ISSN 2581-6217

World Journal of Pharmaceutical Science & Technology

Journal homepage: www.wjpst.com

Review Article

CLINICAL TRIALS: AN OVERVIEW

Mr. Shubham Vitthal Tanpure[1], Ms. Archana Gawade[2]

1. Clinical Research Scholar from Elite institute of Pharma Skills Pune.
2. Managing Director, Elite Institute Of Pharma Skills, Pune

Address for correspondence:

Mr. Shubham Vitthal Tanpure, Clinical Research Scholar from Elite institute of Pharma Skills Pune.
E-mail- shubhamtanpure20000@gmail.com

Received: 15-6-2022, Revised: 29-6-2022, Accepted: 10-7-2022

ABSTRACT

A clinical trial is a research project using human participants to address certain health-related problems. Clinical trials are the quickest and safest approach to discover treatments that benefit patients and ways to enhance health. Investigational studies examine the safety and efficacy of novel applications of conventional therapy in a controlled setting. Observational trials examine health concerns in sizable populations or groups of people in their natural environments. Clinical trials are a significant and highly specialized type of biological experiment that are used to evaluate the efficacy of treatments[1]. Clinical pharmacologists study the phase I pharmacokinetics, safety, and gross effects on human volunteers. If the drug passes the test, it moves on to phase II testing, where clinical pharmacologists study the pharmacokinetics, safety, and therapeutic efficacy of the drug on a small group of patients. If the test is successful, hundreds of small-group patients are now studied in phase III, primarily for safety and therapeutic efficacy. If it is authorized, the medication can now be sold. Even after the drug has been marketed, doctors from various hospitals and clinics provide their feedback on the medication, including any adverse events and phase IV effectiveness[2].

1. INTRODUCTION:

A clinical trial is a research study that examines whether a novel medical procedure or a novel application of an existing procedure would be a more effective means of disease prevention, detection, diagnosis, or

treatment1. Any novel medication must pass preclinical testing in order to begin a clinical trial. Preclinical research includes experiments on animal populations and in vitro (also known as test-tube or laboratory) research. To gather preliminary data on the study drug's effectiveness, toxicity, and pharmacokinetics, a wide variety of doses are administered to animal subjects or an in-vitro substrate[2].

2. PHASES OF CLINICAL TRIAL:

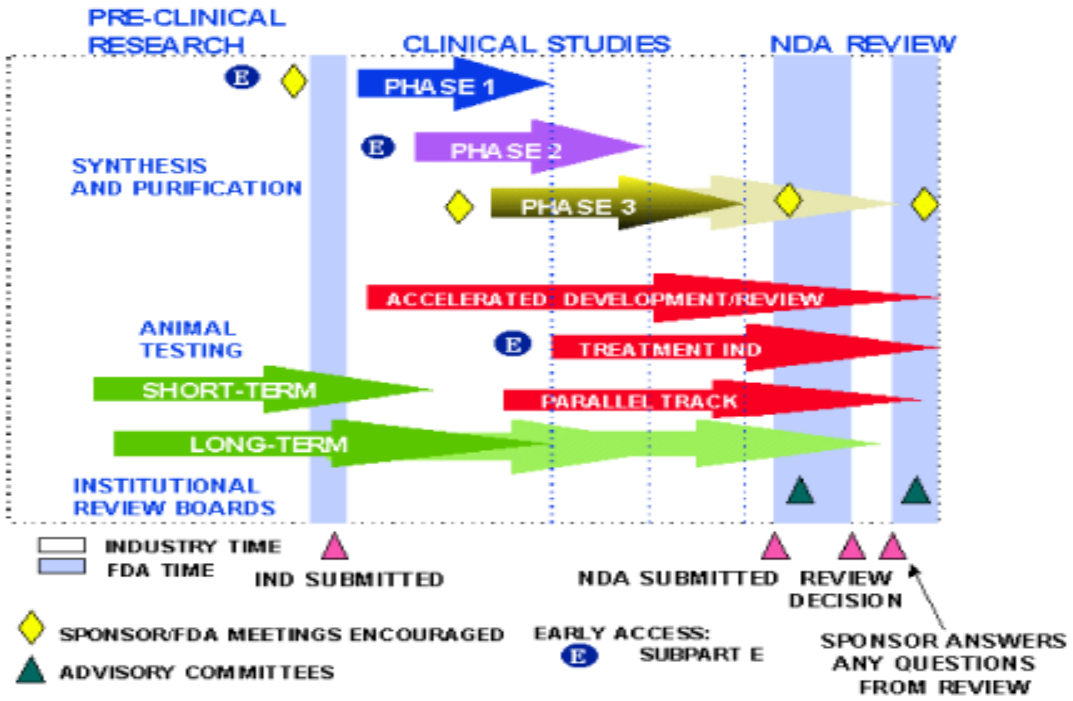

Fig.2. Phases of Clinical Trials

Pharmaceutical firms carry out considerable pre-clinical research before beginning clinical trials on a drug[3].

