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Clinical Trials: National and International Perspective

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Abstract

Due to its expense and unpredictability, outsourcing has gained widespread acceptance in the pharmaceutical industry for the development and global trials of novel medications. Due to its sizable treatment-naive population, human resources, technical skills, adoption/amendment/implementation of rules/laws by regulatory bodies, and shifting economic environment, India would be the most sought-after country for contract pharma research and development. Nonetheless, there are still "miles to go" to meet the requirements to guarantee India's success. India is ambitious and optimistic about luring major pharmaceutical companies to conduct their clinical trials there despite all the obstacles.

Keywords: Clinical Trials, Drugs and Cosmetics Act, Clinical Trial Rules, ICMR Guidelines, International Perspective of Clinical Trials

CHAPTER-1: INTRODUCTION

1.1. INTRODUCTION

A clinical trial is a research project designed to create novel tests and treatments with the goal of evaluating how they affect human health.[1] An investigational product or drug ("New drug") is used to treat human volunteers, and its effects are assessed. A medicine, vaccine, medical device, surgical or radiological technique, behavioral treatment, preventative care, cells, or biological product that has been produced with the intention of receiving marketing permission in the nation could be the subject of the trial. For each new treatment, a clinical trial is specially and carefully crafted depending on the requirements of the stakeholders—patients, physicians, and the experiment's host.[2] The trial procedure is examined, and the trial can only start when it has been approved. The trial procedure is looked over, and after it has been approved, the trial can begin. A clinical trial is the systematic study of pharmaceutical products on human subjects with the goal of discovering or confirming the clinical, pharmacological (including pharmacodynamics/pharmacokinetics) and adverse effects, with the objective of determining their safety and efficacy, prior to marketing the product in India (whether patients or non-patient volunteers). Animals are used as the beginning point for new drug research before moving on to people.

[1]World Health Organization, Clinical Trials, Available At: Https://Www.Who.Int/Health-Topics/Clinical-Trials#Tab=Tab_1 (Last Accessed on January 13, 2023).
[2]Sanofi, Clinical Trials and Results, Available At: Https://Www.Sanofi.Com/En/Science-And-Innovation/Clinical-Trials-And-Results (Last Accessed on January 13, 2023).

One argument in favour of using animals is that since animal and human systems are so similar, we can predict how drugs will impact people by looking at how they behave in animals. The majority of human effects can be expected from research on animals because people share almost 95–98% of the DNA present in mice or rats. However, not all effects can be predicted using animal studies. As a result, no government or organisation is likely to accept animal data as the only source of support prior to the drug's release for clinical use, even though there is a general similarity between medicine effects in animals and people.

A novel medication cannot be made available for therapeutic use without first undergoing a clinical study. Clinical trials are necessary for the development of novel drugs. Clinical trials are normally carried out using patient participants, with the exception of Phase-I trials, which occasionally but not always employ healthy volunteers. Because of this, it is conceivable for the participant to benefit in the majority of clinical studies even though the outcome in Phase I trials is unlikely. Participants in the phase I experiment may have agreed to take part because of the monetary rewards or out of true charity.

Clinical trials are well-organized, strictly regulated studies that evaluate a new drug or therapy's efficacy and safety in an effort to find cures for those who are ill. According to historical reports, trials on young men utilising meat and vegetables, as reported in the Old Testament of the Bible, date back to the sixth century B.C. Clinical trials have evolved and changed over time, but some aspects have remained constant.

1.2. DEFINITIONS

World Health Organization (WHO): A clinical trial is *"any research study that prospectively assigns human individuals or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes"*.

A legal definition of a clinical trial is provided by **Black's Law Dictionary,** which defines it as *"a systematic study of a new medical treatment, device, or drug in human subjects to determine its safety, efficacy, and optimal use."*

The implementation and upholding of ethical and moral standards and values is one of the most efficient ways to reduce risk and harm brought on by the various stages of medical research. To build trust with both the general public and those who take part in medical studies, specific laws based on ethical norms or standards must be meticulously obeyed by the experiments. A heated discussion regarding the initiative's ethics has been sparked by the deaths of multiple women from low-income households over the course of a 15-year medical research trial that was conducted without providing appropriate information for informed consent. There is little doubt that numerous brutal, heinous experiments and mass murders are carried out to further medical knowledge.For the purpose of gathering data, putting human subjects in potentially hazardous situations opens the door to the possibility of abusing those people in order to advance medical research and, as a result, benefit mankind as a whole.

Clinical trials and the human rights of tribal and poor people are closely linked and their protection is an essential aspect of conducting clinical trials. Clinical trials often target vulnerable populations, such as

tribal and poor people, who are be fully aware of the nature and risks of clinical trials, or who may not have access to adequate healthcare and medical services. The rights and welfare of human subjects involved in clinical trials must be protected, and the trials must be conducted in accordance with ethical principles and the highest standards of safety.

Clinical trials and clinical research activities have a direct impact on a number of human rights. These include the right to free informed consent to medical and scientific experimentation, access to remedy, access to information, quality of life and the right to privacy.

If clinical trials are not conducted according to the highest ethical standards, they may infringe upon the right to informed consent and the right to health. ECCHR believes that the role of transnational enterprises in causing or contributing to human rights violations should be investigated. However, despite frequent reports of irregularities in clinical trials in newspapers and NGO publications, few cases have come under judicial scrutiny.[3]Clinical trial subjects may find it challenging to hold foreign trial sponsors or manufacturers accountable if their rights are violated due to the practise of off-shoring and outsourcing studies. This is because of challenges such a lack of publicly accessible evidence, the expense of litigation, and logistical and cultural problems.

Article 7 of the InternationalCovenant on Civil and Political Rights (ICCPR) recognizes that a lack ofinformed consent constitutes a human rights violation: "No one shall besubjected to torture or to cruel, inhuman or degrading treatment or punishment.In particular, no one shall be subjected without his free consent to medical orscientific experimentation."

Article 12(1) of Convention to Eliminate All Forms of Discrimination Against Women (CEDAW) protects the right to non-discriminatory access to healthservices. Adequate access to health services includes the availability ofinformation about the services, such as the risks and benefits of possible options,which is central to informed decision-making.

1.3 STATEMENT OF THE PROBLEM

Because of its contributions to societal well-being and the calibre of its practitioners' work, the medical profession receives respect and esteem in society of the occupation. This trait is determined by how well the members adhere to the established ethical standards, which include relieving suffering, protecting patient privacy, acting with integrity and fairness, not harming patients with whom they have a fiduciary relationship, and maintaining friendly relationships with other medical professionals. Any medicine use carries hazards, some of which may be eliminated and others of which cannot.Prior to utilising a drug, it is crucial to consider the advantages and hazards. Only when benefits outweigh concerns is drug use warranted, this is analyzed by Clinical trials. People take risks when they take part in trials for the greater benefit. The question of what elements should be taken into account when determining the compensation in order to make it fair to all parties involved needs to be given careful thought. They should be reimbursed for injuries sustained during trials.

