‘’A Review on Seamless Clinical Trials: Accelerating Drug Development and Regulatory Approval in the Post-Pandemic Landscape”

A project was submitted to satisfy several requirements for the Bachelor of Pharmacy (B.Pharm) Degree

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Approval

This project has been submitted to the Department of Pharmacy, Faculty of Health and Life Sciences at Daffodil International University. It has been accepted as satisfactory for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (B.Pharm). The style and contents of the project have been approved.

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I hereby certify that I independently completed this project report to satisfy the requirements for the Bachelor of Pharmacy (B.Pharm) degree under the supervision of Galib Muhammad Abrar Ishtiaque, Lecturer, Department of Pharmacy, Faculty of Health and Life Sciences, Daffodil International University. By signing this, I certify that I am the only author of this work. In addition, I swear that neither this project nor its components have ever been submitted to another university to receive a Bachelor's degree or any other degree.

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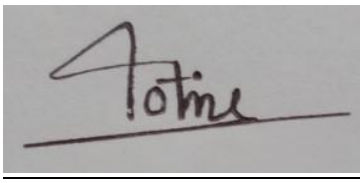

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Tusnim Jahan

Author

Dedication

I dedicate this work to my parents and my teachers. The person who always encouraged me in every sphere of my life and guided me in this process kept me on track.

Abstract:

The cornerstone for assessing the safety and efficacy of medical therapies is clinical trial data, which promotes improvements in healthcare. Conventional trial designs are still important but frequently face obstacles, including long lead times, excessive expenses, and low participant participation. By effectively and cohesively integrating every stage of the trial process from study design to data analysis seamless clinical trials have emerged as a viable solution to these problems. The concept of seamless clinical trials pays prominence to their fundamental elements and benefits. Trials that are seamless span a range of processes with little interruption between them, such as feasibility evaluation, participant recruiting, intervention delivery, data gathering, and analysis. Digital technology, including wearables, telemedicine platforms, and electronic health records, is essential for optimizing trial procedures and improving participant experience. In addition, there are several benefits that seamless trials provide over conventional methods, including shorter research durations, less administrative work, better data, and higher participant retention. Through adaptive trial designs and real-time data analytics, analysts may dynamically modify study settings in response to new knowledge about producing more reliable and individualized results. On the other hand, establishing seamless clinical trials presents difficulties concerning stakeholder participation, data protection, regulatory compliance, and technological interoperability. To overcome such obstacles, collaboration across fields between researchers, medical professionals, policymakers, and tech developers is needed to create standardized procedures and frameworks. A revolutionary strategy for furthering medical research and enhancing patient care is seamless clinical trials. These trials can completely transform clinical studies using integration and innovation, which will hasten the process of turning scientific discoveries into real benefits for people worldwide.

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List of Abbreviations:

COVID 19	**Coronavirus Disease 2019**
FDA	**Food and Drug Administration**
RCTs	**Randomized Controlled Trails**
MRC	**Medical Reserve Crops**
SARS	**Severe Acute Respiratory Syndrome**
RT- PCR	**PCR**
NIAID	**The National Institute of Allergy and Infectious Diseases**
IND	**An Investigational New Drug**
NDA	**New Drug Application**
DNA	**Deoxyribonucleic Acid**
RNA	**Ribonucleic Acid**
MRC	**Medical Research Council**
CSSE	**Computer Science System Engineering**
CDC	**Centers for Disease Control and Prevention**
WHO	**World Health Organization**
ECG	**Electrocardiogram**
LMICs	**Low and Middle-Income Countries**
WIV	**Whole Inactivated Virus**
VLPs	**Virus-Like Particles**
ICH	**The International Conference on Harmonization**
JCO	**The Journal of Clinical Oncology**
EU	**European Union**

Chapter 1
INTRODUCTION

1.1 Clinical Trails:

Clinical research is an essential scientific inquiry that aims to discover effective solutions for human health problems and diseases. This approach involves a systematic study of the pathophysiology of various ailments and conditions to help with their diagnosis, therapy, and prevention. However, the COVID-19 infestation has caused a compelling blow worldwide, resulting in the unfortunate deaths of over 50 million individuals globally. The pandemic has also led to a high rate of morbidity, with no effective medications or therapeutic procedures available to treat and manage the disease [1]. Clinical trials are an integral part of biomedical or behavioral research that seeks to address specific questions regarding the effectiveness of various interventions. These trials can include novel treatments like vaccines, drugs, dietary supplements, medical devices, and established interventions that require further research and comparison [2]. The primary objective of clinical trials is to provide accurate data on dosage, safety, and efficacy, which can help in the development of effective treatments for various health conditions. It is necessary to note that clinical trials are only conducted with the consent of the national ethics commission or health authority of the country where the therapy is being requested. These authorities are responsible for assessing the trial's risk-benefit ratio, and their clearance merely permits the experiment to proceed without implying that the medication is "safe" or successful. Therefore, clinical trials involve small-scale pilot studies with volunteers or patients, followed by larger-scale comparative studies based on the type of product and stage of development. Clinical trials can be conducted in a single research facility or several centers, in one country or several countries, and can differ in size and expense. The purpose of clinical trial design is to ensure the scientific validity and repeatability of the outcomes. This process involves rigorous planning, execution, analysis, and reporting of the results, which can help in the development of effective treatments for various health conditions [3].

1.2 Classifications of Clinical Trials:

After receiving authorization to conduct human research, the U.S.(FDA) categorizes and monitors study results according to the following groups [4].

1. Prevention trials: These aim to stop the spread or recurrence of a disease in people who have never had it. These methods may add prescription drugs, vitamins or other micronutrients, vaccinations, and lifestyle modifications.

2. Suppressing trials: These examine techniques for identifying specific diseases or medical conditions. The purpose of diagnostic trials is to find more precise procedures or examinations for the diagnosis of a certain disease or ailment.

3. Treatment trials: These test innovative drug combinations along with novel surgical or radiation therapy procedures.

4. Quality-of-life trials: It is also known as supportive care trials, which evaluate methods to increase the level of comfort and care given to people with chronic illnesses.

5. Genetic research: This is done to assess the extent to which a person's genetic makeup can predict whether or not they will get sick.
6. Epidemiological trials: These analyze large populations to find common causes, patterns, or disease treatment approaches.
7. Expanded access or compassionate use trials: These allow patients who have no other viable options to receive partially tested, unapproved medications. Patients who are too sick to be considered for randomized clinical trials or have tried every conventional treatment available may qualify. These exemptions typically require individual approval from the FDA and the pharmaceutical company.
8. Fixed trials: These do not modify the trial in any way once it is underway and wait to assess the results.
9. Adaptive clinical trials: These are created with pre-existing data and are adjusted throughout the trial according to interim findings. Changes include those to the "cocktail" mix, patient selection criteria, drug being studied, dosage, and sample size. A Bayesian experimental design is often used in adaptive trials to assess the trial's progress. Studies have frequently developed into an ongoing process whereby patient groups and medications are periodically added or deleted in response to new data. Finding medications with a therapeutic effect rapidly is the aim, as is identifying patient populations for which the therapy is suitable.

1.3 Phases of Clinical Trials:

Clinical trials typically have four distinct phases, each with varying participant counts and different objectives to establish and characterize certain outcomes. Phases are often used to categorize clinical trials of novel medications. A separate clinical study is conducted for each stage of the drug approval process. Phases I through IV of the drug development process often take many years to complete, frequently requiring ten years or more. The national regulatory body generally approves a medicine for use in the general public if it makes it through phases I-III. Phase IV trials are conducted after the newly licensed medication, test, or gadget commercialization to evaluate the advantages, disadvantages, or optimal applications. Pharmacological clinical studies are frequently categorized using phases. Each step of the drug licensing method involves different scientific trials.

