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CLINICAL TRIALS: A STUDY ON THE EXISTING NATIONAL AND INTERNATIONAL LAWS

UNDER THE GUIDANCE AND SUPERVISION OF

DR. LIJI SAMUEL

THE NATIONAL UNIVERSITY OF ADVANCED LEGAL STUDIES, KOCHI

SUBMITTED BY:

PANCHAMY BABU

Register No: LM0320005

LL.M (PUBLIC HEALTH LAW)

CERTIFICATE

This is to certify that **PANCHAMY BABU, REG NO: LM0320005** has submitted her Dissertation titled "**CLINICAL TRIALS: A STUDY ON THE EXISTING NATIONAL AND INTERNATIONAL LAWS**" in partial fulfilment of the requirement for the award of Degree of Masters of Laws in Public Health Law to the National University of Advanced Legal Studies, Kochi under my guidance and supervision. It is also affirmed that the dissertation submitted by her is original, bona fide and genuine.

Date: 11-10-2021

Place: Ernakulam

Dr. Liji Samuel

Guide and Supervisor

NUALS, Kochi

DECLARATION

I declare that this Dissertation titled **"Clinical Trials: A Study on the existing National and International Laws"** is researched and submitted by me to the National University of Advanced Legal Studies, Kochi in partial fulfilment of the requirement for the award of Degree of Master of Laws in Public Health Law, under the guidance and supervision of Dr Liji Samuel, Assistant Professor and is an original, bona fide and legitimate work and it has been pursued foran academic interest. This work or any type thereof has not been submitted by me or anyone else for the award of another degree of either this University or any other University.

PANCHAMY BABU

REG NO: LM0320005

LL.M, Public Health Law

NUALS, KOCHI

Date: 11/10/2021

Place: Ernakulam

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ABBREVIATIONS

1. AIIMS: All India Institute of Medical Science
2. CDSCO: Central Drugs Standard Control Organization
3. CIOMS: Council of the International Organization of Medical Sciences
4. CLA: Central Licensing Authority
5. CT: Clinical Trials
6. CTRI: Clinical Trial Registry of India
7. DCGI: Drug Controller General of India
8. DST: Department of Science and Technology
9. EC: Ethics Committee
10. EU: European Union
11. GCP: Good Clinical Practices
12. HC: High Court
13. ICCPR: International Covenant on Civil and Political Rights
14. ICESCR: International Covenant on Economic, Cultural and Social Rights
15. ICH: International Conference on Harmonization
16. ICMR: Indian Council of Medical Research
17. ICTRP: International Clinical Trials Registry Platforms
18. MoHFW: Ministry of Health and Family Welfare
19. NDCTR: New Drugs and Clinical Trial Rules
20. NGO: Non-Governmental Organization
21. NIMS: National Institute of Medical Statistics
22. NPPA: National Pharmaceutical Pricing Authority
23. PIL: Public Interest Litigation
24. R&D: Research and Development
25. SC: Supreme Court
26. TRC: Technical Review Committee
27. UDHR: Universal Declaration of Human Rights
28. WHO: World Health Organization

LIST OF CASES

1. Achutrao Haribhau Khodwa and Others v State of Maharashtra and Others, AIR 1996 SC 2377
2. Anuj Garg v. Hotel Association of India, (2008) 3 SCC 1
3. Bolam v. Friern Hospital Management Committee[1957] 1W.L.R. 582 (QB)
4. Canterbury v. Spence464 F.2d 772 (D.C. Cir.)1972
5. Dr. Rahul Dutta v. Union of India Misc. Bench WP No: 12280 of 2010
6. GJ Fernandez vs. State of Mysore & Ors AIR 1967 SC 1753
7. Indian Medical Association v V.P. Shantha and Others, 1995 (6) SCC 651
8. Kalpana Mehta v Union of India, (2017) 7 SCC 302
9. Montgomery v. Lanarkshire Health Board, [2015] UKSC 11
10. Narendra Kumar Maheshwari vs. UOI & Ors. [AIR 1989 SC 2138]
11. Parmanand Katara v. Union of India, AIR 1989 SC 2039
12. Samira Kohli v. Dr. Prabha Manchanda and Another, (2008) 2 SCC 1
13. Smt. Vinitha Ashok v Lakshmi Hospital and other AIR 2001 SC 3914
14. Swasthya Adhikar Manch v. Union of India, W. P. (Civil) No. 33 of 2012
15. Syndicate Bank vs. Ramachandran Pillai and Ors., [(2011) 15 SCC 398]

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CHAPTER 1

INTRODUCTION

Medicines play a vital role in the promotion of physical health and welfare. At an individual level, a medicine either helps to prevent certain illnesses, or it serves as a treatment that may reduce the suffering of individuals faced with certain illnesses. Creating a recent medicine is a long and rigorous process, and it takes several years to progress. Drug development is the process of bringing the recent pharmaceutical medicine to the market once a lead compound has been identified through the new process of medicine discovery. It includes pre-clinical experimentation on microorganisms and animals, filing for controlling status for an investigational recent medicine to initiate clinical trials on humans, and may include the step of obtaining controlling acquiescence with a recent medicine request to market the medicine. Clinical Trials is an important aspect of universalizing healthcare, enabling the development of better medicines, devices, surgical procedures, tests, vaccines, and other medical interventions and protocols for their safer and more rational use. The clinical experimentation performed to substantiate the indication for recent medicines, however, absorbs most of the efforts in this field. Clinical trials are carried out to assure, both the safety and effectiveness of a product.

The participation of subjects in clinical trial is crucial to the development of a new drug or device and in better understanding how to treat the disease. And in this process, there is nothing more important than the safety of the clinical trial subjects.But this aspect has been neglected in most of the clinical trials conducted in developing countries like India. A balance should be maintained between medical experimentation and clinical trial subject safety. Ensuring subject safety is an essential requirement for clinical trial. There are some common rules regarding the clinical trials that help to ensure the balance between clinical trial and subject safety. When the clinical trials are not conducted in accordance with the ethical standards, they infringe upon the participant's rights, including rights to informed consent and/or the right to health. The enumeration of ethical and integral rights of research participants is not constrained to a single universal document and the existing provisions have evolved over decades of clinical research experience and are not

exhaustive. Numerous bodies from many countries, including governments, government controlling departments, experimentation organizations, medical professional bodies, and physical health care providers, have issued guidance or legislation like Nuremberg Code 1947, Declaration of Helsinki 1964, Council of the International Organization of Medical Sciences (CIOMS) Guidelines 1982, Convention on Human Rights and Biomedicine 1997, Good Clinical Practices (ICH-GCP) 1997 etc. on the ethical conduct of clinical trials

For the past few years, the pharmaceutical industry has been outsourcing medicine discovery and clinical development programs to Asia, particularly India. It is pertained to mention that India provides unique opportunities for conducting clinical trials because of significant cost reduction and increased speed and productivity of all requisite R&D phases in order to bring effective and safe medicine to market. The New drugs and Clinical trials rules 2019 (New rules) was introduced on 19th March 2019 by the Government of India aim to develop clinical research in India by providing predictable, transparent, and effective regulation for clinical trials and ensuring faster accessibility of the new drugs to Indian population.

India still does not have strict penal provisions in case of violations of the ethical guidelines. An effective legislation incorporating all the rights of research participants and promoting ethical standards in clinical research is the need of the hour.

1.1 SCOPE OF THE STUDY

Experimentation on human subjects as a practice is fairly established and it does provide a beneficial service for millions of people who partake in the successfully approved products, may it be drugs, different drug delivery systems, medical devices, instruments or varied therapies and related technologies. The benefit to millions comes at the participation of people who invariably act as test subjects and suffer certain intrusions upon their physical and mental integrity for the sake of scientific study.

Clinical trials are pivotal for the development of new medicine, treatment or medical device. These trials are required globally to reduce burden of disease by helping

developing safe and effective recent therapies and vaccines. Clinical trials are also necessary to find out the solutions which may help in curing non-communicable diseases for example cancer and diabetes, or, as is especially needed in the poorest regions of the world, infectious disease and also epidemic disorders like Covid- 19. Clinical trials for new medications take place across the world but developing countries generally serve as desired locations for clinical research. Due to lack of commercial viability, developing countries are discriminated in experimentation, yet it is in these poorest regions where medical experimentation- led solutions could bring the greatest impact to high rates of early mortality. Without clinical trials, it is impossible to determine if the new medicines developed by the researchers are effective or safe, or if a diagnostic test or treatment works properly in a medical practice in humans.

Ensuring subject safety is an essential requirement for clinical trial. The participation of subjects in clinical trial is crucial to the development of a new drug or device and in better understanding how to treat the disease. A balance should be maintained between medical experimentation and clinical trial subject safety. There are some common rules regarding the clinical trials that help to ensure the balance between clinical trial and subject safety.

1.2 RESEARCH PROBLEM

There are various issues such as human rights violations, legal, and ethical issues relating to the conduct of clinical trials. Even though there are many International and National legal framework related to the conduct of clinical trials, violations do happen. Indian legal framework related to clinical trials do tackle many of the issues, however a much more structured and comprehensive legislation is required.

1.3 RESEARCH OBJECTIVES

- To understand the concept and development of clinical trials
- To study the ethical and legal issues related to clinical trials
- To examine the International legal regulations relating to clinical trials

- To understand the Indian perspective on regulations on clinical trials
- To provide suggestions for the issues involved in existing legislations on clinical trials.

1.4 RESEARCH QUESTIONS

- What are the legal issues related to clinical trials?
- What all are the international legal framework for clinical trials?
- Are there adequate international legal frameworks available to tackle the ethical and legal issues related to clinical trials?
- What is the legal framework in India?
- Did the New Drugs and Clinical Trial Rules, 2019, solve the ambiguities and issues relating to Clinical Trials in India to a considerable extent?
- Even after enacting the New Drugs and Clinical Trials Rules, 2019, what other concerns need to be addressed to resolve the existing uncertainties and issues connected to Clinical Trials in India?
- What is the approach of the judiciary towards the conduct of Clinical Trials in India?
- What are the suggestions for tackling the problems involving existing regulations on clinical trials?

1.5 HYPOTHESIS

Clinical trials are important for the development of new medicine, treatment or medical device. There are many internationally and nationally recognized and applicable laws and codes with respect to medical experimentation and clinical trials. However, a much more structured and comprehensive legislation relating to Clinical Trials should be enacted to ensure maximum benefit to the patients and also to address the ethical and legal issues relating to Clinical Trials in India.

1.6 METHODOLOGY

The research methodology used in this work is doctrinal legal research as a means to establish the hypothesis in the best suitable way.

1.7 LITERATURE REVIEW

The research has depended on the primary sources including the Constitution of India, WHO constitution, various legislations, executive orders, judgements of Supreme Court and High Courts, International treaties etc. The research has also used secondary resources like books, commentaries for the proper understanding of the subject and analysing the various topics. The research has extensively depended the electronic resources like online databases, websites for gathering resources.

- Patricia M. Tereskerz, 2012 Clinical Research and the Law, pp.33-57.

  This Book comprehensively discusses the topics: standards and duty of care, informed consent, conflicts of interest, research contracts, establishing clinical trials and the disclosure and withholding of clinical trial results. It also provides the answers to many legal questions and potential pitfalls encountered in clinical research.

- Ahmad W, Moeen Al-Sayed (2018) Human subjects in clinical trials: Ethical considerations and concerns. *J Transl Sci* 4

  This article discusses offering incentives for potential subjects and staff who all help in recruiting the research subjects. It also deals with ethical concerns and considerations related to recruiting human subjects in Clinical Trials. Recruitment and retention of the research participants are crucial for clinical trials and medical advancement. And also highlights the ethical issues related to vulnerable groups in clinical trials

- Terwindt, C. (2014). Health Rights Litigation Pushes for Accountability in Clinical Trials in India. *Health and Human Rights*, 16(2), 84-95.

  This article highlights the proceedings before the Indian Supreme Court, which addresses the lack of protection of trial subjects in Clinical Trials.

This article also highlights the 2009 HPV (human papilloma virus) vaccination program was then reviewed to investigate the allegations of informed consent irregularities and inadequate monitoring.

- Aguilera B, DeGrazia D, Rid A Regulating international clinical research: an ethical framework for policy-makers *BMJ Global Health* 2020;

  This article discusses shifting global distribution of clinical trials to low-income and middle-income countries. It also deals with the importance of adequate regulations for protecting the rights and interests of the research participants in clinical trials in these countries. This article proposes a three-step ethical framework which helps policy-makers to navigate this trade-off.

1.8 CHAPTERISATION

- CHAPTER 1 – INTRODUCTION

  This chapter gives a brief idea about the research work by explaining what the research is about and the relevance of the topic. It provides the research questions and the hypothesis of the research. The chapter also says about the method used for research and gives a brief account about the literature used for research.

- CHAPTER 2- DEFINITION AND CONCEPT OF CLINICAL TRIAL

  This Chapter illustrates the definition, concept and clinical trial process. This chapter elaborates upon the various definitions given by the international and national bodies and legislations relating to Clinical Trials. Also explains the concept of clinical trials, then this chapter detail explained all the process involved in a clinical trial and different categorization of clinical trials.

- CHAPTER 3: CHALLENGES IN CONDUCTING CLINICAL TRIALS: LEGAL AND ETHICAL ASPECTS

  This chapter deals with the various issues such as human right issues, legal and ethical issues related to clinical trials and some examples of unethical clinical trials and judicial interventions.

- CHAPTER 4: INTERNATIONAL LEGAL FRAMEWORK ON CLINICAL TRIAL

  This chapter discusses the various international regulations, guidelines and legislations dealing with clinical trials. It gives an overview of the international guidelines, international codes, and code of ethics, international bodies and the related legislations relating to the conduct of clinical trials.

- CHAPTER 5: LEGISLATIONS ON CLINICAL TRIAL: INDIAN PERSPECTIVE

  This chapter begins with a presentation of the Indian controlling oversight system for the governance of clinical trials. This chapter gives an overview of the national guidelines, code of ethics, regulatory bodies and the related legislations relating to the conduct of clinical trials in India. This chapter discuss the establishment of controlling bodies in India. Chapter also discuss the recent controlling instructions issued by CDSCO which is supreme controlling authority in India for clinical experimentation and trails.

- CHAPTER 6- CONCLUSION AND SUGGESTIONS

  The chapter says about conclusions arrived from the research and suggestion made for the tacking the problems involving existing legislations on clinical trials nationally and internationally.

CHAPTER 2

CONCEPT AND DEFINITION OF CLINICAL TRIAL

2.1 INTRODUCTION

Advancement in medical science is the outcome of various research activities undertaken in the field. This involved development of new drugs, technologies, new methods of treatment, etc. Several decades ago, it was almost impossible to even imagine the progress that we have seen today in research. Research in medical science helps understand disease pathology, develop new management strategies and to serve humanity in a proper manner ensuring that no harm is caused to the research participants. Medical research or experimental research involves experiments in animals, cells, physiological, biochemical and genetic investigations, including the study of various properties of drugs and other materials. It involves research studies which are primarily designed to increase the scientific knowledge of diseases and disease conditions (both physical and behavioral), its detection, cause, effect and strategies to promote, prevent or ameliorate the disease. And medical research on human subjects includes research on identifiable human material or data.

Clinical Trials on human subjects as a practice is fairly established and it does provide a beneficial service for millions of people who partake in the successfully approved products, may it be drugs, different drug delivery systems, medical devices, instruments or varied therapies and related technologies. Human experimentation is usually broadly defined as anything done to a person to study and examine how it will affect him. Clinical trials are a kind of research studying new tests and treatments and evaluating their effects and consequences on human body and health outcomes. It involves human participants and people volunteer to take part in clinical trials to test new medical interventions which include drugs, cells and other biological products, surgical procedures, radiological procedures, devices, behavioral treatments and preventive care. Clinical experiments are carefully

designed, reviewed and completed, and have to be approved by the concerned authorities before it can be started. People can take part in clinical trials irrespective of their age, including children depending on the nature and objective of the study. Clinical trials are the primary way to assess the effects of a new drug or medical intervention in humans and find out if it is effective and safe on them.

2.2 CONCEPT OF CLINICAL TRIALS

We have cold many times in our life, We all know the annoying symptoms that we sometimes feel when we have a cold such asa stuffy nose, sore throat, and body aches. Do everybody use medication or other treatments when they get a cold? Most people do seek relief from the symptoms of a cold with some sort of treatment to help them feel better. How do they know which treatments work? We can thank clinical trials for this knowledge.

Researchers use clinical trials to test out recent treatment options. Clinical trials help researchers understand which treatments work and the risks that may be associated with their use. Human clinical trials test these potential treatments on human beingswho agree to participate in the experimentation. There are five phases of human clinical trials. The earliest phases of human clinical trials usually focus on potential side effects of a given treatment while later phases aim to assess efficacy of the recent treatment compared to current treatment options.
Not all phases of a human clinical trial will necessarily be carried out if a potential treatment presents unexpected outcomes.

In a clinical trial, subjects receive a definite intervention according to the plan or protocol of the experiment created by the investigators. These interventions can be anything including medical products, such as medicines or devices; procedures; or changes to participants' behavior, such as diet. In clinical trials, the new medical approach may be compared to a standard one already available that contains no active ingredients, or contains no intervention. Some clinical trials compare interventions that are already available to each other. When a new medical product or approach is being studied, it is often unknown whether it will be harmful, helpful or no different than existing alternatives (including no intervention). Principle

investigators try to ensure the safety and efficacy of the intervention by measuring the result or certain outcomes in the participants. For example, investigators may give a medicine or treatment to participants who have high blood pressure in order to see whether their blood pressure decreases[1].

2.3 RELEVANCE OF CLINICAL TRIALS

There is no doubt that any activity which reforms human welfare or public health is ethically valid, particularly if it promotes a fundamental human right –the right to live. Medicinal product and treatments which enhance the life span and protect the vulnerable from disease is undoubtedly the best request of this right. The development of new medicines and conducting clinical trials to test such advances in medicine are essential. Medical experimentation and trials address a considerable burden of life-threatening diseases that can take away life quickly, specifically those in developing countries. However, the practical benefits which come from these trials may not be good enough. And though the trials in medicine help people in the long run, they can indirectly ignore other human rights.

The main purpose of the clinical trial is to develop generalizable knowledge that improves human physical health or increases understanding of human biology. People who participate in clinical trials make it possible to secure that knowledge. The path to finding out if a recent medicine or treatment is effective or safe, for example, it is to test on patient volunteers, but by placing some people at risk of harm for the good of others, a clinical trial can exploit patient volunteers. Conducting the clinical trials in developing countries is often presents significant ethical, organizational, cultural, and infrastructural challenges to researchers, pharmaceutical companies, sponsors, and controlling bodies. The purpose of the ethical instructions is both to protect patient volunteers and to preserve the integrity of the science.

Behind every and drugs and intervention that people have ever taken there are thousands of participants who have been volunteered to participate in the clinical trials, which have lead the way to many breakthroughs in treatment and disease

[1] Understanding Clinical Trials | Bascom Palmer Eye Institute https://umiamihealth.org/en/bascom-palmer-eye-institute/clinical-trials/understanding-clinical-trials (last visited on September 2nd, 2021)

prevention in the last half-century. Without their willingness, many people would have suffered. And also it is important to note that the clinical experimentation is not always devoted to finding the next blockbuster medicine. Clinical trials also can contribute invaluable statistics about the benefits and safety of existing therapies, providing doctors and patients with reliable statistics for choosing between alternative treatments".[2]

Diagnostic and treatments need to be thoroughly tested in clinical trials to ensure that the benefits outweigh any risks associated with the intervention. In this context: Benefit means any positive effect on the patient survival, quality of life, and physical health outcomes, and Risks means fully understanding any negative impact on individuals and groups of patients.

Clinical trials aim to understand what offers the most significant benefit to the patient with minimum risk. Both benefit and risk are carefully considered in clinical trials. Therefore, a clinical trial must be carried out in a controlled, methodical way so that scientists and doctors can carefully observe the effect of the diagnostic and treatment being tested on patients; thus, a clinical trial advances medical knowledge to benefit future patients potentially.

Generally, clinical trials are designed to improve the medical knowledge related to the treatment, diagnosis, and prevention of illness or health conditions. Some of the important reasons for conducting the clinical trials are as follows:

- To examine interventions one or more (for example, medicines, medical devices, approaches to surgery, or radiation therapy) to treat a disease, syndrome, or condition.
- Discovering ways or finding alternatives to prevent the initial development or recurrence of a disease or condition. These may include medicines, vaccines, or lifestyle changes, among other approaches.
- Assessing one or more interventions that are aimed at identifying or diagnosing a particular disease or condition
- Analyzing new methods for identifying a condition or the risk factors for that condition
- Scrutinizing and measuring new methods to improve the quality of life and

[2]The Importance of Clinical Trials – Policy & Medicine. https://www.policymed.com/2010/05/the-importance-of-clinical-trials.html

comfort through supportive care for people with a chronic disease.[3]

2.4 TYPES OF CLINICAL TRIAL

Clinical trials cover a wide range of different types of experimentation. Trials are often used to test recent medicines or vaccines but can also be used to look at recent combinations of existing treatments or to test whether giving a treatment differently will make it more effective and also reduce any side effects. Clinical trials can also be categorized according to their objectives, like prevention trials, treatment trials or diagnostic and screening trials. Some of the different types of Clinical Trials and their description are as follows; [4]

- *Treatment Trials*

  Treatment trials, also known as interventional trials are clinical trials that set out to test treatments or combinations of treatments that have not yet been officially approved.

- *Prevention Trials*

  Prevention trials means clinical trials which involve tests to find ways to prevent a specific medical condition or, to prevent them from reoccurring for people have them already. The emphasis of this analysis might be on medicines, vitamins, and minerals, or lifestyle changes. Prevention experimentation looks for better ways to prevent disorders from developing or returning. This type of trial determines the recent approaches for preventing or lowering the risk of developing a particular disease. This also involve healthy people who have not had that specific disease, yet may have a higher risk of developing that disease.

- *Observational Trials*

  This is a type of Clinical Trials in which individuals are observed, or certain

[3] Learn About Clinical Studies - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/about-studies/learn (last visited September 2nd 2021)
[4] Clinical Trials: Read About Types, Phases, Pros & Cons. https://www.medicinenet.com/clinical_trials/article.htm (last visited on September 2nd, 2021)

outcomes will be measured. No attempt will be made to affect the outcome (for example, no treatment is given). Observational trials investigate physical health issues in larger group of people. The participants in these kind of trials do not receive any treatment but they may be asked to provide statistics, blood samples. Researchers observe participants by monitoring their physical health over a period of time.

- *Diagnostic & Screening Trials*

  Diagnostic and screening trials aim to find recent ways to diagnose and detect medical conditions (e.g. a more effective procedure, a better test or a more sophisticated tool). The diagnostic trial is research tests or procedures that could use to identify a disease more accurately. Diagnostic trials includes people who have signs or symptoms of a disease. The purpose of the diagnostic test is to establish the presence or the absence of disease as a fundamental for treatment decisions in symptomatic or screen positive individuals (confirmatory test). The primary purpose of these screening tests is to detect early disease or to detect any risk factors for the disease in large numbers of apparently healthy individuals. These trials will be testing the best ways to find the disease at its earliest stage so that hopefully, the chances of the cure are higher, and the amount of treatment needed will be less.[5]

Clinical trials can also classify according to if they are considered therapeutic or non-therapeutic.

- *Therapeutic Trial*

  Therapeutic trials are the type of clinical trials which enroll patients and provide a specific treatment to them to research its impact on the disease. Within these therapeutic trials, there are three different phases used to evaluate recent treatments:

  - Phase I analysis is the most basic of clinical trials. The evaluation of medication dosages and frequency of medicine administration to

[5] Types of clinical trials - Clinical trials - Understanding. https://www.alzheimer-europe.org/Research/Understanding-dementia-research/Clinical-trials/Types-of-clinical-trials (last visited on September 2nd, 2021)

determine the Maximum Tolerated Dosages (MTD). The enrollment of patients in this phase with a variety of diseases is essential to the research to determine the effectiveness. Drugs are given at a gradually increasing dosages until there are unacceptable side effects that is dose-limited toxicities (DLT)

- Phase II analysis uses the results from Phase I research regarding these MTD and DLT. The treatment in this phase targets a population of patients who responded most favorably in Phase I trials.

