CLINICAL TRIALS

Regulative Legal Controls on Bio-Logical Warfare

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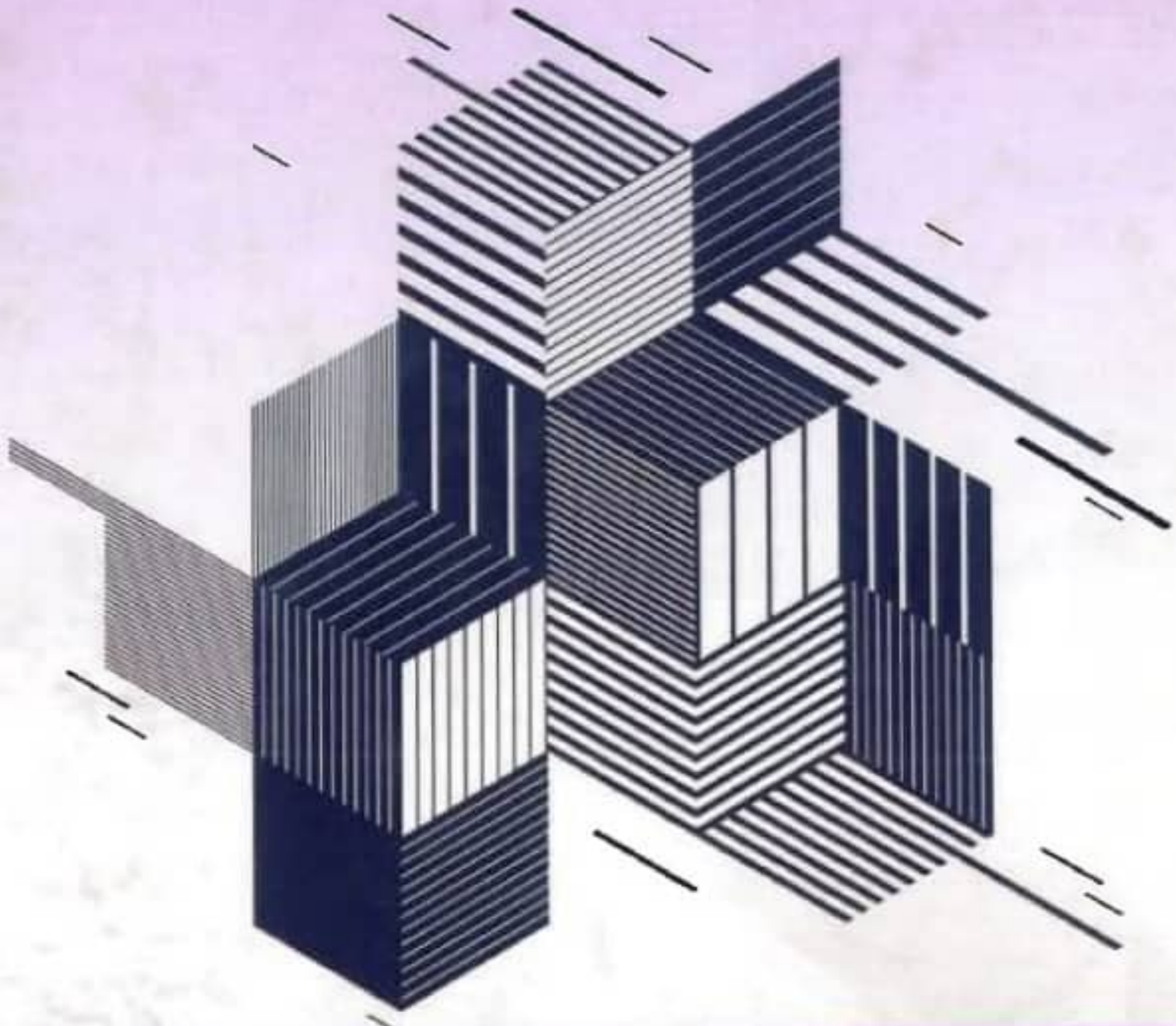

BLOOMSBURY

Contents

Code of Conduct in Clinical Trials and its Historical Perspective and Contemporary Importance

Mr. Saju Jakob*

ABSTRACT: Ever since the dawn of 2020, mankind has only one chant "break the chain" of corona virus infection. In the beginning of the year 2020, many countries were literally shocked at the spread out of covid-19 virus and its impact on their citizen. As on today, 21" of June 2020, the corona infections in India rose to 4.25 lakhs. Globally infection rate is nearing to 9 million. Every day, name of one or another country finds its new place in the front page of all newspapers across the globe with a report of its new ranking in the rate of covid infected patients. The said virus has not only attacked the health of the people but declared emergency on the entire activities of mankind at large. The whole world is at war against the virus of covid 19 pandemic and tall leaders of various countries fell prey to the attack of such virus. Everyone's freedom is largely affected or limited to the minimum requirements of life. Each new dawn begins with the one and same question, "if there is any drug already invented against this viral attack or any vaccination available?" Naturally, the horizon of a human being's interest is expanded to the new areas of wisdom and quite naturally, the term, clinical trial has become a common man's term in their daily vocabulary in today's world of distress and panic due to the covid-19 viruses. Sole objective of clinical trials is to figure out if a new medicine is effective in human body to protect from deceases and to enhance the knowledge of it's working in human biology for the protection of health and thereby of the mankind. Where the extent of medical science has reached its new heights,

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* The author [LL.B (IND), LL.M. (GER), MBA (USA)], is the Advocate practising in the Supreme Court of India. He is the Member of Law Society, London; Member of Bar Council, Cologne, Germany; Life Member of Supreme Court Bar Association; Solicitor of U.K. and Germany, and the Senior Counsel in the law firm Lily Thomas and Saju Jakob. His expertise lies in constitutional law, criminal law and international contracts.

clinical trials have become the prime research tool to check the effectiveness of new drugs. Clinical trial is the experiments conducted on several humans at once to test the reaction of that drug on human bodies within different variables. Whereas its importance cannot be challenged, the process poses a serious threat on the fundamental rights of those humans on whom the drug is tested, known as 'trial subjects', as well as those infected people on whom the new drug is inflicted for the first time, who are known as 'post trial subjects'. Whereas, every person on account of being a human, holds the freedom to impose himself into any situation of his choice, the way of exercising the right to choice holds the constitutional questions of the choice or consent being free and informed. Several questions arise in the mind on this aspect. Whether a trial subject volunteering to undergo the clinical trial due to abject poverty can be considered to have given free consent?