[3] ECCHR, "European Center for Constitutional and Human Rights: Case Summary" available at https://www.ecchr.eu/fileadmin/Fallbeschreibungen/Case_Summary__Clinical_Trials__2014-02-11 (Last Accessed on Jaunary 28, 2023)

1.4 HYPOTHESIS

In India for the regulation of clinical trials there are laws like Drugs and Cosmetics Act, 1940, Drugs and Cosmetics Rules, 1945 and New Drugs and Clinical Trial Rules, 2019 and also Indian Council for Medical Research has issued guidelines in 2017 for Biomedical and Health Research involving Human Participants. However,the ethics and regulations for clinical trial injury compensation in India need to be rationalised for efficient implementation in clinical research because they are not sufficient, uniform, or strong.

1.5 AIMS AND OBJECTIVES

This study focuses on the requirement for rationalization and simplification of compensation regulations and practices in order to uphold the fundamental ethical ideals of fairness, beneficence, and respect. This should establish pay standards that adhere to the finest laws in nations that conduct many trials and boost clinical research in India.

a. Examine the compensation policies in the different nations that have been identified.

b. Research the socioeconomic effects of different regulations. Look into the elements that influence and harm the clinical research environment.

c. Create recommendations for an ideal set of compensation rules in India that will safeguard the interests of all stakeholders, including sponsors, investigators, and participants. These recommendations should be made to governments, organizations, and agencies involved in the conduct of clinical trials.

d. Strengthen the diverse clinical research stakeholders by defending their interests.

e. Describe the functions of government (DCGI) regulations, the media, physicians, etc.

1.6 RESEARCH QUESTIONS

1. How does the "right to health" stand in light of clinical trials and individualized medicine?
2. Can the health system ensure that the right to health is affordable and accessible through drug regulation?
3. Is a person who participates in clinical trials subjected to discrimination and denial of their right to health by the state(s) and society?
4. Are there sufficient regulations for providing compensation to the participants of clinical trial who suffered injury or died during the clinical trial?

1.7 RESEARCH METHODOLOGY

The researcher used the doctrinal method of research primarily relying on primary and secondary sources from global, regional, and Indian levels. The study made an effort to look at all original sources of information, including the Indian Constitution, numerous specialized laws pertaining to health, biomedical, and drug security as well as International Conventions, Resolutions, Guidelines, Reports, Comments, and Guidelines of ICMR. Secondary sources including books, scholarly journal articles, and pertinent website content are also used.An interdisciplinary approach was applied throughout the research process.

CHAPTER-2: HISTORICAL PRESPECTIVE

2.1. EVOLUTION OF CLINICAL TRIAL IN THE WORLD

The history of clinical research is extensive and fascinating. Clinical trials have shown a history that extends back to 500 BC's biblical descriptions. Legumes and lemons are used in dietary therapy on the way to medication. When the basic approach was described in the 18th century, efforts were made to enhance the design and statistical aspects of clinical trials. Following this, the moral and legal landscape changed.

2.1.1 First Clinical Trial in the World

The earliest clinical trial in history is described in the "Book of Daniel" in the Bible. *King Nebuchadnezzar*, a cunning military commander who commanded his people to eat only meat and drink only wine in the belief that this would keep them in fine physical shape, carried out this experiment, which resembled a clinical trial. A few young royal men who loved to eat vegetables objected, though. Only for ten days did the monarch permit such people to consume water and legumes. The king permitted the bean lovers to continue their diet because the experiment's findings suggested that vegetarians were healthier than meat eaters. This was probably the first time in the evolution of the human species that a decision about public health was guided by an open, uncontrolled human experiment.[4]

The renowned surgeon *Ambroise Pare* unintentionally conducted the first clinical trial of a novel therapy in 1537.[5]He was in charge of caring for the soldiers who had been wounded on the battlefield in 1537 while serving with the Mareschal de Motegni.As the number of wounded was high and the supply of traditional treatment - oil was not adequate to treat all the wounded, he had to resort to unorthodox treatment. He goes into great detail about how his oil was lacking and how he was forced to use a digestive consisting of egg yolks, rose oil, and turpentine in its place. He was afraid that without cauterization, the wound on which he had not applied the stated oil would be dead from the poison, and he was unable to sleep that night.Beyond his expectations, he discovered that those to whom he had administered the digestive medication were in just minor discomfort, their wounds weren't swelled or inflamed, and they had slept through the night. The others to whom he had applied the hot oil were feverish and in great agony and swelling around their wounds. He then resolved never again to burn the helpless people wounded by arquebuses in such a horrible manner. But it took a another 200 years for a planned controlled study to be set up.

2.1.2 James Lind and Scurvy Trial: 1747

[4] Bhatt A., "Evolution of clinical research: a history before and beyond jameslind", 1(1), Perspectives in clinical research, 6–10 (2010).
[5]Twyman R A. A brief history of clinical trials.The Human Genome. Available at http://genome.wellcome.ac.uk/doc_WTD020948.html (Last Visited January 16, 2023)

James Lind is credited as being the first physician to undertake a carefully monitored clinical study in the modern period. As a surgeon on a ship, *Dr. Lind* (1716–94) was horrified by the high scurvy mortality rate among seamen. The most effective treatment for scurvy was the subject of his comparative trial. The crucial components of a controlled trial are covered in his vivid account of the trial. He divided the 12 scurvy patients into 6 groups of 2, treated each group differently with cyder, elixir vitriol, vinegar, sea water, oranges, lemons, and electra. As a consequence, the most sudden and visible good effects were perceived from the use of oranges and lemons. After that British Navy eventually made lemon juice a compulsory part of the seafarer's diet.

2.1.3 Arrival of Placebo: 1800

The word was described as "an epithet given to any medicine more to please than benefit the patient" in Hooper's Medical Dictionary of 1811. The first clinical trial comparing an active medication to a placebo, however, was not planned until 1863 by American physician *Austin Flint*. He treated 13 patients with rheumatism using a botanical extract that was suggested rather than an established treatment. "This was given regularly, and became widely known in my wards as the 'placeboic treatment' for rheumatism," Flint wrote in his 1886 book A Treatise on the Principles and Practice of Medicine. The cases' successful developments were such that the solution generally gained the patients' full trust.

2.1.4 First clinical trial that was randomly controlled: 1946

The first experiment with properly randomised treatment and control groups was carried out by the Medical Research Council (UK) in 1946. It involved giving streptomycin as a treatment for pulmonary tuberculosis. In 1947, the trial commenced. The "allocation concealment" at the time patients were enrolled in the trial was a significant benefit of Dr. Hill's randomization strategy over alternation procedure. The trial's use of objective measurements, such as x-ray interpretation by professionals who were unaware of the patient's treatment assignment, was another important aspect. The blind evaluation strategy, which keeps patients and researchers from knowing which therapy group a certain patient was enrolled in at the time of the study, was also used in this trial. This allowed for an unbiased analysis of the results.[6]

2.2 EVOLUTION OF ETHICAL AND REGULATORY FRAMEWORK

The Hippocratic Oath, which established patient safety as a top duty of a physician, is where the ethical framework for protecting human subjects first emerged.

The Nuremberg Code, the first international standard for subject-based medical research ethics, was created in 1947. In May 1947, Dr. Leo Alexander gave the Counsel for War Crimes six points outlining what was deemed appropriate medical research. The "Doctor's Trial" jury found on the six criteria, plus four more points. These ten principles made up the Nuremberg Code. The Code of Federal Regulations,

[6] Yoshioka A, "The Randomized Controlled Trial of Streptomycin in The Oxford Textbook of Clinical Research Ethics", Oxford: University Press Oxford, 46–60 (2008).