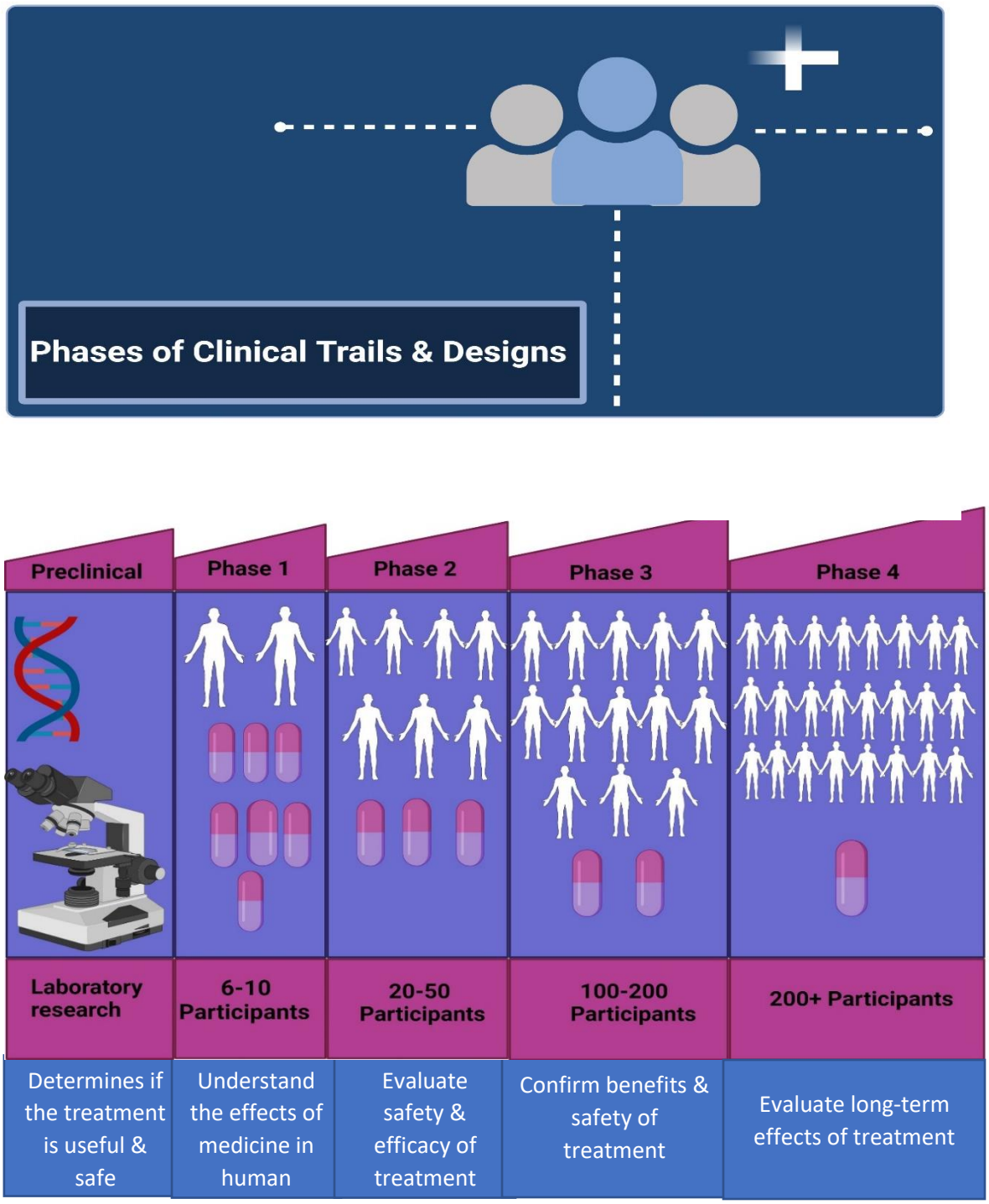

Figure: 1 Phase of Clinical Trails [5].

1.4 Different phases of Human clinical trials:

1. Pre-clinical study

The primary goal of any research study is to evaluate the convincingness of a specific drug or treatment for a particular medical condition. This involves conducting experiments on either animals or cell models within a controlled laboratory setting to determine the optimal dose and toxicity levels of the new therapy. To proceed with human testing, there must be sufficient and convincing evidence of the intervention's safety and efficacy. This may involve conducting preclinical trials to assess the drug's pharmacokinetics, pharmacodynamics, and potential side effects. Additionally, researchers may analyze the drug's molecular structure and mechanism of action to understand its therapeutic potential and limitations better. Ultimately, the success of any research investigation depends on the thoroughness and accuracy of the data collected, analyzed, and interpreted [5].

2. Phase I

Once Phase 0 has yielded good results, the scientists move on to Phase I. During this stage, a broader range of individuals (roughly between the ages of 20-80) who are free of underlying medical issues are used. This stage can take several months to complete. The purpose of Phase I is to determine the highest dosage a human can take without experiencing significant negative effects. Close observation of the participants is required, as well as ongoing reporting and recording of their bodily reactions. During this stage, researchers choose the method of drug delivery - whether it be intravenous, oral, or topical - based on which is most effective or the nature of the illness or infection under investigation. The FDA requires that a drug must come from reliable sources and show a success rate of around 70% for it to proceed to Phase II, the next stage in the process [6].

3. Phase II

Phase II clinical trials are an important part of the drug development process. These trials involve testing new therapies on a larger sample size of participants compared to phase I trials. In phase II trials, over 100 participants with the specific illness or virus being studied are usually included. The dosages used in phase II therapy are the same as those used in phase I therapy. However, the primary goal of phase II trials is to determine the efficacy of the drug rather than its safety. While the safety of a drug is not established in phase II trials, the results provide valuable information that can increase the success rates of phase III trials. The FDA reports that approximately 30% of medications that pass phase II trials and are deemed safe proceed to phase III trials. This means that phase II trials play a crucial role in determining which drugs are safe and effective enough to move on to the next stage of testing. In summary, larger sample sizes are required in phase II trials to ensure the safety and effectiveness of new therapies. While the primary goal of these trials is to determine the efficacy of the drug, the results can also provide valuable information that increases the success rates of phase III trials.

4. Phase III

In the process of authorizing a new medication, there is a phase that involves conducting studies on larger populations in different geographical areas. This phase, known as Phase III, typically involves around 300 to 3000 patients suffering from the ailment for which the drug is intended. Since the trials involve a lot of individuals from different locations, it may take several years to complete. The primary objective of this trial is to compare the effectiveness of the new medicine to the existing treatments available in the market for the same illness. Therefore, scientists must demonstrate that the new medication is equally safe, effective, and efficacious as any currently available medication. During the trial, randomized studies are conducted where participants are randomly selected to create distinct groups. One group is given the new treatment, and another group, known as the controlled placebo group, receives an identical but fictitious substance (sometimes referred to as sugar pills). Phase III studies are often double-blind, meaning that neither the researcher nor the subject is aware of the medicine that the person is receiving. This helps in eliminating bias from the interpretation of the results. Since the Phase III trial involves a greater number of participants and a longer duration, rare and long-term adverse effects are more likely to appear during this phase. If the investigators can demonstrate that the medication is both safe and effective, the FDA can approve the use of the drug. It is worth noting that at least 25-30% of FDA-approved medications are from reliable sources.

5. Phase IV

The stage of drug development referred to as post-market surveillance is an essential aspect of the drug development process. This stage involves conducting research and testing medications on a larger population over an extended period after the medicine has been approved by a regulatory authority. The purpose of this stage is to help investigators gain more insight into the long-term safety, effectiveness, and potential benefits of the drug. During post-market surveillance, researchers monitor the drug's performance in a real-world setting to identify any adverse effects or unexpected outcomes that may not have been evident during the clinical trial phase. This stage can also help identify any long-term benefits of the drug that may not have been apparent during earlier stages of development. The data gathered during post-market surveillance is critical in ensuring the safe and effective use of medications. It is used to update prescribing information, inform regulatory decisions, and provide healthcare professionals with the most up-to-date information on the drug's risks and benefits.

1.5 Importance of Clinical Trials:

- Clinical trials are an essential aspect of medical research that plays a vital role in improving the safety and effectiveness of the healthcare industry.
- These trials provide researchers with valuable insights into the efficacy of novel approaches for detecting, diagnosing, and treating various illnesses.

