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Bioethics and Vaccine Trials in India

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ABSTRACT

Human being consider themselves to be the most suspicious species in the world which give rise to speciesism resulting into the exploitation of other species and natural resources. This exploitation is not only harmful to such species but is also becoming cause of various modern diseases. The most effective tool to combat such diseases are vaccines. Development of vaccine is in itself very complicated process requires years of studies and clinical trials involving human subjects for such trials. The ethical requirement increases when the subject to the trial is involves human being. This ethical requirement also varies from country to country. Conduct of these trial also depends on the laws and regulations prevailing in such country.

The Clinical trial in India follows the ethical Principles of ICMR and is also regulated by various Rules and regulations required the government.

In this paper we will try to analyses the ethical aspect of Human Challenge Trial and in current scenario and various requirements to get approval for clinical trial in India and the laws related to it. Beside this we will discuss the functions and responsibilities of the ethics committee along with the sufficiency of prevailing laws in regulating the ethics of clinical trials in India.

Keywords: Placebo, controlled group, Double blind trial, Human Challenge Trial, vaccine

Introduction

Microorganisms are the smallest living being on this planet. They live inside and outside our body. Some of them are human friendly and are very important for our day to day activities while the others may cause trouble when they replicate in the human body. Such disease causing microbes are called pathogens.

Vaccines are the simplest and most effective weapons which deployed against these pathogens to generate active immune response (antibodies) against these pathogens in human body. A vaccine can either be a live attenuated vaccine (contains live but weakened pathogens) or inactivated vaccine (contains killed pathogens).

The development of vaccine is very slow and complex process. On an average a vaccine takes nearly 10 to 14 years of development before it could be first introduced into the market. In this

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period of development it goes through 3 out of 4 stages of development. However, there are situations like covet-19 where such a long wait for vaccine is could not be afforded at all in any way and the immediate vaccine development is the need of the hour to save the human species. Such immediate development is only possible by adopting the human challenge trial method. However, there are various concerns related to the ethics of this method. Many argues that it is the most unethical method where the subject of the trial is deliberately exposed to the genetically modified pathogens which causes disease in human body sometimes of which no proven cure is available but the others argued that the oldest, effective, cost efficient and especially time efficient method which is perfectly suitable for the development of the covid-19 vaccine.

It is also argued that human challenge trial is often performed on the most vulnerable, poorer and illiterate section of the society who are not even capable of understanding the probable consequences and the risk attached to the such trials and it is also seen as a gross violation of the human rights of people who are subject to these trials.

India being the largest vaccine producer in the world with about 43% vaccine producing capacity of the world is becoming favorite destination for various vaccine candidates to conduct their trials. The other factors responsible for mushrooming of these trials are friendly laws and the easy availability of the cheaper subject for the trials. The increasing clinical trials in last few years raised various concerns related to the ethics of these trials and also questioned the efficiency of various laws and guidelines governing these trials into the country.

Clinical trial

Clinical trials are research studies executed on people that are intended at assessing a medical, surgical, or behavioral intervention with the objective to determine the competence and safety of the new drug or to compare two or more of the already existing drugs. A clinical trial of any drug is pre-conditional to determine the safety and efficiency of the drug.

Clinical trial in relation to new drug is the systematic study of such drug on human volunteers to get data for the discovery or verification of its clinical or, pharmacological including pharmacodynamics, pharmacokinetics or; adverse effects, with the objective of determining the safety, effectiveness or tolerance of such new drug[1]

Clinical trial of drugs is a randomized single or double blind controlled study in human participants, designed to evaluate prospectively the safety and efficiency of new drugs/ new formulations[2]

[1] Rule 2(1)(j) of clinical trial rules, 2019
[2] ICMR ethical guidelines 2006

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Clinical trial of the new drug cannot be conducted without the prior approval of the central licensing authority[3].

Drugs and cosmetic act, 1940 and drugs and cosmetic rues, 1945 authorized CDSCO to permit new drugs[4] or approve the clinical trial[5], laying down the drug standard and control the quality of imported drugs.

A clinical trial is an unavoidable stage of vaccine development which safeguards the safety and competence of vaccine on a human body. India being the major supplier of the vaccines in the world .It required the clinical trials to be conducted on its population before permitting any manufacturing or marketing of any drugs.