Title 45, Volume 46, which was later created by the US Department of Health and Human Services, was based on the Nuremberg Code and the Helsinki Declaration. The ten principles of the Nuremberg Code include things like informed consent, the absence of coercion, consideration for study participants, and more.

In 1948, the General Assembly of the United Nations adopted the Universal Declaration of Human Rights, which expressed concern about the rights of people being violated by unintentional abuse.[7]

The International Medical Association created the Helsinki Declaration in 1964, which is referred to as general principles and detailed recommendations regulating the use of human subjects in medical research. The Helsinki Declaration has undergone changes periodically; the most recent was in 2008. On the other side, there is still debate on post-trial access and using a placebo.

No one shall be subjected to torture or to cruel, inhuman, or degrading treatment or punishment, according to the 1966 International Covenant on Civil and Political Rights. In particular, no one may undergo medical or scientific treatment without his or her consent. Two important initiatives in establishing the ethics of human experimentation were the US National Research Act of 1974 and the Belmont Report of 1979. Good Clinical Practice, which became the de facto benchmark for the moral conduct of clinical trials, was issued by the International Conference on Harmonization in 1996.

Early in the 20th century, as government authorities realised the need to regulate medical interventions, clinical trials began to be incorporated into regulations and ethical standards. When the US Congress passed the Food and Drugs Act in 1906, the FDA, which had been founded in 1862 as a scientific institution, was turned into a law enforcement organisation. The need for performing clinical trials for drugs then became more evident as legislation steadily increased the amount of accountability for the marketing of foods and medications. The regulatory and ethical landscape will evolve as new scientific disciplines and technological developments are included into the drug development process.

2.3 HISTORY OF CLINICAL TRIAL IN INDIA

India is well renowned for being a popular destination for clinical research. The nation has had a troubled history in the area of clinical research, though. Ayurvedic medicine has a lengthy history in India. The traditional ayurvedic texts go into great detail to explain both the causes of ailments and how to treat them. These descriptions were based on direct observations made by the ancient Ayurveda experts. Ayurveda was superseded by Unani and Western medicine as foreign forces came to rule the country, but no clinical investigations have ever been recorded in ancient writings.[8]

[7]Indian Council of Medical Research."Ethical guidelines for biomedical research on human participants." *Ethical Review Procedures,* 11 (2006).
[8]Twyman R A. A brief history of clinical trials.The Human Genome. Available at http://genome.wellcome.ac.uk/doc_WTD020948.html (Last Visited January 16, 2023)

After 1970, India only recently began to seriously consider creating new drugs. Lack of provisions for studies on innovative treatments under the 1940 Drug and Cosmetic Act, the Regulations of 1945, and the 1970 amendment to the Indian Patent Act all hampered research. For a long period, India avoided developing fundamental medicines and became a centre for reverse engineering, in which foreign-developed substances were manufactured there using techniques that were not patented. It should be mentioned that the development of the Indian pharmaceutical business and its leadership in the world are a result of India's chemical engineering, which allowed many substances to be synthesised for a fraction of the cost overseas via alternate non-patented approaches.

When Schedule Y of the Drugs and Cosmetics Rules come into effect in 1988, the rules for new drug research and clinical trials were created. By requiring Phase III clinical research for the registration of new medications, the schedule aided in the growth of the Indian pharmaceutical industry. The company, which had previously focused mostly on producing generic pharmaceuticals, began to concentrate on developing cutting-edge drugs and therapies. Yet, this schedule was limited to clinical studies that were less advanced than those taking conducted elsewhere. This stage prevented India from being included in global clinical development.[9]

As India joined the TRIPS agreement in 1995, pharmaceutical product patents have been required since 2005. This presented a difficulty for the Indian pharmaceutical business. The industry could no longer survive on reverse engineering and stolen knowledge. India needed to keep up with the rest of the world, which was implementing the international standards set forth by the ICH (International Council for Harmonization).

The decision to revise Schedule Y in order to bring it into accordance with international rules was a significant first step. After being changed for the first time in 1995, the schedule underwent a considerable revision in 2005. The 2005 update to Schedule Y established a practical and reasonable method for Phase I to IV trials, in contrast to the 1988 version, which featured wide and logical definitions and requirements for various phases of a clinical study. The responsibilities of the investigator, sponsor, and ethics committee (EC) were described in this Schedule, along with recommended formats for crucial paperwork such consent, reports, EC approval, and the notification of a serious adverse event. The sponsors, multiple trial centres, and participants were given the opportunity to develop the protocol.Moreover, Schedule Y of 2005 makes it mandatory to follow the 2001-released Indian Good Clinical Practices (GCP) guidelines established by the CDSCO (Central Drugs Standard Control Organization). These modifications have provided the GCP regulations with the much-needed regulatory support, and they represent a substantial step in the right direction for GCP-compliant investigations. The Scurvy study had created a standard for conducting clinical trials in a certain manner.

[9]Ibid.

The Guidelines for Biomedical and Health Research Involving Human Participants, 2000, were published concurrently by the *Indian Council for Medical Research(ICMR)*, India's top regulatory organisation for biomedical research, and were updated in 2006. The clinical trial regulatory framework in India was created by these and Schedule Y of the DCR.

This framework created a pro-industry climate for clinical trials. However, the deficient ethical reviewprocedures and lack of compensation mechanism resulted in minimal protection of the clinical trial participants.Subsequently, concerns were raised before the Supreme Court of India[10] regarding insufficient provisionsconcerning patient safety and compensation. This led to a temporary ban on clinical trials in India.

Following that, CDSCO issued a number of instructions incorporating safety and payment systems to be adhered to throughout the clinical study process. An onerous three-tiered clinical trial approval process was implemented, which reduced the number of new entrants into the market. The Parliamentary Standing Committee on Health and Family Welfare then noted shortcomings in the oversight of clinical trials in its report. There was also agreement that, for simplicity of compliance, all administrative, procedural, and reporting requirements needed to be combined into a single regulation. Hence, the New Drugs and Clinical Trials Rules, 2019(CT Rules) were passed to address these concerns and streamlineregulation of clinical trials in India.

The clinical trials framework established by the DCR and the subsequent orders made by the CDSCO were replaced and consolidated by the CT Rules. It regulates all facets of clinical trials in India, including protocols, authorizations, payments, and waivers. The CT Rules specify rules for the formation, registration, and operation of ethical committees, the conduct of clinical trials, and exemptions from regulatory compliances, compensation, and the medical management process.

The clinical trial and clinical research laws in India are now framed by the CT Rules, CDSCO-GCP, and ICMR Guidelines for Biomedical and Health Research Involving Human Participants, 2017 (ICMR Guidelines).

2.4. CLINICAL TRIAL MISCONDUCT IN INDIA

After Schedule Y of the DCR and the 2005 patent law amendments, the Indian clinical trial market had already started to boom. Indian drug development has become popular among multinational pharmaceutical corporations thanks to the sizeable population and lax regulatory environment of the nation. Despite the fact that many important studies were conducted in India in line with the required criteria, there were a few instances where poor, ill, and occasionally illiterate persons were included in tests without providing the appropriate informed permission. Some examples of such unethical clinical experiments are provided below:

[10]SwasthyaAdhikarManch, Indore &Anr.vs. Ministry of Health & Welfare and Ors., W.P. (C) 33/2012.