- By conducting clinical research researchers can determine whether a medication has the desired effect, what dosage is appropriate, how it is metabolized, and how often it should be administered.
- Clinical trials can also identify the adverse effects of a drug, the best methods for treating them, any negative interactions with food or other medications, and how to avoid such unwanted effects.
- Moreover, clinical trials can help researchers identify patients who are most likely to benefit from a particular drug, as well as those who are not.
- This information can help doctors tailor their treatment plans to meet individual patient needs better.
- In addition to these benefits, clinical trials also provide a platform for researchers to gather data on the long-term safety and effectiveness of a new drug or treatment.
- This data is critical in obtaining regulatory approval, which is necessary for the drug to become available for widespread use.

In summary, clinical trials are an indispensable tool in advancing medical research's effectiveness and safety. They provide researchers with valuable insights into the efficacy of new treatments, the best ways to administer them, and any potential risks associated with their use. By participating in clinical trials, patients can help advance medical science and contribute to the development of new and better treatments for various illnesses [5].

1.6 Clinical Trials vs. Clinical Studies:

Clinical studies are research investigations conducted to gain a comprehensive understanding of medicine. There are two primary categories of clinical research:

- Observational clinical research and
- Interventional clinical research.

Observational studies involve observing and analyzing the natural course of a disease or condition, whereas interventional studies involve actively intervening in a disease or condition to assess the effectiveness of the treatment. Interventional studies involve dividing participants into groups and administering one or more treatments or interventions to assess their effectiveness. These interventions may include medication, therapeutic agents, preventative agents, diagnostic agents, medical devices, surgeries, vaccinations, and noninvasive methods, such as diet and exercise modification. In addition, a sugar tablet known as a placebo or no treatment may also be given. Through interventional studies, researchers can evaluate how the prescribed treatment affects biological or health-related variables. One type of interventional study is a clinical trial, where participants are randomly assigned to different intervention groups. A randomized control trial is one type of interventional study. In RCT, an intervention is randomly assigned to human volunteers, who are then divided into two groups:

- The experimental group: which receives the intervention under test.
- The comparison group: It is also known as the control group, which receives conventional treatment, a placebo, or no intervention at all.

In summary, clinical studies are an essential tool for advancing medical knowledge and improving patient care. By conducting interventional studies, researchers can evaluate the effectiveness of different treatments and interventions and identify new approaches to managing diseases and conditions.

1.7 Clinical Research:

Clinical research is usually carried out on human participants to check out the efficacy of therapeutic medications, surgical treatment, or equipment. Clinical research also includes any study conducted on the causes, signs, and risk factors of a disease, in addition to other aspects of the condition. Clinical trials assess the ability of a therapeutic medication or medical technology to control, prevent, and manage disease. The importance of clinical research cannot be overstated, particularly in the context of the increase in both communicable and non-communicable illnesses and the impact of COVID-19 on public health globally. There are two main categories of clinical research design: non-interventional/observational and interventional/experimental studies. Non-interventional studies can be descriptive or analytical studies such as case-control and cohort studies. Randomized or non-randomized experimental investigations are both possible. A variety of designs are available for clinical trials, such as factorial, adaptive, superiority, non-inferiority, randomized withdrawal, parallel, crossover, and factorial designs. There is a crucial difference in evidence-based practice between observational research and randomized controlled trials [6].

Case-control and cohort studies are two types of observational studies that yield less convincing data than randomized controlled trials. A significant amount of design and interpretation error can occur while conducting observational studies since the researchers evaluate relationships between participants' health status and the treatments they received after the fact [7]. Strong proof that the research treatment has an impact on people's health may be found in randomized controlled trials [6].

1.8 Design:

Trail Design Type	Type of Study	Nature of the study
Parallel	Randomized	This is the most frequent design wherein each arm of the study group is allocated a particular treatment (placebo (an inert substance)/therapeutic drug)
Crossover	Randomized	The patient in this trial gets each drug and the patient serves as a control themselves
Factorial	Non-randomized	Two or more interventions on the participants and the study can provide information on the interactions between the drugs
Randomized withdrawal	Randomized	The study evaluates the time/Duration of drug therapy
Matched pairs	Post-approval study	Recruit patients with the same characteristics

Table: 1 Design of Traditional Clinical Trails [7].

1.9 Modern trials:

Sir Ronald A. Fisher, an agricultural researcher at Rothamsted Experimental Station during the 1920s, wrote Principles of Experimental Design, a precise guide for designing experiments [8]. His key concepts include replication to lower uncertainty, repeat measurements and experiments to find sources of variation, blocking to group experimental units into similar sets, and the use of factorial experiments to assess the effects of independent factors [9]. The British MRC acknowledged the importance of clinical trials starting in the 1930s. The council formed the Therapeutic Trials Committee to offer guidance and support in setting up monitored clinical trials for items that show potential in the treatment of disease based on experimental evidence [10]. Sir Geoffrey Marshall conducted the first randomized curative experiment at the MRC Tuberculosis Research Unit, which aimed to determine if streptomycin could treat pulmonary TB [11]. The study included both double-blind and placebo-controlled trials. Sir Austin Bradford Hill, who was part of the streptomycin studies, further established the clinical trials approach [12]. He began

using statistics in medicine in the 1920s and conducted revolutionary research on the link between smoking and lung cancer with Richard Doll. They conducted a long-term prospective study in 1950 that compared lung cancer patients with matched controls and a case-control study in 1950 that looked at the smoking patterns and health of over 30,000 doctors over several years. Hill is known for developing precise experimental methods used in the evaluation of new therapeutic and prophylactic agents in medicine. International Clinical Trials Day is celebrated on the 20th of May [13].

1.10 Drug Trials:

Clinical studies involve testing novel therapies on healthy individuals with no medical issues or on individuals with certain medical conditions who are willing to try a new treatment. Pilot studies are conducted to gather data for subsequent clinical research designs. The aim of testing medical treatments is to determine their safety and effectiveness. Evaluating the safety and effectiveness of treatments involves considering the severity of the illness or condition, alternative therapies, and the intended usage of the treatment [2]. These are not unquestionable norms and benefits must be weighed against risks [14,15]. Cancer therapies, which are designed to treat life-threatening illnesses and are taken under a doctor's care, are permitted despite having substantial adverse effects that would not be accepted for an over-the-counter pain medication [16]. Seniors, who make up 14% of the US population, use almost one-third of all prescription drugs [17]. However, they are often excluded from studies due to their higher likelihood of health issues and drug use, as well as their differing physiological capacity than younger persons. Similarly, children and others with associated medical issues are frequently excluded, and pregnant women are often excluded due to the potential risks to the fetus. The study sponsor determines which patient types will benefit from the study and works with a panel of experienced clinical investigators to determine the trial's design. If the sponsor cannot find enough test participants at one site, investigators from other locations are invited to participate in the study. During the trial, the investigators recruit a specific number of participants, give the therapy or treatments, and collect health-related data from the patients. The data collected includes vital signs, blood or tissue concentrations of the study medication, changes in symptoms, and whether the disease that the drug is meant to treat improves or worsens.

After collecting the data, the researchers send it to the study sponsor, who then performs statistical tests to evaluate the pooled data. The goals of the clinical trial include assessing the safety and relative effectiveness of a medication or device for a specific type of patient, at varying dosages, for a novel indication, assessing enhanced treatment effectiveness about the recommended therapy for a certain ailment, and comparing the study medication or gadget to two or more commonly used or authorized treatments for that ailment.

1.10.1 Prospective Study:

A prospective study is a type of experimental design that involves observing events as they happen over some time. It is also known as a longitudinal study. The study begins with the recruitment of participants who do not have any specific condition of interest. Researchers then collect data and perform measurements at regular intervals to determine the occurrence of specific results and other related information [21]. Prospective studies are often preferred by statisticians over retrospective studies because they have several advantages. They are less susceptible to bias and confounding variables, and they allow researchers to control the study design in a way that maximizes the accuracy and reliability of the results. In a prospective study, researchers have the opportunity to select and control many aspects of the study design, including the techniques, variables, measurement processes, equipment, people, and participants that can best answer their research question. This makes it easier to ensure that the study is collecting the right data and measuring the right variables, which can help to improve the accuracy and reliability of the results. Overall, prospective studies are a powerful tool for researchers who want to study the occurrence of specific events over time. They provide a comprehensive view of the natural history of a disease or condition and can help to identify risk factors, protective factors, and other important factors that may influence the occurrence of the event being studied.