- Phase III analyses are those that most children will receive when newly diagnosed. This analysis will test the standard treatment which is best in the current situation against the promising alternatives which may increase cure rates or decrease side effects or late effects of treatment.[6]

➢ *Non-therapeutic Trial:*

Non-therapeutic trials do not give patients treatment but instead the essential research factors that help advance understanding disease and its impact. Both therapeutic and non-therapeutic clinical trials can be classified in different types, such as randomized trials, blind trials, add-on analysis, open-label trials, or randomized, double-blind placebo-controlled trials. Each type of trial listed above provides data about how the trial is conducted, which may have consequences for the subjects (mainly regarding the inclusion of a placebo group that is relatively common). A brief introduction of some of these terms is presented below:[7]

- *Randomized controlled trials*

  A randomized controlled trial (RCT) is a trial where the subjects are randomly allocated to different treatments. The selection of the group is usually done by a computer and is called randomization. If the participant agree to take part in this type of trial, neither the participant nor the doctor will be able to choose which treatment you are given.

[6] Types of Clinical Trials | Cure Search. https://curesearch.org/Types-of-Clinical-Trials (last visited September 2nd, 2021)
[7] What is non therapeutic research? https://findanyanswer.com/what-is-non-therapeutic-research (last visited September 2nd, 2021)

Specific details about the subjects (for example age, gender or the stage of disease) are put into the computer first. This is to make sure the different groups in a trial are as similar as possible. There are often more than two groups in the trial. Each group is followed up at specific times to see how effective the treatments are.[8]

- *Placebos Trials*

  A placebo is an inactive treatment, sometimes it called as a 'sugar pill. 'In fact, a placebo may be in a pill or in a tablet form. It may be an injection or may be a medical device. Whatever the form, placebos often look like the real medical treatment that is being studied, but they do not contain the active medication. Before they are started, all clinical experimentation programs, including those that involve placebos, are reviewed and approved by an ethical review board. Using a placebo means can measure the effect of the recent medicine much more accurately. Sometimes, people appear to do the better just because they are involved in a trial, even if they are not given the recent medicine. It's not known why this occurs. It may be because they are monitored more closely or because they or their doctor are optimistic about the benefit of the recent treatment. Placebo Trials are not used in clinical trials where patients have life-threatening illnesses, and a proven treatment exists. Even for diseases where treatments are available, some instances might require a placebo. Placebos are also not used in experimentation analysis to harm volunteers if they do not receive real medical treatment for their condition.[9]

- *Blind trials*

  A blind trial is the trial in which the people taking part don't know which treatment they are getting. They could be getting the recent treatment, they could be getting standard treatment or a placebo, which is

[8] Randomized Controlled Trials | Nurse Key. https://nursekey.com/randomised-controlled-trials/ (last visited September 2nd, 2021)
[9] What is a Placebo - University of California, Davis. https://health.ucdavis.edu/ctsc/area/clinicaltrials/documents/What-is-a-Placebo.pdf (last visited September 2nd, 2021)

depending on the design of the trial. All patients may receive identical injections or tablets, so they can't tell which treatment they are having.

- *Double blind trials*

  A double-blind trial is a trial in which neither the researchers nor the patients know what trials they are getting. The computer will give each patient a code number, and this code numbers are then assigned to the treatment groups. The patient's treatment arrives with their code number on it. Neither they nor their doctor knows whether it is the recent treatment or not. The list of participants and their code numbers is kept secret until the end of the trial. In an emergency, the researchers could determine which trial group a patient was in, but generally, no one knew until the trial had finished. Double-blind trials help to eliminate any biased results.

- *Comparative Clinical Trials*

  Comparative Trials, also known as controlled clinical trials, involve one group of patients who receive the recent medicine and a control group who receive a placebo or gold standard treatment. Comparative analyses are typically carried out as double-blind trials, where neither the physician nor the patient knows which group is receiving the recent medicine.

- *Open Label Clinical Trials*

  Open Label clinical trials do not attempt to disguise the recent medicine or treatment, meaning that no standard treatment or placebo is utilized. This leans towards bias, as both the patient and the physician are aware of which groups are receiving what typeof treatment.

2. 5 DEFINITION OF CLINICAL TRIALS

The United Nations' (UN) specialized agency of, The World Health Organization (WHO) that is concerned with international public physical health. It defines the clinical trial as[10]

"Clinical trials are a type of research that studies new tests and treatments and evaluates their effects on human health outcomes. People volunteer to take part in clinical trials to test medical interventions including drugs, cells and other biological products, surgical procedures, radiological procedures, devices, behavioural treatments and preventive care. Clinical trials are carefully designed, reviewed and completed, and need to be approved before they can start. People of all ages can take part in clinical trials, including children."

The definition of Clinical Trials by WHO defines clinical trial as it is any experimentation research that prospectively assigns all human participants or groups of humans to one or more physical health related interventions to evaluate the effects on physical health outcomes. Clinical trial interventions are include but not restricted to: Experimental medicines, Cells and other biological products, surgical procedures and radiological procedures, Medical devices, Behavioural treatments, Process of care Preventive care, etc. Researchers may also conduct the clinical trials to evaluate diagnostic or screening tests and recent ways to detect and treat disease.

This definition of WHO also includes Phase I to Phase IV trials.

- *"Phase I studies usually test new drugs for the first time in a small group of people to evaluate a safe dosage range and identify side effects.*
- *Phase II studies test treatments that have been found to be safe in phase I but now need a larger group of human subjects to monitor for any adverse effects.*
- *Phase III studies are conducted on larger populations and in different regions and countries, and are often the step right before a new treatment is approved.*
- *Phase IV studies take place after country approval and there is a need for further testing in a wide population over a longer timeframe.[11]"*

[10] Definition of clinical trials, WHO, Available at http://www.who.int/topics/clinical_trials/en/, (last visited September 2nd, 2021)
[11] *Ibid.*

In India Clinical Trials is defined under New Drugs and Clinical trials Rules, 2019 is a response to the Supreme Court Orders under *Swasthya Adhikar Manch v Union of India*[12] and various unethical trials in the country. The Ministry of Health and Family Welfare inserted new rule, Rule 122 DAA in Drugs and Cosmetics Rules, 1945, after Rule 122DA

"122 DAA Non-application of certain rules new drugs and investigational new drugs for human use.- Part XA and Schedule Y shall not be applicable in respect of new drugs and investigational new drugs for human use from the date of coming into force of the New Drugs and Clinical Trials Rules, 2019, and the references in respect of human use made in the these rules shall respectively be omitted, and the construction thereof shall be construed accordingly and shall stand amended with all cogent meaning of the grammar"[13]

This new regulations cover provision for promoting clinical research. Under Rule 2(j) it defines Clinical trials as

""clinical trial" in relation to a new drug or investigational new drug means, any systematic study of such new drug or investigational new drug in human subjects to generate data for discovering or verifying its,-

(i) Clinical or;

(ii) Pharmacological, including pharmacodynamics, pharmacokinetics or;

(iii) Adverse effects,

With the objective of determining the safety, efficacy or tolerance of such new drug or investigational new drug;"[14]

"New Drug" is defined under Rule 2(w) as,

i. a drug, including active pharmaceutical ingredient or phytopharmaceutical drug, which has not been used in the country to any significant extent, except in accordance with the provisions of the Act and the rules made thereunder, as per conditions specified in the labelling thereof and has not been approved as safe and

[12] W. P. (Civil) No. 33 of 2012.
[13] Rule 122 DAA, Drugs and Cosmetics Rules, 1945
[14] Rule 2(j) New Drugs and Clinical Trials Rules,2019

efficacious by the Central Licensing Authority with respect to its claims; or

ii. a drug approved by the Central Licensing Authority for certain claims and proposed to be marketed with modified or new claims including indication, route of administration, dosage and dosage form; or

iii. a fixed dose combination of two or more drugs, approved separately for certain claims and proposed to be combined for the first time in a fixed ratio, or where the ratio of ingredients in an approved combination is proposed to be changed with certain claims including indication, route of administration, dosage and dosage form; or

iv. a modified or sustained release form of a drug or novel drug delivery system of any drug approved by the Central Licensing Authority; or

v. a vaccine, recombinant Deoxyribonucleic Acid (r-DNA) derived product, living modified organism, monoclonal anti-body, stem cell derived product, gene therapeutic product or xenografts, intended to be used as drug;[15]

Also in the first schedule of the New DCT Rules, 2019, it deals with enumerates the general principles and practices for clinical trials, in 3(2) states the phases of Clinical Trials[16] Pharmaceutical research on humans is often described in terms of four phases. Phase I trials usually have non-therapeutic objectives and are conducted on a small number of health volunteers and are conducted to test the toxicity or dose of new drugs. Phase II trials are designed to explore the short-term toxicity and therapeutic efficacy of a product on a small group of patients who are suffering from the condition in question. Hence, this is the phase where it is normally administered to patients, but in small numbers. Phase III trials are designed to confirm any therapeutic benefit suggested by a Phase II trial. It usually involves monitoring the effects of supervised use of the product in patients over a long period of time and are usually randomized controlled trial, where one group of participants will receive a different treatment or procedure to the others. A successful phase III study is

[15] Rule 2(w) New Drugs and Clinical trials Rules, 2019
https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/NewDrugs_CTRules_2019.pdf (last visited September 2nd, 2021)
[16] First Schedule 3(2) New Drugs and Clinical Trials Rules, 2019

intended to provide support for obtaining authorization to market the product. After the drug is authorized for use, further studies could be conducted which are referred to as Phase IV trials. These trials go beyond the prior administration of the drug's safety, efficacy and dose definition. Such post marketing monitoring studies are in theory about optimizing the use of the product. But in practice, manufacturers often see such studies as a form of post marketing advertising.

2.6 CLINICAL TRIALS AND HUMAN RIGHTS

Health is deemed our most fundamental asset despite our age, gender, socio-economic, cultural, or ethnic background. When we take the term, 'well-being' no doubt it is healthy, and illness free environment is what we have in our minds. 'Health right' is regarded as the fundamental or essential human right that is consequential for the exercise of other human rights. The right to health, at the least it holds a meaning, a right to certain conditions or facilities which could protect the health of the population. It also encompasses civil and political rights concerning the availability and accessibility of public-based and individual-based health care services. Further, this right includes the invention and manufacturing of new drugs, testing their efficacy, developing new treatment methods and protocols. Therefore, it can safely assumed that clinical trials forms an integral part to secure right to health of the people.

However, clinical trials have not been free from unethical practices that violate the human rights of volunteers. It is clear that clinical trials are fraught with human rights violations, as well as ethical and legal issues.[17]

Human dignity and the integration of the common standards adopted into a human rights framework. All humans are born free, with the same dignity and rights. Every person has the right to life, liberty, and personal security. No one shall be tortured or subjected to cruel, inhumane, or degrading treatment. Certain historical experiences of clinical research upon human subjects like Dachau Hypothermia Study, were unethical and categorically involved torturous, degrading treatment of

[17] Issues & Concerns in Conducting Clinical Trials in India. https://www.pharmafocusasia.com/clinical-trials/issues-concerns-conducting-clinical-trials (last visited September 4th, 2021)

subjects who were by no means participating willingly. Such experiments are in gross violation of human rights. However, it should be recognized that the dignity alone cannot provide a concrete solution to most challenges raised by scientific advances. This can enable to see more clearly why the concept of dignity normally operates through other more concrete notions, like informed consent, bodily integrity, non-discrimination, privacy, confidentiality, and equity, which are usually formulated in rights terminology.[18]

Informed consent is an important concept in a clinical trials involving human participants. Informed consent process protects the individual's autonomy to freely choose whether or not to participate in the research. This basically brings out the most important right of a research participant, to decide voluntarily whether to participate in a particular research study once he is made aware of all the aspects of the research. Every human who is an adult and with sound mind has the right to decide what shall be done with his own body. To take an effective decision, one needs to be aware about the nature, terms, duration, effects and various other aspects of the research study. Informed consent upholds the right to be respected, right to be informed as well as right to voluntarily participate or withdraw from the research.[19]

Vulnerable persons are those individuals who are relatively or absolutely incapable of protecting their own interests because of personal disability; environmental burdens; social injustice; lack of power, understanding or ability to communicate or are in a situation that involving vulnerable groups and individuals. They might have an increased likelihood of incurring additional harm as they may be relatively or absolutely incapable of protecting their own interests. Several characteristics like legal status, clinical conditions, etc. make individuals vulnerable. Examples include children, individuals with cognitive impairment, unconsciousness, economically or socially disadvantaged people, etc. Principles state that vulnerable groups should be included in the research only when the research is directly answering the health needs or requirements of the group. Researchers must keep full and complete research records, including data and notes. Records should be kept for some

[18] Article 1 The Universal Declaration of Human Rights(UDHR)
[19] Meisel A, Kuczewski M: Legal and ethical myths about informed consent. Arch Intern Med 156, 2521-26, 1996.

reasonable period required for post-research monitoring, research assessment, further study (whether by the original researcher or otherwise). While interviewing participants, protection of privacy and confidentiality, specifically related to identity and records, is expressly required.[20]

Privacy and confidentiality, Researchers need the participant's written permission or consent, or someone allowed on their behalf, to reveal individual participant data. Principles which protect the privacy of patients include the principle of informed consent, the principle of privacy and confidentiality, the principle of accountability and transparency and compliance and Principle of informed Consent Investigators must receive informed consent for all scientific research involving human subjects in a document which is known as the Informed Consent Form with Participant / Patient Information Sheet. In a clear and easily understandable way, researchers have to provide sufficient details about the work.[21]

Equity in the selection of subjects: Researchers should exhibit fairness in the selection process of research subjects, such that they should not lure the subjects by offering potentially beneficial research only to some patients who are in the dire need or select only undesirable persons for risky research. The injustice arises from social, racial, sexual, and cultural biases institutionalized in society. The economically disadvantaged, racial minorities, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability, ease of manipulation, and compromised position to exercise informed consent.[22]

These are some examples of human rights related to clinical trials. In order to tackle, regulate and control the above mentioned issues, there are many national and international legislations, regulations and guidelines concerning the conduct of clinical trials.

[20] INDIAN COUNCIL OF MEDICAL RESEARCH, National Ethical Guidelines for Biomedical and Health Research involving Human Participants, 1.1, (2017)
[21] Ethical Guidelines for Biomedical Research on Human Subjects, General Ethical Issues, P. 29 (2006), Indian Council of Medical Research New Delhi.
[22] UNITED STATES (1978), THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH, [Bethesda, Md.], The Commission.

2.7 ISSUES CONCERNING THE CONDUCT OF CLINICAL TRIALS

Despite the benefit or value of clinical trials, such studies are susceptible to ethical and human rights violations. Various ethical and technical guidelines were formulated out under international and national level of a need to ensure the rights of research participants and communities. All through the evolution of the practice of health research on human subjects issues of violation of rights have arisen with dire consequences. A few examples are as follows

- The Willowbrook State Study to know the natural course of infectious hepatitis in children, in willowbrook state school in 1955. The institution was a place for care of physically and mentally challenged children and had a history of infectious disease outbreaks including Hepatitis A. The study proceeded to artificially infect newly admitted children. The researchers tried to justify38, the same by citing the informed consent obtained from the parents of the children and stating even without the artificial infection, the children would have contracted the disease. There can be no justification for intentionally causing harm, for sake of science no matter the importance of the knowledge attained.
- Guatemala syphilis experiment: During the US syphilis experiment in Guatemala[23] from 1946 to 1953, experiments were performed on over 5,500 Guatemalan prisoners, soldiers, sex workers, psychiatric patients, and children about one-quarter of whom which were deliberately infected with syphilis, chancroid or gonorrhoea and all of whom were enrolled in the experiments without their consent. It was later admitted as an unethical study.
- In 1996, the pharmaceutical company Pfizer tested a new drug, Trovan, on a group of young children in Nigeria. Like the case with many clinical trials, the children were divided into two groups, one is receiving the drug Trovan and the other one is a moderate dose of Ceftriaxone (a proven effective drug available at the same clinic). The negative side effects of the drug Trovan were not detected by the staff at their clinic administering the drug. As a result, children whose health deteriorated or did not improve while on

[23] Rogers, Kara, "Guatemala syphilis study", Britannica

Trovan were not moved to an alternative medication. Long-term brain damage and six fatalities were among the terrible outcomes. The affected children approached US Court in Adullahi v. Pfizer[24] under the Alien Tort Statute. This matter was settled out of court for 75 million US dollars.

- In the early 2000s Merck and GlaxoSmithKline tested two vaccines for HPV aimed at prevention of HPV variant causing cervical cancer in girls and women. The led by an organization named PATH was found to have vaccinated school girls in Andhra and Gujarat, without obtaining proper informed consent and other lapses. The Supreme Court halted the research and declared the issue of uncontrolled drug trials on humans by international corporations to be "havoc" in the country, claiming that the government had fallen into "deep slumber" in dealing with this "threat."[25]
- In India, during the 1970s and 1980s, there was a research study conducted in Delhi on 1158 women patients of cervical dysplasia or precancerous lesions of the cervix. These patients were not given any treatment to find out how many lesions progressed to cancer and how many regressed. Seventy-one women had developed malignancies while some had progressed to invasive cancer and they were treated only after they developed localized cancer. This created huge controversies in 1997 which made the ICMR to start developing the guidelines.[26]
- One of the recent alleged unethical trials included allegations that no consent has been obtained from the participants for Covid-19 vaccine trials in Bhopal, who also happened to be Bhopal Gas Tragedy victims. They also state that there was no follow up on their health after the vaccine administration.[27]

[24] 562 F.3d 163 (2d Cir. 2009)
[25] Mills, Edward J, and Sonal Singh. "Health, human rights, and the conduct of clinical research within oppressed populations." Globalization and health vol. 3 10. 8 Nov. 2007, doi:10.1186/1744-8603-3-10
[26] J. Sanmukhani, et.al. Ethics in Clinical Research: The Indian Perspective, 73(2) IJPS (2011 Mar-Apr), 125-130.
[27] No consent, no follow-up claim Bhopal gas tragedy victims in vaccine trial, THE ECONOMIC TIMES (Jan. 10, 2021), https://economictimes.indiatimes.com/news/politics-and-nation/no-consent-no-follow-up-claim-bhopal-gas-tragedy-victims-in-vaccine-trial/articleshow/80200879.cms?from=mdr. 23 Presentation by Dan McDonald, vice president, business development, (last visited October 6, 2021)

Controversial Clinical trials at AIIMS:

AIIMS administration, while responding to the RTI, admitted that out of 4142 enrolments, 2728 babies were below the age of one year, and 49 have died since 2006. In its reply, AIIMS said the deaths amounted to a 1.18% mortality rate. The RTI query was filed by Rahul Verma of Uday Foundation for Congenital Defects and Rare Blood Groups, an NGO.[28]

AIIMS has said five foreign manufacturing medicines were tested during the trials. They were zinc tablets for treating zinc deficiency and serving as a nutritional supplement, olmesartan and valsartan for blood pressure-related problems, rituximab for treating chronic focal encephalitis, and gene-activated human glucocerebrosidase for treating Gaucher's disease, which affects the liver. AIIMS said it had taken clearance for the trials from that's own ethics committee, the Health Ministry Steering Committee (HMSC) on ethics, and ICMR and DBT, national ethics committees.

With most patients in AIIMS being illiterate and extremely low-income families, doubt exists if they even understand what is mean by clinical trial and what their children are being subjected to.

The treating physician read out a consent form that has to be filled by parents for parents who were not able to read it themselves. The question is if the parents can't read or write, do you expect them to understand the implications of these trials.[29]

In India, lot of instances of unethical and illegal trials have been brought to the limelight between the infamous clinical trials on precancerous cervical lesions on about 2250 women in the late 80s (where took no ethical committee acquiescence and the suspension of the clinical trials in July 2004 of the anti-diabetes medicine ragaglitazar being carried out by the Danish multinational, Nova Nordisk after the discovery of urinary bladder tumor in mice the medicine having undergone preclinical and some preliminary toxicology analysis) but not completing the long term toxicological analysis before initiation of human clinical trials as required in

[28] 49 babies die during clinical trials at AIIMS | India News.... https://timesofindia.indiatimes.com/india/49-babies-die-during-clinical-trials-at-AIIMS/articleshow/3374492.cms

[29] Kounteya Sinha, 49 babies die during clinical trials at AIIMS, Aug 18, 2008.

case of anti-diabetes medicine.

HPV Vaccine Case:

In the year 2009, the States of Andhra Pradesh and Gujarat has launched an experimentation project for vaccination against the human papilloma virus (HPV) can cause cervical cancer. "Teenage girls between the ages of 10 – 14 from States of Andhra Pradesh and Gujarat were to be vaccinated. GlaxoSmithKline and Merck provided the vaccines. Received PATH designed and executed the project (Program for Appropriate Technology in Health) and funding from the Bill & Melinda Gates Foundation".

Gardasil vaccine was administered to 16000 individuals in Andhra Pradesh. Within one month of receiving the vaccine, many of the children who received the vaccine fell ill, and also by 2010, five of them had died. Then another two children were reported to have died in Vadodara, Gujarat, were vaccinated another 14,000 tribal children with another brand of the HPV vaccine, Cervarix, manufactured by GlaxoSmithKline (GSK), (they are incidentally, has been accused of the dumping polio virus into a Belgium river.)

Consent forms to administer of the HPV vaccine were 'illegally' signed by wardens form youth hostels, showing that the Gates' prey on the indigent without parents. Most were illiterate for those who had parents, and the true potential dangers of the vaccines were not explained to them. In April 2010, although, the Government of India suspended the program as many violations of ethical standards by PATH were largely reported by human rights organizations and NGO's. Although, by that time, 24,000 girls were already vaccinated.[30]

In the year 2011, a parliamentary enquiry committee found that the process of informed assent was inadequate (especially questioning fact that the school head masters signed assent forms on behalf of the children, calling it wrongful authorization). Informed assent is the process in which trial volunteers are informed about the nature, significance, implications, and risks. Informed assent is crucial to protect people from unwanted experimentation. In the absence of personal physical

[30] CASE SUMMARY.
https://www.ecchr.eu/fileadmin/Fallbeschreibungen/Case_Summary__Clinical_Trials__2014-02-11.pdf

injury, The Article 7 of the International Covenant on Civil and Political Rights (ICCPR) states that a lack of informed assent constitutes a human rights violation: No one shall be subjected cruel, inhuman or degrading treatment, punishment or torture. So in specific, no one shall be subjected without his free assent to medical or scientific experimentation and Clinical Trials. The parliamentary committee then criticized that the monitoring system did not report all the adverse events. Monitoring of clinical trials is, however, important to identify the injuries and to respond adequately. This project was apparently intended to benefit the Indian population, then in August 2013, a second parliamentary committee severely faulted PATH as it concluded that "*Its main purpose has been to promote the economic interests of HPV vaccine producers, who would have earned windfall profits had PATH succeeded in getting the HPV vaccination included in the country's UIP [universal immunization programme]"*[31]

Seeking a decision by the Judiciary on the liability of the trial sponsors and manufacturers of the vaccines

A judicial decision was the need of the hour on the liability of the trial sponsors and manufacturers of the vaccines. Women's physical health activists decided to take the case in to the Court and then in January 2013 they filed public interest petition (PIL) at the Supreme Court of India alleging-[32]

> *"The girls were not informed about the vaccine's nature or purpose. The girls were unaware of the location of the cervix, which had not been mentioned to them. The girls were under the impression that the immunization was being given by the government. Vaccination was seen as obligatory by many young women. They were not told of any potential vaccination negative effects."*

On January 7, 2013, the Supreme Court of India admitted the petition for consideration. Also a second petition on HPV vaccination project was filed by Sama Resource Group for the Women and Health, which is a Karnataka-based Drug Action Forum, and the Delhi Science Forum.

