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Review Article

The dark side of clinical trials and remedial strategies in india

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Abstract

India offers unique benefits to the clinical research fraternity of the world. Breadth of genetic variations, willing subjects due to poverty and abundant research talent brings the world to the door steps of our country. India needs to get its legal framework in to order to check the local exploitation and regulate unscrupulous foreign and domestic researchers. No law is effective unless it is implemented vigorously. Therefore strong executive institutions should be created to implement the laws with severe deterrent punishments. Pharmaceutical practitioners must take this to heart.

Introduction

Over 24,000 clinical trial deaths and (Serious Adverse Events) SAEs in India in ten years have been reported.The time has come to turn the search light on the dark side of clinical trials in India. Disproportionate numbers of lives are being sacrificed on the altars of financial gain and greed. When adequate and promised compensation is not given to the ignorant and unaware subjects then ethical standards get compromised because human value is diluted. Poverty drives people to resort to extreme means in desperation. Therefore they lend themselves to clinical

trials. But powerful purveyors of pharmaceutical practices exploit the vulnerabilities of such poor. When an odd report of blatant loss of life makes it to the main stream media, the whistle blowers are gagged with muscle and money. Truth is hushed and poor suffer silently. Drugs may save a million but kill valuable thousands, nevertheless every effort should be made to save lives. Every human life is worth the same and worth saving. Even those that offer themselves for clinical tests. India has the largest pool of patients suffering from various maladies. This has made India a favourite destination for outsourcing of clinical trials.

Materials and Methods

As India becomes the crux for clinical trials, it is contributing the growth in the fields of health and medicine. Monitoring these clinical trials conducted in communicable and non-communicable diseases is not taken seriously as it is supposed to be. More over Pharma giants are also magnetized by India due to the fact that the country offers nearly 700,000 specialty hospital beds, 251 medical colleges and skilled English-speaking medical personnel. Even with these positive features we still find the monitoring levels of clinical trials as poor. Challenges in conducting safe and productive clinical trials: India is making a name for itself in the international pharmaceutical arena as a preferred destination for leading global companies to conduct clinical trials. It is a challenge for both the government and the private sector to create a balance between ethics and trade. The Indian government has successfully played its part by

standardizing the regulations governing the conduct of clinical trials and the private sector, which includes pharmaceutical companies and contract research organizations. Furthermore, an increased awareness of good clinical practice requirements and a stronger desire for international acceptability of research carried out in India have brought favourable changes in the attitude of Indian clinicians towards participation in clinical trials. Investigators are eager to take part in clinical trials that comply with GCP (expand GCP) and are also willing to adhere to the constraints of protocol. Globalization and trade liberalization can affect health welfare systems directly and indirectly. It is important to take into account the global environment when developing national and domestic health strategies, including clinical trials. The role of the Clinical Trials Registry-India (CTRI) is to register the clinical trials happening in India and more over schedule Y1 is a promising aspect in making the clinical trials beneficial with minimized deaths. Initiated as a voluntary measure, since 15th June 2009, trial registration in the CTRI has been made mandatory by the Drugs Controller General (India) (DCGI). Various bodies connected with clinical trials are shown in table 1.

DCGI	Drug Control General India	Regulatory apex body under the Govt. of India that oversees all clinical trials in the country
ICMR	Indian Council of Medical Research	Apex body that formulates, co-ordinates and promotes biomedical research
GEAC	Genetic Engineering Approval Committee	Clinical trials involving use of biotechnological products would be referred by DCGI to GEAC for recommendations
DBT	Department of Biotechnology	Apex body that oversees the new impetus to develop the field of modern biology and biotechnology in India
AFRB	Atomic Energy Review Board	Authority that exercises regulatory control over the approval of new types of radiation equipment
BARC	Baba Atomic Research Centre	Apex body that oversees and approves all radiation related projects in India
DCC	Drugs Consultative Committee	Provides Technical guidance to the central drugs standard Organization
CDL	Central Drugs Laboratory	National Statutory Laboratory of Indian Govt. for quality control of drugs
CLAA	Central License Approving Authority	Body within CDSCO (expand CDSCO)
DTAB	Drugs Technical Advisory Board	responsible for issuing " no objection certificate" for manufacturing licenses Provides technical guidance to CDSCO

The functioning of these regulatory bodies will become a challenge if money and power get influential. With effective functioning of these regulatory bodies, death rate in clinical trials can be reduced to a very large extent.

