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ETHICS IN CLINICAL TRIALS: ANALYZING INDIA'S ROLE AS A HUB FOR PHARMACEUTICAL RESEARCH AND THE IMPLICATIONS OF UNETHICAL PRACTICES

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Abstract:

Over the past decade, India has emerged as a prime location for clinical trials, attracting pharmaceutical giants due to its vast population, affordable labor, and available expertise. However, this growth has been marred by numerous instances of unethical practices, raising critical questions about the treatment of human subjects in medical research. This essay explores India's role as a hub for pharmaceutical trials, highlighting cases of exploitation, negligence, and violations of ethical standards in clinical experimentation. By examining landmark cases such as the HPV vaccine trial and the use of mepacrine in unauthorized sterilization, this paper delves into the consequences of these practices on vulnerable populations. It also critiques the shortcomings of legal and regulatory frameworks in ensuring informed consent and participant safety. Ultimately, the essay underscores the urgent need for more robust ethical guidelines and enforcement mechanisms to protect human rights while fostering scientific advancement in clinical research.

Keywords: Clinical trials in India, unethical medical practices, informed consent, pharmaceutical research, ethical guidelines, human experimentation, HPV vaccine trial, mepacrine sterilization, participant rights, regulatory frameworks

There has been extensive reporting on the growth of the great pharmaceutical power, its victories resulting in increased life expectancy as well as treatments and cures for many ailments. To the contrary, humans have been exploited and subjected to horrifying forms of torture for the progress of scientific knowledge and financial gain, which is an equally fascinating story of the heinous use of power through compulsion and deception.[228]

Before diving into the ethical nuances, let us look at the meaning of legal ethics. According to Black's Law dictionary[229]Legal ethics is defined as a lawyer's practical observance of or conformance to recognised standards of professional conduct. The statement of how we ought to act as individuals and as a society is embodied in ethical codes or principles. These are moral judgements that can be used in certain circumstances to inform our decision-making and shape our behaviour. They are inextricably related to the cultural values of the moment and are therefore prone to change as attitudes and values do. What was accepted fifty years ago can be viewed as inappropriate today.

The core idea of medical intervention is to enhance the well being of an individual patient or client. But the core activity in medical research essentially is to test an hypothesis, conclusion and thereby to develop or contribute to existing knowledge, expressed, for example, in theories, principles, and statement of relationships. Similarly, medical experimentation refers to relatively untested and usually more innovative medical and

[228] Yee, A. (2012) 'Regulation up with India's trial boom'. The Lancet, Volume 379, Issue 9814, Pages 397 – 398.

[229] B.A. Garner, Black's Law Dictionary,9th edition, 2004 p. 976

surgical procedures which are applied primarily as a means of contributing to the common good in the interests of humanity through anticipated progress in medical science.[230]

A procedure is classified as experimental if the medical community has not accepted it as a conventional treatment for a particular disease or disorder, or for a group of patients, such as newborns or the elderly.[231] Human experimentation can also be broadly defined as 'anything done to an individual to learn how it will affect him.[232]

Some of the earliest literature on earth depicts human experimentation.[233] The Sung Dynasty Chinese examined and documented the effects of vaccination in Sanskrit literature in 590 B.C., and Indian scholars in the second and third centuries A.D. In ancient Persia, it was customary for the ruler to subject those who had been found guilty to scientific experiments. This method was sanctioned in Egypt by the Ptolemaic school, and it also existed in Renaissance Pisa.[234] Hippocrates laid the groundwork for the study of neurology and mental illness when he claimed that epilepsy is a common disease rather than a result of divine intervention. Similarly, Galen formalized medical experimentation in Western society around 1800 years ago by emphasizing experimentation alongside observation.

Galen's former hegemony was replaced in the seventeenth century by Harvey's. In instance, Harvey performed carefully monitored tests on both humans and animals to prove that blood flows through the heart and lungs. Instances of unethical medical research were documented in the early 1960s, most notably in the United States, where volunteers, particularly those who were weak or sick to death, were treated with blatant disdain and put at serious risk of harm. Among these was the infamous Brooklyn Jewish Chronic Disease Hospital project, in which elderly individuals with some form of impairment received an injection of live cancer cells without apparent indications of seeking their consent.