[31] 72nd Parliamentary Committee Report, Department of Health Research, Ministry of Health and Family Welfare, Para. 7.13
[32] Kalpana Mehta v Union of India (2017) 7 SCC 302.

The Court urged the Indian government to advance the controlling framework on clinical trials and improve its acquiescence of licenses. The government was ordered to answer the role of the non-state actors in the protection of the trial participants. What are the responsibilities of these initiating, financing and conducting clinical trials? What are the responsibilities of the manufacturers whose medicine or vaccine is tested? Scholars have pointed out the complexity of the legal relationships among parties in clinical trials.

The Court defined uncontrolled clinical trials of medicines on humans by multinational companies observing that the government had slipped into deep slumbers in addressing this menace. The Court also admonished the Ministry of Health and Family Welfare and the Central Drugs Standard Control Organization (CDSCO) for failing to confront and resolve the problem, and demanded immediate action.

The Court admonished the government for negligence:

"You must safeguard the physical health of the country's citizens." It is your responsibility. Illegal trials must be halted and deaths must be prevented."[33]

The Court criticized the government for its inaction, saying:

"You can return to the courtroom, but what about the individuals who are dying in clinical trials?" People who have lost their lives will never be able to reclaim them. Creating a committee or commission is a simple process. It is done solely to shift attention away from the problem. It's the most effective means of deflecting attention away from serious concerns."[34]

Following the Supreme Court's judgement, the government amended its clinical trial rule on January 30, 2013, making it simpler to obtain compensation in the event of injury or death by clarifying and widening the categories of trial-related injuries, among other things.

Clinical trials are an integral part of inventing and manufacturing new drugs and finding new treatment methods. But, while conducting clinical trials, many factors need to be

[33] *Id.*
[34] *Id.*

considered: human rights should not be violated, it should strictly adhere to the ethical and legal guidelines and regulations. There are several international/national laws/regulations/guidelines concerning the conduct of clinical trials.

Nevertheless, many violations still do take place in the area of clinical trials that need to be addressed. Hence, a detailed study of international or national laws, regulations and guidelines relating to clinical trials is the need of the hour.

2.8 CONCLUSION

This chapter illustrates the definition concept and clinical trial process. So basically Clinical Trials is an indispensable part of the medicine discovery process to ensure the safety and efficacy of any recent medicine. Researchers use clinical trials to test out recent treatment options. Clinical trials help researchers understand which treatments work and the risks that may be associated with their use. Human clinical trials test these potential treatments on human beings who agree to participate in the experimentation. Four phases of human clinical trials are there. The earliest phases of human clinical trials usually focus on potential side effects of a given treatment while later phases aim to assess efficacy of the recent treatment compared to current treatment options. Not all phases of a human clinical trial will necessarily be carried out if a potential treatment presents unexpected outcomes. Then this Chapter detail explained all the process involved in a clinical trial and different categorization of clinical trials.

Clinical experimentation has not only made possible the development of recent and improved treatment for a wide range of human diseases, but it has also provided the knowledge of disease risk factors needed to formulate practical approaches to prevent them.

Clinical trials and analysis are essential to the progress of evidence-based medicine. Healthcare outcomes such as overall survival or quality of life result from a complex interaction between the patient, treatment, and the healthcare system. Clinical trials are the vital link between the recent discoveries related to human biology and the actual delivery of good physical health. They are a crucial link because they are the only valid method by which it is determined if treatment is effective and cost-effective at achieving good physical health.

Also, this process of clinical trials, may have a less direct but valuable effect on those people through healthcare institutions and services providing their care in trials and daily practice through the impact of clinical trials activities upon staff, facilities, and the culture of the institutions.

Clinical Trials on human subjects as a practice is fairly established and it does provide a beneficial service for millions of people who partake in the successfully approved products, may it be drugs, different drug delivery systems, medical devices, instruments or varied therapies and related technologies. The benefit to millions comes at the participation of people who invariably act as test subjects and suffer certain intrusions upon their physical and mental integrity for the sake of scientific study. Clinical trials run by commercial entities are carried out, and appropriately so, to create profits. When the clinical trials are not conducted in accordance with ethical standards, they infringe upon participant rights, including rights to the right to health. The enumeration of ethical and integral rights of research participants is not constrained to a single universal document and the existing provisions have evolved over decades of clinical research experience and are not exhaustive. These analyses are often carried out at high standards and provide valuable statistics to clinicians and policymakers.

CHAPTER 3

CHALLENGES IN CONDUCTING CLINICALTRIALS: LEGAL AND ETHICAL ASPECTS

3.1 INTRODUCTION

Human clinical experimentation trials, by which Pharmaceutical Companies, universities, and experimentation scientists bring recent medicines, devices, and procedures into the practice and marketplace of medicine, have become an enormous business. Pharmaceutical companies develop drugs through clinical trials that may contribute to physical health. Although, not every people has equal access to the drugs and medical products of these companies. This is because of the general inequality within and between the countries. This unequal access to the healthcare is not only problematic in and of itself; it also creates vulnerability in the process of enrolment in clinical trials.

Various international conventions guarantee people a right to enjoy the greatest possible standard of physical and mental health. Ensuring these guarantees, clinical trials are well regulated. It is now a globally accepted principle that no one can conduct a clinical trial on humans, putting them at risk of personal injury without obtaining their informed consent. *"The right to physical health includes the right to control one's physical health and body, as well as the right to be free from interference, such as the right to be free from torture, non-consensual medical treatment, and experimentation,"* according to Article 12 of the International Covenant on Economic, Social, and Cultural Rights (ICESCR).[35] Furthermore, must carefully consider the risks and benefits of clinical trials before such trials are carried out and monitor the physical health of experimentation subjects carefully during and after trials. Monitoring clinical trials is important to identify injuries and respond promptly. Liabilities are likely to arise due to a breach in informed consent rules or adverse reactions due to medicines, negligence of the institution or investigator. When clinical trials are not carried out following ethical standards, they infringe

[35] Article 12 International Covenant on Economic, Social, and Cultural Rights (ICESCR)

upon the participants' rights, including right to physical health. Despite repeated reports of irregularities in clinical trials in newspapers and NGO publications, some cases have been subjected to judicial scrutiny.

3.2 PRIMARY LEGAL AND ETHICAL ISSUES IN CLINICAL TRIALS ON HUMANS*:*

Litigation involving human clinical experimentation trials has escalated rapidly in the past few years. Whereas these suits raise many important theoretical questions, they also have important practical and human dimensions of which many people are unlikely to be aware until, by some unfortunate turn, they must live the reality. Main issues related to litigation in clinical trials are as follows:[36]

- Human Rights Violations
- Informed Consent
- Privacy and Confidentiality
- Vulnerable Groups
- Compensation issues
- Negligence of institution or investigator
- Research and related rules are complex
- Consequences of non-compliance are not understood or well-known

3.2.1 Human Rights Violation

All the human beings are born free and equal in rights and dignity. Everyone has the right to live, security of person and liberty.[37] No one shall be subjected to any torture or to cruel, inhuman or degrading treatment.[38] Certain historical experiences of clinical research upon human subjects like Dachau Hypothermia Study[39], were

[36] Issues & Concerns in Conducting Clinical Trials in India. https://www.pharmafocusasia.com/clinical-trials/issues-concerns-conducting-clinical-trials (last visited September 4th, 2021)
[37] Article 1 The Universal Declaration of Human Rights(UDHR)
[38] Article 3 The Universal Declaration of Human Rights(UDHR)
[39] Berger, R., 1990. Nazi Science — The Dachau Hypothermia Experiments. *New England Journal of Medicine*, 322(20), pp.1435-1440.

unethical and categorically involved torturous, degrading treatment of subjects who were by no means participating willingly. Such experiments are in gross violation of human rights.

The two most distinctive features of international and national legal instruments relating to clinical trials are the central role given to the idea of "human dignity" and the integration of common standards adopted into the human rights framework. In fact, it is difficult, if not impossible, to justify human rights without making any reference, at least implicitly, to the concept of human dignity. This idea is usually associated with the highest interests, fundamental and inviolable values of the human persons. According to Immanuel Kant, dignity means that the people must always treated as an end in their selves and never only as a means[40]. It is true that, the attempts to explain and justify human dignity will encounter enormous theoretical and practical difficulties in our postmodern world. Nevertheless, it seems that, at least for practical reasons, desperately need this concept if want to ensure a civilized social life[41]. In Dworkin's words, anyone who professes to take rights seriously must accept ''the vague but powerful idea of human dignity''[42]. The reference to the human dignity in the two aforementioned international and national legal framework is impressive enough that dignity is ''the shaping principle'' of international and national legal framework of clinical trials. Indeed, these international and national bodies cannot often deal with all human rights violations. However, despite all its weaknesses, the current human rights system is the only mechanism available to protect people. This is why integrating some principles relating to clinical trials into a human rights framework seems entirely justified. In other words, it is clear that, in the case of conflict between preserving humankind from harm and protecting purely financial or scientific interests, the law should give preference to the first option.[43]

[40] Kant I. Grundlegung zur Metaphysik der Sitten. [Foundations of the Metaphysics of Morals.] Berlin: Akademie-Ausgabe, 1911. In German

[41] Andorno R. The paradoxical notion of human dignity. Rivista internazionale di filosofia del diritto 2001;2:151-68

[42] Dworkin R. Taking rights seriously. Cambridge: Harvard University Press, 1977.

[43] Roberto Andorno, Biomedicine and international human rights law: in search of a global consensus, *Bulletin of the World Health Organization 2002, 80 (12)* https://www.who.int/bulletin/archives/80(12)959.pdf (last visited September 30, 2021)

3.2.2 Informed Consent

Informed Consent for medical experimentation is an essential, but challenging, process to assure the protection of the rights of potential experimentation subjects. Informed Consent is the keystone of human research ethics and protects the individual's autonomy to freely choose whether participate or not to participate in the clinical trials. There should be only voluntary participation and participants should not be under coercion, duress or undue influence.

All ethical codes on research involving human beings contains provisions for informed consent in one way or the other. Participants including patients are free to participate or not participate and withdraw from research at any time. They can weigh the risk of harm and potential benefits and decide for themselves. To take an effective decision, one needs to be aware about the nature, terms, duration, effects and various other aspects of the research study. Informed consent upholds the right to be respected, right to be informed as well as right to voluntarily participate or withdraw from the research. This process involves three components: Providing all relevant information to potential participants, ensuring such information is comprehended by them and assuring voluntariness of participation.[44]

In clinical trials, the consent of an experimentation subject is necessary as it creates limitation on biomedical experimentation. Such consent to be acceptable to the community must be free and informed i.e. it should not have been procured by fraud, misrepresentation and coercion. Absence of inducement is another factor for consent to be free. Purchasing an assent by consideration paid or promised taints it as unfree. Informed means informing the prospective enrollee of the objective and nature of the experimentation, the details of the research protocol, the possible effect of the vaccine and probable risks undertaken.

In common law jurisdictions there has developed a rule that where a subject agrees to clinical trial but without having first been informed, warned or advised about the procedure to be undertaken, the patient's apparent assent is ineffective.

In the absence of consent, any deliberate act which leads to physical contact is technically a battery. Consent can be implied or expressed, but it must also be

[44] UNITED STATES (1978), THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH, [Bethesda, Md.], The Commission.

demonstrated to be genuine in the sense that the volunteer must have been adequately informed to the nature and general purpose of the research and have given consent freely without being placed under duress or pressure of any kind.[45]

Informed consent is a well-established doctrine within the treatment regime governing the doctor–patient relationship in most of the common law countries. However, the scope of this doctrine has not been fully explored in the arena of clinical research so as to govern the researcher–participant relationship. The position in India is also not exceptional.

A well-documented informed consent is the signature of any ethical clinical trials[46]. Informed consent gives respect to an individual's autonomy in deciding whether to participate in research or not. It involves seeking permission from a person before making an intervention into his/her body. The researcher is bound to inform the research participant and seek his willingness to participate before the conduct of study or research on him. The subjects have to be informed about the research objectives, status of research, risks involved, potential benefits and other harm or inconveniences involved. They should be made aware of their rights[47].

As per the ethical guidelines laid down by ICMR, in biomedical research that involve human subjects, the researcher or investigator has to obtain the informed consent of the participant or prospective subject or his/her legal guardian where, the individual is not capable of giving a valid consent. Informed consent is relied on the principle that a competent individual is free to decide whether or not to be a subject of research. The concept of informed consent indeed protects the liberty and freedom of choice of an individual.

The prospective subject has to be provided with sufficient information regarding the nature and type of research, in a language which he/she knows. The information must include:

[45] Meisel A, Kuczewski M: Legal and ethical myths about informed consent. *Arch Intern Med* 156, 2521-26, 1996.

[46] Sanmukhani and Tripathi: Ethics in Clinical Research, Indian Journal of Pharmaceutical Sciences, 73 (2), 2011, p.125.

[47] Ruth W. Grant & Jeremy Sugarman, Ethics in Human Subjects Research: Do Incentives Matter?, Journal of Medicine and Philosophy: A Forum for Bioethics and Philosophy of Medicine, 29:6, 2004, pp.717-738

i. the aims, objects and methods of research and the expected duration of participation;
ii. benefits to the subject or others;
iii. any alternative procedures that might be as advantageous to the subject;
iv. any foreseeable discomfort or risk to the subject resulting from participation in clinical trials;
v. the right to prevent use of the subject's biological sample (DNA, cell-line, etc.) at any time during the conduct of the clinical trial;
vi. the extent to which could maintain the confidentiality of records, that is, the limits to which the investigator would be able to safeguard the privacy and confidentiality and the anticipated consequences of breach of privacy confidentiality;
vii. free treatment for the trial related injury by the investigator / institution;
viii. compensation of the subjects for disability or death resulting from such kind of injury;
ix. freedom of the individual / family to participate and to withdraw from trials at any time
x. risk of discovery of biologically sensitive information, etc.[48]

The crucial issue here is whether the participants could understand the risks and benefits of the research project[49]. There exist a number of other barriers in the purview of informed consent, such as the language barrier, that leads to misunderstandings among research participants, influence of religious & cultural beliefs, false expectations as to the outcome of research, etc.

The other issue is that, lack of penalty for failure to take (adequate) informed consent from participants in research has led to abuse[50]. Before 2005, there are only a few documented instances of clinical trials conducted without the informed consent of the research participants in India[51]. A number of incidents of clinical trials with

[48] Informed Consent Process, Ethical Guidelines for Biomedical Research on Human Subjects (2006), Indian Council of Medical Research, New Delhi, p. 24.

[49] Appelbaum, Paul S., Loren H. Roth, and Charles Lidz. The therapeutic misconception: Informed Consent in Psychiatric Research. International Journal of Law and Psychiatry 5.3 (1982), pp: 319-329

[50] S. Nundy and C.M. Gulhati, 'A New Colonialism? – Conducting Clinical Trials in India', The NewEngland Journal of Medicine 352 (2005), pp. 1633–1636.

[51] C.M. Gulhati, 'Needed: Closer Scrutiny of Clinical Trials', Indian Journal of Medical Ethics 12 (2004), pp. 4–5

inadequate or without consent from the subjects came to be reported in the International and Indian media between the years 2000 and 2010[52]. Chief among them are the Indore trials[53], trials involving Bhopal Gas Tragedy victims[54] and the human papilloma virus vaccine (Gardasil and Cervarix) trial[55], etc. Some commentators were called the practice of trials in India by foreign pharmaceuticals and research centers as 'the new colonialism'[56]. And public outrage over these alleged unethical trials ultimately culminated in a PIL titled as Swasthya Adhikar Manch v. Union of India[57] (SAM case). It dealt with the issue of enrolling research participants without proper informed consent[58]. The court in this case, criticized the government for not controlling the illegal and unethical clinical trials especially on the poor, destitute and disadvantaged sections of society and that, inhuman treatment of human subjects by the pharmaceutical companies, amounted to a violation of their basic human rights. It also laid down various regulatory measures such as, any pharmaceutical company seeking approval for the conduct of clinical research has to inform the participants about the potential risks and benefits involved and to compensate the victims in case of any injury[59]. Even in Dr. Rahul Dutta v. Union of India[60], the Allahabad High Court, while taking cognizance of the illegal clinical trials, held the pharmaceutical companies liable for violating the norms of informed consent and thereby causing death of subjects who were not even aware of the fact that they were used as mere guinea pigs. As per the 2017 ICMR guidelines, informed consent must include the "information that a reasonable person would want to know

[52] S. Lloyd-Roberts, 'Have India's Poor Become Human Guinea Pigs?' BBC News 1 November 2012

[53] V. Krishnan, 'MP Govt to Act Against 11 Indore Doctors', Live Mint 22 October 2012. act-against-11-Indore-doctors.html (last visited September 30, 2021)

[54] N. Lakhani, 'From Tragedy to Travesty: Drugs Tested on Survivors of Bhopal', The Independent 15 November 2011.http://www.independent.co.uk/news/world/ asia/from-tragedy-to-travesty-drugs-tested-on-survivors-of-bhopal-6262412.html (last visited September 30, 2021)

[55] Parliament Standing Committee, Rajya Sabha Report No. 72 on Health and Family Welfare, Seventy Second Report on 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 2013/Bhadra, 1935 (Saka). http://164.100.47.5/newcommittee/reports/EnglishCommittees/Committee%20on%20Health%20and%20Family%20Welfare/72.pdf (last visited September 30, 2021)

[56] Nundy and Gulhati, 'A New Colonialism?' – Conducting Clinical Trials in India', The New England Journal of Medicine 352 (2005), pp. 1633–1636

[57] W. P. (Civil) No. 33 of 2012

[58] Roy Chaudhury, R.: Mehta D., "Regulatory Developments in the Conduct of Clinical Trials in India", Global Health, Epidemiology and Genomics. 1: E4, 2016, @ doi:10.1017/gheg.2015.5

[59] Chatterjee S., 'Regulatory changes in conduct of Clinical Trials: A Need for Review', Indian Journal of Pharmacology, 45(4), 2013, pp. 323-4

[60] Misc. Bench WP No: 12280 of 2010.

before making a decision" to be part in the clinical trial[61].

Besides this, the basic requirements of the document seeking informed consent have to be complied with. It should contain an explanation as to whom to approach for research- related queries or in the event of an injury and should give the subjects a choice to discontinue participation at any time without any loss of benefits or penalty[62]. The document should also bear the signature of the research participant.

The Institutional Ethics Committee is entitled to waive off some of these elements where the risk involved is minimal as per the research design. Informed consent could be waived even during an emergency where, prior approval for the study has been conferred by the Ethical Committee.

Broad consent

The concept of broad consent has been added recently by the ICMR 2017 guidelines. Broad consent is defined as the consent for an unspecified range of future research subject to a few contents and/or process restrictions[63]. It is the consent for the secondary use of biological specimen in future with some particular purpose[64]. Studies have shown that around 3-40% participants may not be willing to provide consent for unspecified future use[65]. Broad consent may be more acceptable to the older participants than younger ones, and their level of acceptance might also differ[66]. Most of the participants are consistent with broad consent; they can use it if a proper framework is used, such as initial consent, oversight of the future research projects, and mechanism for the maintenance of contact details and communications with the research subjects.[67].

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[61] Behera SK, Das S, Xavier AS, Selvarajan S, et.al., Indian Council of Medical Research's National Ethical Guidelines for biomedical and health research involving human participants: The way forward from 2006 to 2017, Perspective Clinical Research, 2019; p.110.

[62] Lokesh P. Nijhawan, Manthan D. Janodia, et.al, Informed Consent: Issues and Challenges, Journal of Advanced Pharmaceutical Technology & Research, 4(3), 2013, p. 135

[63] Grady C, Eckstein L, Berkman B, Brock D, Cook-Deegan R, Fullerton SM, *et al.* Broad consent for research with biological samples: Workshop conclusions. Am J Bioeth 2015;15:34-42

[64] McQuillan GM, Pan Q, Porter KS. Consent for genetic research in a general population: An update on the nationalhealth and nutrition examination survey experience. Genet Med 2006;8:354-60

[65] Kettis-Lindblad A, Ring L, Viberth E, Hansson MG. Genetic research and donation of tissue samples to Biobanks.What do potential sample donors in the Swedish general public think? Eur J Public Health 2006;16:433

[66] Trinidad SB, Fullerton SM, Bares JM, Jarvik GP, Larson EB, Burke W, et al. Informed consent in genome-scale research: What do prospective participants think? AJOB Prim Res 2012;3:3-11

[67] Grady C, Eckstein L, Berkman B, Brock D, Cook-Deegan R, Fullerton SM, *et al.* Broad consent for research with biological samples: Workshop conclusions. Am J Bioeth 2015;15:34-42

Therapeutic misconception

Therapeutic misconception is one of the vexatious ethical issues for obtaining a valid informed consent[68]. There are chances of participants getting enrolled to researches misinterpreting it to be a routine medical checkup without understanding the true nature of such experimentation. The subject might be under the impression of a beneficial medical treatment.

Thus, it is inevitable that investigators make deliberate efforts to avoid therapeutic misconceptions in research so as to promote ethics and validity in informed consent. They have to clarify the nature and purpose of research including randomized selection in treatment, random controlled trials, and rationale behind placebo, and how treatment decision making differs from the routine medical care[69]. Therefore, there needs to be an adequate check on therapeutic misconceptions so as to protect the ethical rights of research participants.

Legal issue of informed consent

"No one shall be subjected to torture or cruel, inhuman or degrading treatment or punishment," states the International Covenant on Civil and Political Rights (ICCPR).”[70]. In Specific, no one shall be subjected without his free consent to medical or scientific experimentation’’[71].

The right to informed consent of a research participant could be brought under the right to autonomy as enshrined within Article. 21 of the Indian constitution[72]. Article 21 provides for the protection of ‘personal liberty’ including the protection of personal autonomy. The Supreme Court itself has held autonomy and personality liberty to include “both the positive right of individuals to make decisions about their lives, express themselves, and choose which activities to participate in. And the negative right, that is, not to be subject to any interference others”[73]. Violation of the

[68] Melo-Martín I, Ho A. Beyond informed consent: The therapeutic misconception and trust. J Med Ethics 2008; 34:202-5.

[69] Charles W, Paul S. The Therapeutic Misconception: Problems and Solutions. Medical Care 2002; 40:55-63.

[70] Article 7: The Covenant on Civil and Political Rights, 1966.

[71] Council for International Organizations of Medical Sciences, International Ethical Guidelines for Biomedical Research Involving Human Subjects, prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO).Geneva 2002. http://www.cioms.ch/publications/guidelines/guidelines_nov_2002_blurb.html" \h (last visited September 30, 2021)

[72] Omprakash Nandimath, Consent and Medical Treatment: The legal paradigm in India, Indian J Urol., 25(3): 2009, p. 345.

[73] Anuj Garg v. Hotel Association of India, (2008) 3 SCC 1

right to informed consent was brought before the courts in India, as the violation of the right to life and right to personal liberty[74].

However, the common law application of consent is not fully developed in India and it depends upon the provisions of Indian Contract Act[75] and Indian Penal Code[76]. And an act committed in the absence of proper consent amounts to battery under Tort law[77]. As per the law of torts, battery implies application of force to the person of another without any lawful justification[78].

Reasonable disclosure of information is one of the important elements of informed consent[79]. Courts of different common law jurisdictions use distinct standards for assessing information disclosure, such as, the professional practice standard, the reasonable person standard, etc. The medical professional practice standard, also known as the 'Bolam test', has been laid down in the case, *Bolam v. Friern Hospital Management Committee*[80] and the reasonable person standard, which is also called the 'Canterbury principle' was formed by the U.S court of Appeals in the case, *Canterbury v. Spence*[81]. But in the 2015 case of *Montgomery v. Lanarkshire Health Board*[82], the standard has shifted from the paternalistic, that is, 'what a reasonable practitioner would do' to a patient autonomy standard, enhancing 'what a reasonable person would want to know.