If the procedure of legal/ medical recourse is not known by the trial subject, can his consent be considered as an informed consent? Whether the right to freedom and right to life of an individual can be put under scrutiny for the benefit of the public at large? Whether the consent of a legal heir of the 'trial subject' or 'post trial subject' can be considered as the consent of 'the subject'? When the countries relax the rules of clinical trials, in the light of emergency due to the pandemic, do the need to give up all the constitutional right of individuals or they need to strike a balance at the heart of democratic values? Many more questions with regard to the ethical regulations have arisen in the minds of various jurists and authorities. The need to bring in the morality of democratic ethics was felt way back, which has been discussed later in the research paper. The current research paper aims to find out not only the constitutional aspect of clinical trials, but also the modus operandi of conducting clinical trials in general and resultant injury and deaths, if any. The research paper examines the global code of conduct existing across the globe, and also its historical perspective.

Keywords: Clinical trials, Historical Perspective, Indian Perspective, ICCPR, World Medical Association.

CHAPTERIZATION: The Part I of the paper deals with the introduction to the constitutional aspect of clinical trials. Part II deals with the historical perspective of clinical trials which includes Prussian code, Helsinki declaration, Nuremberg code, ICCPR guidelines, CIOMS guidelines and u.n charter. Part III deals with the global perspective of clinical trials. Part IV deals with Indian perspective and Part V deals with conclusion of the research paper.

INTRODUCTION

The history of clinical trials and ethical regulations can be traced way back to 1747, when first controlled clinical trial was done by James kind to find that citrus fruit could be used to prevent and cure scurvy.[1] The first recorded clinical trial, though not of medicine, was done by king Nebuchadnezzar in babylon,[2] when he ordered his people to eat only meat and wine as their diet. The order of the kind was objected to by some royal blood who preferred a vegetarian diet. For the first ten days, these royal bloods were allowed to eat legumes and water, however after ten days the vegetarian appeared to be healthier than the meat eaters and hence the king allowed them to continue on their diet. Whereas during that era, people were bound by the order of the king and had no alternative but to abide by king's order, today, we are protected by constitutional and enshrined right there under. Our every action is guided by constitutional framework and protected by constitutional right and Indian constitution provides for quality of life as fundamental rights. Informed consent forms the ethical and constitutional backbone of clinical trials and the consequences of a party being subjected to a clinical trial must be known to the patient. The consent of the patient must be gleaned from the person by informing him of varied implications which could arise from the entire process of human experimentation. The term informed consent first was used in Helsinki declaration, 1964[3] which also provided for the subject to withdraw his consent to participate without reprisal. Informed consent was defined as "*informed consent is a decision to participate in research, taken by a competent individual who has received the necessary information; who has adequately understood the information; and who, after considering the information, has arrived at a decision without having been subjected to coercion, undue influence, inducement or intimidation.*"

The two tests which governed the standard of informed consent in medical filed are the prudent patient test and reasonable doctor test are

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[1] Katkade, Sanders and Zou, "*real world data: an opportunity to supplement existing evidence for the use of long-established medicines in health care decision making*", *Journal of multidisciplinary healthcare*, dove press, 2018.

[2] Anonymous, "*The history of clinical trials is fascinating,*" Boston clinical trials: bridging the gap between compound and cure, 2014.

[3] Principle 25 of Helsinki declaration (1964).

two,[4] while in former the doctor discloses only the material information which a patient considers material, the later standards, originated from American case laws,[5] connotes disclosure of all[6] details which another doctor would disclose in the same instance. In these standards, a consideration is kept about the health and effect of the information on the patient, however in clinical trial these standards cannot be adopted. It must be much more than the information sought by the subject, as the patient may not be aware of intricate details and effects for the drug is still on trial stage and the reasonable doctor test cannot be the guiding standard as the subject would be rendered to guinea pigs with no bodily autonomy, if the decision of how much information to be disclosed is left over on the physician. Hence in clinical trials, informed consent signifies a complete disclosure of it, from the method used, to the effect and the aftermaths of the clinical trial.

Another aspect which needs contemplation is body autonomy of an individual which has been recognized by the apex court[7] and it is one's right to decide with respect to one's body that is the idea that people should be able to rule themselves rather than be ruled by others,[8] hence the concept of informed concept relies on one's exercise of his right to bodily autonomy. The un charter mandates the need for consent and lays emphasis on human dignity and informed consent and with the outbreak of covid-19, the importance of informed consent with the need for a vaccine during health emergencies cannot be emphasized. Hydroxychloroquine has been in the news for being a potential drug to treat corona virus infected patients and related side-effects. The instance of use of hydroxychloroquine, with no conclusive proof of its benefit and without testing its effect on a corona-virus infected patient, renders the covid-19 patient as research subject, without consent let alone informed

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[4] International ethical guidelines for biomedical research involving human subjects (2002).

[5] *Canterbury v Spence* (464 f.2d. 772, 782 d.c. Cir. 1972.

[6] *Salgo v Leland Standfordjr. University board of trustees*, 154 cal. App. 2d 560 (1957).

[7] *Nalsa v union of India and puttaswamy (i) v union of India*, writ petition (civil) No. 400 of 2012.

[8] Harigovind, P.C., "*Informed consent in clinical trials and the role of institutional ethics committees: A sociol-legal analysis*", *Christ university law journal*, 3, 1 (2014), 1–16, ISSN 2278–4322.

consent. In this emergency health crisis, the question which needs to be answered is whether the most important and ethical aspect of clinical trials can be surpassed and patients can be reduced as a research subject. Though the theory of utilitarianism may justify subjecting people to pain for the benefit of the larger populace, however in this run for a lifesaving drug, an individual autonomy being protected by constitution cannot be forced to take a back seat. This research paper traces the history of clinical trial and the concept of informed consent. Paper analyses various international guidelines and framework which may or may not be binding yet are ethically to be observed while carrying out a clinical trial. The researcher seeks to analyse the constitutional aspect of clinical trial in light of the various new guidelines issued by the government of India.

HISTORICAL PERSPECTIVE

19th century marked desideratum of human trials, specifically in the field of bacteriology, venereology, immunology and virology to study the effect and consequences of drugs along with the evaluation of its dosage. During this time human experimentations were carried on hospitalised patients without their consent giving rise to the facets of medical ethics and human rights. In 1767, john hunter, a Scottish surgeon, renowned for advocating research and experimentation and propagator of scientific methods in medicine,[9] performed a human experiment, where he injected pus from one patient who was suffering from gonorrhoea into penis of another man who was perfectly normal. But later on it was discovered that the man developed both the disease simultaneously gonorrhoea and syphilis at the same time. This paved the way for surgeons to believe that gonorrhea and syphilis had the same source of origin.[10] later, Philippe Ricord, the French physician conducted almost 2500 experiments on humans in the form of inoculations between 1831–1837. Although with these experimentations, he was able to find out the difference between syphilis and gonorrhea as well as finely trace the three stages.

