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Clinical Trials in light of Covid-19

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ABSTRACT

As we all know with advent of science and medicine world has changed a lot. But this covid 19 era has taught as science and technology is inevitable facet of development but it comes with its own cost. This article discusses about clinical trials and what are the regulations governing it globally and on domestic level. It also emphasis on how covid 19 has changed the landscape of clinical trials.

Keywords- *clinical trial, human rights, covid-19, clinical trial and drug approval in India.*

I. INTRODUCTION

Medicines play a vital role in the promotion of physical health and welfare. Creating a new medicine is a long and rigorous process and it takes several years to progress. Clinical experimentation is an important aspect of universalising healthcare, enabling the development of better medicines, tests, vaccines, devices, surgical procedures and other medical interventions and protocols for their safer and more rational use[3].

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. 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.

There are some common rules regarding the clinical trials that help to ensure the balance between clinical trial and subject safety[4].

Till 1990s, clinical trials were carried out by the government, but with increasing globalisation

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[3] Clinical trial and health care regulations in India, Indian Journal of Medical Ethics, ISBN : 978-81- 909452-0-2.
[4] Pharmaceutical companies must obtain approval from each country's government to market their medicine(s) within the country. The approval process begins at the pre-clinical stages of medicine or device development and continues until the medicine or device is tested as safe and ready for human use. The United State Food and Drug Administration (US FDA) which is a federal agency of the United States Department of Health and Human Services, is the world's foremost regulatory agency which controls safety, efficacy, and manufacturing standards for pharmaceutical products and clinical trials.

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and a booming pharmaceutical industry, commercial interests have overtaken other concerns. India has allowed 100% FDI in the pharmaceutical industry and as a result this industry has been booming post-1990s economic reforms[5].

And in recent past allegations are made that as majority of patients undergoing trials are illiterate and no appropriate compensation or insurance cover is being given to the subjects by CROs or the companies[6].

Without clinical trials, it is impossible to determine whether the new medicines developed in the laboratory or by using animal models are effective or safe the reason behind this is that computer simulation and animal testing can only tell us so much about how a recent treatment might work and are no substitute for testing in a living human body[7].

II. INTERNATIONAL LAW

(A) 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 experimentation laid out by the Nuremberg Tribunal in United States v. Karl Brandt (Nuremberg trials) have come to be known as the Nuremberg Code. In Nuremberg trials, Nazi doctors were convicted of the crimes committed during human experiments on concentration camp prisoners[8].

The goal of the Code is to protect the rights of subjects and to 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 first and most important is that anyone participating in an experiment must give informed assent. This means nobody can be forced to participate in human experiments. All participants must understand the potential risks.

(B) Declaration of Helsinki 1964

"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 she is at liberty to abstain

[5] Lex Hindustan, Clinical Drug Trials on human beings in India, Published on October 1, 2016, Accessed on December 12,2016.

[6] Debjit Bhowmik and Chiranjib.B, Clinical trial in India-An overview, Available from https://www.farmavita.net/documents/CLINICAL%20TRIAL%20IN%20INDIA.pdf.

[7] Australian Clinical trials, Australian government national health and medical research council, Department of industry, innovation and science, Available at https://www.australianclinicaltrials.gov.au/whatclinicaltrial.

[8] It attempted to give clear rules about what was legal and what was not when conducting human experiments. Although not a binding international treaty, the Nuremberg Code became the first international standard defining permissible medical experiments.

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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 should be obtained, preferably in writing.[9]

(C) International Covenant on Civil and Political Rights (ICCPR)

No one shall be subjected without his free assent to medical or scientific experimentation.

(D) Convention on Human Rights and Biomedicine 1997

Article 5 of the CHRB lays out the general rule for informed assent in experimentation.

An intervention in the physical health field may only be carried out after the person concerned has given free and informed assent to it. This person shall beforehand be given appropriate statistics as to the purpose and nature of the intervention as well as on its consequences and risks. The person concerned may freely withdraw assent at any time.

(E) Good Clinical Practices (ICH-GCP) 1997

Good Clinical Practice (GCP) is an internationally recognised ethical and scientific quality standard set for formulating, conducting, recording and reporting clinical trials which involve the human subjects. 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 rules, guidance and industry standards that make up Good Clinical Practice are intended to provide assurance that the rights, safety and well-being of clinical trial subjects are protected. GCP is also intended to assure that the experimentation yields quality scientific data. Fundamentally Good Clinical Practice requires:

- Oversight of the local ethics committee(s)
- Verification of the investigator's qualifications
- A research protocol, investigator's brochure, informed assent, and the documentation that is essential for undertaking a clinical trial
- Monitoring of the clinical trial
- Submission of reports and maintenance of records

[9] Article 26, Declaration of Helsinki, (Amendment 2013).