Now, when it comes to the Indian example of Kohli's case[83] the court rejected the 'Canterbury principle' or the reasonable person standard, for information disclosure and adopted a socio-economic line of reasoning to prefer the Bolam test. The court in this particular case held that the conduct of hysterectomy and SPO without consent was 'an unauthorized invasion and interference with the appellant's body' and that, the respondent was liable for the tort of battery. This case is the existing

[74] In India, the High Courts of various states and the Supreme Court have the jurisdiction to hear cases on violation of fundamental rights. See S. Choudhary et al., eds., Oxford Handbook of the Indian Constitution (Oxford: Oxford University Press, 2016)
[75] S. 13 of the Indian Contract Act, 1872
[76] Sections 87 - 92 of the Indian Penal Code, 1860.
[77] Miola, J., Medical Ethics and Medical Law: A symbolic Relationship, Portland: Hart Publishing, Indian Journal Urol 25(3): 2009; p. 378-80.
[78] Rateesh Sareen, Akansha Dutt, Informed Consent in Medical Decision Making in India, Journal of Counseling and Family Therapy, Vol.1(1), 2019, p.30.
[79] The others being voluntariness and capacity to consent. See R.R. Faden and T.L. Beauchamp, A History and Theory of Informed Consent (New York: Oxford University Press, 1986), p. 155.
[80] [1957] 1W.L.R. 582 (QB)
[81] 464 F.2d 772 (D.C. Cir.)1972
[82] [2015] UKSC 11
[83] Samira Kohli v. Dr. Prabha Manchanda and Another, (2008) 2 SCC 1.

precedent on the law of informed consent in India, which demonstrates India's legal position on informed consent cases, especially in the treatment context[84].

However, as far as lack of consent in clinical research is concerned, the position in India is unclear with respect to the participants' right to claim damages since; there has not been a single reported case in that area. Also, there is not much tort litigation in India due to the high costs of court action[85]. Even the Drugs and Cosmetics Act does not provide for any remedial measures for the failure in observing the procedures of informed consent in clinical trials.

Thus, the research participants, whether rich or poor, have a right to be informed about the research, treatment or any other study and have the right to either give consent or not give consent depending on that information[86]. And any deviation from the procedure is considered as "battery" and the doctor or institute committing it could be held liable before the court of law[87]. Also sufficient time and information should be provided to the patient before taking the decision except, in case of an emergency. For, the Apex Court itself has held that consent is not mandatory in an emergent situation[88].

3.2.3 Patient privacy and confidentiality

The concept has its basis in two ideal principles of respect for one's dignity and the obligation or duty to prevent harm. This implies that all data received during a research process which includes identity of a person, should be maintained within the research circle and not to be shared outside. The process of data collection should be conducted in such a manner that privacy of each and every research participant is protected with utmost care and diligence. Their identities should not be revealed even during publication of research reports unless they explicitly permit to do so. There must be an informed consent from the part of the research subjects. The researcher is not entitled to intrude into the privacy of participants and should respect the boundaries laid down by them so as to protect their integrity. Safety of medical

[84] Himani Bhakuni, Informed consent to clinical research in India: A private law remedy, Medical Law International, Vol. 20(3), 2020, p. 272.
[85] See K.B. Agrawal and V. Singh, Private International Law in India (The Hague: Kluwer Law International, 2010),p. 135
[86] Himani Bhakuni, Informed consent to clinical research in India: A private law remedy, Medical Law International, Vol. 20(3), 2020, p. 268
[87] Edward L Raab. The parameters of informed consent. Trans Am Ophthalmol Soc 2004; 102 : 225–232
[88] Pt. Parmanand Katara v. Union of India, AIR 1989 SC 2039.

records has to be ensured to protect the confidential patient information. Protection has to be assured to information elicited from a person under privileged circumstances of researcher–participant relationship. Voluntarily disclosed Information by the research participant has to be protected from further disclosure since; breach of confidentiality is considered the worse offence.[89]

Breach of confidentiality

The concept of confidentiality applies when the information a person reveals to a professional is private and has limitations on how and when it can be disclosed to a third party[90]. The issue of privacy under biomedical research involves an aspect of consent and limitations on the information that could be gathered and its further use. Consent is mandatory for participation in clinical research and use of personal, medical details and photographic records revealing identity of the patient for the purpose of publication[91]. The Ethical guidelines on Biomedical Research on Human Subjects, 2006 lays down the provisions for protection of privacy during clinical trials and other methods of research.

The privacy-related information in the research subjects information sheet includes, their choice to prevent the use of his or her biological sample, the extent to which could maintain the confidentiality of records and the consequences of breach of privacy and confidentiality, possible current and future uses of the biological material and the data to be generated from the clinical research and if the material is likely to be used for any other secondary purposes or it would be shared with others, or any other risk of discovery of biologically sensitive information and publications which includes photographs and pedigree charts[92].

The conduct of research in human genetics also raises a special concern with regard to maintenance of confidentiality. Therefore, protection of privacy and maintenance of confidentiality, surrounding the subject's identity and records, has to be adequately ensured while using the data or genetic material provided by participants

[89] Lawrence, Dana J. "The four principles of biomedical ethics: A foundation for current bioethical debate. J Chiropr Humanit 14 (2007): 34-40

[90] Mielke H.W. Research Ethics in Pediatric Environmental Health: Lessons from Lead, Neurotoxicol Teratol 2002; 24(4):467–9.

[91] Joga Rao S.V, Medical Ethics, A Ready Reference. 1st ed. Bangalore: Legalaxy Publications; 2004. p. 8.

[92] Informed Consent Process, Ethical Guidelines for Biomedical Research on Human Subjects (2006), Indian Council of Medical Research, New Delhi, p. 21

for research purposes[93]. This is intended to safeguard the subjects against any stigmatization, discrimination or unreasonable harm[94]. These guidelines also require the investigators to maintain the privacy and confidentiality of epidemiological disease related data due to the specific concern that some population based data may also have implications on issues like national security or public safety[95].

There is an exception to the above said provisions. That is, data of individual participants could be disclosed before a court of law under the orders and directions of the presiding judge, if there is any threat to the person's life. Then communicate to the drug registration authority regarding cases of severe adverse reaction and communicate to the health authority if there is any risk to the public health.[96]

Researchers must keep full and complete research records, including data and notes. Records should be kept for some reasonable period required for post-research monitoring, research assessment, further study (whether by the original researcher or otherwise). While interviewing participants, protection of privacy and confidentiality, specifically related to identity and records, is expressly required[97].

Researchers need the participant's written permission or consent, or someone allowed on their behalf, to reveal individual participant data. Principles which protect the privacy of patients include the principle of informed consent, the principle of privacy and confidentiality, the principle of accountability and transparency and compliance and Principle of informed Consent Investigators must receive informed consent for all scientific research involving human subjects in a document which is known as the Informed Consent Form with Participant / Patient Information Sheet. In a clear and easily understandable way, researchers have to provide sufficient details about the work.[98]

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[93] Statement of Specific Principles for Human Genetics Research, Ethical Guidelines for Biomedical Research on Human Subjects 2000, Indian Council of Medical Research New Delhi. p. 62.
[94] ICMR, National Ethical Guidelines for Biomedical and Health Research involving Human Participants, 2017.
[95] General Ethical Issues. Ethical Guidelines for Biomedical Research on Human Subjects (2006), Indian Council of Medical Research New Delhi, p. 29
[96] Statement of Specific Principles for Epidemiological Studies, Ethical Guidelines for Biomedical Research on Human Subjects (2000), Indian Council of Medical Research New Delhi, p. 56.
[97] Ethical Guidelines for Biomedical Research on Human Subjects, General Ethical Issues, P. 29 (2006), Indian Council of Medical Research New Delhi.
[98] *Id.*

3.2.4 Vulnerable groups

Vulnerable research population includes those who are absolutely or relatively incapable of protecting their own interests such as the poor, elderly, illiterate, children, pregnant women, terminally ill persons, etc., who are incapable of giving a valid consent.

As per the Helsinki Declaration 'Medical research involving a underprivileged or vulnerable community or population is only be justified if the clinical trials is responsive to the health needs and priorities of that community or population and if there is any reasonable likelihood that this community or population stands to the benefit from the results of the research'[77]. The Ethical Committee has to justify the inclusion of vulnerable population in research and should ensure that they are not exploited during the generation of clinical data. Some of the ethical guidelines include:

a) prevention of racial inequalities in genetic research;

b) undue advantage of the socially or economically disadvantaged persons should be not be taken for the benefit of those who are better off ;

c) protection of rights and the welfare of the differently-abled and mentally challenged persons and those with behavioral disorders and is therefore incapable of giving a valid consent

d) adequate justification should be provided for research involving those with reduced autonomy such as prisoners, employees, students, etc. as subjects

Special or vulnerable groups that require special concern include

Pregnant or nursing women

While selecting pregnant or nursing mothers as the subjects of research, it has to be ensured that there is no risk involved to the fetus or the nursing infant. The general rule is that, pregnant or nursing women should not be made subjects of research except where; it is to protect and advance the health of the nursing or pregnant women or infants. For instance, tests to prevent the prenatal HIV transmission from mother to child, for the detection of abnormalities in fetus, etc. are permitted.

Also there should not be any intervention discouraging women from nursing the

infants as part of the research. As per the provisions of Medical Termination of Pregnancy Act, 1971, even a woman who undergoes termination of pregnancy, could be made subjects of research. And, research in pre-natal diagnostics should be limited only to detect the genetic disorder or fetal abnormalities as per the provisions of Prenatal Diagnostic Techniques (Regulation and Prevention of Misuse) Act, 1994.

Children

While taking children as research subjects, the investigator must ensure that –

a) they are not involved in research that could be carried out with adults as well;

b) the purpose should be to obtain adequate knowledge on health needs of children and clinical evaluation should be carried out in children only after the phase III trials in adults;

c) consent on behalf of the child should be given either by the parent or legal guardian;

d) the consent of the child should be obtained to the extent of the child's capabilities;

e) research should be conducted in settings in which the child and parent can obtain adequate medical and psychological support;

f) If the child refuse to participate in the clinical trials that must always be respected, etc.

Likewise, a special concern has to be given even when mentally challenged or economically weak persons are made subjects of research.

3.2.5 Negligence

The special relationship between researchers and their human subjects can give rise to specific duties and breach of any such duty would be basis for an action in negligence. The liability formula hence constitutes:

(a) A duty (whether a researcher - subject relationship exists)

(b)Breach of said duty (whether the researcher failed to meet the required standard

of care.)

(c) Causation (if the researchers' breach caused injury to the subject)

(d) Damages.[99]

3.2.6 Compensation issues

The participants of clinical trials deserve compensation for dedicating their time, efforts and in meeting other contingencies. Payment should be made not only for the time spared and inconveniences suffered, but also for the expenses incurred by the subjects for their participation. They should be compensated only for actual expenses and the time, at an hourly rate for unskilled labor but offering higher payment or incentives amounts to inducements.[100] They are also entitled to free medical services. Besides, the Ethical Committee has to approve all the reimbursements, payments and medical services provided to research subjects.

Where the consent is given by guardian there should not be any remuneration other than the reimbursement of out of pocket expenses. Even if the subject withdraws from research, he is entitled to receive the full benefit of participation. The participants have to be informed about the sponsorship of research, so as to be aware of the commercial aspects of research. And, any kind of undue inducements through compensation has to be prohibited. However, this prohibition is not applicable to foreseeable technology transfer, joint ventures, healthcare reimbursements for travel expenses and loss of wages to the research participants, their families or communities. In addition, the research subjects who suffer any physical injury as a consequence of research participation are also entitled to financial assistance. The amount should be equitable in case of permanent or temporary disability. But if it comes to the death of a research participant, the dependents are entitled to material compensation.

Although Compensation is not always necessary, in many clinical trials participants

[99] Morreim, E., 2004. Litigation in Clinical Research: Malpractice Doctrines versus Research Realities. *Journal of Law, Medicine & Ethics,* 32(3), pp.474-484.
[100] Ruth W. Grant & Jeremy Sugarman (2004) Ethics in Human Subjects Research: Do Incentives Matter?, Journal of Medicine and Philosophy: A Forum for Bioethics and Philosophy of Medicine, 29:6, 717-738

receive some form of compensation for their participation. This can mean two distinct things:

- When subjects receive monetary or other benefits for their participation in the clinical trial; or
- If subjects receive a payment or any other services when they suffer some harm from the clinical trial.

Compensation is actually more common in Phase I trials with healthy volunteers and it is usually paid to the participants in recognition of their sacrifice time and as an appreciation of their contribution to science.[101]

3.2.7 Research and related rules are complex

The internal requirements of a pharmaceutical company, academic institution or a federal agency for reviewing multiple aspects of a clinical trial can significantly delay its initiation. In addition to such internal requirements, national and international regulatory requirements affect the conduct of clinical trials. Adhering to these many requirements will be a significant challenge for investigators. Moreover, the delays incurred increase the time cost of a trial and decrease its overall efficiency.[102]

3.2.8 Consequences of non-compliance are not well-known or understood

The regulatory bodies ensure compliances in various legal and regulatory aspects of Clinical Trials. Every country has its regulatory authority responsible for enforcing the regulations and rules and issuing the guidelines to regulate clinical trials drug development process, licensing, registration, manufacturing, marketing, and labeling of pharmaceutical products. But there is not enough law which deals with the consequences of non-compliance with these regulations. It should be clearly and rightly discussed.[103]

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[101] Sivanandan, S., Jain, K., Plakkal, N., Bahl, M., Sahoo, T., Mukherjee, S., Gupta, Y. and Agarwal, R., 2019. Issues, challenges, and the way forward in conducting clinical trials among neonates: investigators' perspective. *Journal of Perinatology*, 39(S1), pp.20-30.

[102] Collins, J, Regulatory Issues for Clinical Trials in Humans. *Epidemiologic Reviews*, 24(1), pp.59-66.

[103] Legal Issues in Clinical Research: What You Need to Know. https://assets.hcca-info.org/Portals/0/PDFs/Resources/library/Legal_Considerations_Clinical_Research.pdf (last visited September 4th, 2021)

3. 3 JUDICIAL INTERVENTIONS IN INDIA

In India, there are no instructions ever published by either Medical Council India, Indian Medical Association, or any other body involved in helm of affairs of clinical enterprises. All over India there are diversities in the way assent are taken and interpreted. What constitutes an ideal consent is not still elusive, nor is it possible to frame it for all cases as a prototype template. The ambiguity in the consent document leads to variable interpretations that have resulted in damages to medical fraternity at large.

The Supreme Court of India has given primacy to the Bolam principle in deciding cases of medical negligence (*Samira Kohli v Dr. Prabha Manchanda*[104], 2008; *Smt. Vinitha Ashok v Lakshmi Hospital and others*[105], 2001; *Achutrao Haribhau Khodwa and Others v State of Maharashtra and Others*[106], 1996; *Indian Medical Association v V.P. Shantha and Others*[107], 1995).

In fact in the V.P. Shantha case, the Supreme Court had an occasion to remark whether the doctrine of informed consent could be applied in India at all. It is clear that "due to the constant reliance on the Bolam principle (as late as 2009 in Martin F. D'Souza v Mohd. Ishfaq, 2009), the position in India continues to be that which existed in the UK when the Sidaway decision was pronounced.

The primary reason for the Supreme Court's paternalistic and protective attitude towards doctors and the medical profession seems to be due to the nature of polity and society in India. India has a large patient pool and most of them are poor and illiterate. Hence it would be a duty of law to put an obligation on the doctors to follow the doctrine of informed consent. Even if doctors were made obligatory to follow the informed consent, such obligation would be meaningless because the patients would not be able to understand the risk associated with a particular clinical procedure." However, the Code of Medical Ethics gives limited recognition to the doctrine of implied consent.

In the case of Samira Kohli Supreme court says that due to ground realities, at present in India only the Bolam and Sidaway principles are amenable but that the doctrine of

[104] 1(2008)CPJ 56 (SC)
[105] AIR 2001 SC 3914
[106] AIR 1996 SC 2377
[107] 1995 (6) SCC 651

informed assent (as recognized in Canterbury v Spence in the US) The Supreme Court has elaborated various aspects of assent taking. It has further laid down specific instructions for taking an accurate or valid consent. As such, it is an attempt to streamline the consent process in India. The judgment was related to a Gynecological case where a Hysterectomy was done as an additional procedure. While the initial consent was obtained for diagnostic laparoscopy, Hysterectomy and removal of both ovaries were performed in the same setting under general anesthesia. The consent for Hysterectomy was, however, obtained from the mother of the patient. The Supreme Court held that the doctor liable for malpractice, overruling the order passed by the National Consumer Dispute Redressal Commission. The Supreme Court opined that additional surgery, however beneficial to the patient, saves time, expenses, pain, and suffering is no ground for defense. It, however, rendered the exception as well. Judgment has further differentiated between Informed consent and Real or Valid consent. Moreover, it has elaborated various aspects of the treatment, including poor patient, long waiting period, lack of infrastructure, and commercialization of medical practice. Hon'ble Supreme Court has expressed significant concern over ignorance on the part of Indian patients in understanding what they would sign and has thus concluded the type of consent that shall practice in India.

New Drugs and Clinical trials Rules, 2019 is a response to the Supreme Court Orders under *Swasthya Adhikar Manch v Union of India*, various unethical trials in the country. An NGO named Swasthya Adhikar Manch prompted by media reports of a series of alleged unethical practices in clinical experiments filed a PIL in the Supreme Court in 2012. The petition requested the court to intervene in cases involving illegal and unethical trials of adults, children, and mentally ill persons across the country. In 2013, after hearing the petition, the Supreme Court observed that the 'uncontrolled' clinical trials of drugs on human subjects by multinational companies were wreaking 'havoc' in the country, noting that the government had slipped into 'deep slumber' regarding this 'menace'. The interim orders of the Supreme Court made the Central Drugs Standard Control Organization issue several directions including a notification making audio–video recording (AVR) of informed consent proceedings during trials mandatory for all clinical trials. It was also decided by the regulatory bodies that only audio and not video of consent would be recorded to protect the privacy of the participants in anti-human immunodeficiency virus or anti-leprosy drug trials. The Court ruled in favor of the organisation and directed the regulatory bodies to make

appropriate regulations. Hence, these rules basically aim at promoting clinical research in the country and tries to change the regulatory landscape for the approval of a new drug and the conduct of clinical trials in India and replaces Schedule Y of Drugs and Cosmetics Rules which had provisions on few rights of research participants. It also contains provisions on informed consent and makes Ethics Committees responsible to safeguard the rights, safety and well-being of all trial subjects including vulnerable subjects

It has significantly shortened the timeline of lengthy regulatory process involved. Hence, compensation has to be provided to the participants in case of any research related injuries. If it results in death, the dependents are entitled to financial compensation. Free medical management should also be provided as long as required or till the time it is established that the injury is not related to the clinical trial. The rules also define post trial access and made post-trial access of the benefits of the research to the participants a requirement, if the investigator recommends it and is approved by the ethics committee.

The lack of penalty or sanction is the major concern with respect to research on human beings in our country. This has led to several abuses in clinical research to an extent that as a reply to Supreme Court's question in *Kalpana Mehta v Union of India*,[108] as to why the government has failed to take any action against unethically conducted foreign-sponsored trials in 2015, the government acknowledged that 'As of now, there are no specific penalties for provisions relating to clinical trials under the Drugs and Cosmetics Act'. This case was filed in the Supreme Court seeking action on the unethical trials of HPV vaccines conducted on adolescent girls. India still does not have strict penal provisions in case of violations of the ethical guidelines

3.4 CONCLUSION

This Chapter discussed about the challenges in conducting clinical trials and legal and ethical issues of clinical trials. Also discusses about instance of unethical clinical trials and recent judicial trends in clinical trial litigations. This chapter has also presented some case analysis where clinical trial resulted into deaths and no

[108] (2017) 7 SCC 302.

compensation was granted to the legal heirs of the victims. New laws or rules may not be a practical response to the conduct of clinical trial. While in some instances legislation or regulation may be the only alternative to protecting the rights of the experimentation subjects. In order to control and regulate the clinical trials, some countries have amended their rules governing clinical trials while some have brought entirely recent laws to regulate the clinical trials.

There are many international guidelines for clinical trials, the benefit of such updated guidelines is defeated if this is not integrated into the national regulatory framework. Yet, in jurisdictions with lax regulation or enforcement of regulations coupled with poverty, feeble health infrastructure etc there is potential for violations. The rights reflected in all the relevant documents like right to life, right to health, right to respect of autonomy and bodily integrity, right to informed consent, confidentiality, privacy etc needs to be universally recognised and enforced and cannot be allowed to be swallowed up in considerations of value to science, society and least of all in any consideration of an economic nature. The biggest problem in India is the proper implementation and enforcement of laws and regulations. India is eager to enact laws and not so eager to enforce them. Indian parliament comes with new laws every year. Laws on clinical trial have been amended several times but there is no improvement in situation. On one side, India is trying to meet the international standards in clinical trial industry while on the other side the important question arises that what India is doing to achieve the international standard? In lack of adequate enforcement mechanism, drug companies violate the laws and give bribes to the ethics committees, investigators and other supervising authority. These authorities do not raise concern for such violations.

CHAPTER 4

INTERNATIONAL LEGAL FRAMEWORK ON CLINICAL TRIAL

4.1 INTRODUCTION

Over the recent decades, globalization of clinical trials, particularly those sponsored by global foundation and government funders and pharmaceutical companies has increased rapidly.[109] This increased globalization of the clinical trials has been attributed to multiple factors, including access to well- characterized and often treatment naïve, willing participants, thus expediting enrolment; availability of qualified local investigators who are ready to conduct trials; the enhanced capacity of international sites; and the lower cost of conducting trials in developing countries. Numerous bodies from many countries, including governments, government controlling departments, experimentation organizations, medical professional bodies, and physical health care providers, have issued guidance or legislation on the ethical conduct of clinical trials.

Experimentation on human subjects as a practice is fairly established and it does provide a beneficial service for millions of people who partake in the successfully approved products, may it be drugs, different drug delivery systems, medical devices, instruments or varied therapies and related technologies. The benefit to millions comes at the participation of people who invariably act as test subjects and suffer certain intrusions upon their physical and mental integrity for the sake of scientific study. When the clinical trials are not conducted in accordance with ethical standards, they infringe upon participant's rights, including rights to the right to health. The enumeration of ethical and integral rights of research participants is not constrained to a single universal document and the existing provisions have evolved over decades of clinical research experience and are not exhaustive.

[109] Glickman, S. W., McHutchison, J. G., Peterson, E. D., Cairns, C. B., Harrington, R. A., Califf, R. M., and Schulman, K. A. (2009). Ethical and scientific implications of the globalization of clinical research. New England Journal of Medicine, 360(8), 816-823

4.2 INTERNATIONAL TREATIES AND CONVENTIONS ON CLINICAL EXPERIMENTS AND RIGHTS OF RESEARCH PARTICIPANTS

The Universal Declaration of Human Rights (UDHR)[110] was adopted in 1948, Article 1 proclaiming that *"All human beings are born free and equal in dignity and rights. Everyone has the right to life, liberty and security of person.''* Article 3 states that: *"No one shall be subjected to torture or to cruel, inhuman or degrading treatment."* Certain historical experiences of clinical research upon human subjects like Dachau Hypothermia Study, were unethical and categorically involved torturous, degrading treatment of subjects who were by no means participating willingly. Such experiments are in gross violation of human rights.