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[9] Kelly a Kapp and Glean e. Talboy, "*John hunter, the father of scientific surgery*", American college of surgeon, 2017.

[10] Ameeta e. Singh and Barbara Romanowski, "*Syphilis: review with emphasis on clinical, epidemiologic, and some biologic features*" clinical microbiology reviews, American society for microbiology (1999).

Of syphilis,[11] but he believed that it was absolutely wrong to inoculate healthy people with diseases whose consequences were unpredictable.

Prussian Code and Neisser Case (1901)

In 1892 by Albert Neisser, head of Nematology, at the University of Breslau in Prussia found gonococcus bacterium, which was bacteria causing sexually transmitted genitourinary infection gonorrhea.[12] He developed a study for syphilis' prevention which was achieved through human experimentation. His study was categorised into two categories based on the age of the subject. The first group consist of female subjects between the age of adolescence and maturity i.e. 10–24 years of age these subjects were injected with serum from the infected patients which lead to them developing gonorrhoea and condylomas but none developed syphilis,[13] second group consist of prostitutes of age group between 17–21 years, who were injected with 30 ml of the serum from patients in various stage of syphilis and in time frame of few months they developed syphilis. The study was concluded by Albert Neisser with observation that the development of syphilis infections in the women was due to their exposure to sexual activities.

And not these rum injected to them,[14] the study conducted by Neisser called public attention.

When the same was published as a part of series published on practice of experimentation by daily newspaper, *the munchmerfreiepresse* tiled "poor people in hospitals". The spark of the study did not stop with newspaper article, rather led various rounds of discussion in parliament in context of funding raised for universities and research, with contrary views. The trial carried by Neisser marked history when in 1898, Prussia's public prosecutor began his investigation and presented all the facts and evidence in the court. The court though observed Albert Neeisser to be an authority in medical field and might have a view of the trial not be harmful, however

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[11] Deepak Vashishtand Sukritibaveja, "*Eponyms in syphilis*", Indian journal of sexually transmitted diseases and aids (2015).

[12] Friedrich h Moll, "*Albert Neisser and the first Prussian directive on informed consent*", Skeletons in the closet indignities and in justifies in medicine (1 American urological association).

[13] *Ibid.*

[14] *Ibid.*

he must have obtained explicit consent from the trial subjects. The court made is explicit that held that its concern was not the experiment rather the consent of the patients who were not informed of the risk and consequences.[15]

Later in 1899, the case was discussed by Prussian government based on a report from the commission comprising of leading German physician concluded that the physician had no right to inject the serum and in any case there was necessity of both; the subject bring informed of about the experiment and obtaining consent of subject before the initiation of any such experiment. The experiment was further categorised to be bodily injury under criminal law as the non-therapeutic research was conducted without the consent of the subject.[16]

In 1900, the government of Prussia issued guidelines, which came to be first state directives on human experimentation including responsibility and free consent and was known as the Prussian code (Also called Berlin Code 1900).

The Prussian code pointed out the specific guideline with respect to consent:[17]

> "... That medical interventions for purposes other than diagnosis, therapy, and immunization are absolutely prohibited, even if all other legal and ethical requirements for performing such interventions are fulfilled if: (1) the person in question is a minor or is not fully competent on other grounds; (2) the person concerned has not declared unequivocally that he consents to the intervention; (3) the declaration has not been made on the basis of a proper explanation of the adverse consequences that might result from the intervention..."

Prussian code was the first code which regulated medical ethics and emphasised on consent in clinical trials.

Nuremberg Code (1947): Doctors Trial

With the extensive medical human experimentations in European countries, Germany formulated the guidelines on human experimentation,

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[15] *Ibid.*
[16] *Ibid.*
[17] Principle 25 of Helsinki declaration (1964).

1931 which[18] suggested that any innovative therapy must be justified and conducted according to the principles of medical practices and theory.[19] The guidelines mandated additional requirement of unambiguous consent of the subject or its legal representative, called for extra caution in case of experimentation on minors and clearly reiterated that exploitation of social hardships in order to put a subject under clinical trial will be against the principle of medical ethics.[20] The guidelines clearly prohibited the clinical trials in the cases where consent was not received, where animal trial was not conducted first, on minors where the experiment can lead to lethal consequences and in cases involving dying subjects,[21] the guidelines 1931 were followed till 1945.

In 1945, with the end of World War II, international military tribunal was enacted on November 19th, 1945 to conduct the trail of war criminals. Among the various trials, the first trials was that of 23 physicians, responsible for murder, or impairment of the patients who were suffering from mental illness and physical disability, who were tried for crime against humanity for, they carried experiment of the prisoners of wars. The doctor's trials titled as "*united states of America v Karl Brandt*" took place at the palace of justice in Nuremberg, Germany.[22] The indictment was filed on October 25, 1946 and the trial lasted from December 9, 1946 to august 20, 1947. The presiding judges held the 16 of the defendant doctors guilty and seven were sentenced to death. Despite the German guidelines on clinical trials, 1931, no such consideration was given to the freedom of choice and consent to the war criminals.[23]

The trial and conviction led to the Nuremberg code which was published on august 17th, 1947, which provided for the standards to be followed while a clinical trial on human is conducted. The code emphasised on the informed consent of the trial subject and such consent must not be given under coercion, or deception or by way of fraud being played on the

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[18] Encyclopedia of bioethics, ed. Warren t Reich 2nd edition, appendix, pp. 2762–2763.

[19] German guidelines on human experimentation, 1931.

[20] *Ibid.*

[21] *Ibid.*

[22] Morris low, "*Pathways to human experimentation, 1933–1945: Germany, Japan, and the United States*" Osiris (2005).

[23] Ravindra b Ghooi, "*The Nuremberg code—a critique*" perspectives in clinical research (2011).

subject. The code also gave right to the subject to withdraw his consent at any time and not to continue the experiment. It further lays that the subject of the trial must not be subjected to unnecessary physical and mental suffering and no clinical trial must be carried if there are chances of any harm to the subject; physical or mental. Further the doctor must be ready to terminate the experiment, when and where he fails to apply required professional skill and continuation of the experiment is likely to result in injury, disability, or death of the experimental subject.[24]

Apart from the above principles emphasising on consent and welfare of the subject, the other dictates of Nuremberg code are that the experimental results should be for the greater good of the society, anticipated result should justify the experiment, the risk factor shall not be beyond human control, adequate facilities/precaution must be taken to provide protection to human subjects, the experiment must be conducted in the presence of/by qualified doctors.