The Kerala Regional Cancer Treatment Center conducted a clinical trial in Trivandrum in the years 1999 and 2000 for the drug Nordihydroguaiaretic acid (NDGA) to treat oral cancer. The trial's sponsor was Johns Hopkins University Hospital. The medicine was given to 26 individuals before it was determined to be safe for use in animals. In addition, patients were not told they were a part of a trial and had the choice to decline enrollment. Two patients died in the trial. The administration has recently decided to put this trial on hold for six months rather than penalising those who are guilty. Eventually, Johns Hopkins University acknowledged that the permission form was insufficient and that the drug's safety had not been proven; as a result, they barred the researchers from acting as lead investigators in any further clinical trials.[11]

In 2003, an unauthorised Phase III Trial was conducted in Hyderabad by two renowned Indian companies, Biocon (Insulin) and ShanthaBiotechnics (Streptokinase). Streptokinase and recombinant insulin were being studied for their capacity to dissolve blood clots and treat diabetes and heart attacks. Without the consent of the Genetic Engineering Approval Committee, companies conducted this trial. They also neglected to inform patients of the trial, which unfortunately led to the deaths of eight people. Without conducting a separate study, "causes other than the consumption of the drug" have been given credit for trial participants' deaths. A Delhi-based NGO filed the lawsuit in March 2004, and the Supreme Court decided that the trial was unlawful. Even though the Supreme Court ruled that the trial was unconstitutional, neither the company nor the investigators involved have received any punishment.[12]

From 2004 to 2010, the Madhya Pradesh city of Indore was in the news for the incorrect reasons. A total of 73 clinical trials involving 3,300 patients, including 1,833 children, were being conducted at the Maharaja Yashwantrao Public Hospital at the time. Trials were conducted for various medical conditions, including leg pain, asthma, heart failure, epilepsy, depression, and schizophrenia, in addition to vaccinations. The trials were supported by large pharmaceutical corporations. However, many of these studies were conducted unethically, in accordance with regional laws, and without receiving informed consent. From all these trials, a total of 81 patients, including 18 children, suffered from serious adverse events while 35 patients died. Health activists in Indore filed formal complaints about this tragedy with the state and national human rights commissions. and the DCGI. For their involvement in improper procedures, twelve doctors were fined by the state government for only Rs 5,000 or US$100. The government also did not disclose the investigation report hence, the data on adverse events or death cases are not available.[13]

[11] S. Nundy, & C.M. Gulhati, “A new colonialism? Conducting clinical trials in India”, 352(16), New England Journal of Medicine, 1633-1636 (2005). DOI: 10.1056/NEJMp048361
[12] SOMO, “Examples of unethical trials. Centre for Research on Multinational Corporations- Amsterdam.” (2008), available at https://www.somo.nl/examples-of-unethical-trials/. (Last Accessed on January 20, 2023)
[13] N. Lakhani, “From tragedy to travesty: drug tested on survivors of Bhopal. The Independent” (2011) available at http://www.independent.co.uk/news/world/asia/from-tragedy-to-travesty-drugstested-on-survivors-of-bhopal-6262412.html (Last Accessed on January 30, 2023)

Bhopal Memorial Hospital began using victims of the 1984 gas catastrophe in therapeutic trials in 2004, which is against international ethical norms. These clinical trials also put them in danger because they were already sick and having various problems (like vision, respiratory, and digestive disorders) as a result of the gas tragedy. Around 14 people lost their lives in the eight studies that Pfizer, AstraZeneca, Sanofi, and others undertook. None of the victims were aware they were participating in medical research. The family members of the subjects who were hurt or killed during the course of the trial are given Rs 200 each time they make a visit, but they receive no other kind of payment.Moreover, neither the government nor the hospital ethics committee took strong measures against the investigators or the committee. The only communication delivered to the concerned pharmaceutical businesses were warning letters, the contents and breadth of which are still unclear.[14]

Mumbai, Osmanabad, and Tamil Nadu, these three distinct randomised clinical investigations of cervical screening with Indian women have been carried out since 1998. The Bill and Melinda Gates Foundation supported the other two trials while the US National Cancer Institute provided funding for the Mumbai trial. These studies compared the mortality rate from cervical cancer between people who had the condition screened for and people who had not. Also, the studies looked for a low-cost cervical cancer screening technique that might be used in public health programmes. The screening techniques used were Pap tests, Quagid hybrid capture2, and Visual Inspection with Acetic Acid (VIA). 138,624 women were not screened during the trials, whereas 224,929 women were.The studies found that a total of 254 women passed away in the three clinical trials' unscreened treatment groups. Following a complaint to the US Office for Human Research Protection, it was discovered that women were not given enough information about the experiment in which they were participating. The primary ethical problem with these research was the inclusion of Indian women from lower socioeconomic position in trials and the decision to assign them to the screening group or the controls group depending on their sociodemographic status.[15]

In order to create a vaccine to prevent the human papillomavirus (HPV- which can cause cervical cancer), the states of Gujarat and Andhra Pradesh began research on the topic in 2009. The study's main objective was to estimate the cost and viability of including the HPV vaccination in the country's universal immunisationprogramme. Other reports claim that the trial, which was wrongly referred labelled as "a post-licensure observational study," was a significant safety trial. The study was created and carried out by PATH (Program for Appropriate Technology in Health) with financing from the Bill & Melinda Gates Foundation. Teenage girls between the ages of 10 and 14 received vaccinations as a part of the experiment in the states of Gujarat and Andhra Pradesh. The vaccines were provided by Merck and GlaxoSmithKline (Cervarix).Throughout the trial, a number of ethical standards violations

[14] S.L. Roberts, “Have India's poor become human guinea pigs?” (2012) available at http://www.bbc.com/news/magazine20136654 (Last Accessed on January 30, 2023)
[15] R. Nagarajan, “Row over clinical trials as 254 Indian women die” (2014), available at http://timesofindia.indiatimes.com/india/Row-over-clinical-trial-as-254-Indian-women-die/articleshow/34016785.cms (Last Accessed on January 29, 2023).

were reported by human rights organisations. The Indian government ended the project as a result in April 2010. But, 24,000 girls had already received immunisations when the trial was told to come to a stop. The majority of the participants were tribal girls. The Committee has admitted that numerous ethical lapses and violations occurred during the trial. Initially, the consent or informed agreement of the girls' parents was not requested. The vaccine was mainly given to these females with a hostel warden's agreement.Additionally, some of the girls who participated in the Gardasil trial encountered unfavourable side effects like dizziness, fatigue, weight loss, and menstrual problems, none of which were reported. PATH and ICMR assert that the deaths of three girls were unrelated to the clinical trial, nonetheless. Several female activists went to schools in Gujarat and Andhra Pradesh after the trial to learn more about the trial procedures. They discovered that the girls were not informed of the nature or purpose of the vaccine. The location of the cervix was not disclosed to the girls, therefore they were unaware of its location. The girls thought the government was providing the immunisation. Many girls believed that getting vaccinated was mandatory.[16]