The International Covenant on Civil and Political Rights[111] recognises the right to life inherent in all human beings[112] and provides by Article 7 that *"no one shall be subjected without his free consent to medical or scientific experimentation."* Article 12 of the International Covenant on Economic, Social and Cultural Rights[113], *''calls on States to prevent, treat, and control epidemic, endemic, occupational, and other diseases to achieve the full realization of the highest attainable standard of physical and mental health.''*

Convention on the Rights of the Child[114], Article 6 recognizes that every child has the inherent right to life. Article 24 provides *"States Parties recognise the right of the child to the enjoyment of the highest attainable level of living and to facilities for the treatment of illness and rehabilitation of health. States Parties shall make every effort to guarantee that no child is denied access to such health-care services".*

The Convention on the Elimination of all forms of Discrimination against Women[115] enumerates the various rights of women and staunchly against discrimination of women in attaining and enforcing any of the rights so provided. Article 12 specifically deals with the right to health of women and right to equal access to health

[110] Universal Declaration of Human Rights, G.A. Res. 217 (III) A, U.N. Doc. A/RES/217(III) (Dec. 10, 1948)

[111] UN General Assembly, International Covenant on Civil and Political Rights, 16 December 1966, United Nations, Treaty Series, vol. 999, p. 171

[112] Ibid, Article 6

[113] UN General Assembly, International Covenant on Economic, Social and Cultural Rights, 16 December 1966, United Nations, Treaty Series, vol. 993, p. 3

[114] UN General Assembly, Convention on the Rights of the Child, 20 November 1989, United Nations, Treaty Series, vol. 1577, p. 3

[115] UN General Assembly, Convention on the Elimination of All Forms of Discrimination Against Women, 18 December 1979, United Nations, Treaty Series, vol. 1249, p. 13,

care services. It is as follows: *"States Parties shall take all necessary steps to prevent discrimination against women in the field of health care in order to ensure equitable access to health care services, including family planning services, for men and women."*

According to the Committee on the Elimination of Discrimination Against Women *"Women have the right to be fully informed, by properly trained personnel, of their options in agreeing to treatment or research, including likely benefits and potential adverse effects of proposed procedures and available alternatives,"*[116]

International Convention on the Elimination of All Forms of Racial Discrimination[117] , Article 1 provides that *" In this Convention, the term "racial discrimination" shall mean any distinction, exclusion, restriction or preference based on race, colour, descent, or national or ethnic origin which has the purpose or effect of nullifying or impairing the recognition, enjoyment or exercise, on an equal footing, of human rights and fundamental freedoms in the political, economic, social, cultural or any other field of public life."*

Among regional conventions protecting human rights, the European Convention on Human Rights, 1950 provides for the right to life of everyone and in the Article 3 specifically states that *" No one shall be subjected to torture or to inhuman or degrading treatment or punishment";*

Article 4 of the American Convention on Human Rights, adopted in 1969, affirms the intrinsic right to life, while Article 5 states:

"1. Every individual has the right to have his physical, mental, and moral integrity respected."

2. No one shall be tortured or subjected to cruel, inhuman, or degrading treatment or punishment. All people who have their liberty taken away must be treated with respect for their natural dignity."

Article 11 protects the right to privacy and dignity of individuals.

The African charter of human right**s**[118] also provides for the right to life and integrity

[116] General Recommendation No 24 adopted at the Committee on Elimination of Discrimination against Women, Twentieth session, 1999.

[117] UN General Assembly, International Convention on the Elimination of All Forms of Racial Discrimination, 21 December 1965, United Nations, Treaty Series, vol. 660, p. 195.

[118] Organization of African Unity (OAU), African Charter on Human and Peoples' Rights ("Banjul Charter"), 27

of person, right to the respect of dignity inherent in human beings[119] and the right to health for all and prohibits all inhuman and degrading treatment.

The Convention against Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment[120], Article 16 establishes the state's commitment to protect citizens against cruel, inhuman, or humiliating treatment that does not constitute torture.

According to the 2007 Convention on the Rights of Persons with Disabilities, "States must offer equal recognition of legal competence and protection against non-consensual experimentation, as well as prevent exploitation and safeguard bodily and mental integrity"

4.3 INTERNATIONAL ETHICAL CODES AND GUIDELINES ON CLINICAL TRIALS

Prior to the 1947, "there was no generally accepted code of conduct governing the ethical aspects of human experimentation, although some countries, notably Germany and Russia, had national policies. One of the worst sides of medical experimentation in the history– the horrific experiments carried out by doctors on concentration camp victims in Nazi Germany – was exposed at the Nuremberg trials of 1947. Emerging from the Nuremberg trials was a code of ethics setting standards to which physicians must conform when conducting experiments on human subjects".[121] Many international instruments confer and safeguard the rights of participants in clinical trials. Modern ethics in human experimentation mainly emerged after World War II, when Nazi physicians used prisoners for "inhuman experiments. This is why, in 1947, the Nuremberg Code was enacted, which properly stated that voluntary permission is an absolute prerequisite for human subject experimentation.

June 1981,

[119] Ibid, Article 5

[120] UN General Assembly, Convention Against Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment, 10 December 1984, United Nations, Treaty Series, vol. 1465, p. 85

[121] The Nuremberg Code (1947) In: Mitscherlich A, Mielke F. Doctors of infamy: the story of the Nazi medical crimes. New York: Schuman, 1949: xxiii-xxv.

4.3.1 Nuremberg Code 1947

The Nuremberg Code was the first modern effort by the international community to create instructions governing experimentation on humans. The standards on medical experiments laid out by the Nuremberg Tribunal in the *United States v. Karl Brandt*[122] (Nuremberg trials) have come to be known as the Nuremberg Code. In the Nuremberg trials, Nazi doctors were convicted of the crimes committed during human experiments on concentration camp prisoners. The goal of the Code is to protect the rights of subjects and prevent the horrendous non-therapeutic, non-consensual medical experiments carried out by Nazi researchers during World War II from recurring. The Code consists of ten principles. The important thing is that anyone participating in an experiment must give informed consent. So nobody can be forced to participate in human experiments and clinical trials.

All participants must understand the potential risks. The judges went on in great detail in the first principle to define voluntary consent, and the disclosures physicians must provide before obtaining that consent. In addition, the Code requires in principle nine that the subject have the right to terminate participation. Suppose he has reached the physical or mental state where continuation of the experiment seems to him to be impossible. The Code states that in medical experimentations involving human subjects, voluntary consent of the human subject is essential. The individual must be able to exercise the free power of choice and must have sufficient knowledge of the nature of the experiment to make an enlightened decision. The subject should be informed of the character, duration, and purpose, the methods and means, all problems and risks reasonably to be expected, and the effects upon his physical health or person which may come from this participation in the human experimentation. The duty and responsibility for determining the quality of the consent rest on each individual who bring out, directs or engages in the human experimentation. This duty and responsibility cannot delegate to another with impunity because it is a personal duty to them.

The Code also gives rules for running the experiments. For example, participants can leave the experiment if they want. Doctors must stop the experiment if they realize it

[122] Brandt, Karl. Records of the United States Nuremberg War Crimes Trials: United States of America V. Karl Brandt Et Al. (case I) November 21, 1946 - August 20, 1947.

can harm the patient. Also, no experiment can be done where the risks outweigh the benefits that can be had from it. Other principles of the Code are presented below:-[123]

1. The experiment should be of a nature that provides fruitful results for the betterment of society, unobtainable by other ways, and not random and unnecessary.
2. The experimentation should be designed based on the results of clinical trials on animals and knowledge of the natural background of the disease or other problem under research. The anticipated results will justify the experiment's performance.
3. The experiment should be conducted in a manner to avoid all unintended physical and mental injury.
4. Whether there is any reason for believing that death or disability injury will occur, researcher should not conduct any experiment. Experiment can be carried out in those cases where the experimental physicians also serve as subjects.
5. The risk level should not cross the limit that determined by the humanitarian importance of the problem to be solved by the experiment.
6. There should be proper preparations and adequate facilities to protect the experimental subject from even remote probability of injury, disability, or death.
7. Only scientifically qualified persons are eligible to experiment. Lot of skill and care should be taken through all stages of the experiment.
8. While experimenting, the human subject should have the freedom to bring the experiment to an end, suppose he has reached the physical or mental state, where continuation of the experiment seemed to him to be impossible.
9. During the experiment, the researcher in charge should be prepared to end the experimentation at any stage of the experiment. If he has probable reasons to believe, in the exercise of the good faith, superior skill and careful judgment required of him, the ongoing experiment is likely to result in injury, disability,

[123] The Nuremberg Code (1947) Permissible Medical Experiments. http://areyouwalkingtall.com/Documernts/NUREMBERG%20CODE%201947.pdf (last visited August 28th, 2021)

or death to the experimental subject.[124]

4.3.2 The Belmont report

The report by the United States Office of the Secretary Ethical Principles and Guidelines for the Protection of Human Subjects of Research, is known as the Belmont Report. The Commission and the subsequent report was an immediate result of the unravelling of the details of the Tuskegee Syphilis study[125] conducted between 1930s to the 1970s for almost 40 years. The study chose specifically persons who were from low income, black families infected with the diseases to study the public health menace it was at the time. The discovery of penicillin and its acceptance as effective treatment for syphilis in 1945 after the commencement of the study made the treatment of syphilis easier and the disease less fatal. The study continued, the intervention available was denied to the participants. This caused death of several participants and proven spread of congenital syphilis to the spouses and children of the participants. The Tuskegee Syphilis study violated the principles of autonomy of persons as information was shielded from the participants, against the principle of non-malfeasance by causing harm to the participant and their families and violated principle of justice as the risks of the study was focused on a particular race and community. The Report sets out three basic ethical principles of research, which include:[126]

1. Respect for Persons: ensuring respect for autonomy of test subjects and measures to be taken to protect those with diminished autonomy.
2. Beneficence: health care providers have a duty to be of a benefit to the patient and take positive steps to prevent and remove harm from the patient.
3. Justice: The benefits and risks of the clinical trial have to be distributed equally among the population, especially to protect vulnerable groups of people.[127]

The Part C of the Report provides for the applications of the abovementioned ethical

[124] *Ibid.*
[125] The Tuskegee Timeline:, Centre for disease control and Prevention
[126] Part B Belmont Report, available at Read the Belmont Report | HHS.gov. https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html (last visited, September 27, 2021)
[127] *Ibid*

principles in[128]

1. Informed Consent: Respect for the persons requires that subjects, to the degree, that they are capable, be allowed to choose what shall or shall not happen to them. The concept contains three elements: information, comprehension, and voluntariness.
    - Information disclosed must be to the extent that a standard of "the reasonable volunteer" should be proposed, the nature and extent of information, the persons should know that the procedure is neither necessary for the care nor perhaps fully understood, they can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit is anticipated, the subjects should clearly understand the range of risk and the voluntary nature of participation. Clinical research involving partial disclosure is only justified if it is apparent that:
        - To achieve the research goals, inadequate disclosure is absolutely important.
        - There should be no dangers to subjects that are more than minimally mentioned.
        - When applicable, there should be a plan in place for debriefing participants and disseminating research findings to them.

- Comprehension: The manner and the context in which the information is conveyed is as important as the information itself. The subject's ability to understand is known as function of intelligence, rationality, maturity and language, thereby it is necessary to adapt presentation of the information to the subject's capacities. The category of people with limited comprehension due to immaturity or mental disability like children, mentally disable, terminally ill, comatose patients etc., is to conferred the respect of their wishes as far as possible and beyond that third parties are to be appointed to ensure that no harm is done to such persons during experiments or therapy. Third party must be such a person capable of understanding the situation of

[128] Part C Belmont Report, available at Read the Belmont Report | HHS.gov. https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html (last visited, September 27, 2021)

the participant and act in their best interest.

- Voluntariness: informed consent is to be free from coercion and undue influence. Vulnerable persons are especially susceptible to controlling or other influences.

2. Assessment of Risks and Benefits: The Report underlines three fold use for the systematic review of data related to the proposed research. Firstly, for the investigator such an assessment would help in proper design of the experiment. Secondly to the review committee the assessment of risks and benefits would help see if the risks justify the conduct of the experiment. Thirdly, it helps the prospective participants to decide whether to participate or not. For the experiment or study to be justified the risks or harm that could be caused to the participants be outweighed by the benefits to the partcipant, if any and the anticipated benefit to the society in the form of knowledge to be gained from the research.

   Assessment of the justifiability of research should incorporate at least the following elements, according to the report:

   i. *Brutal or inhumane treatment of human subjects is never morally justified.*
   ii. *Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Although risk cannot be completely removed, it can often be mitigated by paying close attention to alternative procedures.*
   iii. *When research includes a significant risk of serious harm, review committees should be adamant about the risk's rationale (typically the possibility of benefit to the subject — or, in rare situations, the clear voluntariness of the involvement)..*
   iv. *When vulnerable populations are included in research, the necessity of their inclusion should be proved. A number of factors influence such decisions, including the type and severity of the risk, the state of the population in question, and the nature and magnitude of the anticipated benefits.*
   v. *Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.''*[129]

[129] *Ibid*

3. Selection of Subjects: The principle of justice gives rise to moral requirements that there be fair procedures and the outcomes in selecting research participants. Individual justice in the selection of the participants would require that researchers should exhibit fairness. Thus, they should not offer any potentially beneficial research only to some patients in their favor or they should not select only "undesirable" persons for the risky research. Social justice requires the distinction be drawn between classes of subjects that ought. It ought not to participate in any specific kind of research based on the ability of the members of that the class to bear burdens and on the appropriateness of placing further limitations on already burdened persons. The injustice arises from social, racial, sexual, and cultural biases institutionalized in society. Racial minorities, like the economically disadvantaged, the institutionalized and the very sick may continually be sought as research participants, owing to their ready availability, ease of manipulation, and compromised position to exercise informed consent.[130]

4.3.3 Declaration of Helsinki 1964

World Medical Association formulated the 'Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects' which aims to codify the "ethical principles medical research involving human subjects, including research on identifiable human material and data." As general principles, the Declaration recognizes that it is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research and that the progress of medicine is ultimately based on research on human beings. The Declaration provides for the continual evaluation of even the best proven interventions so as to their safety, effectiveness, efficiency, accessibility and quality, that all such studies are bound by the ethical standards protecting the dignity and health rights of humans and that the need to generate new knowledge and progress can never take precedence over the rights and interests of individual research

[130] UNITED STATES. (1978). The Belmont report: ethical principles and guidelines for the protection of human subjects of research. [Bethesda, Md.], The Commission.

subjects.[131]

The Declaration of Helsinki lays out the basic principle that

"In any experimentation on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the research and the discomfort it may entail. He or she should be informed that he or sheis at liberty to abstain from participation in the research and that he or she is free to withdraw his or her assent to participation at any time."

The Declaration further requires that the subject's freely given informed assent shouldbe obtained, preferably in writing.[132]

In its most drastic move away from the Nuremberg Code, the Declaration of Helsinki distinguishes between clinical trials combined with patient care and non- therapeutic clinical trials. In only the latter does the Declaration require that the subject have free assent after he has been fully informed. A researcher need not obtain assent at all in a clinical setting where the researcher believes that it is unnecessary or difficult to obtain.[133]

Declaration has shown a focus on adequate compensation and treatment for subjects who are harmed as a result of participating in the experimentation. Some countries, and in particular those in developing regions, do not currently have in place those requirements, though many other regions already do.[134]

In addition, researchers are required to monitor the trial risk on an ongoing basis and directed to reduce those risks. Traditionally this task was allocated to ethics committees and safety monitors, however the concept itself is already broadly practiced and a part of other general ethical frameworks. So-called vulnerable populations-traditionally defined as the sick, the old, the young and the mentally

[131] WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI. https://history.nih.gov/download/attachments/1016866/helsinki.pdf (last visited August 28th, 2021)
[132] Article 26, Declaration of Helsinki, (Amendment 2013)
Declaration of Helsinki (1975) | Ethics Codes Collection. https://ethics.iit.edu/ecodes/node/3931 (last visited August 28th, 2021)
[133] Supra 24.
[134] Article 15, Declaration of Helsinki, (Amendment 2013)
Declaration of Helsinki (1975) | Ethics Codes Collection. https://ethics.iit.edu/ecodes/node/3931 (last visited August 28th, 2021)

incapacitated-are also given special emphasis in the revision, which calls for special considerations to be given to those populations to ensure that experimentation is first done (if able) in non-vulnerable populations, and that the population stands to benefit.[135]

The document also called for changes to the use of placebo controls, saying, "fit is acceptable in analysis where no proven intervention exists, or where for compelling and scientifically sound methodological reasons the use of any intervention less effective that the best proven one … is necessary to determine the efficacy or safety of an intervention." Under such a paradigm, it would need to be shown that patients would not be subject to any additional risks, the document adds.[136]

Even though it is a landmark for ethical experimentation standards, but countries, industry or individuals are not legally bound to follow. An example to this, FDA the US Food and Drug Administration is not signatory to any revision made since 1996 after changes were made to abandon the use of placebo controls in analysis where no therapeutic benefit presently exists.

Yet, the declaration of Helsinki is generally referred as a guide for many other ethical frameworks. Till 2008, any clinical trial conducted by US Pharma Company outside US, had to comply with the 1989 iteration of the declaration. Different versions were used by different countries.[137]

4.3.4 Impact of the International Covenant on Civil and Political Rights (ICCPR) 1966

The International Covenant on Civil and Political Rights (ICCPR) is a multilateral treaty that was adopted by the United Nations General Assembly on December 16, 1966, and has been in effect since March 23, 1976. It commits its parties to respect *"individuals civil and political rights, including the right to life, freedom of religion,*

[135] Article 13 , Declaration of Helsinki (Amendment 2013)
Declaration of Helsinki (1975) | Ethics Codes Collection. https://ethics.iit.edu/ecodes/node/3931 (last visited August 28th, 2021)
[136] Article 33, Declaration of Helsinki (Amendment 2013)
Declaration of Helsinki (1975) | Ethics Codes Collection. https://ethics.iit.edu/ecodes/node/3931 (last visited August 28th, 2021)
[137] Declaration of Helsinki (1975) | Ethics Codes Collection. https://ethics.iit.edu/ecodes/node/3931 (last visited August 28th, 2021)

freedom of speech, freedom of assembly, electoral rights and rights to due process, and a fair trial." The ICCPR admit the basic dignity of each individual and take responsibility to promote conditions within the states to allow the enjoyment of civil and political rights. Countries that have ratified the Covenant are obligated "to protect and preserve fundamental human rights and Compel to take administrative, judicial, and legislative measures to protect the rights enshrined in the treaty and to provide an adequate remedy.

ICCPR (International Covenant on Civil and Political Rights) seriously focused on human rights in clinical trials. According to this covenant, no one shall be subjected to torture or cruel, inhuman, or degrading treatment or any other punishment. Especially, no one shall be subjected without his free consent to medical or scientific experimentation.[138] All the signatories are legally binding to this obligation. This covenant guarantees individuals the right to be free from non-consensual medical experimentation. Restrictions are imposed not only to the state actors but also to private actors, or state and private actors working together. Therefore, under the ICCPR, sponsors are responsible for obtaining informed consent from the participant. Though the ICCPR bestows absolute rights, it is not self-enforcing and must be claimed in any human rights lawsuit against a non-state actor. Moreover, while the United States recognizes the ICCPR's status, the ICCPR is not self-executing and does not create a binding international legal obligation enforceable in federal court.[139]

4.3.5 Council of the International Organization of Medical Sciences (CIOMS) Guidelines 1982

The Council for International Organizations of Medical Sciences (CIOMS) was established jointly by the United Nations Educational, Scientific and Cultural Organization (UNESCO) and the World Health Organization (WHO) in 1949. It was established as an international, non-governmental, non-profit organization and now

[138] Article 7 of ICCPR
OHCHR | International Covenant on Civil and Political Rights.
https://www.ohchr.org/EN/ProfessionalInterest/Pages/CCPR.aspx (last visited August 28th 2021)
[139] OHCHR | International Covenant on Civil and Political Rights.
https://www.ohchr.org/EN/ProfessionalInterest/Pages/CCPR.aspx (last visited August 28th 2021)

includes international, national, and also associate member organizations, which are representing many of the biomedical disciplines, national academies of sciences, and medical experimentation councils.[140]

The important objectives of CIOMS are to facilitate and promote international activities in biomedical sciences in collaboration with the United Nations and WHO. To these ends, CIOMS has undertaken significant work in the areas of bioethics, international physical health policy (this includes consideration of social justice and individual dignity to physical health policy), and medicine development (which means safety, pharmacogenetics, reporting of adverse reactions, ethics of medicine promotion). In the 1970s, CIOMS undertook experimentation on bioethics in cooperation with the WHO, which resulted in Proposed Ethical Guidelines, published in 1982.[141]

The CIOMS guidelines are the first to regulate specifically how researchers funded by developed countries perform experiments with subjects in developing nations. First, they require that experimentation subjects from growing communities not be used in experimentation that could be carried out reasonably well with subjects from developed countries. "Second, they provide that experimentation be responsive to the physical health needs of the community in which the experimentation is to take place. Lastly, the CIOMS Guidelines require that externally funded experimentation obtain acquiescence from ethical review committees in home and host states.[142]

The Guidelines identify 26 separate statistics items an investigator must provide to trial participants before getting their informed consent. For instance, the investigator must inform the participants about the potential risks, advantages, purpose, methods, alternative procedures, or available treatments. Subjects also have the right to withdraw from the trial without penalties. These Guidelines also provide participants the right to free treatment for injuries caused during experimentation and the compensation right for accidental injury resulting from the trial.

These guidelines primarily focus on ethical justification and scientific validity of

[140] Johannes J. M. van Delden and Rieke van der Graaf, Revised CIOMS International Ethical Guidelines for Health-Related Research Involving Humans

[141] CIOMS - COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL https://cioms.ch/ (last visited August 28th 2021)

[142] Guideline 15, Cioms guidelines pdf. https://zokilare.weebly.com/uploads/1/3/4/7/134767859/ramijoki.pdf (last visited August 28th 2021)

experiment; ethical review requirements and informed consent requirements; consideration of trial subjects; equity concerning burdens and benefits; choice of control in clinical trials; confidentiality; injury compensation; strengthening of national or local capacity for ethical review; and obligations of sponsors to provide physical health care services.

According to the CIOMS guidelines, informed or valid consent should address the following three questions:

- Whether the patient has the ability or capacity to give consent to require consideration of issues such as age, maturity, cognitive ability
- Whether the consent is voluntary (i.e., without coercion, inducement, or intimidation including pressure from a family member); and
- Whether sufficient data has been provided to the patient on which to base their decision?

Guidelines also stress that assent is a process and not an event. Patients need to have time to look into the research statistics and clear their doubts by asking questions before making the final decision.

CIOMS also defines vulnerable groups as adults without the ability (relative, absolute, or temporary) to give or make a voluntary consent and children, who are generally considered to lack the ability to provide consent. CIOMS presents various guidelines, particularly on experimentation in vulnerable populations. For instance, the benefit of the vulnerable group to which the patient belongs should be the motto of experimentation. Also, the experiment should be therapeutic or, if nontherapeutic, it should pose minimal risk.