The Nuremburg trial resulting to Nuremburg code emphasised upon human life and that no one can be denied of it by lowering them as mere trial subjects. Humans can be subjected to only those procedures where there are no harm and hurt. Though the code defined the concept of consent with ethical, moral and legal satisfaction of clinical trial yet it was silent on what happens, if even after following all precautions, any harm, injury or death was sustained by the subject.

Declaration of Helsinki

In 1964, Declaration of Helsinki was adopted by the 18th world medical association (WMA) in general assembly, in the form of ethical principles for the protection of humans from experiments.[25] **The declaration of Helsinki for the first time, provided binding standards in case of involvement of human subjects in any research.** With the word such as "*a physician shall act in the patient's best interest when providing medical care*"[26]

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[24] Principle of Nuremberg code (1947).

[25] World medical association, wma declaration of Helsinki – ethical principles for medical research involving human subjects, available at: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects

[26] Declaration of Helsinki: ethical principles for medical research involving human subjects, 1964.

emphasise upon the binding nature of the principles enshrined in the declaration. Further the declaration put the complete responsibility of the safeguards of the clinical subjects on the physician and health care professionals even if the consent has been obtained from the subject. Whereas the declaration permits the adherence to the national guidelines of one's own country, however it stipulates clearly that "*no national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this declaration.*"[27]

The declaration part from laying down the protocol for the conduct of clinical trial further provides for the research protocol to provide for "*incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.*" Further the declaration also made a reference to vulnerable groups likely to be exploited and thus, made sure that no experimentation is done to the vulnerable groups and only when there is a necessity of the experiment to be conducted on the vulnerable group, it would be permitted to be conducted. The declaration provides for the constitution of research ethics committee which would approval to the research prior to its beginning, it would keep a check during the trial and check the final report of the trial conducted and concluded. Before the study begins every research, protocol must be submitted to the ethics committee for "*consideration, comment, guidance and approval*".

The Helsinki declaration addressed "the issue of clinical trial and come to be as of the most influential documents and is considered as *the property of all humanity*".[28] It has been an influential in national legislation and is considered as the cornerstone for conduct of human research ethics.

International Covenant on Civil and Political Rights (ICCPR)

The international covenant on civil and political rights (ICCPR) enter into force on March 23rd, 1976 and recognised "the inherent dignity and of the equal and inalienable rights of all members of the human family as the

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[27] *Ibid.*

[28] Badri Man Shrestha, "*The declaration of Helsinki in relation to medical research: Historical and current perspectives,*" *Journal of Nepal health research council* (2012).

foundation of freedom, justice and peace in the world".[29] ICCPR provides for three non-derogable rights to person; right to life[30], freedom from non-consensual medical experimentation on humans[31], and non-discrimination[32] right ealth being facet of right to life, which is a non-derogable right under ICCPR, ICESCR develops the idea of "core obligations" on the part of the state in the aspect of human rights.[33] The covenant vividly provides the accountability of the state in the words "a state party cannot, under any circumstances whatsoever, justify its non-compliance with the core obligations...which arenon-derogable."[34] The accountability of state extent to regulate the domestic and foreign clinical trials conducted by pharmaceutical companies and hence is the prime ensure of human rights.

Ethical guidelines for clinical trial on human subject by council for international organisation of medical science (CIOMS):[35]

> In 1949, "...council for international organisation of medical science (CIOMS) was established by the world health organisation and united nations educational, scientific and cultural organization (UNESCO) for the representation of the biomedical scientific community, which in turn developed international ethical guidelines for biomedical research involving human subjects. The first version of CIOMS guidelines was guideline of 1982 which was revised in 1993 (period which followed the outbreak of HIV/Aids). The ethical issue resulting from the sponsored clinical trials being carried out at low resource setting, resulted in revision of 1993 guideline and the third version of CIOMS guidelines were drafted and finished in 2002 (which was further broadened in 2016 guidelines in light of

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[29] Preamble, international covenant on civil and political rights, 1966.
[30] Article 6, ICCPR.
[31] Article 7, ICCPR.
[32] Article 26, ICCPR.
[33] Article 12.1, ICESCR.
[34] Committee on economic, social and cultural rights, general comment no. 14, the right to the highest attainable standard of health, un doc. No. E/c.12/2000/4 (2000).
[35] Council for international organizations of medical sciences, "*international ethical guidelines for health-related research involving humans*" (2016). Available at: https://cioms.ch/publications/product/international-ethical-guidelines-for-health-related-research-involving-humans.

major changes and revision of declaration of Helsinki in 2008). CIOMS guidelines have been conceived to facilitate the practical implementation of the wma's declaration of Helsinki and to regulate such implementation in low- and middle-income countries. The aim of the guidelines was to provide internationally vetted ethical principles and detailed guidelines on ethical principles should be universally applied, with attention to conducting research in low-resource settings..."[36]

The reiterations of the guidelines are as follows:

1. ***Scientific and Social Value and Respect for Rights***[37]***:*** It presupposes the relations between the scientific and social values in the form of the moral ethics by researchers, scientists, sponsors, and other competitive authorities, which recognise human and respect human dignity. It simply suggests that any scientific advancement cannot surpass the human value and could not open doors to injustice and mistreatment of the human subjects, thus in turn forming the moral ethics of the authorities.
2. ***Research Conducted in Low-Resource Settings***[37]***:*** The guideline provides for the pre-requisites to be ensured before research in a community with low resource is undertaken. The researcher and sponsor as part of their obligation must first analyse that the research being carried is for the public good and research has been carried on small population before it being initiated in a human community. It is the responsibility of the concerned authority to ensure that the experiment to be conducted is safe for public health and the research must be preceded by a deep study of the testing. Prior consultation with the authorities engaged in doing that experiment must been ensured.
3. ***"Equitable distribution of benefits and burdens in the selection of individuals and groups of participants in research"***[38]***:*** The guideline provide for all the stakeholders (researcher, sponsors, governmental authorities) to ensure that the burdens and the benefits of the

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[36] Declaration of Helsinki (1964). Timothy J. Doenges, Bryan J. Dik, available at: https://www.britannica.com/topic/declaration-of-helsinki

[37] Guideline 1-2, CIOMS.

[38] Guideline 3-6, CIOMS.

research must be shared equitably. The members involved in the experiment/trial, must be involved with not more than fair share of the risks and burden. The government authorities, researchers, and doctors and human subjects involved in the trials must have full knowledge of the risk and consequences of the trial. Human subjects must also benefit from the trial, hence surpassing the exploitation as cheap human objects.