2.1. PRE-CLINICAL STUDIES:

Pre-clinical research includes experiments on animals and in vitro (also known as test tube or laboratory) research. To gather preliminary information on the study drug's efficacy, toxicity, and pharmacokinetics and to help pharmaceutical companies decide whether it is worthwhile to move forward with additional testing, a variety of dosages of the study drug are administered to the animal subjects or to an in-vitro substrate[2].

2.2. Clinical Trials:

2.2.1. PHASE 0:

In line with the U.S. Food and Drug Administration's (FDA) 2006 Guidance on Exploratory Investigational New Drug (IND) Studies, exploratory, first in human studies are now referred to as phase 0 trials. By determining very early on whether the medication or agent behaves in humans as was predicted from

preclinical research, phase 0 trials are intended to hasten the development of potential medicines or imaging agents. In order to acquire preliminary information on the agent's pharmacokinetics (how the body processes the medication) and pharmacodynamics (how the drug functions in the body), a limited number of individuals (10 to 15) receive a single subtherapeutic dosage of the study substance.

2.2.2. PHASE l:

The initial stage of testing on human volunteers is called a phase I trial. A modest (20–80) number of wholesome volunteers will often be chosen. This stage comprises tests intended to evaluate a drug's tolerability, pharmacokinetics, pharmacodynamics, and safety (pharmacovigilance). These studies are frequently carried out in an inpatient clinic where the individual may be examined by staff members who work full-time. The patient who receives the medication is often monitored for a number of drug half-lives.

Phase I trials sometimes contain dosage-ranging, also referred to as dose escalation, investigations to determine the ideal dose for therapeutic usage. The dosage range that is examined will often be a small portion of the level that is harmful to animals. Healthy volunteers are most frequently used in phase I studies. Real patients may, however, be employed in some situations, such as those who have advanced illness and have no other available treatments. The most common instances of this exception to the norm are in oncology (cancer) and HIV medication trials. For the time they spend in the volunteer center, volunteers are compensated with an inconvenience charge. Depending on length of involvement, pay might range from a modest sum for a brief period of residency to a bigger sum of up to around £4000 (4,00,288.56 rupees)[2].

There are different kinds of Phase I trials:

a. SAD (Single Ascending Dose):

Single ascending dose studies include giving a single dosage of the medicine to a limited number of people who are then monitored and assessed over an extended period of time. The dose is increased, and a new set of participants is subsequently given a larger dose, if they do not experience any negative side effects and the pharmacokinetic data is approximately in line with expected safe values. The medicine is considered to have achieved the Maximum Tolerated Dose (MTD) when either the precalculated pharmacokinetic safety limits are attained or unacceptable side effects manifest[2].

b. MAD (Multiple Ascending Dose):

Several Ascending Dose studies are carried out to learn more about the pharmacokinetics and pharmacodynamics of the medication at various doses[2].

2.2.3. Phase II:

Phase II studies are conducted on bigger groups (20-300) and are intended to evaluate the efficacy of the study drug as well as to continue Phase I safety evaluations in a larger number of volunteers and patients after the initial safety of the study drug has been validated in Phase I trials. When the development of a novel medicine fails, it typically happens during Phase II trials when it is revealed that the drug does not function as intended or has hazardous consequences. Sometimes Phase II studies are split into Phase IIA and Phase IIB. Phase IIB is especially meant to research effectiveness (how effectively the medication works at the recommended dose(s), as opposed to Phase IIA, which is primarily designed to evaluate dosage requirements (how much medicine should be given). Efficacy and toxicity are tested in certain trials that combine Phase I and Phase II.

2.2.4. Phase III:

In order to provide a conclusive evaluation of the drug's efficacy in relation to the existing "gold standard" of care, phase III studies are large-scale, randomized controlled multicenter trials including patient populations of 300–3,000 or more. Phase III trials are the most expensive, time-consuming, and complex studies to plan and administer, especially in therapy for chronic medical diseases, because of their scale and comparably lengthy duration. It is standard procedure for certain Phase III studies to continue while the regulatory submission is being processed by the relevant regulatory agency.