CIOMS indicates how fundamental ethical principles and the Declaration of Helsinki can be applied effectively in medical experimentation worldwide in different cultures, religions, traditions, and socio-economic circumstances, particularly for developing countries.[143]

[143] Cioms guidelines pdf. https://zokilare.weebly.com/uploads/1/3/4/7/134767859/ramijoki.pdf (last visited August 28th 2021)

4.3.6 Oviedo Convention

The only legally enforceable document on human experimentation is the Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine of 1997. The Preamble of the Convention by the European Council indicates that it aims at the realisation of human rights and fundamental freedoms while accelerating developments in biology and medicine. The preambles also shows that the members of the Council, signatories of the Convention and the European Community is "convinced of the need to respect the human being both as an individual and as a member of the human species and recognising the importance of ensuring the dignity of the human being" and is "conscious that the misuse of biology and medicine may lead to acts endangering human dignity"[144]

Article 1 of the Convention gives the guarantee of protection of human dignity by saying that "Parties to this Convention shall protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity and other rights and fundamental freedoms with regard to the application of biology and medicine."[145] Article 2 holds the importance of individual human over any benefit to the larger society, it states that, "The interests and welfare of the human being shall prevail over the sole interest of society or Science."[146]

In relation to undertaking research Article 4 provides that "Any intervention in the health field, including research, must be carried out in accordance with relevant professional obligations and standards."[147]

Chapter V of the Convention specifically deals with scientific research. Article 15 provides the general rule that, "Scientific research in the field of biology and medicine shall be carried out freely, subject to the provisions of this Convention and the other legal provisions ensuring the protection of the human being."[148]

Article 16 provides for provisions for protection of persons participating in research

[144] CETS 164 - Convention for the Protection of Human Rights https://rm.coe.int/168007cf98 (last visited September 27, 2021)
[145] Article 1 Oviedo Convention and its Protocols
[146] Article 2 Oviedo Convention and its Protocols
[147] Article 4 Oviedo Convention and its Protocols
[148] Article 15 Oviedo Convention and its Protocols

as subjects and provides that research upon human subjects be undertaken only certain conditions are fulfilled. The condition under the Article includes:

i. There is no similar alternative to human research in terms of effectiveness;

ii. The hazards that that person may face are not excessive in comparison to the research's potential advantages;

iii. After an independent analysis of its scientific value, including an assessment of the importance of the research's goal, and a multidisciplinary review of its ethical acceptability, the competent body approved the research proposal.

iv. The subjects of study have been advised of their rights and the legal measures in place to protect them;

v. Article 5 requires that the essential consent be given expressly, specifically, and in writing. This permission can be revoked at any moment.[149]

4.3.7 Good Clinical Practices (ICH-GCP) 1997

Good Clinical Practice (GCP) is an internationally recognized ethical and scientific quality standard set for formulating, conducting, recording, and reporting human subjects' clinical trials. GCP guidelines assure that the statistics and outcomes are credible and accurate. It respect and protect the rights, integrity and confidentiality of the subjects. Sponsors, investigators the ethics committees and any clinical experimentation organizations which are involved in the clinical trial are obliged to follow the relative GCP standard irrespective of the size of trial or the conditions of subjects. The International Conference on Harmonisation (ICH), which was founded in 1990 and is a cooperation between government regulators and industry to rationalise and harmonise pharmaceutical legislation, created Good Clinical Practice guidelines (GCPs). The investigator's duties for good clinical practice.[150]

According to the ICH GCP guidelines, the investigator must be qualified to conduct

[149] Article 16 Oviedo Convention and its Protocols
[150] GUIDELINE FOR GOOD CLINICAL PRACTICE.
https://media.tghn.org/medialibrary/2011/10/ICH_GCP_1996_Guidelines.pdf (last visited September 27, 2021)

the clinical trial and he must have adequate resources to conduct the trial. Further, the investigator is obliged to provide for the medical care of the trial participants, Regularly report to the IRB regularly with regard to the trial, follow the research protocol, account for the use of the investigational treatment used in the trial, follow the randomization and un-blinding procedures, get valid informed consent from the participant, and provide for the suspension of a clinical trial and premature termination. Furthermore, the investigator is obliged to develop, submit, and retain the records and reports on the progress, safety, and final investigator reports for the trial. The documents that are required to be on file in the investigator's research office before the clinical trial formally starts, during the conduct of the clinical trial, and after completion or termination of the clinical trial are listed in tables 4–6, respectively.

Core Principles of (ICH-GCP*)*

The ICH-GCP contains 13 principles which are intended to guarantee the safety of participants and also to ensure the accuracy of data in clinical trials. The first principle states that clinical trials should be carried out following the ethical principles which are developed from Declaration of Helsinki and are consistent with the GCP and applicable controlling requirements. In following principles, ICH/GCP refines the informed assent requirements contained in the Declaration. Specifically, the guideline identifies protocols for obtaining assent and disclosing required statistics to prospective trial participants. GCP enforces tight instructions on ethical aspects of a clinical research. High standards are required in terms of comprehensive documentation for the clinical protocol, record keeping, training, and facilities, including computers and software. Quality assurance and inspections ensure that these standards are achieved. GCP aims to ensure that the analysis is scientifically authentic and that the clinical properties of the investigational products are properly documented.[151]

GCP instructions includes protection of the human rights for the subjects and volunteers in a clinical trial. It also assures the safety and efficacy of the newly developed compounds. Core principles of ICH-GCP are:

[151] *ibid*

1. Clinical trials should be conducted according to the ethical principles originated from the Declaration of Helsinki, and that are compatible with GCP and the applicable controlling requirement(s).

2. Before initiating a trial, potential risks and issues should be measured against expected benefit for the trial subject and society. If the anticipated benefit and risks are balanced then only the trial should be initiated and continued.

3. The most important considerations for clinical trials are the rights, safety and wellness of the subjects. These considerations should prevail over interest of science and society.

4. Clinical and non-clinical data on an experimental product should be sufficient to support the proposed clinical trial.

5. Clinical trials must be technically sound, and described in clear, detailed protocol.

6. A trial should be carried out in compliance with the protocol that has received prior institutional review board (IRB)/ independent ethics committee (IEC) acquiescence/favourable opinion.

7. A qualified physician is always responsible for the medical care given to the subject, and medical decisions made on behalf of subjects.

8. Persons involved in designing and conducting a clinical trial must be qualified by education, training, and experience to perform their respective task(s).

9. Before enrolling a subject into a clinical trial, free informed consent should be obtained.

10. All data pertaining to clinical trial being it clinical or pre-clinical, should be recorded and stored in a manner that permits its correct reporting, interpretation and verification.

11. Confidentiality of the trial subject should be maintained, respecting the privacy and confidentiality rules according to the applicable controlling requirement(s).

12. Experimental medical product should be manufactured and stored according to the applicable Good Manufacturing Practice (GMP) and should be used according to the approved protocol.

13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.[152]

These principles are in the nature of self-explanatory and, when summarized, simply mean: GCP: Related rules and guidance documents These guideline adopts the fundamental principle outlined by the International Committee on Harmonization of Good Clinical Practice (ICH-GCP) with some changes and modifications to suit local requirements

4.3.8 International Clinical Trials Registry Platform (ICTRP)

"WHO regards trial registration as the publication of an internationally-agreed set of information about the design, conduct and administration of clinical trials. These details are published on a publicly-accessible website managed by a registry conforming to WHO standards."[153]

The International Clinical Trials Registry Platform (ICTRP) is the platform for the registration of clinical trials which the World Health Organization operates. It links clinical trials registers globally to ensure a single point of access and the unambiguous identification of trials. This will enhance access to information by patients, families, patient groups and others improve the completeness, comprehensiveness and also the accuracy of registered clinical trial data. And also communicate and raise awareness of the need to register clinical trials, ensure the accessibility of registered data, build capacity for clinical trial registration, and encourage the utilization of registered data.

[152] ICH E8 Guidelines PDF | millones de. https://menjen-kozos.com/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E8/Step4/E8_Guidelinex88-wu5918bp5t1.pdf (last visited on August 28th, 2021)
[153] Clinical trials - WHO. https://www.who.int/news-room/q-a-detail/clinical-trials (last visited August 28th 2021)

4.4 ISSUES OF VIOLATION OF THE GUIDELINES

The various ethical and technical guidelines as above discussed were formulated out of a need to ensure rights of research participants and communities. All through the evolution of the practice of health research on human subjects issues of violation of rights have arisen with dire consequences. A few examples are as follows:

The Willowbrook State Study to know the natural course of infectious hepatitis in children, in willowbrook state school in 1955. The institution was a place for care of physically and mentally challenged children and had a history of infectious disease outbreaks including Hepatitis A. The study proceeded to artificially infect newly admitted children. The researchers tried to justify[154], the same by citing the informed consent obtained from the parents of the children and stating even without the artificial infection, the children would have contracted the disease. There can be no justification for intentionally causing harm, for sake of science no matter the importance of the knowledge attained.

Guatemala syphilis experiment: During the US syphilis experiment in Guatemala[155] from 1946 to 1953, experiments were performed on over 5,500 Guatemalan prisoners, soldiers, sex workers, psychiatric patients and children about one-quarter of them were deliberately infected with syphilis, gonorrhea, or chancroid and all of whom were enrolled in the experiments without their consent. It was later admitted as an unethical study.

In 1996, Pfizer's pharmaceutical company tested a new drug, Trovan, on a group of young children in Nigeria. As with many clinical trials, the children were divided into two groups. The first one received the drug Trovan and the other one a moderate dose of Ceftriaxone (a proven effective drug available at the same clinic). The adverse side effects of Trovan were not detected by the researcher at the clinic administering the drug. As a consequence, children whose health did not improve on Trovan were not switched to the next alternative drug. The results were severe, and included long-term brain damage and six deaths. The affected children approached

[154] Krugman S. The Willowbrook Hepatitis Studies Revisited: Ethical Aspects. Rev Infect Dis. 1986; 8:157–62.
[155] Guatemala syphilis experiment". Encyclopedia Britannica, 18 Mar. 2018, https://www.britannica.com/event/Guatemala-syphilis-experiment. (last visited 27th September 2021)

US Court in *Adullahi v. Pfizer*[156] under the Alien Tort Statute. For 75 million US dollars settled the matter out of court.

In the early 2000s Merck and GlaxoSmithKline tested two vaccines for HPV aimed at prevention of HPV variant causing cervical cancer in girls and women. The study sponsored by ICMR and led by an organization named PATH was found to have vaccinated school girls in Andhra and Gujarat, without obtaining proper informed consent and other lapses. The Supreme Court shut down the study and recognized the issue of uncontrolled clinical trials of the drugs on humans by multinational companies like "havoc" in the country, observing the government had slipped into the "deep slumber" in addressing this "menace."[157]

4.5 CONCLUSION

Despite the benefit or value of research, such studies are susceptible to ethical and rights violations. The various ethical and technical guidelines as above discussed were formulated out of a need to ensure rights of research participants and communities. All through the evolution of the practice of health research on human subjects issues of violation of rights have arisen with dire consequences. However there are some international guidelines for the ethical standards in clinical trials. Many countries have adopted these ethical standards in their domestic laws but these standards are also not much effective as there are no punitive measures in case of any breach.

Factors that help grow the offshoring of clinical trials include easier access to potential subjects, the ability to recruit patients more quickly from an expanded potential subject pool, lower overall trial costs, the availability of eager and qualified investigators; and the increased likelihood that enrolled subjects will complete the study. There is a need for universal acceptance of the principles of the above discussed provisions and Guidelines and integration into national laws to ensure that the risks of health research are not shipped off to a less regulated country with more leeway to abuse. Many of the Guidelines have been amended through the years to

[156] 562 F.3d 163 (2d Cir. 2009)
[157] Mills, Edward J, and Sonal Singh. "Health, human rights, and the conduct of clinical research within oppressed populations." Globalization and health vol. 3 10. 8 Nov. 2007

accommodate and resolve the new issues that have cropped up. Nuremberg Code incorporated and declared the predominance of dignity and safety of individuals over the benefits to science. Sensibilities of race and the prejudices needed to be dealt with as a particular community was seen to suffer the risks for benefits conferred on another community. As regulation on health research on human participants became more stringent in the developing world, we witnessed the offshoring or outsourcing of clinical trials by companies. The Helsinki Declaration, CIOMS Guidelines and the subsequent regulations have been amended to ensure the protection of vulnerable populations and communities all over the world. Research outsourced to other countries needs to justify the need for the study and the benefit for the participant community.

The benefit of such updated guidelines is defeated if the same is not integrated into the national regulatory framework. These provisions also form the recognized industrial standard that the companies adhere to in their markets. Yet, in jurisdictions with lax regulation or enforcement of regulations coupled with poverty, feeble health infrastructure etc. there is potential for violations. The rights reflected in all the relevant documents like right to life, right to health, right to respect of autonomy and bodily integrity, right to informed consent, confidentiality, privacy etc. needs to be universally recognized and enforced and cannot be allowed to be swallowed up in considerations of value to science, society and least of all in any consideration of an economic nature.

As examined in this chapter there is no universally accepted standard for conduct of clinical trial. Different countries follow different Laws and Regulations to conduct clinical trial of a new medicine, medical device or medicinal product. Countries like UK and USA have very stringent regulations to control the clinical trial while on the other hand the countries like India are still in process to enact effective laws to govern clinical trials.

CHAPTER 5

LEGISLATIONS ON CLINICAL TRIAL: INDIAN PERSPECTIVE

5.1 INTRODUCTION

Clinical trials are an important aspect of universalizing healthcare, enabling the development of better medicines, tests, vaccines, devices, surgical procedures, and also other medical interventions and protocols for safer and more rational use. However, today it is considered merely as a business investment with high returns. In the past few years, the pharmaceutical industry has been outsourcing medicine discovery and clinical development programs to Asia, particularly India. Since clinical trial costs are about two-thirds of the cost of developing a medicine, off-shoring clinical trials offer unique opportunities, especially in terms of access to research subjects, trained personnel, lower-cost infrastructure, and labor pools. It is pertained to mention that India provides unique opportunities for conducting clinical trials because of significant cost reduction and increased speed and productivity of all requisite R&D phases in order to bring effective and safe medicine to market. India has a huge patient pool, well-trained and qualified investigators, premier medical institutions, low trial subject cost and a highly favorable controlling climate.[158]

However, the growing clinical trial market in India face challenges, particularly in the area of quality control measures, availability of well trained professionals, controlling timeline predictability and data protection. Although India has been a leading generic medicine producer for several years, world's fourth largest bulk medicine producer. The medicine acquiescence process in India has faced challenges in recent years, some around compulsory licensing of patents, government price control and narrow standards for patentability. Other issues have also occurred in the clinical trials area, which, despite India's high treatment-naïve population and emerging economy, have reduced pharmaceutical sponsors' interest in India as a priority area in which to conduct clinical analysis.

[158] P. Sree Sudha. How ethical are clinical trials in India?, *India Law Journal*, Volume 2, Issue 3

Drugs and Cosmetic Act 1940 along with Drugs & Cosmetics Rules of 1945, the Pharmacy Act of 1948 and the Drugs & Magic Remedies (Objectionable Advertisements) Act of 1954 deal with various controlling provisions regarding to import, manufacture, sale and advertising of medicine in India. Among all of these, the Drug & Cosmetic Act (Act) of 1940, which led to the Drugs & Cosmetics Rules (Rules) of 1945, is central legislation that regulates India's medicine and cosmetic import, manufacture, distribution and sale. And now New Drugs & Clinical Trials Rules 2019 is there to deal with clinical trials in India. A set of instructions prepared by ICMR, are also in place in India for the ethicalconduct of analysis to safeguard the interests of patients or volunteers participating in the research.

5.2 CLINICAL TRIALS PRACTICE IN INDIA

Clinical trials assign human participants to one or more health-related interventions such as vaccines, drugs, biosimilars, or diagnostic or other health interventions so as to evaluate their effects on them. It refers to the systematic study of new drugs on human subjects to generate data for discovering or verifying the clinical, pharmacological or adverse effects determining safety and efficacy of the new drug. So clinical trials are to be carried out by proper and reliable organizations by strictly adhering to the national and international guidelines regulating clinical trials.

So the Clinical Trial practices in India, the main aspect that sets the country at an advantage is the notable momentum adopted by the Indian Council of Medical Research (ICMR) and by the Central Drugs Standard Control Organization (CDSCO) - Directorate General of Health Services, Government of India, in tandem with global controlling instructions – in building up a robust controlling system, considering India's involvement in global GCP has only happened in the past decade. There are various Acts or Orders related to Clinical trials in India which includes New Drugs & Clinical Trials Rules 2019, Drugs and Cosmetics Act, 1940; Central Council for Indian Medicine Act 1970; Right to Information Act, 2005; Guidelines for Exchange of Biological Material (MOH order, 1997), etc. Apart from these legislations related to clinical trials, the Indian Council of Medical Research (ICMR) which was set up to foster a research culture in India, improve and develop infrastructure and foster community support. As stated in the Drugs and Cosmetics Rules, 1945, all clinical trials conducted in India should be conducted in compliance

to the ethical principles of the Declaration of Helsinki. All clinical trials in India should follow Good Clinical Practice Guidelines issued by Central Drugs Standard Control Organization, Ethical Guidelines for Biomedical Research on Human Subjects issued by ICMR from time to time, requirements under Schedule Y and approved protocols. ICMR has issued various guidelines pertaining to clinical trials involving human participants. ICMR issued 'Ethical Guidelines for Biomedical Research on Human Subjects' in the year 2000 and was revised subsequently over the years. It was lastly revised in 2017 as 'National Ethical Guidelines for Biomedical and Health Research involving participants'. The guidelines lists out various principles focusing on respect for person, beneficence and justice. Then New Drugs and Clinical trials Rules, 2019 is a response to the Supreme Court Orders under Swasthya Adhikar Manch v Union of India[159] and various unethical trials in the country.

5.3 REGULATORY MECHANISMS TO GOVERN CLINICAL TRIALS IN INDIA

Regulations are mechanisms to ensure that the quality and integrity of data collected in clinical trials is maintained and that the rights, safety and welfare of experimentation participants are protected. For conducting clinical trials in India there are several laws, rules.

5.3.1 Regulatory Bodies

Regulatory bodies and instructions to plan and monitor trials in a fair and ethical way. The high cost of medicines limits access to physical health care around the world. The role of regulatory bodies in clinical trials is to ensure quality medicine supply and maintaining physical health and well-being of trial participants. In India, the central government's Central Drugs Standard Control Organization (CDSCO) under the Ministry of Health and Family Welfare (headed by the Drug Controller General of India) develops standards and controlling measures for medicines, diagnostics and devices; lays down controlling measures; and regulates the market authorization of recent medicines. The Department of Chemical and Petrochemicals

[159] W. P. (Civil) No. 33 of 2012.

of Ministry of Chemicals and Fertilizers, through National Pharmaceutical Pricing Authority (NPPA) sets the prices of medicines; maintains data on production, exports and imports; and enforces and monitors the supply of medicines and also gives opinions to parliament on the related issues.[160] Principal authorities in India related to clinical trials are:-

- Ministry of Health and Family Welfare (MoHFW)
- Central Drugs Standard Control Organization (CDSCO)
- Indian Council of Medical Research (ICMR)

5.3.1.1 Ministry of Health and Family Welfare (MoHFW)

The Indian Government's, Ministry of Health and Family Welfare, is charged with the health policies in India. It is also responsible for all government programs relating to the family planning in India. The Drugs Controller, India appointed by the Central Government in the Ministry of Health and Family Welfare shall be the Central Licensing Authority for the purposes of clinical trials. The principle authority of clinical trials Central Drugs Standard Control Organization (CDSCO) is headed by the Ministry of Health and Family Welfare.[161]

5.3.1.2 Central Drugs Standard Control Organization (CDSCO)

Central Drugs Standard Control Organization (CDSCO) is headed by the Ministry of Health and Family Welfare. It is the principle body which develop the controlling procedure and standards for medicines, cosmetics, diagnostics and devices. The CDSCO has laid down standards and measures to ensure the safety, efficacy and quality of medicines, cosmetics, diagnostics and devices in India. It regulates the market approval of new medicine and clinical trials standards; supervises medicine imports and approves licenses to manufacture the above-mentioned products.[162] Its main objective is to standardize clinical experimentation and bring safer medicines to the Indian market.

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[160] Saxena, R. and Saxena, P., 2021. Clinical trials: Changing regulations in India. https://cyberleninka.org/article/n/1086551 [last visited 2nd September 2021].

[161] About the Ministry | Ministry of Health and Family Welfare. https://main.mohfw.gov.in/about-us/about-the-ministry (last visited September 29, 2021)

[162] Parvathi K. Iyer, Regulatory Issues in the Indian Pharmaceutical Industry, India, *Science and, Technology*, 2008

With this controlling agency, it is the Drug Controller General of India (DCGI) who is regulating all the pharmaceuticals and medical devices. DCGI is the main licensing authority, which directly issues permission for recent medicines and devices. It oversees clinical trials as well. As such, the DCGI is being advised by two other bodies which are:

- Drug Technical Advisory Board
- Drug Consultative Committee

Central and state government receive advice on all technical matters arising out of medicine control enforcement from the Drugs Technical Advisory Board Experts. With the permission of the board, government can make amendment in the rules. The Central Drug Standards Control Organization is maintaining a good track record with 'World Health Organization'.[163]

5.3.1.3 Indian Council of Medical Research (ICMR)

The Indian Council of Medical Research the apex body in India for the formulation, coordination and promotion of biomedical experimentation, is one of the oldest and largest medical experimentation bodies in the world. The Indian Council of Medical Research, the apex body for clinical trials, was set up to promote experimentation culture in India and develop infrastructure for clinical trials. The ICMR is funded by the Government of India through the Department of Health Research, Ministry of Health and Family Welfare. The governing body of this organization is presided by the Union Health Minister. And, this agency is being assisted by the scientific advisory board. Various eminent experts in biomedical disciplines will assist ICMR in both scientific and technical matters. ICMR is the government body which has formulated instructions for several aspects that are relating to national physical health. Treatments for conditions like malaria, cancer, type 2–diabetes, retinoblastoma and Covid- 19 have been covered by various instructions by Indian Council of Medical Research.[164]

[163] Introduction. https://cdsco.gov.in/opencms/opencms/en/About-us/Introduction/ (last visited September 29, 2021)
[164] About ICMR. https://icmr.org.in/about-us/about-icmr (last visited 2nd September, 2021)

5.4 REGULATORY FRAMEWORK

5.4.1 The Drugs and Cosmetic Act, 1940

The Drugs and Cosmetic Act, 1940 came into force on 1st April 1947. Later on, in 1962, the government extended the controlling provisions to the cosmetics, and finally, the Act came to known as the Drugs and Cosmetic Act 1940. Drugs and Cosmetic Act has been divided into Chapters, Rules, and Schedules and is amended from time to time to control the medicines' safety, efficacy, and quality.[165]

The rules to be followed when conducting clinical trials in India are clearly documented to a large extent in this document." Schedule Y for India is a law and not simply a guideline.[166]

The enforcement which came into existence in 1988 was a significant provision for providing support to the upscale of generic pharma scenic present in those days. With the entry of large pharmaceutical companies and the multiple multinationals in clinical experimentation, the needs changed and put a revised version of Schedule Y in line with the ICH-GCP (International Council of Harmonisation and Good Clinical Practice) standard forth in 1995. Since that time multiple revisions to schedule Y took place to provide a healthy environment for clinical experimentation to be carried out in India. Implementation of these; raises the bar for the industry to function as per quality standards expected by the foreign regulators. Mandatory registration of clinical trials in the Clinical Trial Registry of India (CTRI) has made the process more transparent and evolved it to the next level. Schedule Y of the Drug and Cosmetics Rules, 1945 regulated clinical trials in India; however, after enacting the New Drugs and Clinical Trials Rules 2019, Schedule Y was replaced by the said rules, 2019.[167]

While conducting a clinical trial, new chemical entities can be given to human subjects only with the permission of the Drugs Controller General of India. In order to obtain such approval, an application is required to be submitted to the DCGI. The application should contain the detailed protocol, informed consent documents, list of

[165] Important Information of Clinical Research | Icri India Blog. https://www.icriindia.com/blog/regulatory-environment-of-clinical-research-in-india/ (last visited 2nd September,2021)
[166] Schedule Y Guidelines For Clinical Trials Pdf https://arc2climate.org/for-pdf/11463-schedule-y-guidelines-for-clinical-trials-pdf-593-994.php (last visited 2nd September 2021)
[167] Recent Changes in Regulations Related to Clinical Trials, http://rifapharma.com/clinicaltrialapprovalIndia.pdf (last visited 2nd September, 2021)

proposed investigators and background data of medicine according to the New Drugs and Clinical Trials Rules 2019.