4. ***"Potential individual benefits and risks of research"***[38]

   "*To justify imposing any research risks on participants in health research, the research must have social and scientific value. Before inviting potential participants to join a study, the researcher, sponsor and the research ethics committee must ensure that risks to participants are minimum and appropriately balanced in relation to the prospect of potential individual benefit and the social and scientific value of the research.*" It envisages a two-step process; first "*the potential individual benefits and risks of each individual research intervention or procedure in the study must be evaluated*" and second "*the aggregate risks and potential individual benefits of the entire study must be assessed and must be considered appropriate.*"

5. ***Choice of Control in Clinical Trials***[38]***:*** Whenever the clinical trial is about to start, all the concerned participants must be informed about the consequences and effective risk. The participants (human subject) must not be exposed to danger only because they have consented for the trial. Before inoculation, the study must be conducted completely diagnosing the condition of participants. "*The research ethics committee must ensure that research participants in the control group of a trial of a diagnostic, therapeutic, or preventive intervention receive an established effective intervention.*" Hence all risks and benefits must be evaluated as per the criteria set out under this guideline.

6. ***Caring for Participants' Health Needs***[38]***:*** While conducting a clinical trial effective measures must be ensured to make adequate provisions to address the health need of the participants of the trial. If the health care need of the participants during and after the trial cannot be taken care of by the local health care facility, the researcher and sponsor must ensure prior availability of adequate health care for the participants. "*...the guideline requires a five-fold plan to be undertaken by the researcher and the sponsors:*

- *How care will be adequately provided for the condition understudy.*
- *How care will be provided during the research when researchers discover conditions other than those under study ("ancillary care").*
- *Providing continued access to study interventions that have demonstrated significant benefit; and*
- *Consulting with other relevant stakeholders, if any, to determine everyone's responsibilities and the conditions under which participants will receive continued access to a study intervention, such as an investigational drug, that has demonstrated significant benefit in the study..."*

7. ***Community Engagement***[39]***:*** The researchers concerned authorities and the sponsors should take into consideration the; local factors while carrying research in a community and must build confidence with the leader of community to negotiate various aspects of research. There must be transparency and disagreement if any must be solved through negotiation. Hence the community must be engaged in conduct of clinical trial.
8. ***Collaborative partnership and capacity-building for research and research review***[39]***:*** The government authorities, being the guarantors of fundamental rights to its citizens, must review the research and reports from time to time. The independent research organisation and research committees must review the research done by the private sector/institutions involving human subjects so that the implementation of international guidelines on medical ethics and human rights can be followed.
9. ***Individuals Capable of Giving Informed Consent***[39]***:*** The moral as well as legal obligation of the sponsors and researchers includes selecting potential participants who have attained an age of maturity, are of sound mind and are capable of understanding what is wrong and right. The participants must be informed of the effect and consequences of the trial so that they are able to give free and informed consent for the experiment. There must not be any deception and withholding of information with the participants given enough time to consider their participation.

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[39] Guideline 7-9, CIOMS.

10. ***Modifications and Waivers of Informed Consent***[40]***:*** The participant must be free from all obligations before or during the trial to waive the right to consent. However before such waiver of informed consent is granted, the ethics committee should "*establish whether informed consent could be modified in a way that would preserve the participant's ability to understand the general nature of the investigation and to decide whether to participate.*"

    Waiver of informed consent would be approved if:

    "The research would not be feasible or practicable to carry out without the waiver or modification;

    - *The research has important social value; and*
    - *The research poses no more than minimal risks to participants."*

11. ***Collection, storage and use of biological materials and related data***[40]***:*** The collection of data and information must be done by the researchers and sponsors in order to provide the information to government authorities. The biological material i.e. Residual tissue is stored for future research with the consent of the patients. All the research data is kept in a record book and some of the research results as a specimen so that it can be shown to the patient and references can be made from it.

12. ***Collection, storage and use of data in health-related research***[40]***:*** The collection of data is done in the form of research paper and research results, the experiments in the past are used as reference so that failure can be ignored. The reason behind the storage data in health-related research is that the data stored will provide a source to get accurate information and what is the essential part to respond. Data collection and storage must not affect the right and welfare individual. The researcher must obtain either specific informed consent for the use of data for specific purpose or broad informed consent for unspecified future use must be obtained from the person. The collection and storage of data is guided by the guideline 12.

13. ***Reimbursement and compensation for research participants***[41]***:*** The participants involved in trial must be reimbursed with the expenses of travelling, lodging and time spent in the experiment. The

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[40] Guideline 10-12, CIOMS.
[41] Guideline 13-16, CIOMS.

compensation must be done if there is loss of any organ or harm to any part of the body. That compensation can be monetary or non-monetary. The monetary value fixed must be reasonable and according to the risk factor at the time of experiment.

14. ***Treatment and compensation for research- related harms***[41]*:* The sponsors and researchers must compensate the participants for any physical, psychological or social harm resulting from participation in the research. The researcher must ensure that the participant receives the required treatment for free along with compensation for loss of wages. The participants must be compensates with reasonable amount and sufficient medical care, wherein the research ethics committee would determine upon the adequacy of the compensation and arrangement for treatment.

15. ***Research involving vulnerable persons and groups***[41]*:* In some trials there is a requirement of some vulnerable group of persons e.g. Children, persons with disabilities or persons suffering from dangerous diseases to be participants. While conducting such clinical trial there must be adequate safeguards and extra protection equipment to neglect any harm to human health of these vulnerable groups. It is the responsibility of the research ethics committee to ensure that human subjects are not exposed to any risk which may result in any kind of loss or death.

16. ***Research involving adults incapable of giving informed consent***[41]*:* The researchers and sponsors must follow the ethical guidelines to conduct a trial wherein the participants are adults who are incapable of giving informed consent. However, such trials are to be carried following the research ethics committee guidelines so as to protect the interest and rights of such participants. The guideline provides that "*before undertaking research with adults who are not capable of giving informed consent, the researcher and the research ethics committee must ensure that:*

A legally authorized representative of the person who is incapable of giving informed consent has given permission and this permission takes account of the participant's previously formed preferences and values (if any); and

The assent of the subject has been obtained to the extent of that person's capacity, after having been provided with adequate information about

the research at the level of the subject's capacity for understanding this information."