1.10.2 Randomized Controlled Trials:

Prospective study designs involve RCT where participants are randomly appointed to different treatment groups. They are then monitored over time to evaluate the effectiveness of the treatment.RCTs are considered the best design for clinical research due to their robustness. RCTs ensure that any observed effects are due to the intervention itself and not influenced by external factors. This is achieved by randomly allocating participants to intervention and control groups, which helps to adjust for both known and unknown confounding variables. The randomization process also minimizes selection bias by ensuring that each participant has an equal chance of being in any given group.

1.10.3 Prospective Cohort Study:

Researchers collect data over time in prospective cohort studies to compare the appearance of the desired result between persons exposed to a risk factor and those who were not. This approach facilitates the identification of any possible correlation between the risk factor and the result. This research is done over time.

1.10.4 Advantages of a Prospective Study:

When comparing prospective studies versus retrospective designs, the following benefits are typically observed:

- Selects the research design, methods, and participants that will most fully address the study topic while reducing bias.
- To generate better data, it regulates circumstances and standardizes processes.
- To lessen confusion, one might opt to assess control variables.
- Capable of estimating relative risk and population prevalence of outcomes.
- By not depending on the recollections of the individuals, recall bias is minimized.

1.10.5 Retrospective Study:

A comparison study involves the examination of two groups: cases and controls. Cases refer to individuals with the condition or disease being studied, while controls are groups of individuals who do not have the same condition or disease. Researchers analyze the medical and lifestyle histories of each group to determine the variables that may be associated with a particular disease or condition. This type of study is also known as a study with a control group.

1.10.6 Retrospective Cohort Study:

A retrospective cohort study, also known as a historical cohort study, is a type of longitudinal cohort study that is commonly used in psychology and medicine. The study involves comparing a group of individuals who share a common exposure factor that affects the occurrence of a condition such as illness or death, to another similar group of individuals who were not exposed to the same factor. Retrospective cohort studies have been around for approximately the same amount of time as prospective cohort studies, dating back to around 22 years ago [22].

1.10.7 Advantages:

- A reduced size is used for them [23].
- Generally, they take less time to finish [23].
- Since data collection takes up the majority of resources, they are often less expensive [24].
- They perform better in the multi-outcome analysis [24].
- In a medical setting, they could be able to treat uncommon illnesses, for which very big cohorts would be needed in prospective research [23].
- Retrospective studies are typically less expensive than prospective investigations [6].

Since the individuals afflicted have already been identified, retrospective investigations are particularly useful in tackling illnesses with low incidence [25]. And it has almost all the advantages of a cohort study.

1.10.8 Comparison with Case-Control Study:

The purpose of case-control research is to identify potential exposure variables after a known disease incidence has been established. On the other hand, retrospective cohort studies compare the probability of contracting an illness to certain known exposure factors. In case-control studies, only the odds ratio can be used to fix the association between vulnerability and disease. However, in retrospective cohort studies, both the relative risk and the odds ratio are relevant measures to evaluate the relationship. Although case-control studies are often conducted retrospectively, they can also be prospective in the sense that participants are enrolled based on the incidence of the disease when new cases occur.

1.10.9 Prospective vs Retrospective Studies:

Prospective studies	Retrospective studies
A prospective study watches for outcomes, such as the development of a disease, during the study period and relates this to other factors such as suspected risk or protection factor(s).	A retrospective study looks backwards and examines exposures to suspected risk or protection factors in relation to an outcome that is established at the start of the study.
The study usually involves taking a cohort of subjects and watching them over a long period. The outcome of interest should be common; otherwise, the number of outcomes observed will be too small to be statistically meaningful. All efforts should be made to avoid sources of bias such as the loss of individuals to follow up during the study.	Retrospective investigations are often criticized. If the outcome of interest is uncommon, however, the size of prospective investigation required to estimate relative risk is often too large to be feasible. In retrospective studies the odds ratio provides an estimate of relative risk.
In prospective studies, individuals are followed over time and data about them is collected as their characteristics or circumstances change.	In Retrospective studies,individuals are retrospectively provide information on their lives since the previous interview.

Table: 2 Prospective vs retrospective studies [26].

1.10.10 Prospective & Retrospective Cohort Study Design:

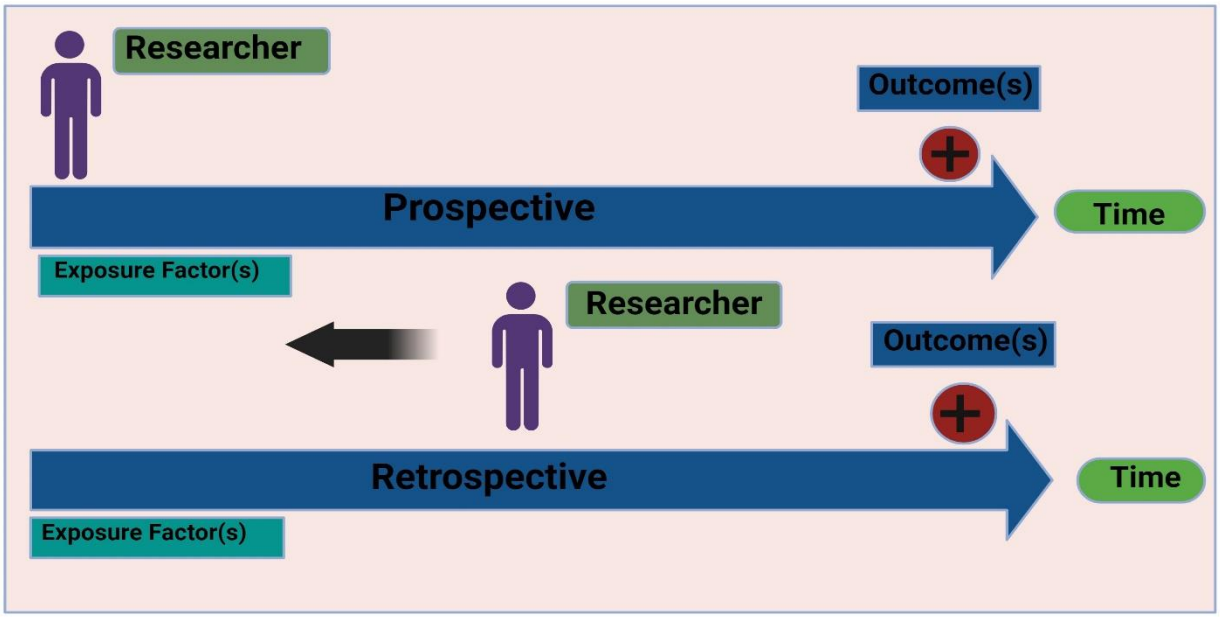

Figure: 2 Prospective & Retrospective Cohort Study Design [27]

According to their exposure status, research participants are identified in cohort studies, and they are either followed over time to see which people experience the desired consequence or outcomes, or they examine data collected earlier, before the creation of the outcome. According to several studies [27, 43, 28, 44, 45, 46], prospective cohort studies are the best kind of observational research. To classify exposure and identify patients at baseline, these investigations start with a cross-sectional investigation. Next, those who are free from the disease are monitored, and the progression of cases is recorded. Cross-sectional research to classify exposure and identify patients is also the first step in retrospective cohort studies.

Recordkeeping from that period is then used to calculate exposures. The case status is also monitored utilizing previous data that was generated at that time in an ideal retrospective cohort. Records of exposure and results are generated for commercial and regulatory objectives, making occupational groups especially well-positioned for retrospective cohort studies. Examples of these groups are Commercial Truck Drivers, who are subject to frequent monitoring and have certificates [44]. Instead of identifying related factors, as may be done in other types of studies, these investigations can illustrate temporality and identify real risk factors.