India experienced a considerable effect from the HPV vaccine trial. Following the deaths of seven girls, health advocates and influential members of the media pushed the ICMR to examine all the unethical trials conducted around the country. The Indian Parliamentary Standing Committee on Health and Family Welfare heard testimony from the director general of the ICMR in April 2010, who admitted that the DCGI's rules had not been observed during the HPV study. The government did not, however, enact any strict regulations. Finally, the proponents of women's health who had brought the issue before the Indian Parliament filed a Public Interest Litigation (PIL) petition with the Supreme Court. A lawsuit was brought up against PATH International, the ICMR, the states of Gujarat and Andhra Pradesh, the DCGI and the vaccine manufacturers Merck and GlaxoSmithKline.[17]The petition was accepted for review by the Court on January 7, 2013. A second petition regarding the HPV vaccine programme was also submitted by the Delhi Science Forum, the Drug Action Forum, and the Sama Resource Group for Women and Health. These petitions were actually a timely response to two other PIL cases concerning clinical trials conducted in India that Dr. AnandRai and SwasthyaAdhikarManch (Health Right Forum) had previously filed. Those petitions had asked the court to ask the Indian government to strengthen trial subject protection by raising the standard of conduct. In summary, the petition claimed that "more than 150,000 people were participated in at least 1,600 clinical trials and that between 2006 and 2011, at least 2,163 people reportedly died in India while, or after, engaging in such trials".[18]
The Court referred to pharmaceutical corporations' unauthorised human research trials as "havoc" throughout the nation in January 2013. The Court demanded prompt action after criticising the Ministry of Health and Family Welfare and the Central Drugs Standard Control Organization (CDSCO) for

[16] P. Bagla, “Indian parliament comes down hard on cervical cancer trial” (2013), available at http://www.sciencemag.org/news/2013/09/indian-parliament-comes-down-hardcervical-cancer-trial (Last Accessed on Febuary 7, 2023)
[17] A. Nair, “Clinical research: regulatory uncertainty hits drug trials in India”, 294(7853), The Pharmaceutical Journal (2015).
[18] A. Moure, “The struggle of regulating clinical trials in a developing nation: India's experience” (2015), available at http://scholarship.shu.edu/student_scholorship/774 (Last Accessed on February 7, 2023).

failing to take any strong measures in response to earlier issues. Also, on September 30, 2013, the Court ordered that no clinical studies for investigational drugs should be conducted until a system to monitor them was in place. The Court also suspended the Drug Controller General of India's authority to approve clinical trials. The Supreme Court's decision dramatically reduced the number of clinical trials. According to data from the clinical trial registry, 207 applications were received in 2013 compared to 480 in 2012.[19]

As a result of the Supreme Court decision in case of ***SwasthyaAdhikarManch v. UOI***,[20] 3 Rules (Rule 122 DAB, 122DAC, 122DD) were added to Drugs and Cosmetics Rules, 1945 and its Schedule Y was substituted. And later on the basis of order in the same judgment, finally New Drugs and Clinical Trial Rules, 2019 were issued by the Central Government after consultation with the Drugs Technical Advisory Board.

CHAPTER-3: CLINICAL TRIALS: INTERNATIONAL AND NATIONAL PERSPECTIVES

3.1 INTERNATIONAL COUNCIL FOR HARMONISATION GUIDELINE FOR GOOD CLINICAL PRACTICE (ICH-GCP)

A global ethical and scientific quality standard for clinical trial design, conduct, performance, monitoring, auditing, recording, analysis, and reporting is known as "Good Clinical Practice" (GCP). Also, it assists to safeguard the privacy, honour, and rights of test subjects. Understanding the history behind the creation of the ICH-GCP principles is crucial since it provides justification for their necessity. In this essay, we discuss the historical context and the occasions that gave rise to the creation of these recommendations. Nowadays, the ICH-GCP standards are utilised in clinical trials throughout the globe with the main purpose of protecting and defending human rights.

There are 13 core principles of ICH-GCP and they are as follows:

1. Clinical trials should be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety and well-being of the trial subjects are the most important considerations and should prevail over interest of science and society.
4. The available non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound, and described in clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/ independent ethics committee (IEC) approval/favourable opinion.

[19] A. Nair, "Clinical research: regulatory uncertainty hits drug trials in India", 294(7853), The Pharmaceutical Journal (2015).
[20] Writ Petition(S) (Civil) No(S). 33 Of 2012

7. The medical care given to, and medical decisions made on behalf of subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational products should be manufactured, handled and stored in accordance with applicable Good Manufacturing Practice (GMP). They should be used in accordance with the approved protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

All clinical trials should be conducted in accordance with ethical standards, reliable scientific evidence, and explicit, thorough protocols. These principles are self-explanatory. Trials should be conducted if the advantages outweigh the dangers. The rights, safety and well-being of trial participants are of paramount concern and these should be safeguarded through getting informed permission and protecting anonymity. The care must be provided by persons who are suitably qualified and have sufficient experience. To ensure correct reporting, verification, and interpretation, records need to be quickly available and retrievable. Good Manufacturing Practices should be followed when producing investigational items.[21]

3.2 WORLD WIDE SCENARIO

3.2.1. Sweden

In Sweden, personal injuries that may be treated and are either physical or mental in character (a mental injury must have a medically proven effect) are referred to as "compensable injuries". The injury must be a direct effect of the therapy for it to be compensable.[22]The adoption of a different treatment that would have met the current research need in a less risky way would have prevented a medical intervention, according to a later evaluation. The compensation scheme in Sweden is based on this. Sweden abides with the insurance-requirement statute. Depending on the cause of the injury, the Patient Insurance Association or Pharmaceutical Insurance pays the reimbursement. A "Patients' Claim Panel" reviews all claims and renders impartial decisions on each one. On demand, this panel also counsels the claimant, insurer, or court. According to Section 1 of the Tort Liability Act, the Patient Insurance Act offers compensation equal to 80% of the cost of the damages.Compensation might be granted if an

[21] A. Vijayananthan, & O. Nawawi, "The importance of Good Clinical Practice guidelines and its role in clinical trials", 4(1), e5, Biomedical imaging and intervention journal (2008).
[22] Patricia L. Munhall, "Revisioning phenomenology: Nursing and health science research", No. 41, Jones & Bartlett Learning (1994).

accident-related injury is linked to routine medical procedures. The tort law may be applied generically to other kinds of injuries.

3.2.2. New Zealand

Government-sponsored compensation for research injuries is available in New Zealand. The "Injury prevention, Rehabilitation, and Compensation Act" covers the treatment of wounds received during clinical studies. The Act also covers childcare, home modifications, rehabilitation costs for pharmaceuticals, disability aid, and occupational retraining in addition to compensation. The majority of the cost of delivering healthcare is borne by the country's universal healthcare system. To be eligible for reimbursement under the Act, a clinical trial must receive ethical committee permission before it can begin.

The list of covered injuries also includes death, denture damage, and physical and mental harm brought on by bodily harm. A compensable damage does not include injuries brought on by the participant's pre-existing conditions or unduly withholding consent for treatment. For lost pay for wounded participants, 80% of the applicant's salary at the time of the injury is paid out. A lump sum payment up to a predetermined amount is paid in the case of permanent impairment. In the event of death, the dependents are also taken care of. When deciding whether an injury is compensable in New Zealand, the "degree" factor is not taken into consideration. The level of the participant's handicap determines the amount of compensation.[23]

3.2.3 USA

The USA has conducted the most clinical trials of any nation to date. However, because there is no system for universal compensation in the USA, wounded participants must file a lawsuit in order to be compensated. The informed consent form for clinical trials involving more risk than minimal risk must include all relevant information, such as whether compensation or medical care is available, contact details for the contact person, and the patient's rights in the event of research-related injuries, as per Code of Federal Research, Title 45, part 46, subpart A.