17. ***Research involving children and adolescents***[42]***:*** Children and adolescents must be involved in health research so that requirements for the proper growth can be analysed and development and research can be done in that direction. The researchers must follow the concerned guidelines in order to safeguard the interest, rights and welfare of the children.
18. ***Women as a research participant***[42]***:*** Women must be included in health related research, however women are usually excluded from these research because of their child bearing potential. When a woman is involved in the trial then only the researchers can know the requirement of the drugs for the disease which are mainly affecting women's health. A woman must be informed of all health risk and it is only the consent of a woman which must be taken into account.
19. ***Pregnant and breastfeeding women as research participants***[42]***:*** The women who are pregnant and breastfeeding babies have distinct health requirements. The involvement of these women will give new ideas and reasons to understand the dietary needs, medical requirements and data will also build so that the patients suffering from any of these health problems can be treated easily, however research on such women must be carried out as per the guideline 19.
20. ***Research in disasters and disease outbreaks***[43]***:*** Places where disasters have been observed must be involved in the health related activities for the better understanding of the genomic mutation. Disaster like extreme cold, summer or rain, which requires a good immune system to survive. This all will give a good research point to know better about the conditions of the people living in that area. The research ethics committee guidelines must be followed for the protection of their rights and interest, which cannot be foregone, even during the times of disasters. The ethical principles embodied in the guideline must be followed even during the disease or disaster outbreak.
21. ***Cluster randomized trials***[43]***:*** Whenever there is any cluster trial, it is the responsibility of the researchers and authorities to identify the

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[42] Guideline 17-20, CIOMS.
[43] Guideline 21-25, CIOMS.

people and group who will be affected from that trial. Cluster trials result in the large data and information about the experiment.

22. ***Use of data obtained from the online environment and digital tools in health-related research[43]:*** The data obtained from an online environment is a secondary source and is not reliable until supported with sufficient strong scientific data. This data is related to the experimented data for the reference so that a proper analysis can be done, and a conclusion can be made.
23. ***Requirements for establishing research ethics committees and for their review of protocols[43]:*** Research ethics committee must establish some guidelines so that researchers can follow and implement them during experiments. The trial process is guided by the ethic committed. Every protocol of a research trial is approved by the ethics committee.
24. ***Public accountability for health-related research[43]:*** The general public must be involved in the clinical trial by giving them a proper explanation about the experiment. The researchers and sponsors must comply with recognised public ethics and must be accountable to the general public if any harm is caused due to the experiment.
25. ***Conflicts of interest[43]:*** Each individual may have conflicting interest, however there exist a common welfare for a society and if there is a conflict between individual interest and societal interest, importance is given to the welfare of the society and people. In a clinical trial conflict may arise due to long term benefits of the research. The research ethics committee must review the interest of the researchers and sponsors so that welfare of the society can be observed first.

GLOBAL PERSPECTIVE – GOOD CLINICAL PRACTICE

Good clinical practice is a globally approved quality guidelines for trials, by the international council for harmonisation of technical requirements for pharmaceutical for human use (ICH), an international body generally known as international conference on harmonization of good clinical practice or ICH-GCP. It details the necessity of globally approved standards for the protection of human beings from exploitation of various stakeholders while conducting the trials. It requires strict documentation of every step of clinical protocol and ensures the quality control, protection of basic human rights, and regular inspection for strict adherence of clinical guidelines. It is approved as scientifically authoritative guidelines as

it is scientifically tested and proved. However, it is criticised for lack of morality and hence less authoritative in comparison to declaration of Helsinki.

The WHO provides a handbook[44] for good clinical research practice (GCP) reiterating "development of the trial protocol; development of standard operating procedures (sops); development of support systems and tools; generation and approval of trial related documents; selection of trial sites and the selection of properly qualified, trained, and experienced investigators and study personnel; ethics committee review and approval of the protocol; review by regulatory authorities; quality, handling and accounting of the investigational product(s); trial data acquisition while conducting the trial; safety management and reporting; monitoring the trial; managing trial data; quality assurance of the trial performance and data; and the reporting of the trial." The responsibility for GCP is shared by all the parties involved, which includes sponsors, investigators and site staff, contract research organizations (CROS), ethics committees, regulatory authorities and research subjects. Regarding informed consent, GCP involves the summation of the Helsinki declaration, Belmont report, CIOMS guidelines, ICCPR as well as other international guidelines. Not only does the handbook specifically state the information that is required to be given to the trial subject to form an informed consent, but also specifies the eligibility criteria for the administrator of taking the consent. Whereas the handbook states the categories of people as vulnerable groups, it also clears the process of documentation of taking the consent, which cannot be completed just with a signature. Additionally, the WHO also has published international standards for clinical trial registries, which mandates the registration of clinical trials and aims to accumulate the information of all the clinical trials, in order to prevent the repetition of mistakes and to gain the knowledge from the other researches as well. World Health Organization (WHO) aims to state various guidelines already mentioned in the Helsinki declaration and other ethical principles and guidelines and thus formulate a common guideline for all the countries to follow. Moreover, who aims to man date the global registration of clinical trials at one stop and also to provide the results of those clinical trials, so the possibility of errors, harm and injury

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[44] Handbook for good clinical research practice (GCP), available at: https://www.who.int/medicines/areas/quality_safety/safety_efficacy/gcp1.pdf

can be minimised. As a result, who states four phases of clinical trials, which are as follows:[14]

- 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.

In European Union, good clinical practice has been regulated by directive 2001/20/EC. European Union has approved the guidelines of ISO 14155 as a harmonised principle. In the United States, ICH-GCP is not statutorily mandated, though it is approved by the food and drug administration (FDA). The national institute of health demands all clinical investigators and staff are to be qualified as trainers of good clinical practice.

The food and drug administration (FDA), a federal agency of us department of health and human services, handles the landscape of clinical tests in us, with an intention to protect the safety, and efficiency of clinical tests and the health rights of trials participant.

There are many conferences being held every year in the realm of clinical trials. The recently held conference on clinical trials in Amsterdam, has mainly tried to handle the "evolution of clinical research in advanced life". There is a patient involvement conference, to be held in the month august 2020 to understand the patient's voice in planning clinical trials.

INDIAN PERSPECTIVE

In India, the clinical trials are governed by guidelines of Indian council of medical research (ICMR), drugs and cosmetics act and rules' 1945, and Indian medical council 1956, central council for Indian medicine act, 1970 and drugs and clinical trial rules 2019. The central drugs standard control organisation (CDSCO) is the national regulatory authority of India, the department of drug controller general of India (DGCI) being the

prime licensor. The Indian council for medical research (ICMR) publishes a national handbook of ethical guidelines for biomedical and health research involving human participants, making changes from time to time providing the standard of ethics to be followed for conducting clinical trials and other research.