Stages of vaccine trial

Vaccine development is a long and time taking process. the development of vaccines on an average takes about 10 to 15 years of clinical trials to ensure that the vaccine is safe for the use (have no long term or short term side effects) and is efficient against the the target pathogen. In this process a vaccine goes through four stages of development to determine its safety as well as its biological effects including immunogenicity.

Phase 1

The first phase includes the study of dose and route of administration and should involve subjects of lower risk. For example – first phase of covid 19 vaccine trial should not include children or, diabetic patients as the subject of trials.

The phase 1 study is a small study involving few subjects of the trial which are observed for a short period of time. The primary objective of this trial is evaluate the safety and the immunogenicity of the vaccine candidate in addition to it this phase of trial also helps in evaluating the dosage and the preferred route of its administration.

This phase of trial generally involves high risk and hence should not include a large number of human subjects.

The documents required for this trial are –

1. Systematic toxicity studies which includes dose range studies, single dose toxicity studies and repeat dose systemic toxicity studies
2. Male fertility study

[3] Rule 21 drugs and cosmetic rules, 2019
[4] Section 2(1)(w)(v) new drug and clinical trial act, 2019
[5] Section 2(1)(j), new drugs and Clinical trial act, 2019

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3. In-vetro genotoxicity studies with proposed route of clinical application
4. Allergenicity/ hypersensitivity test.
5. Photo allergy or dermal photo toxicity test

Phase II

Phase 2 trial is usually a double-blind trial in which both the researcher and the participant is unaware whether they have been treated with the vaccine candidate or with a placebo;

Phase II trial verifies the safety and the immunogenicity of the vaccine candidate which is already been discovered from the previous phase of the trial. It may also include subjects risk subject to observe their responses. In this phase a challenge trial could also be performed where the healthy participant after being vaccinated is deliberately infected with the pathogen in question in order to assess the ability of the vaccine to confer protection against experimental challenge. The result of this pilot study provides the useful data for the third phase of the trial.

However no human challenge trial has been known to be performed so far in any stage of trial as there is no proven treatment of this disease and the mortality rate is very high.

The phase 2 trial should be carried out on the specialized place having adequate facilities for the safety of the subject.

The documents required for phase 2 clinical trial are

1. Summary of previously submitted non clinical safety data.
2. Repeat dose systemic toxicity studies of appropriate duration to support duration of proposed human exposure.

This is the longest and the final phase of trial after the successful completion of it the vaccine could be introduced into the open market for general public. This phase includes thousands of volunteers from various centers is required a lot of time and money. These trial is usually conducted in conducted in a double- or single-blind, placebo-controlled, randomized manner.

Phase 3

If the results from phase II are encouraging, phase 3 trial would be started. This is the largest trial, often involving thousands of participants coming from from various different centers. Generally it would be conducted in more than 10 centers.

The principle objectives in phase III are to:

- To determine the safety and efficiency of the new medicine or vaccine in the typical patient likely to use it
- To confirm actual dosing levels

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- To identify side effects or reasons why the treatment should not be given to individuals with another condition (known as 'contraindications')
- To build knowledge of the welfares of the medicine or vaccine and compare them with any risks
- To compare results against any presently achieved by existing treatments[6]

Phase 4

It is the post licensing trial in which the results of the already available vaccine in the market has been observed in long over the long period of time on a large and diverse population. In this trial a rarer or unexpected events can be detected which may not be detected in small phase 2 or phase 3 trials.

This trial can determine the age of vaccination and adverse effect due to change in vaccine strains.

Ethics Committee

Ethics committee is panel of seven or more than seven members which could be from medical, non-medical, scientific and non-scientific area with at least one lay person, one woman member, one legal expert and one independent member from any other related field such as social scientist or representative of non-government voluntary agency or philosopher or ethics or theologian[7]

At least fifty percent of the members of the ethics committee should not be connected to the institution in which it is constituted and the chairperson of the committee should not be affiliated with such institution or organization[8]. The member secretary of the committee should a person who is affiliated to the institution and should be appointed by such institution[9]. There should be at least one non -scientific and one independent member in the committee[10].