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III. LEGAL FRAMEWORK IN UNITED STATES (US)

These part overviews the legal framework for conducting clinical trials in the US and outside US conducted by US institutes involving Food and Drug Administration (FDA)-regulated trials or conducted by US entities that are not subjected to FDA regulation such as Academic Medical Centers (AMC). There are some other laws which also affect certain aspects of the clinical trial and its conduct. Overview also includes the data about important controlling guidelines introduced by international bodies such as the International Conference on the Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH).[10]

IV. LEGAL FRAMEWORK IN UNITED KINGDOM (UK)

In 2001 the European Union adopted the EU Clinical Trials Directive (2001/20/EC) as a framework for good management in trials of medicines for human use. The subsequent UK Medicines for Human Use (Clinical Trials) Regulations became law in 2004.[11]

The regulations are intended to protect the rights, safety and well-being of research participants and to simplify and harmonise regulatory processes. They apply to trials designed to generate information on the efficacy or safety of medicines.

The MRC's policy on the UK clinical trials regulations details our requirements of MRC-funded researchers in universities or other research organisations who take on the role of investigator in a Clinical Trial of an Investigational Medicinal Product (CTIMP)

If you are planning a clinical trial but are uncertain whether it falls within the scope of the regulations, please contact the MHRA directly.

V. INDIAN LAW

(A) History of Drug Regulations in India

The medicine regulation history in India can be traced back to British era when the most of medicine were imported. During the early decade of 20th century, Indian market was flooded with deceptive and adulterated medicines by many foreign drug manufacturers. "In reply to widespread Gigantic Quinine Fraud; a drug inquiry committee was formed under the chairmanship of Sir Ram Nath Chopra also known as Chopra Committee. Recommendations

[10] Maureen Bennett and Jan Murray, Conducting Clinical Trials in the US and Abroad: Navigating the Rising Tide of Regulation and Risk, Squire, Sanders & Dempsey L.L.P, Published on www.ssd.com.

[11] The Directive requires the competent authorities of the Member States to perform certain functions in relation to clinical trials. The UK competent authority responsible for those functions is the licensing authority. The licensing authority was established under the Medicines Act 1968; it consists of Ministers who act through The Medicines and Healthcare products Regulatory Agency (MHRA).

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of this committee were later on tabled amidst growing protest in legislative assembly as The Drug Bill. In the year 1940, India's first Drugs and Cosmetics Act came into enforce and was further amended as the Drugs and Cosmetics Rules of 1945. The 1945 amendment established the CDSCO and the DCGI. The Drugs and Cosmetic Act, 1940 came into force from 1 Apr. 1947. The Indian Council of Medical Research (ICMR) was created in 1949 to guide and manage medical experimentation. Later on, government, in 1962, extended the controlling provisions to the cosmetics, and finally the Act came to known as Drugs and Cosmetic Act 1940.

Drugs and Cosmetic Act has been divided in Chapters, Rules and Schedules and is amended from time to time to control the safety, efficacy and quality of the medicines. The Central Drugs Standard Control Organization (CDSCO), headed by the Drugs Controller General (India) (DCGI), discharges the functions allocated to the Central Government (similar to the US Federal Government) under the Act. CDSCO is attached to the office of the Director General of Health Services in the Federal Ministry of Health and Family Welfare[12]. This Act regulates the import, manufacture, distribution and sale of the medicines and cosmetics. Manufacture and sale come under the control of respective states governments and union territories through their respective medicine control organization, whereas setting standard, import, marketing authorization and monitoring of adverse medicine reactions of a recent medicine is under Central Government.

To regulate the conduct of clinical trial, a particular sub-Drugs and Cosmetics Act, called Schedule Y, was enacted. In order to facilitate the various aspects of biotechnology, the Department of Biotechnology was developed in 1986.India have adopted international controlling instructions regarding clinical trials; and the Drug controller general of India and the Indian Council of Medical Research (ICMR) have developed Indian versions of these instruction. Ethical Guidelines for Biomedical Research on Human Subjects were issued by ICMR in the year 2000 and Indian version if GCP instructions were released by CDSCO in Dec. 2001. Licensing authorities are assisted by CDSCO and ICMR in giving final marketing authorization of new medicine.

VI. TIMELINE

1. **1988**: The local clinical trials were made mandatory in the year 1988, with a Phase lag, such that, the clinical trial in India will be one stage behind when compared to rest of the world.

[12] Clinical trial and health care regulations in India, Indian Journal of Medical Ethics, ISBN : 978-81- 909452-0-2.

2. **2000**: Many incidents due to the violations of ethical issues related to informed assent were reported. Based on these incidents Central Ethics Committee on Human Research (CECHR) and Indian Council of Medical Research (ICMR) took a controlling initiative & conceptualized and issued Ethical Guidelines for Biomedical Research on Human Subjects in 2000. Trials were allowed to conduct only after acquiescence from Ethics Committees, apart from DCG (I) and the informed assent of the subject participating in the trial was made mandatory.

3. **2001**: Good Clinical Practice (GCP) "instructions were developed in line with ICH and GCP.

4. **2005**: DTAB made Good Laboratory Practices (GLP) mandatory for all the laboratories. CDSCO made elaborate revisions to Schedule Y to bring it on at par with internationally accepted definitions and procedures."