Only observational studies using cohorts can compute incidence, including cumulative incidence and incidence rate [27,45,46]. Furthermore, point prevalence and period prevalence may be computed in a cohort study as their start is the same as in a cross-sectional research. Cohort study data may be used to compute a wide range of risk metrics. Once again, cohort studies may also be used to compute the risk measures for the exposure-outcome link, which include odds ratio, prevalence odds ratio, prevalence ratio, and prevalence difference. These measures are also calculable in cross-sectional research designs. Risk ratios, hazard ratios, relative risk, and incidence rate ratios are examples of risk measurements that make use of a cohort study's capacity to compute incidence.

1.11 Observational Studies and Interventional Studies:

Observational studies and interventional studies are the two primary types of research. Observational studies, also known as epidemiological studies, involve the researcher observing the natural connections between causes and outcomes without taking any action on behalf of study participants. Diagnostic studies are a subcategory of observational studies and will be discussed separately. Interventional studies, or experimental studies, are research studies in which the researcher intervenes as part of the study design. Data collection methods used in the study can be classified based on how time affects them, either retrospectively or prospectively. Retrospective studies collect data from the past by asking participants to recall their exposures or results or by examining records made at the time. Retrospective studies are more susceptible to various biases, such as recollection bias, and are less able to establish causality. Prospective studies track people over time while collecting information, which makes it easier to show that the exposure preceded the illness, strongly suggesting causality. They are less susceptible to some forms of bias.

1.11.1 Interventional Study Designs:

An interventional study design is a type of research study where the researcher intervenes at some point during the investigation, similar to an experimental study design. Besides the most widely used and robust type, the RCTs, there are other interventional research designs such as quasi-experiments, pre-post-study design, and non-RCTs [27, 28, 29]. Experimental investigations are utilized to evaluate preventive or therapeutic drugs. Examples of therapeutic agents include preventive measures, cures, surgical techniques, and diagnostic procedures. Preventive measures can include modifications to engineering controls, management, policy, protective gear, and any other element that may be considered a possible cause of illness or injury.

1.11.2 Pre-Post Study Design:

A pre-post study involves observing the frequency of an outcome before and after a specific intervention is implemented. For instance, observing car collision fatalities before and after

seatbelt laws were enforced can be a good starting point. Pre-post studies can be either single-arm, where a group is assessed before and after the intervention, or multiple-arm, where groups are compared. Typically, there is an arm where no action is taken, which serves as the control group for multi-arm pre-post studies. Pre-post studies have temporal validity, which means they can demonstrate that the intervention has an impact on the outcome. However, since pre-post studies lack control over other factors that may change concurrently with the intervention, it is not possible to entirely attribute the differences in illness occurrences during the study period to the specific intervention. Pre- and post-intervention studies can use mean values of continuous outcomes, such as systolic blood pressure, or binary health outcomes, such as incidence or prevalence. Different analytical methodologies are used in pre- and post-intervention studies based on the outcome being evaluated. If there are several treatment arms, it is also possible to observe differences in each treatment arm from the beginning to the end of the study.

1.11.3 Non-randomized Trials Study Design:

Trials that are not randomized are a type of interventional research design. These trials involve comparing two groups: one that received an intervention and another that did not. These research designs are practical and are often prospectively carried out. They can identify potential links between the intervention and the outcome. However, these designs are not considered robust as they are susceptible to various forms of bias and error.

1.11.4. Randomized Controlled Trials Study Design:

Interventional studies are commonly conducted as (RCTs), which may be modified in various ways [30,31,32]. In RCTs, a group of research volunteers is randomly divided into two groups. If the randomization is successful, both groups should have the same measured and unmeasured confounders. The efficacy of the intervention in one group is compared to that of the other after the intervention is implemented in one group but not the other. The intervention is the only thing that should separate the two groups for the entire study. A good randomization process is one of the most significant benefits of the RCT [30,31,32]. RCTs use other methodological components to strengthen the causal inference of the intervention's effects. These include concealing the allocation, blinding, monitoring compliance, accounting for co-interventions, quantifying dropout, interpreting outcomes based on the intention to treat, and evaluating each treatment arm uniformly and at the same time point.

1.11.5 Crossover Randomized Controlled Trials Study Design:

Crossover RCT is a type of interventional research design where participants are reassigned to the other treatment arm after the first treatment period. This is different from the observational case-crossover design. The secrecy of the randomization technique is ensured by allocation

concealment, where a third party creates the schema and sequentially numbered opaque envelopes are used to conceal the treatment allocation. Blinding in randomized controlled trials refers to withholding the treatment arm from research participants. This could be achieved through sham therapy or placebo tablets to maintain the isolation of the variation in results across groups from the intervention alone. Compliance is measured to assess the extent of research participants' adherence to the recommended intervention. This may have a significant effect on the study's findings. If compliance differs between the intervention arms, this variation may conceal real differences or lead one to incorrectly believe that there are differences between the groups when none exist. Co-therapies or interventions that affect the outcome in addition to the primary intervention may lead to incorrect conclusions in clinical studies. The study's results might be off if the number or kind of extra therapy components varied throughout the treatment groups. Dropout rates could lead to incorrect study results if they are high overall or vary between the intervention arms. Although studies with dropout rates below 20% may draw incorrect conclusions, 20% is the generally recognized dropout rate. Intention-to-treat (ITT) analysis is a quantitative approach to analyzing deviations from random allocation. It evaluates each person according to the intervention that was assigned to them, irrespective of whether or not the intervention was received as a result of the protocol.

1.12 Recruitment Status:

- **Not yet recruiting:** The study has not started recruiting participants.
- **Recruiting:** The study is currently recruiting participants.
- **Enrolling by invitation:** The study is selecting its participants from a population, or group of people, decided on by the researchers in advance. These studies are not open to everyone who meets the eligibility criteria but only to people in that particular population, who are specifically invited to participate.
- **Active, not recruiting:** The study is ongoing, and participants are receiving an intervention or being examined, but potential participants are not currently being recruited or enrolled.
- **Suspended:** The study has stopped early but may start again.
- **Terminated:** The study has stopped early and will not start again. Participants are no longer being examined or treated.
- **Completed:** The study has ended normally, and participants are no longer being examined or treated (that is, the last participant's last visit has occurred).
- **Withdrawn:** The study stopped early, before enrolling its first participant.
- **Unknown:** A study on ClinicalTrials.gov whose last known status was recruiting; not yet recruiting; or active, not recruiting but that has passed its completion date, and the status has not been last verified within the past 2 years.

1.13 Blinding in Clinical Trials:1.13.1 Blinding:

All participants and groups have access to information on the allocated interventions in a non-blinded, or "open," study [47]. The practice of concealing information from one or more research study participants that could have an impact on the findings is known as blinding, or "masking." It is important to differentiate between allocation concealment and blindness. Allocation concealment, which is essential for avoiding selection bias, is the practice of keeping clinical research participants and investigators oblivious of impending group allocations until the actual assignment time [48]. Blinding, on the other hand, is the practice of not revealing to trial participants any knowledge of the allocated interventions from the moment of the group project until the experiment is over [49]. Proper randomization minimizes the disparities between treatment groups at the beginning of a trial, but it does not prevent study groups from being treated differently throughout the experiment or from being analyzed and interpreted differently after the trial [50].

