Unethical Clinical Trials in India: A Selective preliminary overview

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Abstract
This paper attempts to study the phenomena of clinical trials in India with a specific focus on the conduct of unethical trials. There has been a widespread chronicling of the rise of the great pharmaceutical power, the triumphs leading to improvements in life expectancy along with treatments and cures for numerous diseases. But there has also been the equally fascinating tale of the appalling usage of power in the form of coercion and deceit, with human beings exploited and subjugated to horrific forms of torture for the advancement of scientific knowledge and financial gains.

1. Introduction
There are legal and ethical provisions relating to the clinical trials sector and these provisions have been formulated both at the international and national levels and one of their major aims is to provide protection to the participants of clinical trials. However, despite the existence of a number of ethical guidelines as well as the legal stipulations, there have been numerous instances of clinical trials being conducted unethically and illegally in India. While such trials have been reported from other parts of the world as well, there have been quite a few Indian cases recently which continue to be in focus- thereby providing the basis for this research work.

India has been hailed as an emerging clinical trial location over the last decade or so and the different advantages it offers have been repeatedly highlighted (Yee 2012). Pharmaceutical companies are the major sponsors of clinical trials and as more and more of these companies venture into drug development and clinical trials, there is a need to have access to a large pool of participants for the trials. Along with the population advantages and the availability of lower cost of labour and expertise available in India, the facilities promised by the Government have also played an important role in setting up India as an attractive location. However, the reports of trials being repeatedly carried out unethically and illegally have raised certain questions about the functioning of the clinical trials sector in India.

This study seeks to investigate the clinical trials sector in India as, over the last few years, the question of clinical trials in India has been a contentious one. This is largely because a number of trials were found to have been conducted on Indian patients without following the necessary legal and ethical principles (recently, for instance, the HPV Vaccine trial, Indore Public Hospital and Bhopal Memorial Hospital trials). It is this area within the clinical trials sector which forms the focus of this work- however, the scope of this paper is only limited to an overview of some of the earlier reports of unethical trials in India. For this purpose, the publication of the ICMR Ethical Guidelines has been taken as the integral development, and hence, only trials which were reported prior to the development of the guidelines have been included in this short review.

2. The ethical questions: unethical clinical trials in India
In order to gain an insight into the clinical trials sector in India, we need to try and understand the context in which it was established and the subsequent path of its development. This necessitates identifying the historical cases of unethical trials in India along with documenting the recent cases.

The cervical dysplasia trial was perhaps the first well documented case of trials being conducted in India. In 1970s and 1980s researchers at the Institute for Cytology and Preventive Oncology which is an institute under the Indian Council of Medical Research (ICMR) in New Delhi, carried out a study on women patients who presented with different stages of cervical dysplasia or what were suspected to be precancerous lesions of the cervix. The women were not informed that they were participating in a trial, and hence, none of them were asked for consent. Nonetheless, it should be noted that the researchers said that they took verbal consent from the women who were illiterate. They also argued that the study was justified in that there was 'no conclusive evidence' that all severe dysplasias develop into cancer. However, while the study was underway, a major North American medical journal published the findings of a longitudinal study of cervical cancer.

The study concluded that cervical dysplasia was indeed a precursor for cervical cancer, and thus that all forms of dysplasia were to be treated. However, despite these new findings, the Indian researchers continued with the study. The subject participants were left untreated to see how many

lesions progressed to cancer and how many regressed. By the end of the study seventy-one women had developed malignancies and lesions in nine of them had progressed to invasive cancer. Sixty-two women were treated only after they developed localised cancer. It was largely due to the controversy that erupted after the study was highlighted in the 1990s, that the ICMR Ethical Guidelines for Biomedical research in Human was formulated in 2000 (Srinivasan, 2005).

Although India adopted Schedule Y and Schedule XA of the Drugs and Cosmetics Rules 1945 which relates to clinical trials in 1988, the study highlights the ethical issues that can emerge in clinical trials, and therefore establishes why such trials need to be closely regulated. Further, the principles enshrined in the Helsinki Guidelines were not adhered to. While the investigators asserted that they had acquired verbal consent, there was no evidence that the women had been informed about their potential participation in a clinical research study. Further, despite the fact that the research published in the journal clearly established that all forms of dysplasia warranted treatment, the Indian investigators continued with the study. This is clearly not in keeping with Article 7 of the Helsinki Guidelines (1964) which establishes that 'physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits'. Further, it had been clearly stated in the introduction to the guidelines that the mission of the physician was to safeguard the health of the people.

It also needs to be clarified that in the presentation of this case as well as the other subsequent cases, the term 'subject participant (s)' is being used. What is being referred to is, the process of the constitution of the trial participant as a 'subject participant' rather than merely a volunteer participant. This is especially true in case of unethical trials where the patients may not be aware of or fully comprehend their status as experimental sites. However, the intrinsic unequal power relations between the trial organizer and the participant also constitute her/him as a subject participant even if she/he is aware of the trial. The vulnerability and defenselessness of their position is more markedly revealed since it is their *own resource of life* which is leased out *as resource* matter for trial activities which are carried out to ostensibly improve life existence and yet, may paradoxically lead to diminishing of their own life existence.