The permission granted by the Central Licensing Authority to conduct clinical trial under shall be subject to following conditions, namely: _
(I) Clinical trial at each site shall be started after approval of the clinical trial procedure and other related papers by the Ethics Committee of that site, registered with the Central Licensing Authority under rule 8;
(ii) Where a clinical trial site does not have its own Ethics Committee, clinical trial at that site may be started after procurement approval of the procedure from the Ethics Committee of another trial site; or an independent Ethics Committee for clinical trial established in accordance with the provisions of rule 7:

[6] https://www.gsk.com/en-gb/research-and-development/trials-in-people/clinical-trial-phases/
[7] Rule 7 of Drugs and clinical trial rules, 2019
[8] Rule 7(3) of Drugs and clinical trial rules, 2019
[9] Rule 7(4) of Drugs and Clinical trial rules, 2019
[10] Rule 7(5) of Drugs and Clinical trial rules, 2019

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Provided that the approving Ethics Committee for clinical trial shall in such case be accountable for the study at the trial site or the Centre, as the case may be:

Provided additional that the approving Ethics Committee and the clinical trial site or the bioavailability and bioequivalence Centre, as the case may be, shall be located within the same city .[11];

The ethics committee is responsible to grand primary approval or denial to a particular clinical trial, bioavailability or bio equivalence study after considering the safety and rights of the subject trial in accordance with the good clinical trial guidelines and other other regulations. The ethics committee is also responsible to periodically review the progress reports furnished by the investigators or monitoring and internal audit reports furnished by the sponsor[12]. In case if the committee is of the opinions that the trial is likely to compromise the right, safety and wellbeing of the subject, the committee may discontinue the trial and convey the same to the head of the committee conducting the clinical trial and to the central licensing authority.

Rule 12 of the drugs and clinical trial rules, 2019 specifically requires the presence of at least five of its members to review the protocol and relevant documents related to the clinical trial or bioavailability or bioequivalence study. These five members should include a medical scientist, a clinician, a legal expert, a social scientist or representative of non-governmental voluntary agency or philosopher or ethicist or theologian or a similar person; lay person.

The data, record, registers and other documents pertaining to the functioning and review of clinical trial of the committee is required to be maintained for a period of five years after the completion of the trial[13].

Rights of the subjects to the trial

The position of enrolment of the trial subjects shall be submitted to the Central Licensing Authority on periodical basis or as suitable as per the duration of treatment in accordance with the permitted clinical trial protocol, whichever is earlier[14].

Any report of grave adverse event happening during clinical trial to a subject of clinical trial, shall, after due examination, be forwarded to the Central Licensing Authority, the chairperson of the Ethics Committee and the organization where the trial has been conducted within fourteen days of its incidence.[15]

[11] Rule 25 of Drugs and clinical trial rules, 2019
[12] Rule 11(2) of Drugs and clinical trial rules, 2019
[13] Rule 13 of clinical trial rule, 2019
[14] Rule 25(vii) of Drugs and Clinical trial rules,2019
[15] Rule 25(x) of drugs and clinical trial rule, 2019

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In case of damage during clinical trial to the subject of such trial, whole medical management and compensation shall be provided in accordance with Chapter VI and details of compensation provided in such cases shall be informed to the Central Licensing Authority within thirty working days of the receipt of order issued by Central Licensing Authority in accordance with the applicable provisions.[16]

In case of clinical trial linked death or permanent disability of any subject of such trial during the trial, compensation shall be provided in accordance with Chapter VI and details of compensation provided in such cases shall be intimated to the Central Licensing Authority within thirty working days of receipt of the order issued by the Central Licensing Authority in accordance with the provisions.[17]

As per ICMR guideline and Helsinki declaration [18]the individual who is the subject to trial should be allowed to the aids which arise out of such trial. I.e. if a individual took part in vaccine trial and later the vaccine got license, it is suggested that the individual who is the subject of trial should be given such vaccine at the reduced rate if not for free.

Ancillary care

In 2002 guidelines issued by council for International organization for medical science It was clearly declared that the sponsors are not obliged to provide health care services beyond what is necessary for the conduct of research, but it is morally praiseworthy to do so[19] clearly indicating that there is no ethical obligation on the sponsor to provide medical care for the health issues which are not directly related to the trials. Even there were no mention of the ancillary care in the Helsinki declaration. As per ICMR ethical 2006 guidelines "If the applicant requires treatment for complaints other than the one being studied essential free ancillary care or appropriate recommendations may be provided[20]." Clearly signifying that it was just a recommendation and there was no ethical accountability to provide ancillary care to such applicants. But the government taking in to consideration the evolving ethics and the need to recognize the rights of the participants to attract more people to participate in clinical trials introduced **no fault compensation** in new drugs and cosmetic rules, 2019 where the sponsor is liable for interim compensation up to 60% of total amount incurred within 15 days of ethics committee's opinion.