Ever since, the procedure of conducting clinical trials in India was envisaged in drugs and cosmetic rules, 1945, till the time the need to regulate the policies was strongly felt. In 2012, a Pil[45] was filed by an NGO describing the problems in the compensation granted to trial subjects in case of injury or death of the subject. The 2013 amendment bill[46] to the drugs and cosmetics act was released proposing changes in the regulation of the import, export, manufacture, distribution and sale of drugs, cosmetics and other medical devices as well as to ensure safety, efficacy, quality and conduct of the clinical trials. This was the first bill in India that proposed the penal provisions with regard to the violations of the guidelines formulated by ICMR. However, the bill was not passed due to the reasons that it still needed contemplation on various issues.

The provisions regarding the compensation to the subjects in case of death or injury in a clinical trial is governed by the ethical guidelines of ICMR,[47] which suggests that the sponsor of the clinical trial shall compensate the injured trial subject or the legal heir of the dead trial subject up until the extent of direct relation of the injury to the clinical trial. The direct injury may include physical, psychological, social, legal or even economical. According to the drugs and cosmetics rules' 1945 the decision to decide the granting as well as extent of compensation shall be in the hands of the ethics committee. Despite the provisions for careful regulations and compensation, it was reported that a total of 1443 participants of clinical trial died between 2015–2018, whereas only 88 of them were given compensation suggesting their injury was directly related to the trial.[48]

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[45] "Swasthya Adhikar Manch, Indore vs. Union of India", W.P (c) No. 33 of 2012.

[46] The drugs and cosmetics (amendment) bill, 2013.

[47] Handbook on national ethical guidelines for biomedical and health research involving human participants.

[48] See Ch. VI, rule 39, draft new drugs and clinical trials rules, 2018 (2017), http://www.cdsco.nic.in/writereaddata/draft%20ct%20rules%20sent%20for%20publication.pdf [hereinafter "2018 draftrules"]

In order to overcome the difficulties faced by the existing provisions, to encourage bringing more clinical trials and to promote the indigenous drug development in India, the new drugs and clinical trial draft rules were formulated in February, 2018. One of the significant aspects of the draft rules was the reception of no fault compensation by the government of India, through adding a provision to grant mandatory interim compensation, amounting to 60% of the total amount incurred in the injury, within 15 days of the opinion of ethics committee.[49] However, such provision was realised to be against the objective of the rules which is to encourage the sponsors for bringing in the trials. The new drugs and clinical trial rules' 2019 hence became the most significant legislation promising the favourable and expeditious reception of trials.

Under the new rules,[50] significant changes have been made, which are enumerated below:

1. ***Pre and post-submission meetings*** – in order to facilitate the process of application for approval to conduct the clinical trials, a provision has been framed for the sponsors to have an advisory pre-submission meeting with the central licensing authority (CLA) or the officers appointed by CLA. Similarly, in case of any further queries from CLA or CDSCO, the sponsor may even apply for a post-submission meeting.
2. ***Expedited and deemed approval/licensing*** – the rules provide for the time period of 30 days in case of domestic companies to get the license to conduct the trials and moreover, states that in case of no response from DGCI within 30 days suggesting a rejection or deficiency, it shall be deemed to be approved. In case of foreign companies, the time period is of 90 days, provided that the time period of 30 days is to be followed in case the drug is discovered in India or the research and development of the drug have been carried out in India and also the drug is proposed to be manufactured and marketed in India.[51]

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[49] Rupak de Chowdhuri, "India's new clinical trial rules weaken safety nets for participants" scroll.in, April 4' 2019 *available* at: Https://scroll.in/pulse/918874/new-clinical-trial-rules-weaken-safety-nets-for-trial-participants-to-promote-research

[50] New drugs and clinical trial rules' 2019.

[51] *Id.* At Ch V, Rule 22 and 23.

3. ***Local clinical trial waiver*** – another provision regulating the market of drugs is the waiver of local clinical trials in case the drug has already been approved by any other country, provided the country is approved by DGCI, who has the authority to approve it on a case-to-case basis.
4. ***Fast-track orphan drug registration*** – orphan drug is the drug inflicted to cure a rare disease. Under the current rules, it is defined as a drug intended to treat a condition which affects not more than five lakh persons in India.[52] The regulatory pathway, of conducting a trial in case of rare diseases or in the case of unmet needs of India, is fast tracked and less stringent restrictions are applied.
5. ***Post-trial access*** – the rules tend to deliver distributive justice by requiring sponsors to provide post-trial access to a drug at no cost to the trial participant if the following circumstances are fulfilled:
   (a) The trial relates to an indication for which no alternative therapy is available and the drug has been found beneficial to the subject by the investigator;
   (b) The continued access has been approved by the ethics committee;
   (c) The subject or legal heir consents to post-trial use of the investigational drug; and
   (d) The investing at or has certified and the trial subject declares in writing.

   That for such post-trial use the "sponsor shall have no liability for post-trial use of investigational new drug or new drug."[53]
6. ***Accelerated approval for drugs*** – the idea behind this type of approval is to render the availability of new drugs in case of serious conditions based on their severity, rarity, high prevalence, lack of alternate treatment and also if the new drug is more beneficial than the already existing one. Under this kind of approval, the surrogate end points are used to gather the efficiency of a new drug, rather than standard outcomes. In other words, rather than relying on the proven results of clinical trials, a predictive opinion is formed anticipating the clinical benefits of the new drug. The 2019 rules provide for the condition of approval in these cases of new drugs subsequent to the phase ii of the

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[52] Id. At Ch I, rule 2(x).
[53] *Id.* At Ch V, rule 27.

trial and therefore, post marketing trials are required to validate anticipated medical benefit.[54]

7. ***Doctor's predicament in case of life-threatening diseases*** – in case of life- threatening diseases, the rules give away the authority as well as the duty to the doctors and officers of government hospitals and institutions to seek the permission of CLA in order to import the unapproved drugs from different countries, which are approved for marketing in the country of origin. Nevertheless, it also yields power to manufacture in India, unapproved drugs of other countries in case of life-endangering situations.

The patents act' 1970 already provides the power to the government of India to grant compulsory licences to non-patent holders to manufacture patented drugs without any legal implications in case of national emergency, extreme urgency or public non-commercial use.[55]

The Laws of Consent and Compensation in Indian Scenario

It has already been discussed earlier in the research paper that the guidelines related to the compensation and consent ethics are enumerated in the national handbook of ethical guidelines by ICMR, whereas the mechanism to receive the compensation is still debatable in the country. As per the consolidated reading of the guidelines as well as the new rules, every sponsor bears the responsibility to undertake the consent of each subject prior to the clinical trial. In case of injury or death of the subject, the new rules limit the liability of the sponsors to provide medical management as per the discretion of the investing at or till the time it is established that the injury was not directly related to the trial.[56] It envisages the investigator as the final authority to decide whether the compensation or medical management to be provided and if yes, then to what extent. In case of death as well, the compensation may be provided if the investigator discreets the death to be the direct result of the trial as well as the extent of compensation shall also be the investigator's decision. Another change made in the new rules was the report of death to be given by sponsor and the investigator to DGCI, has to be now given within

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[54] *Supra* at 6.