Obtaining clearance from the proper regulatory bodies (FDA (USA), TGA (Australia), EMEA (European Union), etc.) is normally assumed to need at least two successful Phase III studies confirming a drug's safety and efficacy, however this isn't always the case. When a medicine has successfully completed Phase III trials, the trial data is often compiled into a sizable document that includes a detailed explanation of the processes and outcomes of human and animal research, manufacturing practices, formulation information, and shelf life. The "regulatory submission" is made up of this assortment of data and is sent to the relevant regulatory bodies in various nations for examination.

The majority of pharmaceuticals entering Phase III clinical trials can be marketed in accordance with FDA standards, with the appropriate recommendations and guidelines, but the drugs must be quickly removed from the market in the event that any adverse effects are documented anywhere. It is not unusual to find several medications in Phase III clinical trials on the market, despite the fact that the majority of pharmaceutical corporations abstain from this approach[2].

2.2.5. PHASE IV:

The majority of pharmaceuticals entering Phase III clinical trials can be marketed in accordance with FDA standards, with the appropriate recommendations and guidelines, but the drugs must be quickly removed

from the market in the event that any adverse effects are documented anywhere. Following a drug's approval for sale, phase IV studies require continued technical support and safety surveillance (pharmacovigilance). Regulatory agencies may mandate phase IV studies, or the sponsoring firm may carry them out for competitive (identifying a new market for the medicine) or other reasons (for example, the drug may not have been tested for interactions with other drugs, or on certain population groups such as pregnant women, who are unlikely to subject themselves to trials).Unlike what was achievable during the Phase I-III clinical studies, the safety surveillance is intended to discover any uncommon or long-term side effects over a much larger patient group and longer time period. Recent examples include cerivastatin (brand names Baycol and Lipobay), troglitazone (Rezulin), and rofecoxib (Vioxx). If harmful effects are identified through Phase IV studies, a medicine may no longer be sold or restricted to certain applications[2].

3. TYPES OF CINICAL TRIAL:

A. Treatment trials:

Test experimental treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.

B. Prevention trials:

Look for better ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include medicines, vitamins, vaccines, minerals, or lifestyle changes.

C. Diagnostic trials:

Conducted to find better tests or procedures for diagnosing a particular disease or condition.

D. Screening trials:

Test the best way to detect certain diseases or health conditions.

E. Quality of Life:

Trials (or Supportive Care trials) explore ways to improve comfort and the quality of life for individuals with a chronic illness[2].

INVESTIGATIONAL NEW DRUG (IND) / CLINICAL TRIAL EXCEPTION (CTX) / CLINICAL TRIAL AUTHORIZATION (CTA) APPLICATION:

Examples of requests made to the proper regulatory authorities for authorization to conduct experimental research are INDs (in the United States), CTXs (in the United Kingdom), and CTAs (in Australia). This research may examine a novel dosage form or a fresh application of a medication that has previously been given marketing approval.

An Institutional or Independent Review Board (IRB) OR Ethical Advisory Board must also approve the testing methodology and the informed consent forms that participants must sign before taking part in a clinical trial, in addition to receiving approval from the necessary regulatory bodies. A clinical trial's ethical conduct and the protection of research participants rights are ensured by an impartial committee made up of doctors, community activists, and other individuals[14].

NEW DRUG APPLICATION (NDA) / MARKETING AUTHORIZATION APPLICATION (MAA):

Applications to sell a novel medicine include, for example, NDAs (in the U.S.) and MAAs (in the U.K.). This application contains all the data gathered during the medication development process and documents the safety and effectiveness of the experimental medicine. This collection of documentation is submitted to the FDA in the United States or to the relevant regulatory body in other countries following the end of successful preclinical and clinical testing. The application must include convincing proof that the medicine will really work as intended when taken by humans or under the circumstances outlined in the labelling or recommended for use. A new drug's marketing approval typically takes between six months and two years[4].

MONITORING CLINICAL TRIALS:

The purposes of trial monitoring are to verify that:

- The rights and well-being of human subjects are protected.
- The reported trial data are protected.
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s)[4].

4. ETHICAL CONSIDERATION:

An independent body (a review board or a committee, institutional, regional, national, or supranational) made up of medical professionals and non-medical members is in charge of ensuring the protection of the rights, safety, and well-being of human subjects involved in trials and giving the general public assurance of that protection, among other things, by reviewing and approving/giving a favorable opinion on the trial protocol, the suitability of the investigations,

Although independent ethics committees legal standing, make-up, operations, and legislative restrictions may vary from country to country4, they should be able to operate in accordance with GCP as outlined in this recommendation[4].