Human challenge trial

It is a type of clinical trial where the subjects are deliberately been infected with the genetically modified or less active pathogens. These type of trials are generally performed to evaluate the

[16] Rule 25(xi) of drugs and clinical trial rule, 2019
[17] Rule 25(xii) of
[18] Helsinki Declaration of the World Medical Assembly, 2008(2)
[19] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5612421/#cit0008
[20] ICMR 2006 Ethical guidelines for biomedical research and human participants

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efficiency of the vaccines. It also helps in comparing the efficiency of two or more vaccines simultaneously. The rule of general ethics for clinical trial which requires minimum risk and maximum benefit cannot alone be applied in human challenge trial as it involves a very high risk. WHO in its 2020 guideline [21] discussed the criteria for the ethical acceptability of SARS-CoV-2 challenge trial

Scientific justification – the trial should have strong scientific justification for conducting SARS-CoV-19 human challenge trial. The trial should propose to give the important results which could not be obtained from other studies with such efficiency and accuracy in such limited time. The trial could also be done on multiple vaccines to find out the best available vaccine.

Assessment of the risk and the potential benefit – it is the general ethical principle that the potential benefit should always overweight the risk involved in it. There should be a rigorous assessment of risk and potential benefit of the sarc-cOv-2 Human challenge trial. Potential benefit and the risk involved should be compared with the other alternative trials. The risk and benefit should not only be studied on the subject but should also be studied on the community as well.

Consultation and engagement – view of the general public and expert consultation should be taken time to time. Prior consultation for the research should be taken from the locals to avoid any delay for the trial.

Coordination of research – the sponsor should have a prior consultation and coordination with the local health authority to avoid any compromise with the health of general public in the trial. The study should be transparent and should be monitored by other health authorizes as well like WHO. The study data should be properly stored and should be made available to the public.

Site selection - Human challenge trial should only be conducted in center's which has a prior significant experience in conducting such trials as there is high risk and uncertainty involved in it. Centre should have the appropriate facilities and should be comfortable and safe for the trial.

Participant selection – safety of a participant is the most important ethical requirement for the conduct of the trial. Initially, the selection should be made from the health and younger population (18-30) to avoid any serious health issues. People with high background probability of infection (such as doctors and other health care workers) should be priority for the trial as these people faces less marginal risk.

Expert review – In addition to the review of institutional ethics committee the human challenge trial should have a specialized independent review involving high level of expertise and should be conducted rapidly without compromising the quality of review.

[21] Key criteria for the ethical acceptability of COVID-19 human challenge studies

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Informed consent – since there is a high risk and uncertainty involved in SRRS-CoV-2 HCT study the informed consent should be rigorous and repeated consent should be taken throughout the trial and all the development and new information's pertaining to trial should be conveyed to the participants of the trial.

Arguments on Human Challenge trials

Human trial challenge was always been in controversy. Many argues that it is the highly unethical method where the subject of the trial is deliberately exposed to the genetically modified pathogens which causes disease in human body sometimes of which no proven cure is available but the others argued that it is the oldest, effective, cost efficient and time efficient method which is perfectly suitable for the development of the covid-19 vaccine.

It is also argued that human challenge trial is often performed on the most vulnerable, poorer and illiterate section of the society who are not even capable of understanding the probable consequences and the risk attached to the such trials and it is also seen as a gross violation of the human rights of the population which are subject to these trials.

Since exposure occurs in controlled laboratory settings, human challenge trials could potentially be completed in just a few weeks and require very few people. It can also help to quickly evaluate the efficacy on a case-to-case basis, and the another advantage is that it can help compare different vaccines head to head and understand the individual immune response in people.

There are many global experts including those who were present in that webinar were disagreed with his views and were in favor of the human challenge trial for SARS-CoV-2. But there are other experts of the same view as including Peter Piot, Director, London School of Hygiene and Tropical Medicine, UK, who himself battled the painful experience of Covid.

Professor of Human Genetics, University of Oxford said, "This (HCTs) has stood for viruses like malaria and cholera without any problems, so I don't see why we cannot do this for Covid-19."