1.13.2 Blinding Types :

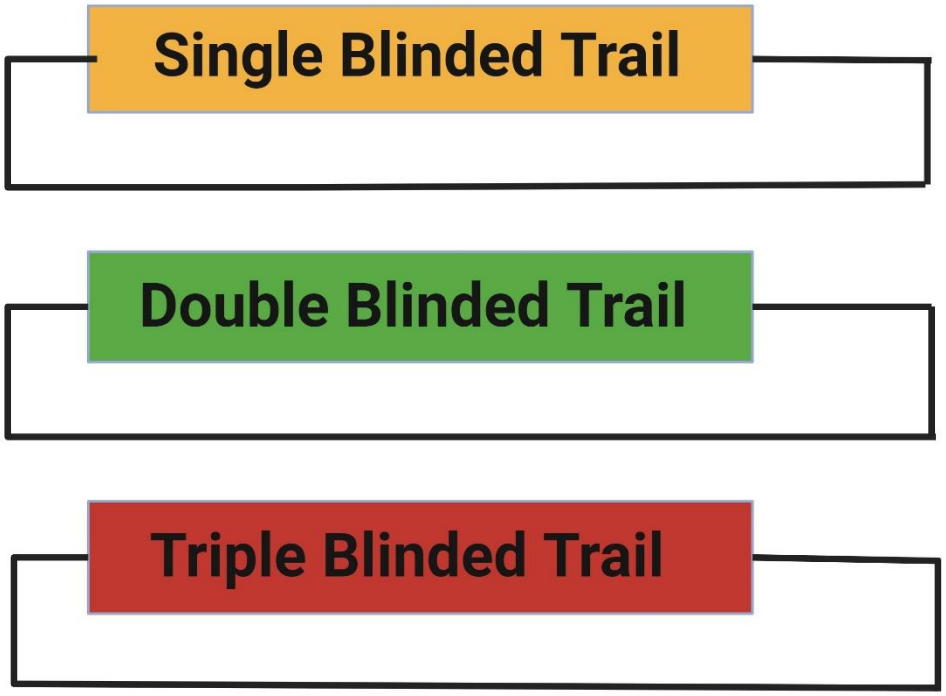

Figure: 3 Types of Blinding [50].

1.13.3 Single-Blind Study:

Participants in a type of clinical trial receive a treatment or intervention in secret, with only the researcher leading the study being aware of it until the trial is over. This type of research is called single-blind and aims to minimize the chances of biased results. By doing so, it decreases the likelihood of results being influenced by factors unrelated to the therapy or intervention being assessed. During the study, participants are not informed about which group they are assigned to until it is over.

Control group participants may alter their behavior to reduce their risk of contracting the flu, such as frequent hand washing, avoiding crowded places, etc. if they become aware that they have gotten a phony vaccination and are not immune to the virus. The vaccination may appear less effective than it is as a result of this behavior, which might close the illness rate difference between the analysis and control groups. In single-blind trials, the vaccinations that each subject received real or fake—are concealed from them to avoid this kind of result [51].

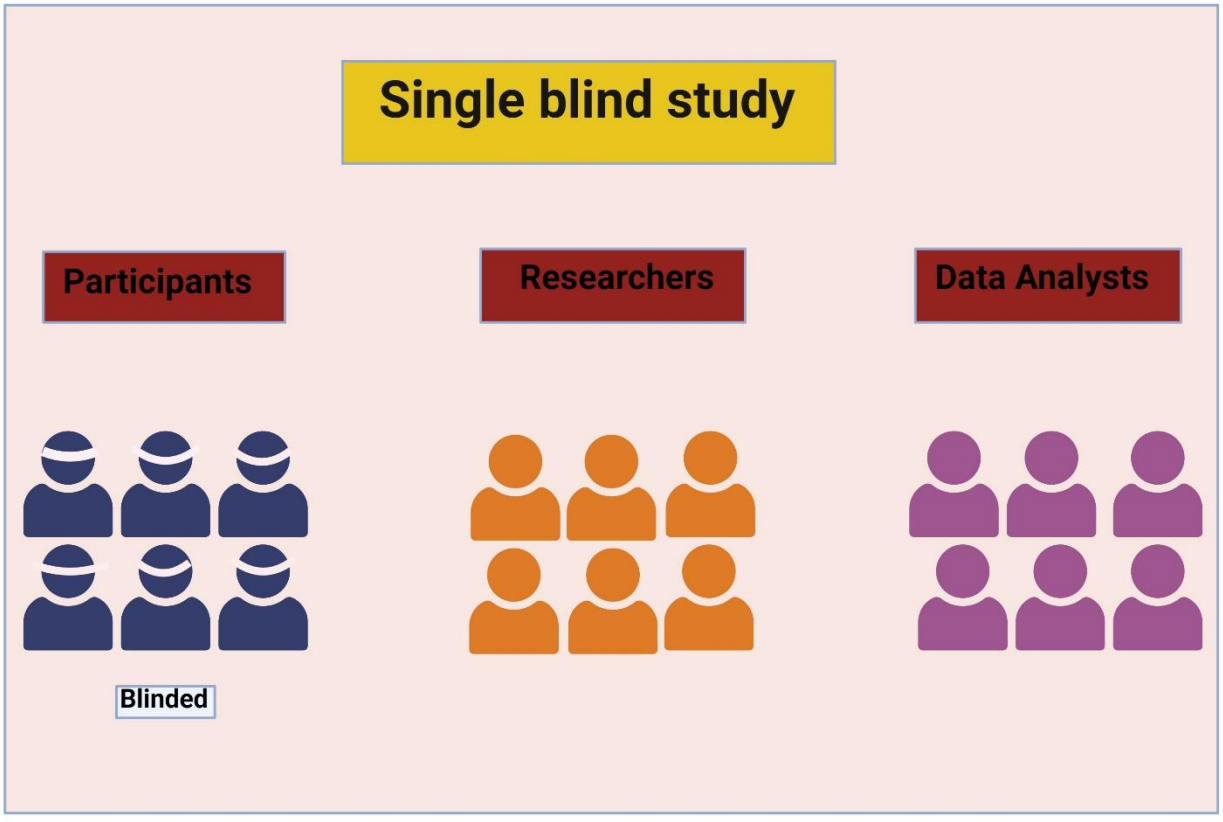

Figure: 4 Single Blind Study [51].

1.13.4 Double-Blind Study:

If the researchers experimenting are as hip to a participant's group assignment, they may unintentionally treat the control group differently than the treatment group. This can directly impact the result and even disclose the participant's assignment. In a double-blind experiment, the subject and experimenter are both heedless of the group assignment to prevent this from happening [51].

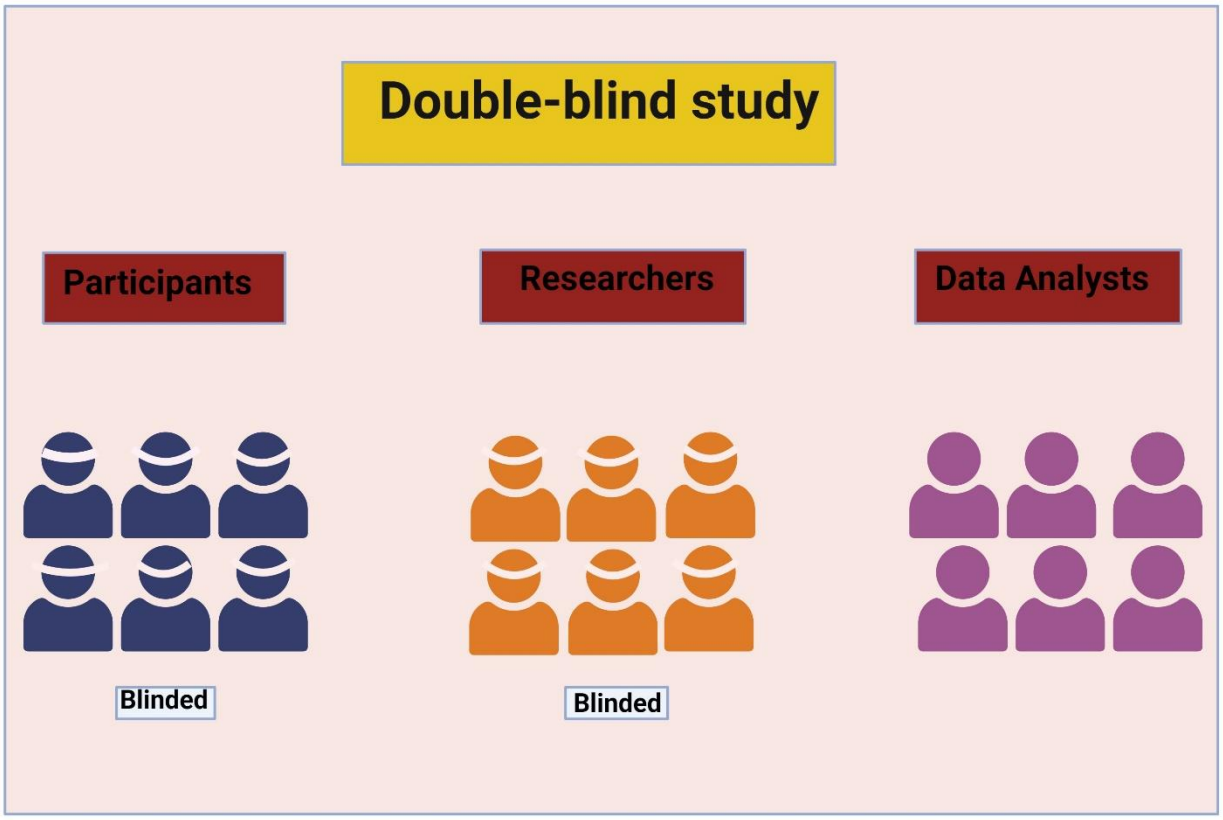

Figure: 5 Double-Blind Study [51].