5. **2006**: CDSCO issued draft rules which included- Checklist for filing Global Clinical Trial Applications and Categorization of acquiescence of protocol amendments.

6. **2007**: Schedule Y revisions in 2007 permitted Phase I trials to be carried out concurrently in India along with the rest of the world. This removed the stage lag and clinical trial registry was launched.

7. **2008**: CDSCO started inspection of clinical trial centers in India. A full fledge onsite inspection by US-FDA trained Indian Inspectors & controlling experts started[13].

8. **2011- 2012**: Several steps have been taken by the Government, to strengthen the clinical trial acquiescence procedures and their monitoring mechanism to ensure that the safety, rights and well-being of clinical trial subjects are protected:

   i. Clinical trials registration in the ICMR's registry (through the official website www.ctri.in) has been made compulsory.
   ii. For conducting inspection of clinical trial sites and sponsor / Clinical Research Organizations (CROs), separate guidelines have been issued.
   iii. Investigational new drugs are the new substances which have not been used earlier in human beings. IND committee, headed by the Director General of Indian Council of Medical Research (ICMR), evaluate the applications of Investigational New Drugs (IND).

[13] National Health Accounts Cell: National Health Accounts India 2004–05. 2009, New Delhi: Ministry of Health and Family Welfare, Government of India.

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iv. 12 NDAC's and 7 MDAC's comprising of leading experts mostly from the Government medical colleges and institutes from all over the country have been constituted to advise the CDSCO on matters related to acquiescence of clinical trials and recent medicines. 5.Proposals to amend the toxicity research data requirements for acquiescence of clinical trial / recent medicines to make it harmonized with the international instructions have been approved by DTAB.

(A) Clinical trial and Drug Approval in India

1. Permission from the Drugs Controller General, India (DCGI).

2. Approval from respective Ethics Committee where the research is planned.

3. Mandatory registration on the ICMR maintained website www.ctri.in

VII. CLINICAL TRIAL IN LIGHT OF COVID 19

The COVID-19 pandemic's threat to global security and the economy has captured the entire world's attention. The number of COVID-19 cases continues to rise globally with little sign of slowing down.

The COVID-19 pandemic has mobilised researchers worldwide on a scale and timeframe that have never been seen before for one specific disease. In hopes of rapid discovery of therapeutics, vaccines, and diagnostics for COVID-19, a substantial amount of money is being invested towards clinical research. Despite the sheer volume of research and discussion on the research related to COVID-19, we will illustrate in this Series paper that we are not fighting this common fight very efficiently.

Most clinical trials that have been done for COVID-19 have been too small in scale to provide conclusive evidence. Investing in large-scale clinical trials that can facilitate international collaboration will be important to generate high-quality data efficiently that can inform policy and change clinical and public health practices.

Although sharing of individual participant-level data has historically proven to be challenging from both private and public researchers, as shown by the COVID-19 pandemic, there is a need to mandate data sharing, expedite systems to apportion credit for data sharing, and preserve commercial interests[14].

Amendments to the patient information and ICDs necessitated by the COVID-19 pandemic must comply with applicable regulatory requirements. Amendments and approvals for trials

[14] *How COVID-19 has fundamentally changed clinical research in global health*, THE LANCET (JULY 20, 2021, 12:40 PM) https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(20)30542-8/fulltext.

investigating the management of COVID-19 and related conditions should be prioritized. Obtaining physical informed consent from participants in such trials may be particularly challenging because of isolation measures required for COVID-19 patients. Participants with COVID-19 who are in isolation may not be able to provide written consent. Oral consent observed by an impartial witness may be obtained according to the applicable regulations. The impartial witness must sign and date the consent document.

Monitoring and quality assurance activities should take into account the national and state restrictions, the necessity and availability of trial staff, and other limitations of resources during the COVID-19 pandemic. Changed monitoring plans should aim for an optimal balance between adequate oversight, practicalities at sites, and compliance with the relevant regulations. Modifications to monitoring can include[15]:

- Increased use of central and remote monitoring.
- Virtual on-site monitoring plans using telephone or video calls.
- Adaptive monitoring plans with increased use of remote or central monitoring.
- Postponing or cancelling on-site monitoring visits.

These were the few highlighted problems among many other problems faced during covid-19 while conducting clinical trials.

VIII. CONCLUSION

India is losing out of opportunities to other nation because of uncertain controlling framework and acquiescence mechanism for conducting trials. There is strong requirement for liberalizing the controlling environment in favour of sponsors and at the same time balancing interest of subjects involved in such trial. Law should be more for regulations in clinical trials rather than restricting it.

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[15] Panda, P., Stockler, M. and Gulia, A., 2021. *Clinical research during coronavirus disease pandemic: Challenges and way forward*. [online] Available at: <https://ijmsweb.com/clinical-research-during-coronavirus-disease-pandemic-challenges-and-way-forward/> [Accessed 20 July 2021]..