Pharmaceutical Firms

Set up for manufacturing drug or death? Core conceptualization is exchange of money or goods for research participation as compensation. Coercion is also an important concern in research with prisoners and other captive populations forced to participate and on refusal are punished or retaliated. Undue inducements involve offers that are so attractive that they lead people to participate to which they would normally have important objections. Poor people who have limited access to health care facility are induced to enter research studies for their health care. As per the official list with health ministry, 44 companies reported 668 cases in 2010, while 50 companies were involved in such cases during 2009. The Indian law for clinical trials - the amended Schedule Y of the Indian Guidelines for Clinical Trials and the ICMR Ethical Guidelines for Biomedical Research on Human participants, 2006, have specified the need for provision of compensation of participants for research-related injuries[3]. The guidelines apply to all clinical research, whether sponsored by the pharmaceutical or medical device industry, government or academia or individual investigators.

The compensation, it says, could be in the form of payment for immediate medical/ surgical management of research-related injuries or for permanent disabilities. It says the Informed Consent Document (ICD) should state that the research participant has a right to claim compensation in case of research-related injuries and whom to contact for their rights as research participants. The draft says compensation has to be paid, irrespective of whether injury was foreseeable or predictable and that the research participant had given her/his consent in writing about participating in the research study. "The payment will be the responsibility of the investigator or institution," the draft says. Fear of unethical trials, being conducted by multinational drug companies on naive Indian villagers, has been a serious concern over many years. Claims made by the research participant should be settled within a reasonable timeframe not exceeding 90 days. Any disputes will have to be settled within a reasonable timeframe preferably within 90 days. The guideline adds, "Compensation will not be paid to research participants receiving placebo in consideration of its failure to provide a therapeutic benefit or for natural progression of an underlying disease."

OVERCOMING THE CHALLENGES

It is high time India sets off on a journey to overcome the challenges put forth by the task of conducting clinical trials. The journey could probably not be a high way but a road with many potholes and by-lanes. But still it is never too late to strive and bring about a change for the better. These could probably be some of the ways through which the challenges can be won over with effort. A separate checklist of documents required to be submitted for the conduct of Global Clinical Trials has been published on the CDSCO's website. As per these requirements, the applicant has to submit details on, among other things:

1. Name of the applicant
2. Sponsor authorization letter
3. Drug name
4. Regulatory status in other countries
5. Trial objective
6. Phase of study
7. Participating countries and sites
8. Details of patient enrolment globally and in India
9. IRB approvals
10. Any reported suspected unexpected serious adverse reactions from other participating countries
11. Data as per Form 44 (clinical trial application) and Form 12 (application to import drugs for use in clinical trials).

Requirements are meant to be fulfilled at any cost as they help to avoid undesirable situations.

Results

Death a serious issue in clinical trials: As per the clinical trials registry of India maintained by the office of Drug Controller General of India, 1868 clinical trials are being carried out currently. No. of people volunteering for clinical trials is 11 between July and December 2007; 137 between January and December 2008; 548 between January and December 2009; 806 between January and December 2010 (note the increase in the number of people volunteering for clinical trials over the last three years). As numbers can create a larger impact, the number of deaths in 2007 accounted to an enormous 132 and this number increased to horrifying 288 and this did not stop here. In 2009 the number was a dreadful 637 and in 2010, the death toll hit the alarming figure of 668 producing alarming total of 1725, a number that the health ministry cannot turn a blind eye to. These are the figures that have come into light based on the reports given by the trial investigators. But the dark side always prevails owing to which gross under-reporting of actual number of deaths taking place.

Children Are No Exception To Unreasonable Death Owing To Trials

As per an article published in a Sunday magazine on April 18, 2010, clinical trials performed for HPV given for cervical cancer claimed the lives of 7 girls between the ages of 10-14 years. These girls were from tribal groups in AP and Gujarat. A women's health rights group called SAMA instigated the central government to inquire into the issue. The report revealed that the deaths occurred owing to minor deficiencies in planning and conduct of study. There was no indication of the company that conducted the study. Although the age of the girls was justified owing to the nature of the drug being tested, the inquiry committee questioned the legality and morality of the study. Consent by proxy is that although the committee does not indict either the drug company or the organization that conducted the study, and also concludes that the inclusion of girls between the ages of 10 and 14 was justified given the nature of the drug, it has questioned the "legality and morality" of the circular from the Andhra Pradesh government permitting hostel wardens and head masters to sign the consent forms on behalf of these girls without informing their parents. It has gone further by stating: "The committee stresses that everyone shall desist from research on tribal population, unless of specific benefit to them." The company got away without paying compensation. The loop holes in this study were inefficient health monitoring after immunization, the girls having no health insurance and the parents not being informed about the study. This is one such case where even minor deficiencies in performing clinical trials can spell death. Unethical standards are highly pronounced in this case and the fact that life has lost its value is evident. Lack of transparency is another issue that has to be seriously taken into consideration. Another case that came into light in August 2008 created a country wide controversy. This case shows that reputation of the institution or company has nothing to do with respect for life and its value. AIIMS, the most reputed institute

claimed the life of 49 children over the past 3 years before 2008. The inquiry committee reported that the drugs were safe and not known for fatal complications. Once again AIIMS jumped the bone in the court by justifying that the children were victims of serious diseases. This shows that law in India needs revival.