No-fault compensation is a feature of the well-known National Vaccine Injury Compensation Program (NVICP) in USA. Everyone who has had a vaccination and experiences injury as a result of participating in a vaccine research programme is eligible to submit a petition. The U.S. Department of Health and Human Services' medical staff then reviews this petition, determines whether the petitioner is eligible for compensation, and recommends that the court approve it. The court chooses the compensation after carefully weighing the evidence presented by both parties. The amount of compensation for eligible

[23]BismarkM ,Dauer E , Paterson R , et al, "Accountability sought by patients following adverse events from medical care: the New Zealand experience" 175, CMAJ 889–94(2006). doi:10.1503/cmaj.060429

participants is determined by a special panel, and the court then recommends that the U.S. Department of Health and Human Services award compensation.

3.2.4.Europe

Clinical Trial Compensation Guidelines, effective as of January 1, 2015 provides two distinct categories in the clinical trial compensation standards.

1. Payment for Phase I clinical studies
2. Compensation for clinical studies in phases II, III, and IV.

The goal of the compensation guidelines for Phase-I clinical trials is to eliminate any pay disparity between Phase-I healthy volunteers who are free of the target disease and Phase-I patient volunteers who are diagnosed with the target disease and can reasonably be expected to benefit directly from the research.

Guidelines for Phase-I clinical trials were initially published in 1970 for "healthy (Non patient) volunteers," and guidelines for Phase-II, III, and IV trials were released in 1983. Since then, these recommendations have been periodically reviewed and modified by the Association of British Pharmaceutical Industry (ABPI).

- **Guidelines for Phase I Clinical Trial Compensation**

According to ABPI regulations, the sponsor company of Phase-I studies that do not directly benefit the study participants must now legally and compulsorily provide a straightforward but necessary form of compensation. The topic information sheet and necessary consent form, which should include details on how participants will be paid in the event of physical harm, should be sent to the volunteer by the sponsor. Participants who suffer injuries should receive compensation as soon as possible without having to prove their own responsibility or that the product they were using was defective. The rights of volunteers should be fully upheld, and any disagreements over who will foot the bill for compensation should be settled on an individual basis by each party involved in the study.[24]

- **Clinical Trial Compensation Guidelines for Phases II, III, and IV**

The ABPI recommends that, without entering into any binding legal agreements, the sponsoring company of Phase II, Phase III, and Phase IV clinical trials provide a written assurance to the investigators and, through him, to the appropriate research ethics committee that the Guidelines will be followed. Regardless of any legal requirements, the corporation is required to make restitution to patient volunteers who suffer injury as a result of taking part in the experiment. Compensation must be offered when harm results from administering a medicine that is being studied or from any clinical intervention or procedure that would not have occurred if the patient had not signed up for the research.

[24]Shenoy P., Harugeri A. (2015). Elderly patients' participation in clinical trials. Perspectives in Clinical Research, 6, 184-189.

Compensation should not be given for momentary pain and suffering, but only for more severe injuries that are long-lasting and crippling. Compensation should be given to the injured if they suffered harm as a result of a procedure used to treat a medication adverse reaction, regardless of whether the injury was anticipated or foreseeable and regardless of the patient's free consent. Compensation ought to be offered to the subject whether or not the patient can prove the business' fault or the flaw in the product. These criteria do not apply to PhaseIV, with the exception of harm caused by actions taken in compliance with the protocol that the patient would not have been exposed to had treatment not been a part of the study.

3.2.5. Australia

In Australia, a legislative body known as the National Health and Medical Research Council (NHMRC) Act was established to oversee and develop public health issues. The main responsibility of NHMRC was to suggest guidelines for the ethical conduct of medical research. "Guidance on Good Clinical Practice," a revision to the National Declaration on Ethical Conduct in Research Involving People that was initially made available by the NHMRC in 2007 The "Guidelines for Compensation for Damage Related to Participation in a Business Supported Clinical Trial" state that financial compensation for harm caused by research participation should be given without creating legal responsibilities.

3.2.6. Russia

Russia is one of the newly growing locations for clinical trials as the number of international clinical studies is significantly increasing. Clinical trial insurance is necessary in Russia. The company supporting the research is responsible for making up any shortfall in the event of an SAE or death.

Since 2008, none of the 1,000 insured participants have received payment, claims Zavidova, the executive director of ACTO (Association of Coach Training Organizations) in Russia. She thought this was because no one required recompense. It is interesting that a Russian administrator would say something like that, but without more details, it is impossible to comment.[25]

3.2.7. Germany

Germany employs the no-fault compensation system. As a result, because the sponsor pays for compensation, neither the study subject nor the government must bear the expense of payments. The sponsor must establish an insurance fund to pay for research injuries. Insurance does not cover pain or suffering; it only covers financial losses. The trial participant must show a causal relationship between the harm and the research intervention within three years of the study's end and that no other party is to blame for the injury.

[25]Zvonareva, Olga, et al. "Risks and benefits of trial participation: A qualitative study of participants' perspectives in Russia", 12.6, *Clinical Trials*, 646-653 ((2015).

3.2.8. France

In France, sponsors of clinical trials are responsible for providing "no-fault compensation" to compensate injured study participants, albeit the sponsor has the option to shirk this responsibility by claiming duty. The French Parliament enacted the Huriet Law, commonly known as the law for the "Protection of People Undergoing Biomedical Research," to protect research participants in biomedical studies. This law makes it so that any compensation payments made by the mandated insurance system are the sponsor's responsibility.[26]

3.2.9 China

To protect the rights and welfare of trial participants, the ethics committee must evaluate the protocol in line with Chinese laws and regulations on foods, drugs, and cosmetics. The EC is required to carefully review any documents relating to trial-related insurance, medical care for injured participants, or death benefits. The sponsor is obligated to have insurance, provide legal and financial protection, and aid medical management as part of remuneration, as stated in Chapter VI, Article 42 of the Chinese Laws and Regulations. Another expectation from the sponsor, with the exception of situations involving medical malpractice, is indemnification for the investigator. According to Chinese law, the manufacturer or seller of the goods is held vicariously accountable for the subpar quality of the goods.[27]

3.2.10 India

India has always been a popular market for clinical trials due to its sizable, diverse population and acceptable regulatory framework. Clinical research regulation in India was initially established by the Drugs and Cosmetics Act, 1940 (DCA), which is governed by the Ministry of Health and Family Welfare and is the country's primary drug control statute. Only the import, manufacture, distribution, and sale of drugs in India were initially subject to regulation under the DCA and the 1945 Drugs and Cosmetics Rules ("DCR"). Clinical trials in and of themselves were rare and outside the purview of the CDSCO.