1.13.5 Triple-Blind Study:

A study can be triple-blind, meaning that group assignment is concealed from all participants, administrators, and data analysts responsible for analyzing the results. Even if the outcome is due to chance, researchers may have a preconceived idea and use different data analysis methods to support their conclusions [51].

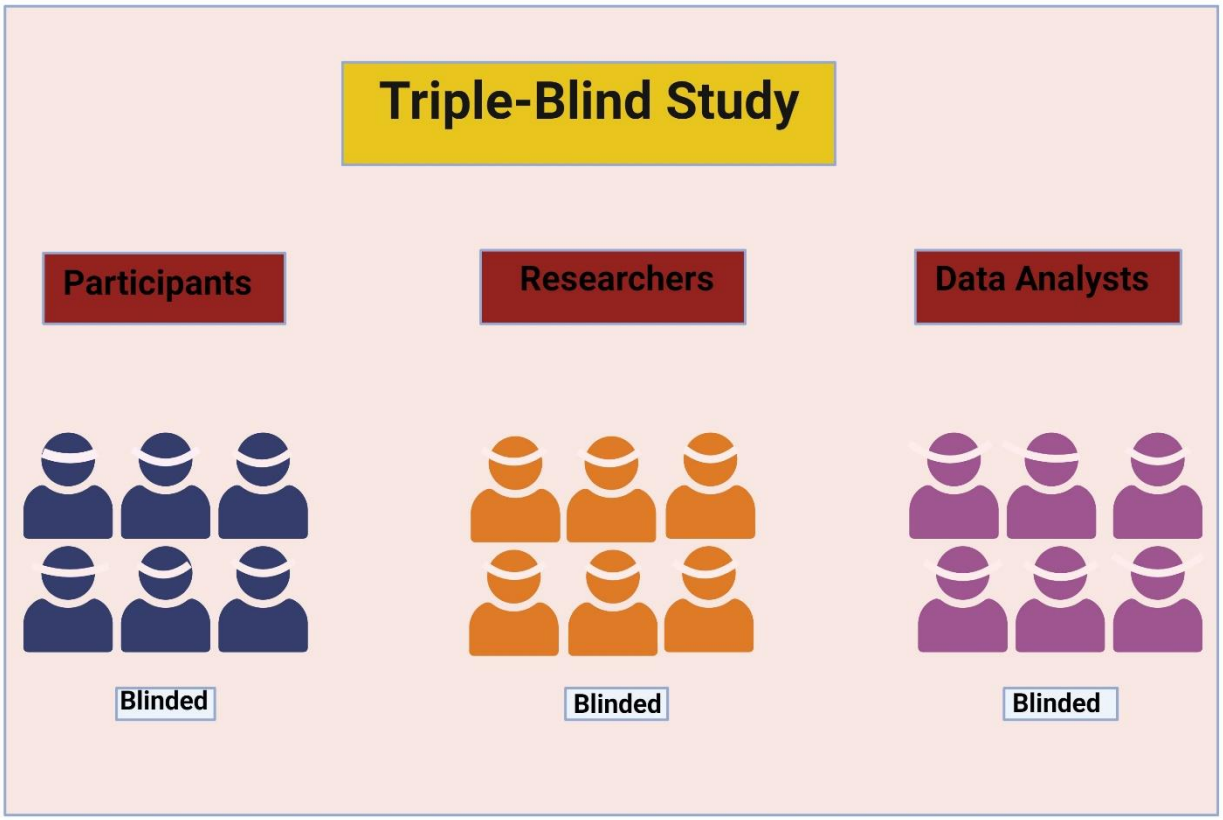

Figure: 6 Triple Blind Study [52].

1.13.6 Reasons for Blinding:

If there is potential for prejudice, bias may arise. When research study participants are informed about the medicines they have been assigned, this may occur. This knowledge can cause bias in several ways, including expectations, adherence to trial protocols, seeking therapy outside of trials, and assessments of the effectiveness of interventions [52]. The application of differential treatments, attention, or attitudes toward participants by healthcare teams or research workers who are not blinded presents a danger to the objectivity of the findings [53]. There are no analytical techniques that can reliably get around this constraint if bias has been introduced from any of these sources [54, 55]. Numerous empirical data points demonstrate the direct influence of non-blinding on clinical trial outcomes, according to a thorough study conducted by Hróbjartsson et al. Subjects assigned to the experimental group have higher attrition in participant-blinded trials than do subjects in non-blinded trials. The discrepancy between participant-reported findings in non-blinded vs blinded research is typically 0.56 standard deviations, and it is much more pronounced in studies that look at invasive procedures [51]. Hróbjartsson and colleagues carried out three distinct meta-analyses on observer bias in randomized clinical trials [56, 57]. According to these

analyses, studies with binary outcomes, measurement scale outcomes, and time-to-event outcomes produced exaggerated odds ratios by an average of 36%, 68%, and 27%, respectively, when non-blinded versus blinded outcome assessors were used [59]. The four meta-analyses by Hróbjartsson et al. taken as a whole show that participant and assessor blinding cause inflated effect sizes [60]. According to the three analyses on observer bias, blinding may have different effects on study findings depending on the kind of variable evaluated. When it comes to minimizing bias in research, especially subjective results, blinding is the most easily understood idea. However, many outcomes that appear objective but depend on how participant data is interpreted—for example, interpreting an ECG scan to rule out myocardial infarction—also have subjective components. Furthermore, variables including the degree of follow-up, concurrent drug use, and acceptance of advance directives might have an indirect effect on objective outcomes like the time to death [61]. Studies on subjective vs objective outcomes have revealed more substantial evidence of bias, but they have not found any discernible variation in the estimated treatment impact based on the degree of subjectivity in the results [62]. Thus, the research so far indicates that blinding is necessary to minimize bias for both subjective and objective results [59,63].

1.13.7 How To Do Blind:

Different methods are available for blinding clinical study participants, both individuals and groups [64]. Ultimately, the blinding method chosen by the researcher will depend on the parties being blinded, the research question, and the intervention being studied [65]. There is a lot of flexibility when it comes to blinding, and researchers can even create their unique blinding approach as long as they can ensure that all relevant information about the groups is successfully concealed and the method does not compromise the accuracy of the results [66]. A thorough review of blinding in randomized controlled trials evaluating pharmaceutical treatments was conducted by Boutron et al., who provided a useful inventory of strategies for establishing participant and provider blinding, maintaining blinding, and blinding outcome assessors. Common techniques for participant/provider blinding include double-dummy procedures, flavoring to mask the unique taste of active oral medications, and central production of comparable capsules or tablets, bottles, and syringes. When multiple groups may receive a placebo, a double-dummy approach is often used to maintain blindness by using several placebos [67]. Reduced unblinding risk strategies include using an "active placebo," centrally evaluating for side effects, partially disclosing side effect information, and adjusting the dose as needed. Clinical exams, centralized evaluation of supplementary investigations, and adjudication of clinical events are common techniques used to blind outcome assessors [68]. Blinding in non-pharmaceutical trials presents several unique problems due to the complexity and physical nature of these interventions, participant and physician acceptability, and ethical and safety concerns [69,70]. As a result, blinding is generally used less frequently in studies involving surgery, medical equipment, and participatory therapies (like rehabilitation) than in pharmacological trials [71,72]. Nevertheless, blinding is just as

important in these studies as it is in pharmacological trials in the pursuit of evidence that shapes real-world practice [73]. Blinded interventional studies are often feasible and might even include a placebo group [74].

