 years after first tests and costs involved in establishing a drug vary from 50 million USD to 800 million USD.[1,2] Because of the high cost and long process of developing, incentive is high to cut the costs and speed up the process. This has lead to formation of Human Experimentation Corporations which are commercial organizations with specializations in biopharmaceutical testing in humans. Such corporations have increased dramatically in the past 2-3 decades and have grown to a 20 billion USD industry in 2008 with annual growth rates of 15-20%.

Because of constraints of high expenditure, high literacy rates, human rights awareness, strong legal and judicial systems, free media to report blankly any untoward incidents, better economy and per capita income and overall strong integral Institutional Review Board (IRB's) and health departments, drug trials were and are becoming increasingly difficult in developed countries. All these factors along with cut throat competition among pharmaceutical companies to build up and market new drugs more rapidly, has lead to shifting of focus to poor countries of South.

Poverty, illiteracy, lack of human rights bodies and awareness, corrupt and inefficient health controllers and practitioners in poor and developing countries of 3rd world, have gradually led to drug trials being moved to target the poor and gullible masses of these countries, and patients are made guinea pigs in unawareness.

The atrocities conducted by Nazi doctors in concentration camps during World War II lead to the need of some International guidelines to safeguard the rights of patients/participants from such exploitations.[3] First such guidelines were formulated by Nuremburg tribunal popular as Nuremburg code.[4]

Atrocities of human experimentation in the 20th century became public due to efforts of some upright personnel from health profession and medical journalists prompted the development of Universal Ethical principles to govern all such research in future.

The prime example of such unethical trials was Syphilis trials in Guatemala where 700 Guatemala prison inmates, mental patients and soldiers were deliberately infected with spirochetes to produce the disease and later on to test 'Penicillin' in them to study its efficacy

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(1946-1948). Even American NIH switched to inhuman practices by using paid prostitutes infected with syphilis to sleep with prisoners to transmit the disease to them. Not only that bacteria obtained from skin lesions of patients were poured into artificial wounds on skins of these victims, they were even injected intra spinally to produce the disease.[5]

Another such example is seen in case of the famous AIDS trials in Thailand brought to the forefront by the commendable journalistic effort of Washington Post. (6) This trial was aimed to determine the vertical transmission of HIV funded by the US army and approved by the National Institute of Health (NIH) even with out prior availability of antiretroviral drug AZT to any of the participants. Researchers at the Harvard University also conducted a similar trial simultaneously who wisely considered that non availability of AZT to the participants in the control group would be unethical. The efficacy of AZT had already been proved in reducing the incidence of vertical transmission of HIV and had become a standard treatment in France and US before these Thai studies. The army researchers curtailed some of their grant (a modest $1 million) for purchase of AZT (cost of $15000).[6]

India seems to be another ground for pharmaceutical companies using humans as guinea pigs. According to a published article in 2012, more than two thousand people in India succumbed due to drug trials over the period of 4 years.[7] The first example concerns tribal girls who were volunteered for immunization tests on the say-so of the warden of the hostel in which they lived.[8] This project was sponsored by Bill and Melinda Gates and several girls later died. Another extreme example has been drug trials on survivors of the world's worst poisonous gas disaster in Bhopal in at least 11 trials without proper informed consent.[9] Streptokinase trials in India in 2003 where drug had been tried (phase III) on unaware patients and resulted in the death of 8 patients, displays yet another crash of ethics.[10] Phase III trials without prior information and proper consent involving Clinasetron were also permitted by Drugs Controller General of India despite of the fact that Phase II trials had been carried out of India and such practices were not permissible in India at that time.[11]

Hepatitis E vaccine trial in Nepal (2001-2003) by GlaxoSmithKline and the Walter Reed Institute of Research presents a similar situation where phase II trials were conducted on 2000 soldiers offered by the Royal Nepalese Army as volunteers.[12] Despite of the fact that vaccine was declared unsuitable for American soldiers by Walter and Reed it was used in poor Nepaly soldiers.

Ethical Guidelines for Drug Trials

The Nuremberg war crimes tribunal formatted and compiled ethical standards for medical research.[4] This was the first guideline towards ethics of drug trials. The Helsinki declaration adopted in 1964 is the most authentic and accepted document on research ethics updated regularly. In year 2000 the declaration was revised fifth time to rectify the controversial issues which were raised by media on the trials conducted in developing countries .The World Medical Association, the formulating body, especially prohibited the use of placebos in such situations when best current methods are available in developed countries. Also research in developing countries is to be allowed only when it is likely to benefit the local population, is appropriate culturally, and provides equal treatment to all participants and finally fair access is given to post trial treatment.

The three cornerstones of Belmont report are **(a) Respect for persons:** respecting humans as autonomous and voluntary decision makers on their free will. **(b) Beneficence** and non-maleficence to protect individuals from any harm due to acts of commission or omission and up keeping individuals best interest **(c) Distributive justice** that is ensuring benefits to the patients in the research group & equity in care to all during and after trials.[13]

If a drug is intended for the U.S. market, it must be approved by the FDA. Studies conducted under an Investigational New Drug (IND) designation have to fulfill FDA regulating guidelines which include informed consent and Institutional Review Board requirements, while those foreign studies not conducted under an IND are governed by another rule.[14,15] Universal Principles are based on clear and detailed informed consent and true voluntary and unbiased participation, beneficence for the participants and ultimately equity and justice. Strong health departments lead by Government; honest and integral IRBs should govern the Pharmaceuticals / human drug trial corporations.

Globalization- beyond the dark side

The FDA says that at least 80% of drugs approved in USA and other developed countries are based on data from clinical trials abroad. As reported by Department of Health and Human Services (HHS) Office of the Inspector General most of the foreign clinical trials participant and sites are from Western Europe but heights number of participants per sites were from Central and South America.[16]

Almost 50% of clinical trials are done outside USA. One-third of the investigators are from foreign sites. An average pharmaceutical company is expected to save up to 600 million dollars annually by shifting 50% of its drugs trials from western countries like USA & Europe to poor countries of South America & India.[17]

Most of the trials are now being conducted in Africa, Asia, and Latin America. Mainly included countries are Peru, Colombia, Chile, Panama, Venezuela, Nicaragua, Dominican Republic, African countries and India. Exploitation is almost inherent in these trials as there is always lack of proper informed consent, direct and indirect coercion, lack of equality and lack of resources. Companies are not liable for even intentional let alone unintentional harm caused by experimental drugs.

CONCLUSION

Continuing Clinical research is vital for growth of Medicine. Pharmaceutical industry has clearly a vested interest in developing and marketing profitable therapies .Obstacles faced by them in developed countries has led to shifting of the focus of human trials to poor countries of the South from North. Often ethical norms for participants in developed countries are deliberately and conveniently not followed resulting into human accesses which should honestly be punishable under criminal act. It is high time that health authorities in developing countries wake up and lay down necessary rules and regulations for fair business, make independent and integral Ethical Review Boards for prior approval and supervision of all such trials and make overall unethical conduct and malpractice in this regard a punishable offence.

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