The colonial patent rules were replaced by the Indian Patents Act, 1970 in an effort to create a "process patenting framework" and boost domestic production. As a result, the production of generic medications shifted to India, and foreign pharmaceutical firms were deterred from penetrating the Indian market. Then, in 1988, Schedule Y was included in the DCR in order to regulate clinical trials in India and promote the growth of a primarily generic pharmaceutical industry there. Schedule Y mandated that

[26] Toulouse, Elisabeth, et al. "French legal approach to clinical research.", 37.6, Anaesthesia Critical Care & Pain Medicine, 607-614 (2018).
[27] Gray, Whitmore, and Henry RuihengZheng,"General Principles of Civil Law of the People's Republic of China.", 34.4, The American Journal of Comparative Law, 715-743 (1986).

manufacturers do Phase III clinical trials before registering new medications and requesting marketing authorizations.[28]

India ratified TRIPS in 1994, establishing the "product patent system" and ensuring some degree of intellectual property protection. The government relaxed Schedule Y in 2005 as a result of realising the potential of clinical research for new therapies, which led to an influx of pharmaceutical companies entering India. This amendment established a reliable regulatory framework for clinical trials by approving the Guidelines on Good Clinical Practice in India, 2001 (CDSCO-GCP) and introducing a four-phase clinical trial design.

The Indian Council for Medical Research ("ICMR"), India's main regulatory body for biomedical research, released the Guidelines for Biomedical and Health Research Involving Human Participants in 2000. The guidelines were amended in 2006. Along with Schedule Y of the DCR, these served as the framework for the clinical trial regulatory system in India.

Today's clinical trials take place in a business-friendly environment. Due to the poor ethical review procedures and absence of a compensation mechanism, clinical trial participants only received a basic level of protection.

The Supreme Court of India[29]thereafter received concerns concerning the insufficient patient safety and reparation measures. As a result, clinical trials were temporarily outlawed in India. After that, the CDSCO issued a number of instructions integrating payment and safety rules that have to be followed throughout the clinical study process. The number of new competitors in the market was decreased by the implementation of an onerous three-tiered clinical trial approval process. In its report, the Parliamentary Standing Committee on Health and Family Welfare then identified supervision issues with clinical trials. There was also agreement that all administrative, procedural, and reporting requirements needed to be consolidated into a single regulation for ease of compliance. The CT Regulations were passed as a solution to these problems and as a means of streamlining clinical trial regulation in India.

The CT Rules have integrated and superseded the clinical trials framework created by the DCR and the following guidance provided by the CDSCO. It controls all aspect of clinical studies conducted in India, including protocols, approvals, payments, and waivers. The CT Regulations specify clear rules for the formation, registration, and functioning of ethical committees, as well as for the execution of clinical trials, the payment of remuneration, and the medical management procedure.

[28] Parliament Of India, Department-Related Parliamentary Standing Committee RajyaSabha On Health And Family Welfare, Alleged Irregularities In The Conduct Of Studies Using Human Papilloma Virus (Hpv) Vaccine By Path In India (Department Of Health Research, Ministry Of Health And Family Welfare), August 30, 2013, Available At: Http://164.100.47.5/Newcommittee/Reports/Englishcommittees/Committee%20on%20 Health%20and%20family%20welfare/72. Pdf (Last Accessed On January 13, 2022)
[29]SwasthyaAdhikarManch, Indore &Anr. Vs. Ministry Of Health & Welfare And Ors., W.P. (C) 33/2012.

The clinical trial and clinical research laws in India are defined by the 2017 ICMR Guidelines for Biomedical and Health Research Involving Human Participants ("ICMR Guidelines"), CDSCO-GCP, and the CT Rules.[30]

3.2.10.1. Phases of Clinical Trials

Clinical trials are carried out in four phases. Clinical trials of drugs developed in India have to undergo all four phases of trials in India.

Phase I or clinical pharmacology trials or "first in man" study: This is the first time where the new drug is administered to a small number, a minimum of 2 healthy, informed volunteers for each dose under the close supervision of a doctor. The purpose is to determine whether the new compound is tolerated by the patient's body and behaves in the predicted way.

Phase II or exploratory trials: During this phase, the medicine is administered to a group of approximately 10-12 informed patients in 3 to 4 centers to determine its effect and also to check for any unacceptable side effects.

Phase III or confirmatory trials: Purpose is to obtain sufficient evidence about the efficacy and safety of the drug in a larger number of patients, generally in comparison with a standard drug and/or a placebo as appropriate. In this phase, the group is between 1000-3000 subjects. If the results are favorable, the data is presented to the licensing authorities for a commercial license to market the drug for use by the patient population for the specified and approved indication.

Phase IV trials or post-marketing phase: Phase of surveillance after the medicine is made available to doctors, who start prescribing it. The effects are monitored on thousands of patients to help identify any unforeseen side effects.[31]

3.2.10.2. Clinical Research Categories in India

For the purposes of regulation, medical research in India can be roughly divided into the following categories:

i.Interventional Clinical Studies: Interventional clinical trials are defined as studies that administer an investigational new drug or an interventional new drug for a commercial purpose and are governed by the CT Rules.

ii. Academic and Biomedical Clinical Studies: The ICMR Guidelines also apply to academic clinical trials and biological and health research. The gathering of scientific knowledge about conditions and diseases is the main objective of biomedical and health research. This covers studies that don't use novel or novel-for-investigation medicines. On the other hand, academic clinical trials are conducted for drugs

[30] Indian Council For Medical Research Guidelines For Biomedical And Health Research Involving Human Participants, Available At: Https://Main.Icmr.Nic.In/Sites/Default/Files/Guidelines/Icmr_Ethical_Guidelines_2017.Pdf (Last Visited On 13,Jan, 2023).

[31] Drugs and Clinical Trials Rules, 2019, available at https://www.drishtiias.com/to-the-points/Paper2/drugs-and-clinical-trials-rules-2019 (Last Accessed on January 28, 2023)

that have previously received approval for a certain claim and are initiated by an academic or research organisation or an investigator for a new indication, dosage form, or route of administration.

3.2.10.3. Clinical Trials for AYUSH Drugs (Ayurvedic, Siddha, Unani, and Homeopathic Medicines)

Ayurveda, Siddha, or Unani drugs, as well as homoeopathic therapies, are likewise covered by the D&C Act. The D&C Guidelines mandate that AYUSH treatments, like allopathic drugs, must report safety and efficacy data. The ICMR Guidelines will apply if human subjects are utilised in the study, rather than the CT Rules, which govern clinical trials and studies that generate this type of data. The Ministry of AYUSH has developed the General Guidelines For Clinical Assessment Of Ayurveda Treatments for use with ayurvedic, siddha, and unani medicines.

3.2.10.4. Clinical Trial Setup and Entry Procedures

Clinical trials may only be carried out in India by a sponsor or a person, institution, or organisation that has authority. A sponsor must follow all regulations governing the manufacture/import of the study drug and the submission of pre-clinical data in order to be authorised to conduct a clinical trial. The sponsor will have to demonstrate that the study protocol and CT Rules are still being followed once the trial has begun.

3.2.10.5. Clinical Trials and the COVID era

SARS-CoV-2 has quickly spread throughout the world. People first suffered since there were no effective medications available to treat patients with serious illnesses. Global scientific research has significantly changed as a result of the COVID-19 pandemic. In India as well as other countries throughout the world, numerous strategies are being investigated for the prevention and treatment of COVID-19.Until March 2021, 4952 clinical trials have been registered in ClinicalTrials.gov toward the drug and vaccine development for COVID-19. These clinical trials have received funding from more than 100 different nations. In addition to the registered (medium to large-size) clinical trials, a few small-size clinical trials have also occasionally been carried out to assess the COVID-19 treatment.