COMPLIANCE WITH PROTOCOL:

The researcher or institution must carry out the study in accordance with the protocol that was accepted by the sponsor and, if necessary, the regulatory authority (IES), and which was given approval/a positive

opinion by the IRB/IEC. The protocol, or an analogous contract, should be signed by the sponsor, the investigator, and the institution to demonstrate understanding.

With the exception of situations where it is imperative to remove an immediate risk to a trial subject or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor (s), change in telephone no.), the investigator should not implement any deviations from or changes of the protocol without agreement from the sponsor and prior review and documented approval / favourable opinion from the IRB / IES of an amendment (s).

Any departure from the authorized procedure should be noted and justified by the investigator or a representative chosen by the investigator. Without seeking previous IRB/IEC clearance or a positive opinion, the investigator may adopt a departure from the protocol or a change to it in order to remove an urgent risk to trial participants. The implemented deviation or change, the justifications behind it, and, if necessary, the suggested protocol amendment(s) should be reported as soon as feasible.

- To the IRB/IEC for review and approval/favourable opinion.
- To the sponsor for agreement.
- To the regulatory authority (IES)[4].

5. PLANS OF CLINICAL TRIAL:

Trials may be open, blind or double-blind.

5.1. Open trial:

In an open study, both the patient and the researcher are aware of every aspect of the therapy. These studies don't do anything to lessen the placebo effect and are subject to accusations of bias. However, as placebo therapies are not always feasible, they occasionally cannot be avoided (see Blinding). Typically, bioequivalence studies employ this type of study design[6].

5.2. Blind trials:

A. Single-blind trial:

In a single-blind experiment, the patient is blinded to the treatment's specifics but the researcher is not. There may not be a placebo effect since the patient does not know if the new therapy or another treatment is being given. Since the researcher is aware, it is conceivable for him to treat the patient differently in practice or to subtly indicate to the patient about key treatment-related information, altering the study's outcome[6].

B. Double-blind trial:

One researcher assigns a set of numbers to the "new therapy" or the "old treatment" in a double-blind experiment. The numbers are disclosed to the second researcher, but she is not informed of their intended use. Since the second researcher is in the dark, he is unable to inform the patient directly or indirectly and cannot yield to pressure from the patient to provide the novel medication. Additionally, the distribution of patients' ages and sexes in this system frequently reflects reality more closely. Therefore, as they frequently produce the most reliable results, double-blind (or randomized) experiments are favoured[6].

C. **Triple-blind trial**:

Although the definition of triple blinding may change depending on the specifics of the research design, certain randomized controlled trials are thought to be triple blinded. The most prevalent interpretation of this phrase is that the subject, researcher, and person giving the therapy (typically a pharmacist) are unaware of what is being administered. It might also imply that the patient, the researcher, and the statistician are all blind. The group administering the intervention in the control and research groups might not be aware of it. The phrase "triple-blinded" is rarely used because these extra safeguards are typically in place with the more widely known term "double blind trials." It does, however, imply an additional level of security to prevent any direct participants in the study from improperly influencing the study's findings[6].

6. ICH GCP GUIDELINES:

The principals of ICH GCP:

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

8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective tasks.
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement.
12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approval protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implanted[5].

7. ROLE:

7.1. ROLE OF PLACEBO:

The Latin word "placebo" means "I may pleasure you." The placebo effect is a side effect that can be attributed to a medication as a treatment and is not caused by a drug's unique pharmacodynamic properties for the ailment being treated. The placebo effect is "how the patient's impression of therapy effects his / her reaction," according to one definition. Placebos are employed in clinical trials to rule out the possibility that a drug's benefits are the result of pure chance alone and as psychologically effective therapeutic agents.

Placebos frequently result in the alleviation of subjective symptoms linked to psychological problems. This also includes relief from dyspnoea, anxiety, discomfort, and headaches. As a result, placebos are frequently used in the treatment of several diseases where the mental component is thought to be the cause of subjective symptoms. Sometimes with placebos, objective reactions such an increase or reduction in eosinophils and Europhiles can be observed. The placebo preparation, when administered for therapeutic effects, must seem to be relevant to the illness, must be safe, should ideally meet the patient's expectations, and to be effective, the preparation's "potency" must be demonstrated by some signs, such as a strong taste, a colorful capsule or a tablet with an unusual shape, and occasionally even by obvious but safe side effects.