5.4.2 Report of the Prof. Ranjit Roy Chaudhury expert committee:

This report put forward in July 2013 by the Expert Committee constituted by the Ministry of Health and Family Welfare enlists practices that would be conducive forthe growth of clinical trial industry in India while meeting the controlling standards.[168] It formulated policy and instructions for acquiescence of recent medicines, clinical trials and banning of medicines. The actions taken by the Ministry based on the recommendations hereon included-[169]

- Clinical trials should be carried out in accredited sites by an accredited Investigator with the oversight of accredited Ethics Committees (ECs). The Accreditation would be provided by a Quality Council of India.
- As discussed above with Rule 122 DD, Registration of Ethics Committee is made mandatory but the proposed accreditation required a special procedure which calls for amendments in Drugs and Cosmetics Act.
- Regarding the procedure for review and request of recent medicines, New Drug Advisory Committees are renamed as Subject Expert Committees. Applications for recent medicines will initially be evaluated by these followed by review from the Technical Review Committee (TRC). CDSCO will take the final decision based on recommendations from the TRC.
- A computerized database of experts in each area will be generated which will be updated every year based on specific selection criteria.
- If India takes part in a global clinical trial for a recent medicine, acquiescence should be sought from the CDSCO before marketing the medicine.

[168] Kulkarni NG, Dalal JJ, Kulkarni TN. Audio-video recording of informed consent process: Boon orbane. Perspectives in Clinical Research. 2014; 5(1): 6-10.
[169] Supra 11

- The CDSCO will review applications for acquiescence of clinical trials withinsix months and ultimately bring down the timeline to one month.
- If at all, a placebo controlled trial needs to be done, it should be efficient; ethical and appropriate.
- Audio-visual recording of the assent process will be undertaken. Violation of the informed assent process can cause debarment of the investigators.
- An investigator cannot take part in over three trials at a time. All details about payment of the investigator by the Sponsor should be made available to the DCGI.
- Use of statistics technology shall be used at all points in the clinical trial to ensure total transparency
- If an investigator fails to report an SAE within 24 hours, he should give the reason for delay to the satisfaction of the DCGI along with the SAE report.
- Amendments in Rules 122 DAB and Schedule XII are called upon regarding compensation in injury or death discerned at a later stage.
- Academic clinical trials may be approved by the Institutional Ethics Committee. If a recent medicine is being tested or a recent use for an existing medicine is being evaluated, then acquiescence of the CDSCO is required.
- There is no restriction as to the number of clinical trials carried out in the country and no deletion of existing medicines needs to be done in case a recent medicine is approved for a particular disease.
- A waiver of clinical trial in Indian population for acquiescence of recent medicines, which have already been approved outside India, can be considered only in cases of national emergency, extreme urgency, and epidemic and for orphan medicines for rare diseases and medicines indicated for conditions/diseases for which there is no therapy.
- Post marketing surveillance is to be carried out for 4 years as per

Schedule Y which needs to be extended for 6 years.[170]

These instructions definitely improvised the shortcomings of the clinical trial industry in India by clearly specifying how and when recent medicines would be approved. But much of this need to be put in practice and change is still a long way to go.

The rules are as follows-

1. For recent medicine being developed in India, clinical trial have to be carriedout in India from stage I
2. For marketing acquiescence of medicines already approved in others countries, a multicentric stage III clinical trial is required to established the medicine impact on the Indian ethnic population.
3. A request for recent indication of an already approved medicine is treated as a request for recent medicine's acquiescence.
4. New formulation of approved medicine may be subjected to bioequivalence research.
5. Phase I trial of foreign medicines were not permitted except for medicine of special relevance to India.

All the mentioned controlling requirements, whether National or International law, rule or instructions are basically having a same target

1. Respect and protection of Human rights of trial subject.
2. Reasonable compensation of trial subject.
3. Participation of subject with assent.
4. Full scientific, medical and ethical justification to conduct the trial.

The trial sponsor must obtain acquiescence from DCGI before starting a trial. The trial cannot be started without clearance from the local ethics review committee at each site.

[170] Actions on the recommendations of Prof. Ranjit Roy Chaudhury expert committee to formulate policy and guidelines for approval of new drugs, clinical trials and banning of drugs https://www.iscr.org/wp-content/uploads/2019/04/Actions_on_the_recommendations_of_Prof._Ranjit_Roy_Chaudhury_Report._59.pdf (last visited 2nd September 2021)

5.4.3 New Drugs and Clinical Trial Rules 2019

New Drugs and Clinical trials Rules, 2019 is a response to the Supreme Court Orders under *Swasthya Adhikar Manch v Union of India* and various unethical trials in the country. An NGO named Swasthya Adhikar Manch prompted by media reports of a series of alleged unethical practices in clinical experiments filed a PIL in the Supreme Court in 2012. The petition sought judicial interference with respect to illegal and unethical trials being conducted on adults, children and mentally ill people in the country. In 2013, after hearing the petition, the Supreme Court observed that the 'uncontrolled' clinical trials of drugs on human subjects by multinational companies were wreaking 'havoc' in the country, noting that the government had slipped into 'deep slumber' regarding this 'menace'.

The interim orders of the Supreme Court made the Central Drugs Standard Control Organization issue several directions including a notification making audio–video recording (AVR) of informed consent proceedings during trials mandatory for all clinical trials. It was also decided by the regulatory bodies that would be record only audio and not video of consent to protect the privacy of the participants in anti-human immunodeficiency virus or anti-leprosy drug trials. The Court ruled in favor of the organization and directed the regulatory bodies to make appropriate regulations. Hence, these rules aim to promote clinical research in the country and try to change these regulatory landscape for the conduct of clinical trials and approval of new drugs and in India and replace Schedule Y of Drugs and Cosmetics Rules, which had provisions on few rights research participants.

The New drugs and Clinical trials rules 2019 (New rules) was introduced on 19th March 2019 by the Government of India. New rules have set specific requirements for the ethics committee (EC). The EC must follow requirements set as per New rules and forward their report to Central Licensing Authority (CLA). The new rules aim to develop clinical research in India by providing predictable, transparent, and effective regulation for clinical trials and ensuring faster accessibility of the new drugs to Indian population. New rules have also reduced the time for approving applications, which has come down to 30 days for the drugs manufactured in India and 90 days for those drugs which was developed outside the country. In case, if there is no communication from Drugs Controller General of India, then the

application will be deemed to have been approved.[171]

The Drug Controller General of India will decide the compensation in death, permanent disability, or other injury to a trial subject. The ethics committee will monitor the Clinical trials and decide on the amount of compensation in adverse events. In the case of injury to the clinical trial subject, it has been mandated that medical management will be providing as long as required as per the investigator's opinion. New drugs approved in select developed markets will be automatically allowed in India, provided global trials include Indian patients. This waiver would also extend to the drugs that receive these marketing approvals even while a trial is underway in India. New rules have removed regulations on tests conducted on animals in case of drugs approved and marketed for more than two years in well-regulated overseas drug markets. It also contains provisions on informed consent and makes Ethics Committees responsible to safeguard the rights, safety and well-being of all trial subjects including vulnerable subjects. Compensation is another important aspect and Chapter VI deals with serious adverse events and its compensation. It has significantly shortened the timeline of lengthy regulatory process involved. Hence, compensation has to be provided to the participants in case of any research related injuries. If it results in death, the dependents are entitled to financial compensation. Free medical management should also be provided as long as required or till the time it is established that those injury is not related to the clinical trial. The rules also define post trial access and made post-trial access of the benefits of the research to the participants a requirement, if the investigator recommends it and is approved by the ethics committee.

Salient features of the new rules, 2019

- In this new drugs and clinical trials rules, 2019 definitions of many previously undefined terms included. The definition of "New drug"[172] has been broadened, it now covers new therapeutic options like NDDS, SR/MR, Living modified organisms, stem cells derived products, monoclonal antibodies, xenografts, gene

[171] New Drugs and Clinical Trial Rules, 2019 https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/NewDrugs_CTRules_2019.pdf.(last visited September 29, 2021)
[172] Rule 2(w) New Drugs and Clinical Trial Rules, 2019

therapeutic products, etc. Definition of an "orphan drug"[173] is a drug used to treat a condition that affects not more than 5 lakh people in India.

- New rules deals with the Provision of waiver of local phase III clinical trials. A drug approved and marketed in specific countries as per the requirements is subject to certain conditions to conduct a Phase IV study. But in the case of drugs of particular relevance, for example, in case of unmet need, orphan drugs, for rare diseases for which drugs are not available or available at a high cost, etc., could reduce the Phase IV study requirement.[174]

- Suppose a new drug is available for more than 2 years in certain countries. In that case, Animal toxicology, teratogenic studies, reproduction studies, perinatal studies, carcinogenicity, and mutagenicity studies may be modified and relaxed case of imported products. But in the case of locally manufactured products, this relaxation may be allowed only if the drug is marketed in other countries for many years.[175]

- In the new rules, Provision of Pre-submission meetings is included in which by paying some certain fee, before making the actual submission to the regulator, the Applicants can discuss their projects with the regulators and subject experts, for seeking the guidance about the requirements of procedure and law applicable for their research. Then Provision of Post-submission meetings included in which the applicant can make an application for a post-submission meeting with officer designated by the Central Licensing Authority within fifteen days from the date the questions was received for seeking guidance with regards to the questions concerning the pending application if they desires to seek clarification in person in respect of pending application and

[173] Rule 2(x) New Drugs and Clinical Trial Rules, 2019
[174] Rule 101 New Drugs and Clinical Trial Rules, 2019
[175] Rule 75 New Drugs and Clinical Trial Rules, 2019

queries related to that.[176]

- Provision of Post-Trial Access included. The investigator may recommend post-trial access for the patient in the case of whether the drug is beneficial, and there is no other alternative therapy. Ethics Committee approval and patient or legal heir's consent are required. There will not be any liability on the sponsor for post-trial use by the patient in that case.[177]

- The validity of clinical trial permissions has changed in new rules. The permission to initiate Clinical Trial will be valid till two years from the date of issue unless the licensing authority extends it.[178]

- New Drug Approval: demonstration of safety and efficacy of the medicine product for use in humans is essential before the medicine product can be approved for import or manufacturing and marketing in the country. The recent medicine acquiescence process in India is standardized and well-controlled, involving multiple steps and the organizations. At central level, the DCGI, under the Ministry of Health and Family Welfare, approves the medicine or medical device for marketing. Manufacturing licenses are approved at the state level by state medicine control authorities. State agencies also perform monitoring in coordination with the CDSCO.[179]

- Clinical Trial Approval Process: Clinical Trial process in India is divided into two parts. First part gives the path of request from applicant to Health authority, i.e. CDSCO. The other part gives the alleyway of documents from the applicant to the Ethics Committee. The timelines forthe acquiescence process vary from request to request, in some it may be more than 90 days. But The new rules state that any drug discovered in India, or research

[176] Rule 98 New Drugs and Clinical Trial Rules, 2019
[177] Rule 27 New Drugs and Clinical Trial Rules, 2019
[178] Rule 26 New Drugs and Clinical Trial Rules, 2019
[179] SECOND SCHEDULE New Drugs and Clinical Trial Rules, 2019

and development of the drug has been done in India, and which is proposed to be manufactured and marketed in the country, will be deemed approved for clinical trials within 30 working days by Central Licensing Authority (CLA).[180]

- Chapter III of the new rules deal with ETHICS COMMITTEE. The composition of the Ethics Committee, 50 percent of its members, should be persons not affiliated with the institute or the organization in which that committee is constituted. Ethics Committee registration certificate shall be granted in the form of CT-02 within a time period of 45 working days. The validity will be for a time period of five years from that date of its issue unless cancelled or suspended by the Central Licensing Authority. Ethics Committee can apply for renewal of registration, which is done 90 days before the date of expiry of registration. It is to ensure the deemed continuity. Suppose a clinical trial site does not have its own Ethics Committee. In that case, can initiate clinical trial at that site only after obtaining approval of protocol from the Institutional Ethics Committee of another Clinical trial site and an independent Ethics Committee. The Ethics Committee approving shall be responsible for the study at the clinical trial site, which should be located within 50 km of the clinical trial site or the same city.[181]

- Compensation: Rule 122DAB of Schedule Y of Drugs and Cosmetics Rules, 1945 was the compensation rule in India, till March 2019. The current compensation rules appear in Chapter VI of the New Drugs and Clinical Trial Rules 2019. These rules have replaced part XA and Schedule Y of Drugs and Cosmetics Rules 1945. The requirements are given in rule 39, 40 and 41. Rule 42 describes the procedure to be adopted for the payment of compensation for injuries (including death) during clinical trials under the condition that they are due to participation in the trial[182]

[180] *Ibid.*
[181] Chapter III of the New Drugs and Clinical Trial Rules 2019.
[182] Chapter VI of the New Drugs and Clinical Trial Rules 2019.

Approximately 70 million population of India suffer from rare disorders and many of those disorders still not curable and also their treatment is very high. And then now Covid- 19 pandemic has changed everything and yes the research in India before pandemic is more curved towards non-communicable diseases. The new rules are promoting clinical trials and research in India through a transparent process that yields faster approvals like drug discovered in India, or research and development of the drug has been done in India, will be deemed approved for clinical trials within 30 working days by Central Licensing Authority (CLA).

Clinical Trial Registration in India

In order to make clinical data and reports available to all, an online clinical registryhas been initiated by the Indian Council of Medical Research (ICMR) for the registration of any interventional trial to ensure the following goals:

- Transparency and accountability of clinical experimentation
- Internal validity of clinical trials
- To oversee the ethical conduct of clinical trials
- Reporting of results of clinical trials[183]

The clinical trial registry of India (CTRI) is the online registry of the prospective clinical trials in India. This is one of the initiative started by the National Institute of Medical Statistics (NIMS) of the Indian Council of Medical Research and is supported by the Department of Science and Technology (DST) and the World Health Organization (WHO)[184] Initially, the clinical trial registration was only voluntary and not mandatory. "With increased irregularities in conducting clinical trial, by June 15th 2009, CDSCO has mandated the registration of clinical trial. Clinical trial should be registered before the actual enrolment of research subjects. The responsibilities of the clinical trial registration must be shared by principal investigator or sponsor.

[183] India Law Journal. https://www.indialawjournal.org/archives/volume2/issue_3/article_by_sreesudha.html

[184] Indian clinical trial Registry maintains a database of on-going clinical trials. Any professional or general public can access the data, reports and status of the registered clinical trial free of cost; only requirement is that they should do a formal registration on the CTRI website.

Problems with new rules new drugs and clinical trials rules.

It was a significant document since it laid down the procedures to introduce new drugs in the country for the first time. Before its introduction, the new drug was haphazard and unpredictable, at the hands of the power that be. Detailed study of the rules shows that changes are very few, but the arrangement and presentation of the rules have changed significantly. If one were to evaluate whether the new rules are better than the earlier ones, an honest answer would be a mixed bag. Some of these changes are for good, but some new problems have cropped up. These are:

- New Rules created more problems through vague or faulty drafting. This has led to the issues that prevent the overall progress that the new rules would have brought about. The New rules contain 107 rules numbered 1 to 107 whether the Drugs and Cosmetics Rules 1945 consisted of 169 Rules, numbered 1 to 169. Thus, while mentioning or quoting any rules, one must specify whether the rule number referred to the Drugs and Cosmetics rules or the New Drugs Clinical Trial Rules.
- The New Drugs Clinical Trial Rules do not recognize any Independent EC. Rule 7 is only about the composition of the Ethics Committee for Clinical Trials, bioavailability and bioequivalence studies (BA, and BE) and not about independent ethics committees. About the composition of the EC for Clinical Trials, BA, and BE studies, the composition recommended is different[185]. The description is incomplete and vague and raises more questions than it answers.
- The EC had powers to approve, require modifications, or reject a research proposal in the past. Once the Institute's EC rejected or disapproved a proposal, the only remedy for the investigator was an appeal for reconsideration. The EC could subsequently approve the proposal if the investigator provided adequate grounds to do so. The NDCTR has provided an additional mechanism of relief to

[185] Rule 7 The New Drugs and Clinical Trial Rule, 2019

such an aggrieved investigator.[186] An investigator could find another EC that would approve of the proposal and conduct the study at the institute who's EC had rejected the proposal. Further, the investigator must submit the EC decision details to the CLA before approaching another EC. The rule does not say that the approval of the CLA is necessary. The problem with this rule is that it encourages EC shopping. One wonders why the new rules have brought in such a clause and how this will aid ethical research in the country.

- Compensation for clinical trial injuries is an essential aspect of subject protection. Compensation, in clinical trials, we have to understand the terms nominee and legal heir. They are not interchangeable, but the NDCTR has used them in this sense. On the death of a participant, the sponsor must pay the compensation to the legal heir.[187] The mechanism by which the sponsor or the investigator would identify the legal heir of the participant is not clear. A simple and effective compensation rule is essential for ethical clinical research, and any complication in this is likely to affect the quality of clinical research in the country.
- The need for Periodic Safety Update Reports becomes clear, but when is the manufacturer supposed to do the Phase IV trial or the Post Marketing Study is not clear. Clarification on these issues will be helpful for sponsors, investigators, and EC members.[188]

5.5 ICMR GUIDELINES

ICMR is the primary authority issuing ethical guidelines and various other principles in conducting biomedical research in India. ICMR issued such guidelines for the first time officially for the establishment of ethics committees in all medical colleges and research centres in 1980 which was named as 'Policy statement on Ethical

[186] Rule 25 (iii) New Drugs and Clinical Trials Rules
[187] Chapter VI, Rule 39(1) New Drugs and Clinical Trials Rules 2019
[188] Rule 77 New Drugs and Clinical Trials Rules 2019
Rule 82 New Drugs and Clinical Trials Rules 2019

Considerations involved in Research on Human Subjects'. The Ethics Committee (EC) acts as the bridge between a researcher and the ethical guidelines of the country. The primary responsibility of ECs is to ensure an independent, competent and timely review of all ethical dimensions of the project proposals received and ensure that it is in compliance with the ethical standards. However, these guidelines were not followed or respected by many researchers in India and India was always a part of some controversial research works. There were some unethical research works conducted which resulted in Ethical Guidelines for Biomedical Research on Human Subjects, 2000. Due to the technological advancements and changing trends in the research field, the guidelines were revised in 2006. It was lastly revised in 2017 as 'National Ethical Guidelines for Biomedical and Health Research involving participants' and by the start of the current pandemic, ICMR issued National Guidelines for Ethics Committees reviewing Biomedical & Health Research During Covid-19 Pandemic in April 2020 listing out relevant portions from the 2017 guidelines with additional new ethical guidelines for matters related to COVID-19 pandemic. The lastly revised ICMR guidelines aim at safeguarding the dignity, rights, safety and well-being of the research participants involved in biomedical and health research. All stakeholders are supposed to follow these set of guidelines and it is applicable to all biomedical, social and behavioural science research for health conducted in the country involving human participants, their biological material and data. As mentioned above, the guidelines lay down four basic principles which has to be followed while conducting biomedical and health research. They are respect for persons, beneficence, non-maleficence and justice and it must guide research in order to protect the dignity, rights, safety and well-being of research participants.[189] These four principles are expanded to twelve most important principles which play a major role in laying down the rights of research participants. Out of these 12 principles, the principles that put forward the rights of research participants are as follows:[190]

PRINCIPLE OF VOLUNTARINESS: It provides a research participant with the rights to make a decision, to be or not be part of the research. A person has the right

[189] HANDBOOK - ethics.ncdirindia.org. https://ethics.ncdirindia.org/asset/pdf/Handbook_on_ICMR_Ethical_Guidelines.pdf (last visited 2nd September 2021)

[190] INDIAN COUNCIL OF MEDICAL RESEARCH, National Ethical Guidelines for Biomedical and Health Research involving Human Participants, 1.1, (2017).

to agree or not to agree to participate in research, or to withdraw from the study at any time and this right is paramount. The informed consent process is of utmost importance and it ensures that participants' rights are safeguarded.

PRINCIPLE OF NON-EXPLOITATION: It states that research participants have to be equitably selected to ensure that the benefits and burdens of the research study are distributed in a fair and equitable manner and without any arbitrariness or discrimination. Sufficient safeguards to protect vulnerable groups should also be ensured. It tries to ensure that the research participants are given adequate remuneration for their participation in research.

PRINCIPLE OF ENSURING PRIVACY AND CONFIDENTIALITY: The participant's identity and records be kept confidential and access to these records must be limited to only those who are authorized. Also, the potential limitations to strict confidentiality have to be explained to the participant like in certain situations when it involves suicidal ideation, homicidal tendency, HIV positive status, when required by court of law etc the right to life of an individual supersedes the right to privacy of the research participant. In such situations, privacy of the information can be breached in consultation with the EC for valid scientific or legal reasons.

PRINCIPLE OF RISK MINIMIZATION: It is ensured that all stakeholders take due care at all stages of the research and thereby make sure that the risks are minimized and appropriate care and compensation is given if any harm occurs.

PRINCIPLE OF MAXIMIZATION OF BENEFIT: While efforts are made to minimise the risks, it should also be ensured that the research is designed and conducted in such a way the benefits to the research participants and society are maximised.

PRINCIPLE OF TRANSPARENCY AND ACCOUNTABILITY: It ensures that the research plan and outcomes emanating from the research are brought into the public domain through registries, reports and scientific and other publications while safeguarding the right to privacy of the participants.

PRINCIPLE OF TOTALITY OF RESPONSIBILITY: It states that all stakeholders involved in research are bound by various ethical guidelines and regulations including the rights of research participants. They are responsible for their actions and have to act in compliance with ethical guidelines and related regulations.

Apart from these rights, various other rights of patients as research participants as discussed under Section 2 of the ICMR Guidelines, are:

RIGHT TO PAYMENT FOR PARTICIPATION: The expenses incurred with respect to their participation in research like travel related expenses has to reimburse to the research participant. They should also be compensated for any inconvenience incurred, time spent and other incidental expenses like loss of wages and food supplies in either cash or kind or both.

RIGHT TO COMPENSATION FOR HARM: Participants have the right to compensation in the form of financial or other assistance if they suffer any direct physical, psychological, social, legal or economic harm as a result of their participation. Dependents of the participant are entitled to financial compensation in the event of death.

RIGHT TO ANCILLARY CARE: Participants have the right to free medical care for non-research-related conditions or incidental findings if such conditions occur during the period of research participation. However, it has to be made sure that such compensation does not amount to undue inducement as determined by the EC.

POST-TRIAL ACCESS OF RESEARCH BENEFITS TO PARTICIPANTS: It is important that the researchers make necessary arrangements wherever applicable for post-research access and sharing of academic or intervention benefits with the research participants which includes those in the control group.

Ethics Committees are supposed to ensure that these basic principles are being strictly adhered to while conducting research. It is the basic responsibility of the researcher to obtain the written, informed consent of the prospective participant or legally acceptable or authorized representative (LAR). Vulnerable groups should be included in research only when the research is directly answering the health needs or requirements of the group. They also have an equal right to be included in research so that benefits from the research apply to them as well. Patients who are terminally ill are also considered as a vulnerable group. Terminally ill patients or patients in search of new interventions after having exhausted all available therapies are regarded as vulnerable as they are ready to give consent for any intervention that can give them a ray of hope. Since the possibility of therapeutic misconception is high in such situations, there should be appropriate consent procedures and the EC should carefully review such protocols and recruitment procedures. Additional monitoring should also be done to detect any adverse event at the earliest. Benefit-risk assessment should be performed considering perception of benefits and risks by the potential participant and the EC should carefully review post-trial access to the

medication, especially if it is beneficial to the participant.