A study of contagious hepatitis C at the Willow Brook Home for Children with Mental Retardation, where patients were purposefully exposed to the virus, not only caused grave public concern but also endangered the honourable character of the medical industry. The New England Journal of Medicine published an article by Henry Beecher titled "Ethics and Clinical Research"[235] in 1966 that listed 22 instances of medical research involving subpar ethical treatment of human participants. The U.S. National Health Service conducted a study termed the Tuskegee study of untreated syphilis in the black male for nearly 40 years (1932–1972) Over 600 black men participated in the study, and 399 of them had syphilis. Although their informed consent was obtained, the participants were never made aware that they were a part of a research study. Notwithstanding the progress made with regulations on human experimentation, there are advanced levels of unethical practices of experimentation still taking place in the United States which needs to be addressed before it relates into war crimes.

As a statement of ethical standards for medical research involving human subjects, including study on identifiable human material and data, the World Medical Association (WMA) established the Declaration of Helsinki. The declaration is mainly directed towards physicians, in line with the WMA's mandate. The WMA exhorts others involved in medical research involving human subjects to follow these guidelines:

[230] Coleman C.H, Menikoff J.A, Goldner J.A, et al. The Ethics and Regulation of Research with Human Subjects. Newark: Matthew Bender Co, 2005:3–50
[231] 1National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research, The Belmont Report (Washington, DC: Government Printing Office, 1978), p. 2, cited in A.M. Capron, "Human Experimentation" in Robert M. Veatch (ed.), Medical Ethics (Boston: Jones & Bartlett, 1989), p. 132Ronald Munson.Intervention and Reflection Basic Issues in Medical Ethics, 4th ed. (Belmont, CA: Wadsworth Publishing, 1992), p. 320. A.M. Capron, "Human Experimentation" in Robert M. Veatch (ed.), Medical Ethics (Boston: Jones & Bartlett, 1989), pp. 137-8.
[232] Capron, "Human Experimentation", pp. 138-139.
[233] Bollet, Smalox: The Biography of a Disease-I, Resident and Staff Physician Aug. 1978, at 47, 48.
[234] Ibid, 6
[235]Robert M Veatch, https://pubmed.ncbi.nlm.nih.gov/27499481/, National Centre of Biotechnology Information.

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The International Code of Medical Ethics states that "A physician shall act in the patient's best interest when delivering medical care," which binds the doctor to the WMA's Declaration of Geneva's tenet that "The health of my patient will be my first consideration."[236] More comprehensive, frequently updated ethical codes produced by national medical organisations, such as the AMA Code of Medical Ethics (first adopted in 1847) and the British General Medical Council's Good Medical Practice, have supplanted the Hippocratic Oath as a statement of professional ethics. These materials offer a thorough summary of the duties and professional conduct expected of doctors towards their patients and the larger community. Infractions of these codes by physicians may result in disciplinary actions, including loss of licence.[237]

There is no direct punishment for breaking the Hippocratic Oath, although an arguable equivalent in modern times is medical malpractice, which carries a wide range of punishments, from legal action to civil penalties. In the United States, several major judicial decisions have made reference to the classical Hippocratic Oath, either upholding or dismissing its bounds for medical ethics:

Roe v. Wade,[238]

Washington v. Harper,[239]

Compassion in Dying v. State of Washington (1996),[240] and

Thorburn v. Department of Corrections (1998).[241]

The unethical trials in India

Looking at the trials that were conducted in india: The environment in which it was made and the developments that followed necessitates uncovering earlier instances of unethical trials in India in addition to reporting current cases. The study found that cervical dysplasia was a risk factor for cervical cancer and that all kinds of dysplasia should be addressed. The Indian researchers persisted with the investigation despite these fresh discoveries. To determine how many lesions turned into cancer and how many reverted, the subject subjects were left untreated.[242] Women had malignancies by the end of the research, and nine of their lesions had progressed to aggressive malignancy. Only after developing localised cancer were sixty-two women treated. The dispute that erupted was a major factor.[243]

Although India approved Schedule Y and Schedule XA of the Pharmaceuticals and Cosmetics Rules 1945, which relate to clinical trials, in 1988, the study illustrates the ethical difficulties that might arise in clinical trials and underscores the need for strict regulation of such experiments. Furthermore, the Helsinki Guidelines'[244] guiding principles were not followed. The women had not been notified about their potential involvement in a clinical research project, despite the investigators' claims that they had verbally obtained agreement from the women. However, the Indian researchers persisted with the investigation despite the journal article's obvious conclusion that all forms of dysplasia required treatment.