Social Bodies Concerned And The Role Of Health Ministry

The Health Ministry's role is quite less critical over a period of years keeping in view the number of deaths that have occurred owing to unethical clinical trials. It is high time this government body that has to function the most in view of the health welfare of its people, starts functioning. The various social bodies catalyze the functioning of this ministry in relation to the accountability and transparency of the firms conducting trials by instigating inquiries into the aftermath of the trials to be conducted by its sub-bodies .The social bodies put forward their desire to provide protection for clinical trial subjects by making amendments to the GCP guidelines to purchase a comprehensive 5year health insurance for all volunteers in clinical trials. The Health Ministry should take a hard look at what it wants to achieve by promoting India as a cradle for clinical trials. In view of recent trends, there is quiet a good reason for bringing about temperamental changes in the current enthusiasm to promote clinical trials in India with strong regulatory mechanisms. It takes people like the Directorate General of Health Services to Hisar – based RTI (Right to Information) activist Mr. Ramesh Verma, to actually open the blind eye that the Health Ministry turned to the alarming rates of death in clinical trials. He raised the following questions in his RTI application like the drugs that have been registered for clinical trial approval, the name of the pharmaceutical company heading the trials, the drugs for which clinical trials have been approved, the mandatory requirements of an organization to perform clinical trials, provision of a sample copy of approval by a member of the family of the volunteer and details of compensation in case harm to the volunteer, number of complaints received pertaining to clinical trials, number of deaths occurred. The Ministry should not limit its functioning to just reporting but also consider inquiring into issues which actually agonize the social bodies functioning to promote health welfare of these volunteers.

Discussion

India being a cradle for clinical trials with several factors accounting for it being a hot spot for clinical trials. Out of the many factors, few of which are illiteracy, economic status, increasing population, prevalence of many diseases, greater genetic disparity, inefficient law etc. Is there any hope? Yes, there is as the National Human Rights Commission (NHRC) is dealing with the issue of the rise in mortality rate related to clinical trials in India. The drug control authorities are to make an official statement regarding the proposed Schedule Y1 for the efficient streamlining of the sector. This amendment seeks to initiate registration of not just the clinical trials but also the research subjects. Various organizations like the Indian Council of Medical Research's Ethical Guidelines for Biomedical Research on human participants, Indian Society for Clinical Research (ISCR) and Forum for Ethics Committees in India are dealing with issues concerning compensation for the research participants of harm. The Informed Consent Document (ICD) is supposed to state the rights of the participant and also information regarding who to contact for their rights as a clinical trial participant. These are the seeds of hope but hope lies where there is a scope for change.

Conclusion

The number of deaths would be much more than we will ever know unless there is a system of independent auditors to investigate the cause of death of subjects involved in clinical trials. Whatever the investigator says is believed even if he attributes the cause of death to a prior disease. "Now-a-days people know the price of everything and the value of nothing" as Oscar Wilde states. Life is a precious gift to be cherished and should be valued equally without any discrimination. The Indian healthcare sector can be viewed as a glass half empty or a glass half full. The challenges the sector faces are substantial, from the need to improve physical infrastructure to the necessity of providing health insurance and ensuring the availability of trained medical Personnel .But the opportunities are equally compelling, from developing new infrastructure and providing medical equipment to delivering telemedicine solutions and conducting cost-effective clinical trials. At this juncture awareness seems to be the only channelling route for finding an answer to this problem of death of human subjects during clinical trials.

Though the clinical trials done in India are registered, it's the subjects being used in the trials not been registered causing improper scrutiny of the deaths or the serious health consequences that happen when clinical trials go wrong. Today, world over, a need has been felt on the imperative for transparency, accountability and accessibility in order to re-establish public trust in clinical trial data and this would be feasible only if all clinical trials conducted are registered in a centralized clinical trials registry along with the people or subjects being used in the trials after their informed consent is accepted.

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Conflicts Of Interest

There are no conflicts of interest between the authors.

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