5.6 GCP GUIDELINES BY CENTRAL DRUGS STANDARD CONTROL ORGANISATION

In India, GCP Guidelines[191]were issued for biomedical research studies and to encompass the design, conduct, termination, audit, analysis, reporting, and documentation of human subjects' studies. The main objective of GCP is to ensure that the interest of science and society never takes precedence over considerations related to the well-being of the study subject while conducting research on human beings. This set of guidelines seek to establish two cardinal principles which are protection of rights of human participants and authenticity of biomedical data generated. The guidelines put emphasis on various rights of the research participants in a biomedical research such as right to privacy and confidentiality, concept of informed consent, right to be informed on various aspects of the research, right to payment for participation and compensation in case of any harm, etc. As per the GCP guidelines, all clinical experiments involving human subjects must be carried out in compliance with the Declaration of Helsinki and should respect the basic principles, namely justice, respect for persons, beneficence and non-maleficence as defined by "Ethical Guidelines for Biomedical Research on Human Subjects" issued by ICMR and any other laws and regulations of the country, which ensure a greater protection for subjects. GCP Guidelines for clinical trials in Ayurveda, Sidha and Unani medicine, 2013 was issued by Department of Ayush on the basis of the original GCP guidelines. Apart from the differences in technical aspects as the same is on a different field of medicine, the ethical principles and the rights available to the patients are the same.

5.7 CLINICAL TRIALS AND COVID 19 PANDEMIC

The global pandemic of COVID-19 has resulted in an unprecedented collaborative effort involving industry, academia, regulatory bodies, and governments, as well as significant financial investments. The only goal is to accelerate developing and

[191] CENTRAL DRUGS STANDARD CONTROL ORGANISATION, Good Clinical Practices for Clinical Research in India, 2013.

deploying a safe and effective vaccine to control the pandemic. One can draw on the experience of accelerated vaccine development, such as the H1N1/swine flu vaccine in 2009 that took 93 days to begin clinical trials after identifying the vaccine candidate. In 2014, the Ebola vaccine had a similar interval of 167 days. The H1N1 vaccine could be used while the epidemic was still ongoing. The clinical testing of the Ebola vaccine took five years. It was approved in 2019 by the European Medicines Agency (EMA) and the US Food and Drugs Administration (FDA) long after the outbreak got over. The vaccines for severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and Zika viruses are still under clinical testing. To control novel pandemics (or similar epidemics and large outbreaks), it is essential to get approval for vaccine/s while the outbreak is actively spreading in the community. The combined collaborative effort for SARS-CoV-2 has significantly accelerated vaccine development through the discovery phase, lead candidate optimization, preclinical studies, and clinical trials within two months of pandemic onset. More than 25 vaccine candidates are already in different phases of clinical trials in the second half of 2020.

5.7.1 ICMR guidelines in the context of Covid-19

Section 12 titled "Research during humanitarian emergencies and disasters" of the ICMR Guidelines, 2017 provides ethical guidance to conduct biomedical research in humanitarian emergencies. National Guidelines for Ethics Committees reviewing Biomedical & Health Research During Covid-19 Pandemic issued in April 2020 lists out relevant portions from the 2017 guidelines with additional new ethical guidelines for matters related to COVID-19 pandemic. This document reiterates several rights of the research participants as mentioned in the ICMR guidelines. Participants have the right to free health care and referrals if they suffer any direct physical, psychological, social, legal or economic injury or harm as a result of participating in the research. COVID-19 being a pandemic, the information related to it may be highly sensitive in nature and there is a large scope for stigmatization, discrimination, violence etc. In such a situation, researchers have to ensure that confidentiality and privacy of the participants are protected and any discrimination is avoided. The concept of distributive justice plays a significant role in biomedical research and the participants invited for research must be selected in a manner where the benefits and burdens of research are equitably distributed without leading to

social, racial or ethnic inequalities. It is also important that participants are paid for their participation in research and all related expenses. Compensation should also be awarded for any research related injuries. With respect to the successful investigational drug/ vaccine for COVID-19, post-trial access of these drugs should be facilitated free of cost to the trial participants till the same is available in the market. It is also important to ensure appropriate safety, funds, care and compensation, including insurance coverage as well as training at individual, societal and/or community levels for patients, health care workers and others engaged in COVID-19 research. It is the responsibility of the ECs to make sure that the research is conducted ethically in accordance to national guidelines and regulations and safeguard the dignity, rights, safety and well-being of research participants. There should also be efforts to protect the research participants from any possible stigma or discrimination. Informed Consent process has to be followed in clinical trials related to COVID-19 also. The guidelines also acknowledge that obtaining valid informed consent in humanitarian emergencies such as COVID-19 is a challenge because of the practical difficulties associated to it including reaching out to a patient in a COVID ward, isolation or quarantine facility. The capacity of a hospitalised patient with moderate or critical disease condition to decide would also be very low and he may not be possible to differentiate between reliefs offered and research components. Alternative procedures like electronic consent may be considered to avoid direct interaction with the patient in isolation. If the consent of the research participant or LAR cannot be obtained due to the emergency situation, informed consent can be administered at a later stage, when the situation permits. However, it is important that prior permission is obtained from the EC if it is so envisaged.

The guidelines state that there needs to be additional safeguards for participants as COVID-19 patients may be additionally vulnerable to being stigmatized because of the contagious nature of the disease and they may be under duress and traumatized. It should also be ensured that research addresses the needs of participants and justify inclusion of vulnerable persons. Benefits and risks of the research must be carefully determined and the risk minimization strategies must be examined. Efforts should also be made to set up support systems to deal with associated medical and social problems and ancillary care must be provided whenever possible. Persons tested positive for COVID-19, their families, health workers who get in contact with COVID positive cases have to be provided due psychosocial support wherever

possible. The guidelines emphasize on the importance and need to show respect, empathy and compassion and not subject them to any kind of stigma or discrimination.

5.8 ISSUES IN IMPLEMENTING GUIDELINES

A guideline is a statement or plan that is used to determine the best course of action. A guideline seeks to streamline specific processes in accordance with a predetermined routine or sound practice. It is not mandatory to follow a guideline if adhered to by definition. Guidelines are not legally binding and are not enforceable. An organization may issue guidelines to make the actions of its employees or divisions more predictable and presumably of higher quality[192].

The principles and regulations which is established in a community by some of the authority and it is applicable to its people, whether in legislation or custom and policies recognized and enforced by judicial decision. Any written or positive rule or set of rules imposed by the authority of the state or nation, such as by the people in its Constitution. The controlling influence of such rules; the condition of society brought about by their observance. System or collection of such rules are defined as law.[193] The ambiguity is whether the guidelines issued by various departments of the Government of India or by the contracts entered into by public bodies fall under general law and are thus enforceable through judicial intervention, or whether they are simply executive instructions subject to deviations. Are they legally binding or merely advisory?

The Indian Courts have addressed these issues in a number of cases[194], often in the context of petitions filed against the government seeking strict enforcement and compliance of these government policies/contracts as a matter of right, and have held that guidelines or executive orders that are not statutory or under some provision of the Constitution are not 'laws,' and thus cannot be enforced by the courts.

Compliance cannot be enforced through courts, and the competent authority might

[192]Guideline vs Legal Requirement, available at https://www.tempe.gov/home/showpublisheddocument/41925/636026197629000000 (last visited September 2, 2021)

[193]Law, https://dictionary.law.com/Default.aspx?selected=1111(last visited September 2, 2021)

[194] *Narendra Kumar Maheshwari vs. UOI & Ors. [AIR 1989 SC 2138]; Syndicate Bank vs. Ramachandran Pillai and Ors., [(2011) 15 SCC 398]*

depart from these guidelines where the proper exercise of discretion warrants.

This is due to the fact that such guidelines, by their very nature, do not fall within the categories of direct, subordinate, or ancillary legislation.

They merely serve as guidelines, and disobedience or divergence from them is always and implicitly permissible if the circumstances of a particular fact or legal situation merit it. Judicial control takes over as it were where the deviation either includes discretion or discrimination or is as crucial as to undermine a fundamental public purpose which the guidelines and the statute beneath which they are issued are intended to achieve.

Also, the Supreme Court of India in *GJ Fernandez vs. State of Mysore & Ors,*[195] considered the question of whether the instructions contained within the Mysore Public Work Department Code, has statutory force or not. The Court held that so as for executive instructions to possess the force of statutory rules, must show that they have been issued either under the authority conferred on the Government by some statute or under some provision of the Constitution providing therefore. Since, within the present case, the code had not been issued either under the authority conferred on the Government by some statute or under some provision of the Constitution, the Court held it to be within the nature of administrative instructions and not statutory rules. Such administrative instructions, which haven't any statutory force, can therefore confer no right on any general public member to invite a writ against Government by a petition under Article 226 of the Constitution.

Therefore, it can be concluded that Government policies, guidelines, instructions that haven't been framed under any provision of the Constitution of India or in any statute aren't considered statutory in nature and are instead within the nature of executive instructions/administrative guidelines and compliance thereof cannot be enforced through courts. Deviation or Non-adherence from them is necessarily and implicitly permissible if the circumstances of any particular fact or law situation warrants the same.

As discussed before the various guidelines relating to clinical trials in India are ICMR Guidelines and GCP Guidelines. Thus, since the above-mentioned are guidelines, no legal status can be accorded to them. Despite the existence of these guidelines, there is no substantial data on compliance (or lack thereof) by research

[195] *AIR 1967 SC 1753*

organizations or companies. There is hardly any compliance check of these guidelines. The fact is that ICMR has released these guidelines, and researchers are expected to follow these guidelines. The lack of legislation means even the evidence of violations is low. In the face of limited regulatory oversight, the repercussions that a researcher, a journal, or an institute might face following misconduct are limited. Even though these administrative measures by government agencies have helped define the ethical boundaries in Indian clinical trials, increased vigilance and implementation of guidelines, such as through legal avenues, would ramp up the quality of research done in the country.

5.8.1 Attempts to provide binding effect to ICMR Guidelines

There have been various efforts to bring legal power to these principles for conducting clinical trials and upholding the rights of participants. The Biomedical Research on Human Subjects (Regulation, Control and Safeguards) Bill, 2005 aimed at promoting and regulating biomedical and behavioural research on human subjects to ensure safety and well-being of the research subjects, to restrict unscrupulous clinical trials on unsuspecting patients, provide legislative power to the ICMR Ethical Guidelines, setting up of a National Biomedical Research Authority. National Biomedical Research Authority is expected to promote & ensure that research on human subjects is in accordance with the four basic ethical principles in the whole country, provide relief in cases of violation and exploitation of research participants, etc. The Bill was vetted by the Law Ministry, however, it could not be cleared due to various objections from different quarters.[196]

Biomedical and Health Research Regulation Bill, 2013 was another effort to put a binding effect on the ICMR guidelines. The Bill focused on the entitlements of a human participant during research making him eligible to be paid due remuneration, compensation or reimbursement for the time lost, besides reimbursement of travelling and other incidental expenses incurred in connection with his participation in research. The investigator and the institution have to take appropriate steps to safeguard the interest of special or vulnerable groups while the ethics committees

[196] Ramesh Shankar, Health ministry finalises 'Biomedical Research Human Subjects Promotion and Regulation Bill', 28 Oct. 2013, http://www.pharmabiz.com/NewsDetails.aspx?aid=78425&sid=1.(last visited September 2, 2021)

shall ensure that individuals, groups or communities proposed to be subjected to research are selected by the investigator in such a way that the "burden and benefits'' are equally distributed. It is also important that strict confidentiality of all research data is maintained so as to prevent any identification of the participant and avoid any consequent stigmatization and discrimination unless he/she is under obligation to disclose the information to any official or the government department concerned under the provisions of any law. With respect to informed consent, the investigator is obliged to obtain voluntary, documented, informed consent after being fully informed of the participant's involvement in the research and also to withdraw the consent given earlier.26 This Bill was also not successful and the need of a legislation regulating trial and providing binding effect to the ethical standards is still left unattended.

The Drugs and Cosmetics (Amendment) Bill, 2013 was introduced in the Rajya Sabha in 2013. This Bill tried to rename the Act to the Drugs, Cosmetics and Medical Devices Act, 1940 and proposed to bring changes to the regulation of import, export, manufacture, distribution and sale of drugs, cosmetics and medical devices and to ensure safety, efficacy, quality and conduct of clinical trials.[197] The Bill also had provisions for the medical treatment and compensation in case of injury or death of a person during participation in a clinical trial or due to it. However, the Bill was withdrawn by the Union Cabinet in 2016.

5.9 CONCLUSION

This chapter begins with a presentation of the Indian controlling oversight system for the governance of clinical trials. This chapter discuss the evolution of clinical trial rules and establishment of controlling bodies in India. Chapter also discuss the recent controlling instructions issued by CDSCO which is supreme controlling authority in India for clinical experimentation and trails. The fledgling clinical trials industry in India has been hit by recent revelations of a lack of regulation. Until 2013, India was considered a preferred destination for conducting clinical trials. But After the new drugs and clinical trial rules 2019, The new rules state that any drug

[197] Aarti Dhar, At last, a Bill to control unethical practices in biomedical, health research, THE HINDU, 25 Sep. 2013, https://www.thehindu.com/sci-tech/health/at-last-a-bill-to-control-unethical-practices-in-biomedical-health-research/article5167810.ece. (last visited September 2, 2021)

discovered in India, or research and development of the drug has been done in India, and which is proposed to be manufactured and marketed in the country, will be deemed approved for clinical trials within 30 working days by Central Licensing Authority (CLA). New rules will end the unnecessary repetition of trials and speed up the availability of new drugs in the country, lower the cost of drugs and will improve the ease of doing business for drug makers. In the Covid- 19 pandemic we have witnessed the speed and efficiency of the laws and authorities related to clinical trials in India. The lack of penalty or sanction is the major concern with respect to research on human beings in our country. This has led to several abuses in clinical research to an extent that as a reply to Supreme Court's question in *Kalpana Mehta v Union of India*[198], as to why the government has failed to take any action against unethically conducted foreign-sponsored trials in 2015, the government acknowledged that 'As of now, there are no specific penalties for provisions relating to clinical trials under the Drugs and Cosmetics Act'. This case was filed in the Supreme Court seeking action on the unethical trials of HPV vaccines conducted on adolescent girls.

India still does not have strict penal provisions in case of violations of the ethical guidelines. Various attempts to provide binding effect to the principles under ICMR guidelines were in vain as all the bills with respect to the matter were not successful. An effective legislation incorporating all the rights of research participants and promoting ethical standards in clinical research is the need of the hour. The abuse and exploitation are more prevalent with the vulnerable sections which includes patients especially because they are not aware about their rights and privileges. Awareness campaigns or seminars should be organized to educate the public about their rights while participating in a clinical research. It has to be ensured that the ethical principles are strictly complied by the authorities by enacting a law giving binding effect to the ICMR guidelines and imposing punishments in case of violation.

[198] (2017) 7 SCC 302.

CHAPTER 6

CONCLUSION & SUGGESTION

6.1 INTRODUCTION

Innovation in medicine development is one of the most important components of public physical health improvement. Clinical trials are the experimentation analysis that explore whether a medical device, treatment or strategy is safe and effective for humans or not. It is very complex endeavor which involves hundreds of steps that must be taken, numerous decision points, and multi-layered and iterative review processes because multiple supervisory bodies with different objectives and responsibilities have jurisdiction over clinical trials. Clinical trials are not mainly intended for the direct benefit of the experimentation subjects. Researchers first test the safety and secondly factors like proper dosage and side effects. The previous chapters has dealt with the concept of clinical trials and many internationally and nationally recognized and applicable laws and codes with respect to medical experimentation and clinical trials. However, a much more structured and comprehensive legislation relating to Clinical Trials should be enacted to ensure maximum benefit to the patients.

6.2 CONCLUSION

Chapter I gives an introduction to the topic and brief idea of the research. This chapter also deals with the relevance of the topic, and the importance of clinical trials.

Chapter II illustrates the definition concept and the relevance of clinical trial process. Then this Chapter detail explained all the process involved in a clinical trial and different categorization of clinical trials. So basically Clinical Trials is an indispensable part of the medicine discovery process to ensure the safety and efficacy of any recent medicine.

Chapter III deals with the challenges in conducting a clinical trials, and ethical and legal issues of clinical trials. Then this chapter discusses the examples of unethical practices of clinical trials and judicial interventions.

Chapter IV provides an overview of the global controlling oversight system, and presents statutory provisions of clinical trial in different countries. The chapter begins with international conventions and conferences regulating clinical trials all across the world. These conventions include, The Nuremberg Code, The Declaration of Helsinki, Council of international organization of medical sciences (CIOMS), convention on human rights and biomedicine, Good clinical practice (ICH-GCP).
Chapter V begins with a presentation of the Indian controlling oversight system for the governance of clinical trials. This chapter discuss the clinical trial rules and establishment of controlling bodies in India. Chapter also discuss the recent controlling instructions issued by CDSCO which is supreme controlling authority in India for clinical experimentation and trails. This Chapter mainly focuses on New Drugs and Clinical Trials Rules, 2019. The important changes brought under this rules. Chapter also delas with ICMR guidelines related to clinical trials.
Unfortunately, there have been some isolated incidents of alleged unethically and unregulated carried out trials. These incidents have made the patient community to believe that they are treated like guinea-pigs. The Supreme Court of India has criticized the body that oversees clinical trials for its inaction in the face of these unethical practices.

From the above mentioned chapters, the following conclusions can be drawn:

1. There are many human rights violations related to human dignity, are there while conducting a clinical trial like, Informed Consent, Privacy and Confidentiality, Selection of Vulnerable Groups.[199]

2. The various international ethical and technical guidelines as discussed in chapter IV were formulated out of a need to ensure rights of research participants and communities. All through the evolution of the practice of clinical trials on human subjects issues of violation of rights have arisen with dire consequences.[200]

3. India has adopted these international guidelines ethical standards in their

[199] See Chapter 3 of the dissertation
[200] See Chapter 4 of the Dissertation

domestic laws but these standards are also not much effective as there are no punitive measures in case of any breach.[201]

4. In India, the central government's Central Drugs Standard Control Organization (CDSCO) under the Ministry of Health and Family Welfare (headed by the Drug Controller General of India) develops standards and controlling measures for medicines, diagnostics and devices; lays down controlling measures; and regulates the market authorization of recent medicines. Clinical Trial in India is regulated by ethical guidelines and research regulations, which overlap in many situations.[202]

5. The New drugs and Clinical trials rules 2019 (New rules) was introduced on 19th March 2019 by the Government of India. The analysis of these new rules shows that changes are very few, but the presentation and arrangements of these rules have changed remarkably. Some changes introduced in these new rules are for the better, but some of these create new problems that have cropped up like vague or faulty drafting, unrecognized Independent Ethics Committee, encourages Ethics Committee shopping, there is no differentiation of the terms nominee and legal heir for the purpose of compensation, No clarity on Periodic Safety Update Reports.[203]

6. New laws or rules may not be a practical response to the conduct of clinical trial. There have been isolated incidents of alleged unethically and unregulated carried out trials. One of the recent alleged unethical trials included allegations that no consent has been obtained from the participants for Covid-19 vaccine trials in Bhopal, who also happened to be Bhopal Gas Tragedy victims. They also state that there was no follow up on their health after the vaccine administration.[204]

7. The ICMR guidelines have been accepted as the standard operating manual by the Institutional Ethics Committees (IEC) in India. Even though these administrative measures by government agencies have helped define the ethical boundaries in Indian clinical trials, increased vigilance and

[201] See Chapter 5 of the Dissertation
[202] *Id.*
[203] *Id*
[204] *Id*

implementation of guidelines, the guidelines don't have any legal status.[205]

8. The Central Drugs Standard Control Organization (CDSCO) is the National Regulatory Authority in India for clinical trials. But Supreme Court or the judiciary have intervened in the issues of clinical trials adverse reactions and scrutiny which could have well been addressed by the drug regulator or a regulator as the case may be.[206]

9. The Judiciary has criticized the body that oversees clinical trials for its inaction in the face of these unethical practices, but they are just making rules and regulations they fail to implement these.[207]

6.3 SUGGESTIONS

1. There is a need for universal acceptance of the international principles of the international guidelines and integration into national laws to ensure that the risks of health research are not shipped off to a less regulated country with more leeway to abuse.
2. Clinical trials not only contribute to the scientific experimentation and medicine development but also ensure better patient care than normal clinical practice in hospitals and in long run it is a boon for the society as it eventually leads to the development of recent generic medicines and medicines. But India is losing out the opportunity for clinical trials by foreign companies because of the uncertainties in the controlling framework and acquiescence mechanism for conducting clinical trials. It is time to give some certainty to this. While making laws and rules it should be note that Clinical Trials is important for the development of the country.
3. Without undermining the need of amending the existing rules relating to the clinical trials thereby making the clinical trials safer and preventing the exploitation of vulnerable subjects participating in such trials, it is necessary to appreciate that we as a developing economy with the conditions so suitable for clinical trials like diverse population, cost effective facilities and

[205] *Id*
[206] *Id*
[207] *Id*

resources, presence of reputed pharmaceutical companies including subsidiaries of such multinational corporations willing to act as a sponsor and trained investigators, should not restrict the growth of clinical trials and instead try to promote a strong culture of experimentation and development in the physical health sector in India.

4. Pharmaceutical companies or institution involved in clinical trials, do not want any negative publicity. They do not want to defend themselves over ethical issues such as human rights violation or unethical treatment of patients, unethical practice etc. In today's diverse and cut throat competitive environment, one must acknowledge that law generally incorporates ethical principles, but law and ethics are far from co- extensive. While framing laws, other elements such as social utility, economic growth etc. should be taken into consideration. However, it is not necessary that law would always prohibit something which is considered as unethical and the vice versa holds well.
5. There is a strong requirement for liberalizing the controlling environment in favor of the sponsors conducting such trials and at the same time balancing the interest of the subjects involved in such trials. Further the acquiescence mechanism needs to be more transparent and time efficient. Concerns raised by the human rights activist and NGOs are genuine, but rejecting or delaying the acquiescence to the applications for conducting clinical trials is in no way a solution to the problem. Law should be for the regulation of the clinical trials and not for restricting the clinical trials. Instead of dismissing clinical trials or delaying the acquiescence process, what is required is to identify and fix the loopholes in the controlling framework and implement existing laws effectively to ensure that clinical trials are carried out with utmost transparency and diligence. Otherwise we would end up losing the prospects of growth of clinical experimentation activities in India, which would certainly be a huge loss to our physical health care sector.
6. The biggest problem in India is the proper implementation and enforcement of laws and regulations. India is eager to enact laws and not so eager to enforce them. Indian parliament comes with new laws every year. Laws on clinical trial have been amended several times but there is no improvement in situation. On one side, India is trying to meet the international standards

in clinical trial industry while on the other side the important question arises that what India is doing to achieve the international standard? In lack of adequate enforcement mechanism, drug companies violate the laws and give bribes to the ethics committees, investigators and other supervising authority. These authorities do not raise concern for such violations.

7. India still does not have strict penal provisions in case of violations of the ethical guidelines. Various attempts to provide binding effect to the principles under ICMR guidelines were in vain as all the bills with respect to the matter were not successful. An effective legislation incorporating all the rights of research participants and promoting ethical standards in clinical research is the need of the hour.
8. The abuse and exploitation are more prevalent with the vulnerable sections which includes patients especially because they are not aware about their rights and privileges. Awareness campaigns or seminars should be organized to educate the public about their rights while participating in a clinical research. It has to be ensured that the ethical principles are strictly complied by the authorities by enacting a law giving binding effect to the ICMR guidelines and imposing punishments in case of violation.
9. There have been various efforts to bring legal power to the ICMR and GCP guidelines for conducting clinical trials and upholding the rights of participants. Should bring legal power to these guidelines for conducting ethical clinical trials.

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APPENDIX

THE NATIONAL UNIVERSITY OF ADVANCED LEGAL STUDIES

Kalamassery, Kochi – 683 503, Kerala, India

CERTIFICATE ON PLAGIARISM CHECK

1.	Name of the Candidate	Panchamy Babu
2.	Title of Thesis/Dissertation	CLINICAL TRIALS: A STUDY ON THE EXISTING NATIONAL AND INTERNATIONAL LAWS
3.	Name of the Supervisor	Dr. Liji Samuel
4.	Similar Content (%) Identified	11%
5.	Acceptable Maximum Limit (%)	20%
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