Still various Covid-19 vaccines are under clinical trial in India:

1. COVAXIN: The National Institute of Virology and the Indian Council of Medical Research (ICMR) collaborated on the development of COVAXIN, an indigenous COVID-19 vaccine produced by Bharat Biotech (NIV). The BSL-3 (Bio-Safety Level 3) high containment facility at Bharat Biotech serves as the development and manufacturing site for this locally produced, inactivated vaccine. After getting approval by the DCGI, the vaccine's Phase III clinical trials are now complete.

2. Covishield:A Phase II/III, Observer-Blind, Randomized, Controlled Study to Evaluate the Safety and Immunogenicity of Covishield is being conducted in collaboration between the Serum Institute of India (SII) and the Indian Council of Medical Research (COVID-19 Vaccine). Also, it has finished Phase III clinical trials and received approval from DCGI for restricted usage.

3.ZyCoV-D: ZydusCadila, a company that specialises in finding and creating NCEs, Novel Biologicals, Biosimilars, and Vaccines, announced that its plasmid DNA vaccine to prevent COVID-19, ZyCoV-D, had been found to be safe in a Phase I clinical trial in healthy volunteers and had received approval from the independent Data Safety Monitoring Board (DSMB). It is now undergoing Phase III trials after completing Phase II trials.

4. Sputnik V: A multi-centre, phase II/III adaptive clinical trial is being conducted by DrReddys Laboratories Ltd and Sputnik LLC to evaluate the immunogenicity and safety of the combination Gam-COVID-Vac vector vaccine. It has been given approval for Phase II/III trials as well as for restricted use during emergencies.

5. BBV154 - Intranasal vaccine: A multicenter study is being conducted by Bharat Biotech to assess the immunogenicity, reactogenicity, and safety of an intranasal adenoviral vector COVID-19 vaccine (BBV154) in healthy volunteers. A wide immune response is elicited by the intranasal vaccine BBV154, which neutralisesIgG, mucosal IgA, and T cell responses. Blocking COVID-19 infection and transmission requires immune responses at the infection site (in the nasal mucosa). Phase I clinical trials are now being conducted, with DCGI's approval.

6. COVOVAX: A phase 2/3, observer-blind, randomised, controlled study is being conducted by the Indian Council of Medical Research and the Serum Institute of India to evaluate the immunogenicity and safety of COVOVAX (the SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with Matrix-M adjuvant) in Indian adults. Phase II/III trials are currently being conducted, and DCGI has given its approval for limited emergency usage on adults.

7.CORBEVAX: The Texas Children's Hospital Center for Vaccine Development, Baylor College of Medicine, and Dynavax Technologies, based in Emeryville, California, created the protein subunit COVID-19 vaccine known as Corbevax. For development and manufacture, it is licenced to Indian biopharmaceutical company Biological E. Ltd (BioE). Phase I and Phase II clinical trials have been completed, and DCGI has approved its restricted usage on adults during emergencies.[32]

8. PFIZER: The cost and availability of the COVID-19 vaccine, created by Pfizer Inc. and its German partner, BioNTech SE, are currently the subject of a legal dispute in India. Pfizer-BioNTech COVID-19 Vaccine and Pfizer-BioNTech Emergency Uses The FDA has issued an Emergency Use Authorization (EUA) allowing the COVID-19 Vaccination, Bivalent, to be used as needed to prevent Coronavirus Disease 2019 (COVID-19) in people aged 6 months and older. The declaration that conditions exist that warrant the authorization of emergency use of the medical product under Section 564(b)(1) of the FD&C

[32]ICMR, "WORLDWIDE COVID-19 CANDIDATE VACCINES", available at https://vaccine.icmr.org.in/covid-19-vaccine (Last Accessed on February 5, 2023).

Act must remain in effect for the period of the declaration before it is terminated or the authorization is revoked.[33]

On September 25, 2020, Brook Jackson, a former employee of Ventavia Research Group, a Texas-based company engaged to conduct clinical studies for Pfizer's covid-19 mRNA vaccine, filed a complaint with the US Food and Drug Administration (FDA). Jackson, a regional director, saw issues at three of the trial sites she was in charge of, and she complained to an FDA inspector about them. She listed a number of issues, such as falsified data, patients who weren't blinded, and poorly trained vaccine providers who were slow to follow up on adverse events. Yet, the aforementioned study sites were not inspected by the FDA.

This instance of negligence was not unique. Only nine of the 153 Pfizer trial sites were inspected by the FDA before the mRNA vaccine received a licence, according to regulatory papers. Similar to this, only five of the 73 remdesivir trial sites and 10 of the 99 Moderna trial sites were inspected.

The vaccine created by Pfizer and BioNTech is not wanted to be taken off the market by Moderna, a pharmaceutical and biotechnology business. Sales of the cancer vaccine in the low- and middle-income countries covered by the global COVAX initiative are also not its main goal.

Pfizer and BioNTech were the targets of a patent infringement lawsuit brought by Moderna on August 26, 2022, in a district court in the US. Moderna says its mRNA rivals in developed markets will, however, "respect its intellectual property rights and would consider a financially reasonable licencing." Pfizer and BioNTech allegedly "failed" to request such a licence, according to the company. Two "essential elements" of Moderna's patented technology, according to its accusations, were copied by Pfizer and BioNTech. One of the defences offered by the business is that Pfizer and BioNTech started testing four candidates on humans before the outbreak even started. Others were spared from allegations of patent infringement, but Moderna asserts that its rivals developed a therapy that is similar to Spikevax's "exact mRNA chemical alteration" in several ways.[34]

The second accusation made by Moderna is that its rivals illegally utilised its know-how to encode a full-length spike protein in a lipid nanoparticle formulation for a coronavirus. Modernaclaims that they were developing that technique during the Middle East Respiratory Syndrome outbreak years ago.

Pfizer and BioNTech will "weaponize their own patent portfolio," according to analysts at Silicon Valley Bank (SVB) Securities, in reaction to Moderna's legal action. The SVB team believes that it will take years to settle the legal disputes. Although every instance is unique, the investment bank claimed that the history of IP disputes involving oligopolistic corporations "suggests the most likely outcome

[33]"Coronavirus COVID-19 Vaccine Updates", available at https://www.pfizer.com/science/coronavirus/vaccine/rapid-progress (Last Accessed on February 6, 2023)
[34]Scott Berinato, "Moderna v. Pfizer: What the Patent Infringement Suit Means for Biotech", available at https://hbr.org/2022/09/moderna-v-pfizer-what-the-patent-infringement-suit-means-for-biotech (2022), (Last Accessed on February 3, 2023).

would be small royalties paid by both companies, with little net favourable gain for anyone save the law firms involved."

This is not the first court case involving a pandemic, by any means. Alnylam Pharmaceuticals is suing Pfizer and Moderna for allegedly violating a patent for a "breakthrough class of cationic biodegradable lipids exploited to generate lipid nanoparticles" for mRNA-based vaccinations. Alnylam demanded royalties on the sales of the best COVID vaccines.

At the time, Moderna claimed that the case "would fail" because Alnylam's patent does not cover the COVID-19 vaccine. In "an endeavour to earn improper economic profit," Alnylam was trying to enforce intellectual property, according to Pfizer.

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