In clinical trials, placebos are used to reduce physician and patient bias. This is especially important when assessing novel medications for illnesses including bronchial asthma, angina pectoris, pain, and mental disorders. In these situations, the actual medication and the placebo should be identical in terms of physical attributes including color, smell, taste, and shape.

7.2. ROLE OF PHARMACISTS IN CLINICAL TRIALS:

First and foremost, pharmacists play a vital role in research and clinical trials by providing the facilities needed for the safe storage of investigational medical products (IMPs), either in the refrigerator or at a regulated ambient temperature. Temperature monitoring is guaranteed and documented on a regular basis.

The pharmacist must also make sure there is always a steady supply of IMPs and that they are given to patients as needed. In addition to any written information that is provided, such as the Informed Consent Form or the Patient Information Leaflet, patients are counselled on the proper use of the IMPs. To assess treatment compliance, patient IMP returns are tallied and recorded. Additionally, pharmacists will make sure that injectable IMPs are prepared in line with the trial's instructions and are administered correctly.

In addition to overseeing clinical trials, oncology pharmacists frequently conduct studies with the goal of enhancing patient outcomes when given pharmaceuticals, such as chemotherapy or other supportive therapies like anti-emetics, blood growth factor injections, etc.

Pharmacists frequently perform research initiatives called Drug Utilization Evaluations (DUEs). These initiatives seek to encourage our patients to utilize medications responsibly. Basically, giving information on patient drug consumption and tracking our doctors' prescription behaviour. Because pharmacists check to see if medication is being used appropriately, DUEs are occasionally referred to as drug audits.

Additionally, pharmacists carry out observational studies to learn more about how patients or doctors see and feel about drugs. The information from surveys is utilised to enhance the services we offer to our patients. Two surveys are being carried out by the oncology pharmacy at NCC right now. They seek to learn more about how patients use complementary and alternative medicines as well as what patients think about using oral anti-cancer medications safely. Patients are frequently surveyed by pharmacy students who have received the necessary training to conduct research. We would like to take this chance to express our gratitude to each and every one of our patients who agreed to participate in the survey[10].

- After the clinical research there are several types of vaccines and their effects on human body was studied.

<u>Examples of vaccines are as follows:</u>

1. Covaxin – Bharat Biotech
2. Covishield – Serum Institute of India (Oxford/AstraZeneca formulation)
3. ZyCoV-D – Zydus Cadila
4. mRNA-1273 – Moderna
5. Sputnik-V - Gamaleya

6. Ad26.COV2. S – Janssen (Jonson & Jonson)
7. AZD1222 – Oxford/AstraZeneca

8. COVAXIN™:

1. WHAT IS COVID-19?

SARS-CoV-2 is a coronavirus that causes COVID-19 illness. There has never before been a coronavirus of this sort. Through interaction with another individual who has the virus, you can get COVID-19. Although it can affect other organs, the sickness is mostly respiratory in nature. People who have COVID-19 may suffer a variety of symptoms ranging from moderate to severe. 2 to 14 days after viral exposure, symptoms could start to show up. Aside from a fever or chills, symptoms may also include a cough, shortness of breath, exhaustion, muscular or body pains, headache, recent loss of taste or smell, a sore throat, congestion or a runny nose, nausea or vomiting, and diarrhoea[11].

2. WHAT IS THE BHARAT BIOTECH COVID-19 VACCINE (COVAXIN™)?

The COVID-19 vaccine (COVAXIN™) from Bharat Biotech has been approved for limited use in emergency situations and may prevent COVID-19. The sale or distribution of COVAXIN™ for limited usage in urgent situations in the public interest as a strong precaution has been authorized by the Central Licensing Authority. Additionally, the trial phase that evaluated and established COVAXIN™'s capacity to generate immunity against COVID-19 is now complete. However, clinical trials are currently being conducted to determine the effectiveness of COVAXIN™. Recognizing that having the vaccination does not exempt one from additional Covid-19 precautions is crucial since the clinical effectiveness of COVAXIN™ is now being investigated during a phase-III investigation[11].

3. WHO SHOULD NOT GET BHARAT BIOTECH COVID-19 VACCINE (COVAXIN™)?

You should not get the BHARAT BIOTECH COVID-19 VACCINE (COVAXIN™) if you:

- Have any history of allergies.
- Have fever.
- Have a bleeding disorder or are on a blood thinner.
- Are immune-compromised or are on a medicine that affects your immune system
- Are pregnant.
- Are breastfeeding.
- Have received another COVID-19 vaccine.