Article 7 of the Helsinki Guidelines (1964), which states that "Physicians should abstain from engaging in research initiatives involving human beings unless they are satisfied that the hazards involved are regarded to be predictable,"[245] is obviously not being followed in

[236] Merino, Aruanno, Gelpi, Rancich (2017). "THE PROHIBITION OF EUTHANASIA" AND MEDICAL OATHS OF HIPPOCRATIC STEMMA" (PDF). *Acta Bioethica*. **23**: 171-178 (176). doi:10.4067/S1726-569X2017000100017
[237] Ibid,9
[238] 410 U.S. 113 (1973)
[239] 494 U.S. 210 (1990)
[240] 1994 May 3;850:1454-68.
[241] 66th CAL. App. 4th 1284
[242] World Medical Association, Human Experimentation: Code of Ethics of the World Medical Association, 2 Brit. MED. J. 177 (1964); Declaration of Helsinki, adopted first by the World Medical Association in 1964, Declaration of Helsinki: Recommendations Guiding Doctors in Clinical Research, 197 J.A.M.A. 32 (1966).
[243] While some have criticised the Helsinki Declaration (for watering down the consent provisions of the Nuremberg Code) it gained more publicity than the Nuremberg Code and was more influential within the medical profession. see Kuhse H, Singer P, Paul M. McNeill, Experimentation on Human Beings: A History, and Discussion of Current Regulations a Companion to Bioethics. Blackwell: Companions to Philosophy, Blackwell Publishers: 369-378. (1998)
[244] "Declaration of Helsinki History Website". *Ethical Principles For Medical Research*. The JAMA Network. Retrieved 20 February, 2023..
[245] These ethical issues such as informed consent, confidentiality, research misconduct, respect and responsibility, data protection Act 1998, Declaration

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this case. In the event that the risks are proven to outweigh the possible benefits, doctors should stop their research. Also, the purpose of the physician was made very plain in the introduction to the guidelines: to protect the public's health. It should be made clear that the word "subject participant (s)" is used in the presentation of both this instance and the other examples that will come after it. The mechanism through which a trial participant is formed is what is being discussed.

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.[246] 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. While the trials had been stopped in the West, the compound had been directly distributed to medical practitioners in India.

This prohibited and unproven approach had been used to sterilise over 30,000 women in India, with at least 10,000 of those procedures taking place in West Bengal. This trial serves as an example of how ethical norms are interpreted differently depending on the nation. Notwithstanding the fact that the studies in the west had been discontinued, the intervention was provided to doctors without being legally approved for testing, which was obviously illegal. Although the Supreme Court outlawed its use and sale, the medication was nevertheless accessible in rural Bengal for up to five years after that. Another significant case in the account of India's clinical trial history is the M4N AND G4N trial. The government-run Regional Cancer Center treated 2716 oral cancer patients in 1999.[247]

The patients were given first-in-human experimental medications, such as tetra-O-methyl nor-dihydro-guaiaretic acid (M4N) or tetraglycinyl nor-dihydro-guaiaretic acid, despite the fact that there were known regimens of treatment such as surgery, chemotherapy, and radiation choices (G4N). Finding out if these compounds could halt the spread of oral cancer was the goal. Although the subject participants were required to sign consent papers, neither they nor the other approved therapy options for their ailment were disclosed to them while they were taking part in the research project. The Indian pharma regulator gave its consent to the anti-cancer medicine trial only after it had already begun, and John Hopkins University, a collaborator, had not yet given its ethical permission. After a radiotherapist from the centre raised major concerns about the trial's conduct, the trial was only brought to the attention of the media. While both an Indian and a US-based investigation were launched, only "procedural lapses" were discovered to have taken place. It should be noted, however, that the University prohibited the principal investigator from conducting any additional research on the chemical entities and stipulated that any additional human clinical research to be carried out by the investigator would have to be under

of Helsinki, Nuremberg code etc. will be discussed in the course of the work. See also Veatch R.M. The Patient as Partner: A Theory of Human Experimentation Ethics. Bloomington: Indiana University Press, 1987:16–76

[246] Srinivasan, S. (2005) 'Some Questionable trials' http://infochangeindia.org/publichealth/features/some-questionable-drug-trials.html WHO Technical Consultation (2009) http://whqlibdoc.who.int/hq/2009/WHO_RHR_09.21_ eng.pdf

[247] Krishnakumar, R. 'Trial and Errors' Frontline, Volume 22 - Issue 25, Dec. 03 - 16, 2005 http://www.hindu.com/thehindu/thscrip/print.pl?file =20051216005102200.htm&date=fl2225/&prd=fline & ICMR Ethical Guidelines, 2006

the supervision of someone from the University who had experience managing human trials.[248]

Before the start of Phase 1 trials on humans in the USA, animal testing was done on these substances. In addition, the trial's volunteers were patients who had no other treatment options. With the participants who were Indian, this wasn't the case. This specific trial also serves to draw attention to India's abhorrent trial procedure. First of all, the subject participants were not informed that they were taking part in a clinical trial and were therefore receiving experimental therapy as opposed to treatment that had been approved, effectively depriving them of care.