[55] 'The patents act' 1970, section 92.

[56] [illegible]

14 days of when the death of the subject came into their knowledge, rather than within 14 days of the occurrence of death in previous rules. In case of post-trial liability, the sponsor holds no responsibility as the drug is inflicted on the post-trial subject after receiving the consent from the subject or the legal heir of the subject ratifying the no responsibility of the sponsor.[57]

India's chief authority on drugs standard control organisation (CDSCO) has published the "rapid response regulatory framework for Covid-19 vaccine development, following which the Indian council of medical research (ICMR) issued national guidelines for general ethical issues, and review proceedings for the covid related and non-related research, clinical trials and issues relating to consent. As per the new rules and regulations, sponsors of ongoing projects shall co-ordinate with investigators and ethical committee, strictly adhere to the approved protocol of clinical in accordance with the good clinical trials practice (GCP) and to maintain complete records and submit the records of amendments if any along with the actual report of clinical trials. It also highlights the importance of rights of patients, welfare, and safety aspects. It is to be placed on record that Indian authorities have appreciated the efforts of various multinational companies' sponsors, local pharmaceutical companies and other stakeholders of clinical trials and amended the changes in the process of clinical trials, striking a balance between the health interests of the people and also the fundamental rights of the trial subjects.

After India becomes signatory to trips (agreement on trade related aspects of intellectual property rights, India is become the hotspot of clinical trials due to various factors like professionally qualified skills, availability of huge population of patients, and existence of variety of diseases. Cost effective Indian market is of course the core reason for the exponential growth of clinical markets in India along with clear cut rules and regulations with timely amendments in the rules and legislations. As per the new law, an online application can be filed to central licensing authority as per the rules via sugam, an online portal managed by the CDSCO. Time lines for approval of application has been cut down to 30 days and a system of deemed approval is assumed if no response has come from drugs controller general of India (DCGI). Most importantly,

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[57] *Supra* at 10.

if the drugs clinical trial is approved and tested in any other country, which follows good practice procedures of international standards, in similar to Indian standards, the necessity of local trial may be waived.

DCGI, which is the central licensing agency as per the new rules, can also decide the amount of compensation in cases of death and other permanent disability to a trail participant, along with ethics committee. Amount as to how much compensation to be paid is decided with the support of calculation as formulated in the formula of new rules. If the clinical trial is purely for the academic interests, no such prior approval is required, but the result of such trials shall not be made use of, for the purpose of promotion of any drugs or medicines and it shall not be used for medical use in the market.

Authors prefer to notify some of the important references in the areas of clinical trials as it gives glimpse of the new amendments. The most important handwork on guidance is the handbook published by Indian council of medical research and central drugs standard control organisation, which is titled as 'handbook for applicants & reviewers of clinical trials of new drugs in India (January 2017). Another important reference is the gazette notification f. No. DCGI/MISC/2020(104) government of India, director general of health services, central drug standard control organisation, dated 30th March 2020. There are other two guidelines, which are important to mention here is national ethical guidelines for bio-medical and health research involving human participants (ICMR) and also another guideline for gene therapy product development and clinical trials (2019).

CONCLUSION

With the acceptance of democratic values throughout the world, the human rights of freedom of choice, equality among others and right to life and liberty hold the paramount importance in today's world as they are non-derogable rights. Whereas, it is suggested that with every evolving guideline on clinical trials, efforts have been made to clarify the intricacies in aspects of consent and information available to provide the consent, these guidelines being suggestive, the only binding rules upon the countries, especially India are the rules made by the central government of India. In various under developed countries of Africa and other parts of

developing countries, clinical trials are part and parcel of their economic policies.

They relax the rules and regulation of ethical code to attract multinational companies for doing clinical trials on their citizens. By the glimpse of the various country's rules and regulations, it seems that rules are relaxed to the effect that the individual rights and fundamental rights have been given unwarranted inflictions in order to invite foreign multinational pharmaceutical companies. It seems rubber is pulled through each side and the individual is stuck in between the financial crisis and health crisis.

On one hand, the world is growing with an aim to decrease the gap between the two, on the other

Hand the instances of unregistered clinical trials, trials without proper information and thus tainted consent, limited liability of the state in case of death and injury, authority of investigators over the quantum of compensation, exploitation of citizens of developing countries, vulnerable groups becoming the targets of atrocities of pharmaceutical companies, etc., are growing up. The supremacy of economics over human rights doesn't seem out of the picture where individuals are just objectified into cheap subjects.

We often observe advertisements in newspapers stating that if you don't observe hair gain; your money will be refunded in a limited time. Advertisements of hair gain oil, body weight gainer, and height increasing tablet or vaccine, and many more are not officially approved by any competent authorities. Participants involved in these trials are unknown to the fact that they are a part of the testing which is going on. In some of the cases the researcher and sponsor may be the same person, so he may not have sufficient funds or resources to compensate, so they independently test the drug on themselves.

It is suggested that the government authorities like central licensing authority in India and medical council of India should review the ethics committee and number of researches done by the laboratory or institution. Timeline has to be set by the organisation so that a well detailed report can be analysed for the approval of any testing. Participants must be qualified and free informed and consent has to be obtained. Time to time the authorities must check the record book of every institution for every

research they tested. Final approval shall be given only when a person from that field who has deep knowledge and learning about the subject approves the trial and not on the certificates approved by their own members.

Warning notice shall be issued if any institution found involving participants without their consent and taking undue advantage of the subject. If any institution is found for failing two times consecutively, then their license for testing must be canceled. Guidelines are the framework of the competent authorities, so that development and innovation in the technology must go on, but without losing human lives.

During the last decade, a developing country like India has received impetus in receiving foreign funds for clinical trials from multinational companies as it has relaxed its rules for the purpose of enhancing the number of clinical trials. India is one of major players to reckon with in the conduct of clinical trials and is also one of the largest manufacturing countries of various pharmaceuticals. Various multinational companies have signed joint ventures with local national companies in India to produce drugs and medicines, medical devices and also to conduct clinical trials. India, though tries to make use of all these instrumentalities for the welfare of the people and economic prosperity, also tries to strike a balance in its legal realm between the fundamental rights and economic rights. The Indian democracy and its constitution are fundamentally strong to protect the health interest of its citizens and hence, health is still considered as wealth of the country. India, being a country well known for its yoga, meditation and ayurveda, attaches paramount significance to the health of the people, along with economic interest of the country.