The second case being presented here is from the 1990s. A huge multi-country unauthorized trial was carried out on thousands of illiterate Indian and Bangladeshi women wherein the anti- malarial compound mepacrine was used in pellet form as a means of female sterilization. Once inserted into the women's uterine cavity, it caused inflammation and scar tissue formation which closed off the fallopian tubes permanently.[15] While the trials had been stopped in the West, the compound had been directly distributed to medical practitioners in India. More than 30,000 women in India had been sterilised using this illegal and untested method, at least 10,000 in West Bengal alone. This trial demonstrates the differing ethical standards applied in different country settings. In what was clearly an illegal move, although the trials had been stopped in the west, the intervention was directly distributed to medical practitioners instead of being properly approved for testing. The Supreme Court banned the use and sale of this drug but it continued to be available in rural Bengal for up to five years after that (Dasgupta, 2005).

The M4N AND G4N trial is another important case in the account of India's clinical trial history. In 1999, 27[16] people with oral cancer were under treatment at the government-run Regional Cancer Centre in Thiruvananthapuram. Although there were established protocols of treatment including surgery, chemotherapy and radiation options, the patients were given first-in-human experimental drugs, tetra-O-methyl nor-dihydro-guaiaretic acid (M4N) or tetraglycinyl nor-dihydro-guaiaretic acid (G4N). The aim was to determine whether these chemicals could arrest the growth of oral cancer. Although the subject participants were made to sign consent forms, they were not informed that they were participating in a research study or that there were other approved means of treatment for their condition. While approval for the anti-cancer

[15]Mepacrine is the name of the compound, but it was better known by its commercial name Quinacrine. Although its use in sterilization has passed through several small trials, there has been no overall dismissal of its link to cancers and ectopic pregnancy and hence, WHO convened a technical consultation which decided that Quinacrine should not be used for sterilization purposes in women, either in research or therapeutic settings. (WHO Technical Consultation, 2009)

[16] While the questions on the ethical conduct of the trial are numerous, there also appears to be some confusion on the total number of trial participants. The RCC had initially acknowledged 27 patients but later released data on only 23 of them. Subsequently, only 18 cases were taken into account.

drug trial was taken from the Indian drug regulator only after the trial was underway (Srinivasan, 2005), ethical clearance from the collaborating organization- John Hopkins University had also not been provided.

The trial was only thrust into the media spotlight after a radiotherapist from the centre raised serious questions on the conduct of the trial. While there was an enquiry established in India as well as in the US, only 'procedural lapses' were found to have occurred. However, it must be noted that the University barred the principal investigator from conducting any further research on the chemical entities and also provided that any further human clinical research to be carried out by the investigator would have to be supervised by someone from the University who had experience in dealing with human trials (Frontline, Vol.22 Dec. 2005). Subsequently, animal testing was done on these chemicals before the launch of Phase 1 trials on humans in USA. Moreover, the volunteers in the US trial were patients who did not have any therapy option available to them. This was not the case with the Indian subject participants. This particular trial also serves to highlight the reprehensible process in which trials are organized in India. Firstly, the subject participants were not informed that they were participating in a clinical trial, and thereby receiving experimental therapy as opposed to approved therapy, thereby effectively amounting to denying them treatment.

Moreover, the trial was initiated before permission was sought, which was illegal as per Section 1.2 of Schedule Y of the Drugs and Cosmetics Act, 1945 (GSR 944 (E) 1988). Further, the ethical committee clearance of the collaborating body should also have been obtained as no such clearance had been acquired. It may be pertinent to point out that one of the possible reasons for the ethical clearance not being sought from John Hopkins University, might have been that it would have been unlikely that permission would have been granted because of the serious ethical question on the study itself. Hence, the question cannot be looked at in isolation- what also needs to be focussed upon is the undeniable role of the context of such a trial. This refers to the fact that the trial was being carried out in a third world nation-state which has a history of poor regulatory oversight; also the lack of ethical clearance from the US (first world) makes it an intriguing case and raises the pertinent question of elitism and even, worryingly, racism.

These three trials are illustrative cases of the nature and extent of unethical as well as illegal practices that are widely prevalent in the pursuit of clinical research in India. To state clearly, all of these studies violated the four basic tenets of ethics as per the ICMR Ethical Guidelines- autonomy (respect for person /participant), beneficence (act for the benefit of person/participant), non-maleficence (do no harm) and justice (ICMR Ethical Guidelines). Subjects were not informed that they were participating in clinical research and actual informed consent was not taken. Participants were subjected to the trials while being deliberately deceived that they were receiving standardized therapy as opposed to experimental interventions.

The three cases of unethical trials that were presented- the cervical dysplasia trial, the mepacrine pellet trial and the G4N & M4N trials were all conducted before the ICMR Ethical Guidelines for Biomedical research in Human Subjects was presented in 2000, although the 'Policy Statement on Ethical Considerations involved in Research on Human Subjects' had in fact, been published in 1980. The ICMR Ethical Guidelines for Biomedical research in Human were published first in 2000 while the CDSCO prepared the Indian Good Clinical Practice (GCP) guidelines in 2001. It is to be expected that after the categorical formulation of ethical and clinical considerations necessary for conducting clinical research in India, the situation would be somewhat different.

However, reports over the last few years have not been positive and instead brought to light further examples of unethical conduct of clinical trials. However, that is beyond the scope of this paper.

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