Human challenge trials, in which subjects are deliberately exposed to an infectious agent in a controlled setting, are not always feasible or appropriate. Though, in some scenario it may be useful and suitable to get an assessment of vaccine effectiveness from human test trials. If they are accomplished, human challenge trials may be of particular use:

1. When there is no appropriate nonclinical model. For example when the pathogen against which the candidate vaccine is has to be tested is only confined to human beings. Like in case of sars-cov-2 virus
2. when there is no known ICP;
3. when vaccine efficacy trials are not feasible

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ICMR ethical principles on research involving human participants

1. Principles of essentiality- a Human participant should only be used for the trial only if human participation is considered to be absolutely necessary after the due considerations of all alternatives in proposed area of research and after the proposed trial has been duly considered by the ethics committee and the research is necessary for advancement of knowledge or for human benefit or ecological benefit.
2. Principle of voluntariness, informed consent and community agreement - The human trials should be fully aware of the risk and possible consequences of the trial whether on them or on community. They should also be free to quit at any time from the trial without the fear of any legal consequences and there should be only minimum restrictive obligations on them. And if the participant is incapable of giving the consent for any reason and it is essential to conduct the research, the consent could be taken from his guardian legally capable of giving consent on his behalf. The principle of consent is a cardinal principle and should be continue throughout the research i.e. the participant should be informed of any change or new findings of the trial and consent should be taken time to time.
3. Principle of non-exploitation – The participants should be reasonably remunerated for their involvement in research or experiment irrespective of their social or economic condition or educational status. They should be fully informed about all the danger pertaining to their participation so that they can be able to appreciate all physical or psychological risk attached to it. The participants should be chosen in such a way that the burden and benefit of research is distributed without any bias. There should be in a build compensation mechanism whether through insurance or any other method to compensate any miss happening attached to the trial.
4. Principles of privacy and confidentiality – the identity and documents related to the human subject should be kept confidential and no such information should be released without any legal or scientific requirement. Even before releasing such information for any scientific or legal reason a prior written consent should be taken from the concerned person.
5. Principle of precaution and risk minimization – All the due care and caution should be taken throughout the research to ensure that the subject of research should be at the minimum risk and should not be suffered from any known irreversible adverse effect.

Some other principles like principle of professional competence, accountability & transparency, maximizing public interest & distributive justice, totality of responsibility, public domain and institutional arrangements are the other principles given by WHO which are required to be followed while involving a human subject to the trial.

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Legal developments in laws related to clinical trial

Government of India realizing the reason of reluctance of sponsors to conduct new clinical trials relaxed the regulatory pathway to conduct such trials by taking various steps like introducing the new Drug and Clinical Trial Rules, 2019 in which it relaxed various rules for marketing foreign drug in India

In the new drugs and clinical trial rule, 2019 the government took into consideration various problems in conducting clinical trials and relaxed various laws related to clinical trials including rules for making foreign drugs in India where it reduced the time limit for central drug licensing authority (DCGI) from six months to 30 days in case the drug is manufactured or marketed in India.

The provision of deemed approval is also introduced where in case the sponsor has received no response within 30 days of filing of the application it shall be considered as if drug has been approved by DCGI but in such a case the sponsor has to give the prior notification to the central licensing authority (DGCI) informing about the conduct of the trial trial.

Also if the drug has already been approved by the DCGI approved country, accelerated approval of drugs in case of serious conditions based on severity, high prevalence, lack of alternative treatment and also if the new drug is more beneficial than the already existing one or to fulfil an unmet medical need

Conclusion

Vaccines are the most effective preventive tool against the pathogenic diseases which is deployed to reduce human suffering. Lack of vaccine and limited knowledge about the pathogens are the major reason behind today's pandemic. Today the major challenge before us is to rapidly develop an effective and safe vaccine at an affordable price. And for this the speed of the trial need to be increased by deviating from the typical human trial and adopting the human challenge trial but the ethics of these trials has always been remained in questions. Where the world's first HCT for SARS-CoV-2 vaccine is set to be conducted in London, the Indian government has rejected it on the ground that it does not have any additional benefit and hence is unethical to conduct such trial. As we have seen that there is no immediate need to conduct such trial but certainly HCT would be benefit in future for the development and comparison of new vaccines. HCT should only be conducted in such situations where the potential benefits attached to it are more than the risk associated to it. The role of the ethics committee is very crucial in clinical trials involving human participants and hence the selection of members of the committee should be done properly and without any bias. The committee should make sure that all the principles of the good clinical practice had been followed throughout the trial.

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The government has taken various steps to encourage the conduct of clinical trials in India by the time for approval of application of clinical trial from 6 months to 30 days and introducing the concept of deemed approval for clinical trial.

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