Any other serious health related issues, as determined by the Vaccinator/Officer supervising vaccination[11].

4. WHAT ARE THE RISKS OF BHARAT BIOTECH COVID-19 VACCINE (COVAXIN™)?

Side effects that have been reported with the BHARAT BIOTECH COVID-19 VACCINE (COVAXIN™) include:

- Injection site pain
- Injection site swelling
- Injection site redness
- Injection site itching
- Stiffness in the upper arm
- Weakness in injection arm
- Body ache
- Headache
- Fever
- Malaise
- Weakness
- Rashes
- Nausea
- Vomiting

The BHARAT BIOTECH COVID-19 VACCINE (COVAXIN™) has a very slim probability of resulting in a serious allergic response. Rarely, receiving the BHARAT BIOTECH COVID-19 VACCINE may result in a serious allergic response (COVAXIN™). For this reason, your immunization provider will ask you to remain at the location of your vaccination for 30 minutes after each dosage in order to be monitored following vaccination. Signs of a severe allergic reaction can include:

- Difficulty in breathing
- Swelling of your face and throat
- A fast heart beat
- Rash all over your body
- Dizziness and weakness[11]

8.1. INTRODUCTION:

As of December 23rd, 2020, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, also known as the Coronavirus disease-2019 (COVID-19), has spread to more than 216 nations worldwide,

with a total of 79 million confirmed cases and 1.7 million fatalities. There have been 10 million verified SARS-CoV-2 infections in India as of January 6, 2021, and 1,50,000 people have died as a result. Animals and people alike are seriously at risk from coronaviruses. When the Middle East Respiratory Syndrome (MERS) virus first appeared, it infected 2000 individuals with a mortality rate of 35%. Earlier, other members of the same Coronaviridae family, including SARS-CoV, infected 8000 people with a death rate of 10%. The porcine epidemic diarrhoea coronavirus (PEDV) has invaded the country, killing more than 10% of the country's pig population in less than a year and leaving piglets with an almost 100% mortality rate. The encased positive-stranded RNA viruses known as coronaviruses have the biggest genomes of any RNA viruses, measuring between 27 and 32 kb2. The nucleocapsid protein (N), which forms a helical capsid and is encased in an envelope, houses the viral genome inside of it. Version: 4.0. There are a minimum of three structural proteins linked to the SARS-CoV viral envelope: While the spike protein facilitates viral entrance into host cells, the membrane protein and envelope protein are important in virus assembly. These structural proteins include the spike, which causes corona viruses to seem to have crown-like protrusions from their surface. Specifically, through respiratory droplets, the SARS-CoV-2 virus spreads from person to person.

SARS-CoV-2 is an inhaled virus that mostly attaches to epithelial cells in the upper respiratory tract and begins multiplying once inside the cell. Both SARS-CoV-2 and SARS-CoV use the angiotensin-converting enzyme 2 (ACE2) as their primary receptor. The virus spreads locally, but the innate immune response is rather moderate. At this point, nasal swabs can identify the virus. These people are contagious even if their virus load is minimal. The viral RNA RT-PCR result may be helpful in predicting the viral load, subsequent infectivity, and clinical outcome. A more potent innate immune response is activated when the virus spreads and migrates down the respiratory system. Both the virus (SARS-CoV-2) and early indicators of the innate immune response should be detectable in nasal swabs or sputum. After around 5 days of incubation, SARS-CoV-2 infection symptoms start to show. From the time SARS-CoV-2 symptoms first appeared until death, it took an average of 14 days, ranging from 6 to 41 days. The length of this time depends on the patient's age and immune system health. Compared to those under the age of 70, it was shorter for those over 70. Fever, coughing, and exhaustion are the most typical symptoms of SARS-CoV-2 disease, but other signs and symptoms might also include sputum production, headache, haemoptysis, diarrhoea, dyspnoea, lymphopenia, and in certain cases, recently developed anosmia and/or ageusia.[11].