Additionally, according to Section 1.2 of Category Y of the Medicines and Cosmetics Act, 1945,[249] The experiment was started without approval, which was prohibited. Furthermore, as there was no ethics committee clearance from the collaborating body, that clearance should have been obtained as well. It could be important to note that one reason ethical approval from John Hopkins University was not requested could have been that it was doubtful that permission would have been granted due to the significant ethical question surrounding the study itself. As a result, the issue cannot be considered in isolation; rather, attention must also be paid to the undeniable significance of the environment of such a trial.

This alludes to the fact that the study was taking place in a third-world country with a track record of lax regulatory control; in addition, the absence of ethical approval from the US (first world) makes it an intriguing example and highlights the relevant issue of elitism and even, worryingly, racism.

During undergoing the trials, participants were purposefully led to believe that they were receiving standardised therapy rather than experimental interventions. The cervical dysplasia trial, the mepacrine pellet trial, and the G4N & M4N trials were all conducted prior to the presentation of the ICMR Ethical Guidelines for Biomedical Research in Human Subjects in 2000, despite the fact that the "Policy Statement on Ethical Considerations involved in Research on Human Subjects" had actually been published in 1980. The Indian Good Clinical Practice (GCP) guidelines were created by the CDSCO in 2001 after the ICMR Ethical Guidelines for Biomedical Research in Humans were first published in 2000. It is reasonable to assume that the situation would be slightly different after the categorical specification of ethical and clinical considerations required for conducting clinical research in India.

The HPV trial case in Khamman

Gross ethical transgressions are shown in the final report of the three-member committee that was formed by the federal government to investigate the alleged irregularities in the trial of the HPV vaccine. The Indian Council of Medical Research, the governments of Gujarat and Andhra Pradesh, and the NGO Program for Appropriate Technology and Health (PATH) worked together to conduct the experiment, which has been put on hold since March 2010. In the Andhra Pradesh district of Khammam and Vadodra, it was conducted on over 23,500 girls between the ages of 10 and 14 (Gujarat).

It is disturbing that the informed consent forms, which are among the most sacred trial records, were filled out "extremely carelessly" and with "incomplete and presumably erroneous" data. A dormitory warden or headmaster signed over 2,800 consent forms in Andhra Pradesh as the "guardian." The explanation was that it was difficult to contact the parents. Given that, and given that it was a research study and not an emergency, should these kids have ever been enrolled? What moral reason is there for the warden or headmaster acting in compliance with the 1945 Schedule Y of Medicines and Cosmetics Rules as a "legally acceptable representative"? Teachers played a "primary

[248] gained more publicity than the Nuremberg Code and was more influential within the medical profession. see Kuhse H, Singer P, Paul M. McNeill, Experimentation on Human Beings: A History, and Discussion of Current Regulations a Companion to Bioethics. Blackwell: Companions to Philosophy, Blackwell Publishers: 369-378. (1998)
[249] GSR 944 (E) 1988

role" in explaining and "obtaining consent," which meant that the permission was obtained under duress in a way that was legally unacceptable since students had "limited autonomy."

An uproar in the community over the deaths of seven children led to examination of the trial. Notwithstanding the fact that the deaths' underlying causes were later determined to be unrelated to vaccinations, the occurrence showed that the system in place to keep an eye on the "volunteers" for both significant and less serious adverse reactions to vaccinations completely failed. Two deaths in the Khammam district went undetected, while one death was reported after a wait of five months. Contrary to expectations, the Principal and Co-Principal investigators did not notify the sponsor of all adverse events within a day as required by the Medicines and Cosmetics Regulations, despite the fact that these were the "primary end goals of the trial" and were measured and reported. The fact that widespread violations of established practices and standards were found during the trial despite the participation of the top medical organisation and the fact that the investigating committee did little to assign blame sends a very negative message.[250]

Lastly, the need for medical research cannot be overemphasized; it promotes advancement in both the scientific and curative aspects of medicine, which is advantageous to all of humanity. These three trials serve as illustrations of the kind and range of unethical and prohibited practices that are regularly applied in India to perform clinical research. The four key criteria of autonomy (respect for person/participant), beneficence (act for person/benefit), participant's nonmaleficence (do no harm), and fairness were all violated in all of these studies, to be clear (ICMR Ethical Guidelines).

250 https://main.icmr.nic.in/sites/default/files/reports/HPV_PATH_final_report.pdf. Retrieved on 20.02.2023