COVAXIN DEVELOPMENT:

An indigenous entire virion inactivated SARS-CoV-2 virus vaccine has been created by Bharat Biotech International Limited in collaboration with the National Institute of Virology (NIV), a renowned institute of the ICMR (COVAXIN^{TM}). The non-clinical toxicity tests to evaluate the COVAXIN^{TM}'s safety were carried out in accordance with GLP standards (GLP). The COVAXIN^{TM} vaccine was tested for immunogenicity and

safety in three animal models mice, rats, and rabbits and was discovered to be both safe and immunogenic across the board. The trial paper is accessible at bioRxiv as a pre-print. By administering the Rhesus macaque (DOI:10.21203/rs.3.rs65715/v1) and Syrian hamsters with the wild type virus, the COVAXINTM vaccine's effectiveness was assessed in both species. These findings show that two vaccine doses effectively protected animals exposed to the SARS CoV-2 virus and elicited a substantial immunological response (version 4.0).

8.2. OBJECTIVES:

to assess the COVAXIN^{TM} vaccine's safety and reactogenicity while introducing it to limited environments in real life.

to assess the number of COVID-19 patients with RT-PCR positive results following receipt of COVAXIN^{TM} within the required post-vaccination contact days[11].

8.3. ELIGIBILITY:

The potential vaccine recipients fulfilling the following criteria will be eligible for vaccination.

Ability to provide consent.

Vaccine recipients aged 18 years and above.

Vaccine recipients with good general health or stable medical conditions as determined by the Vaccinator/Officer supervising vaccination. A stable medical condition is defined as a disease not requiring significant change in therapy or hospitalization or worsening disease during the past 3 months.

The individuals with the following conditions will NOT be eligible for vaccination.

- Have any history of allergies.
- Have fever.
- Have a bleeding disorder or are on a blood thinner.
- Are immunocompromised or are on a medicine that affects their immune system.
- Are pregnant.
- Are breastfeeding.
- Have received another COVID-19 vaccine.
- Any other serious health related issues as determined by the Vaccinator/Officer supervising vaccination[11].

8.4. VACCINATION PROCEDURE:

- **Visit 1 (Day 0):** The Vaccine recipients will be administered with the first dose of the COVAXIN^{TM} via the intramuscular route.

Following vaccination, Vaccine recipients will remain at the vaccination site for at least 30 minutes of observation to record any adverse event.

Day 1-7: The Vaccine recipients will be given an adverse event form to record the adverse events.

Day 8-27: The Vaccine recipients will inform the vaccination site, if they have encountered any health-related issues or adverse events.

The Vaccine recipients will return the Adverse Event Form during the visit for the administration of the second dose of vaccine (Day 28).

- **Visit 2 (Day 28):** The Vaccine recipients will be administered the second dose of the COVAXIN^{TM} vaccine via the intramuscular route.

Following vaccination, Vaccine recipients will remain at the vaccination site for at least 30 minutes of observation to record any adverse event.

Day 28-35: The Vaccine recipients will be given an adverse event form to record the adverse events.

If vaccine recipients have any health problems or negative side effects, they will let the site know. After seven days have passed since receiving the immunization, vaccine recipients must submit the completed Adverse Event reporting form.

Following the second dose of immunization, all vaccine recipients will be monitored for a period of three months. The report shall be given to the approved immunization officers or healthcare personnel in the event of any negative or major negative effects. The procedures now in place under the government vaccination programmed and the Central Ethics Committee, where applicable, shall be used to determine the causality assessment of all SAEs, medical management, and compensation. Vaccine recipients will get medically accepted standard of care in the government-designated state hospitals in the event of any adverse events or significant adverse events. Based on CDSCO/suggestion, DCGI's the AEFI monitoring's final results and the compensation to be given will be determined[11].

8.5. Study Design:

A. Parallel Study:

EACH PATIENTS RECEIVE ONE TREATMENT

Each patient is assigned to one treatment arm in parallel research. The study therapy, a placebo, the accepted standard of care, a comparator medication, or several dosages of the research treatment can all be included in a study arm. They'll stay in that treatment group for the duration of the experiment[12].

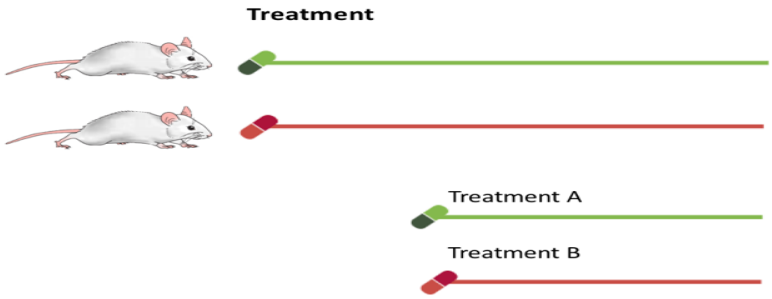

Fig. 8.5.A. Illustration of Parallel Study

B. Cross-over Study:

EACH PATIENT RECEIVES BOTH TREATMENTS

Every patient in crossover research begins in one treatment arm and shifts to another during the experiment.

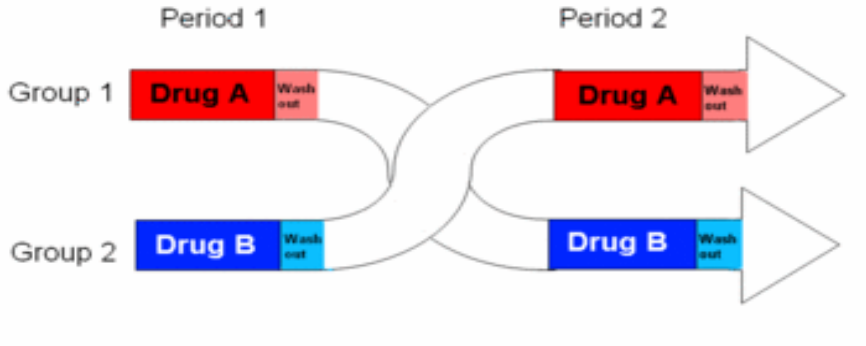

Fig.8.5.B. Illustration of Crossover Study

A washing period—a planned pause between treatments in crossover studies—is common. No medications are used at this time to lessen the impact of the earlier therapies[12.13].

- **CONCEDERATION FOR CROSSOVER STUDIES:**

WHEN THEY ARE USED	RECRUITMENT EFFECTS	OUTCOME EFFECTS
Not well suited for short duration, or acute conditios[12,13]	More patients may withdraw from the study since it takes longer to participate in multiple treatment arms[12]	Carryover effects from prior treatments may impacts results gathered from subsequent treatment arms[12,13]

Better for long-term, or chronic conditions with stable symptoms[12,13]	Recruitments may occur faster because fewer patients are needed and all enrolled will have an opportunity to receive study treatments[13]	Each patient acts as test and control, so comparisons are made within the same patients instead of between patients[12,13]

9. CONCLUSION:

A clinical trial is undertaken in human volunteers to confirm the beneficial features of a novel medicine and is conducted in accordance with ICH and GCP principles. Investigational novel drugs go through clinical stages I, II, III, and IV after preclinical development. These stages include a thorough discussion of pharmacokinetics, pharmacodynamic profile, side effects that may be detrimental or advantageous, unfavourable impact, and post-marketing surveillance.

10. REFERENCES:

1. Information about clinical trial. Available from: URL http://www.temple.edu/pascope/about_trials.html
2. Clinical trial Wikipedia, the free encyclopedia. Jan 28 2008. Available from: URL http://en.wikipedia.org/ wiki/clinical trial. 28 Jan 2008.
3. Kulkarni S. K., Hand Book of Experimental Pharmacology, 3rd ed, Vallabh Prakashan New Delhi, 2004, 21.
4. Itkar S., Pharmaceutical Management, 3rd ed, Nirali Prakashan, Pune, 2007, 13.4-13.5.
5. ICH Harmonized Tripartite Guideline for Good Clinical Practice 'Academy for Clinical Excellence'.
6. Pharmacist Career Profile: Clinical Research / Investigational Drug, Available From: URL: http://en.wikipedia.org/wiki/Randomized_controlled_t rial.
7. Barar, F. S. K., Essential of Pharmacotherapeutics. 4 thed, S. Chand and Company Ltd; New Delhi, 2007, 57-59.
8. Allen, L. V, Poporich, N. G, Ansel H. C., Pharmaceutical Dosage Forms and Drug Delivery System, 8th ed, B I Publications Pvt. Ltd.; New York, 2005, 45, 64-65.
9. Satoskar, R. S., Bhandar, S. D., Ainapure, S. S., Pharmacology and Pharmacotherapeutic. 8th ed, Popular Prakashan, Mumbai, 2003, 64.
10. Pharmacist Role in clinical trial Available from: URL: http://www.nccs.com.sg/pbcation/tomorrow/mar 08/pharmacy
11. BHARAT BIOTECH OFFICIAL PAGE (Article)
12. Remedica. Clinical Trials: A practical Guide, Analysis, and Reporting. 2006. URL: books.google.com/books?id=zgx_YTHny5C&lpg.
13. Piantados S. Clinical Trials: A Methodologic Perspective.2005. URL: books.google.com/books?id=w0vpmFSh4yMC&lpg