1.13.8 Who Do We Blind:

Current literature has identified as many as 11 distinct groups meriting unique consideration when it comes to blinding:

i. Participants

ii. Care providers

iii. Data collectors and data managers

iv. Trials managers

v. Pharmacists

vi. Laboratory technicians

vii. Outcome assessors (study personnel who collect outcome data)

viii. Outcome adjudicators (personnel who confirm that outcomes meet prespecified criteria)

ix. Statisticians

x. Members of safety and data monitoring committees and

xi. Manuscript writers [75].

The assignment of treatments is the information most often left out in blinded clinical investigations [75]. It is still possible to blind some of the groups listed previously to more information. Laboratory technicians, outcome assessors, and result adjudicators, for example, could also be blinded to the general trial goal, as well as to the fundamental clinical and demographic traits of the research population. Since the individuals and information that can be blinded vary widely, it is important to view blinding as a continuous spectrum rather than an all-

or-nothing occurrence [75]. Therefore, "partial blinding," which exposes certain research groups to relevant information only when it is technically feasible, can enhance trial outcomes even in situations where it is not possible to blind all study groups completely. The COVID-19 drug development process presents an array of obstacles. In addition to the scientific challenge posed by our limited understanding of the biology and pathophysiology of the SARS-CoV-2 virus, several social, practical, and logistical issues necessitate a departure from traditional drug development methods.

1.13.9 Factors:

1.13.9.1 Time Pressure:

Clinical trials in phase III can take up to ten years in traditional drug research to identify a target. However, in the current pandemic, where hundreds of thousands of people have died in a matter of months, conventional medicine research doesn't have the luxury of time. Therefore, the focus is on finding medications or therapeutic candidates already on the market for other uses that may be effective against COVID-19. These drugs can be pushed through clinical trials at a faster pace as they have established pharmacokinetic, pharmacological, and toxicity data. While a pivotal trial may include additional dosage assessments, it will need to use complex combinations of clinical and laboratory metrics to be pharmacologically meaningful. Although this acceleration is challenging, it is possible but comes with significant regulatory agency burdens only justified by the pandemic itself [76].

1.13.9.2 Repurposing Drugs:

Medications that are designed to treat RNA viruses such as Ebola may be useful in treating COVID-19 based on what is now understood about the molecular and biochemical characteristics of the SARS-CoV-2 virus [77,78]. Regulatory bodies are well-versed in the clinical development process of established medications suggested for new indications, and this process is generally short. However, since SARS-CoV-2 is a novel virus, medications repurposed for COVID-19 won't have undergone early development optimization for COVID-19 studies. Repurposing of established medications for a new indication often fails due to insufficient data about the drug's exposure-response relationship in the new patient group, even in cases when there is substantial preclinical evidence for prospective efficacy [79].

1.13.9.3 Lack of Information:

The biggest uncertainties when selecting a medication candidate are the dose, dosing schedule, and duration of treatment required. Phase II trials are usually employed to assess these factors, demonstrate proof of concept, and determine the dosage range by investigating the pharmacokinetics, pharmacodynamics, and clinical endpoints of a drug [80]. This process can be accelerated or even avoided by accepting a near-maximum tolerated dose or by applying current therapeutic dosing recommendations for established indications, although this approach heavily relies on the close association between the original and the new indication. To facilitate rapid clinical dose-finding investigations, the translation of antiviral activity from in vitro to in vivo needs to be considered while exploring the range of possible doses. Alternatively, a larger pivotal safety/efficacy study could examine two or more dose levels, but this strategy has its challenges. False-negative outcomes could arise if COVID-19 does not have an optimal therapeutic dosage schedule. Moreover, the therapeutic dose time window for treatment is poorly defined due to the lack of knowledge about the viral dynamics of SARS-CoV-2 and disease progression, which could lead to misleading results. Accurately estimating the time of infection is further complicated by asymptomatic transmission and varying incubation periods [81]. Other infectious diseases such as hepatitis C virus and human immunodeficiency virus have recognized measures of viral activity (such as CD4 count and viral load) that have demonstrated clinical correlations and have been critical to the development of new drugs. However, COVID-19 does not currently have standardized markers or threshold values for viral activity.

1.14 Operational Challenges:

The location of the first observation of COVID-19 was in Wuhan, China. This has led to several clinical studies of repurposed medications being conducted in the area. However, due to the stringent public health measures put in place, the number of new cases dropped significantly in a few months, making Wuhan a poor location for upcoming clinical studies. Following the Wuhan epidemic, COVID-19 instances surged in Europe, particularly in Italy and Spain. Currently, the USA has the highest number of reported cases globally, making it the country with the highest illness burden. When designing clinical trials, epidemiological trends in the global illness load must be taken into account, and future COVID-19 clinical trials will probably need to be planned as international trials. However, the sponsor must create a trial design that is acceptable to several regulatory bodies, which can hinder the conduct of global clinical trials. It is crucial to identify a uniform patient population across all nations using exact inclusion and exclusion criteria. Evidence of ethnic sensitivity may cause regulators in certain countries to demand a higher proportion of patients from their nation than is reasonable. Furthermore, several nations object to the sending of clinical sample analysis within their borders, even if it is ideal to do it in a single central laboratory. Similar issues arise with medicine import and manufacturing regulations. The final significant obstacle to a worldwide clinical trial is the lack of a globally recognized standard of treatment for

COVID-19. Clinical procedures may present additional challenges since home quarantine conditions do not permit routine assessments that require careful patient supervision. Clinical trials are subject to resource rivalry and ethical constraints, which may restrict study conduct and practicality. Extreme strain on professional personnel, a lack of equipment, and patients' demand for efficient care are some of the contributing factors. The majority of clinical staff members are currently nearly solely concerned with saving patients' lives. If they focus their efforts on changing treatment plans and patient selection to perform clinical trials, they may encounter strong opposition. Defining SARS-CoV-2 infection using reverse transcription-polymerase chain reaction (RT-PCR) testing is still scarce and unevenly distributed. Concerns from patients regarding their potential enrollment in a clinical study should also be taken into account. Many patients may decide not to continue in clinical trials while dealing with potentially deadly illnesses, particularly if they are not informed of their therapy. All these concerns must be considered to obtain results that can be put into practice, even in the case of accelerated trials.

1.15 Regulation and Approval:

Approval of clinical trials is based on science and ethics, and the standards for evaluation and approval are well-established, with only minor national variations. IND evaluation and approval process is often used for drugs that aim to reach the clinical phase. National regulatory agencies participate in the evaluation process, which can take several months. Expedited regulatory scrutiny and IND clearance are required due to time constraints and the rapidly evolving incidence of disease. For some COVID-19 medications, approval from a local institutional review board or ethical committee is sufficient to use them in investigator-initiated studies. While this is a quick approach to starting clinical trials, it can be poorly designed without a randomized control group, with patients who are not well selected, or with an insufficient number of patients. Investigator-initiated studies use pre-existing medications that have been repurposed for the treatment of COVID-19. Since they have been previously reviewed for other uses, less regulatory scrutiny is required for the use of these medications in COVID-19. Approval must be obtained for all patients whose characteristics, such as age, size, organ function, pregnancy, genotype (if applicable), and medication interactions, may affect the result of the medicine. This can be accomplished in two ways: by using previous knowledge (e.g., population-based PK) to predict dosing regimens and confirm efficacy-safety later, or by ensuring that the clinical studies include a diverse patient population to cover efficacy-safety analysis, particularly with concentration-effect relationships.

1.16 Clinical Trials Protocol:

A written plan called a clinical trial protocol provides a comprehensive outline of a research study's scientific justification, objectives, design, techniques, statistical considerations, and organizational

structure. Typically, a group of professionals prepares this plan to serve as a guideline for all involved investigators. The protocol includes specific guidelines for conducting the trials and detailed information about the research plan for ensuring the safety and health of trial subjects. Additionally, it specifies the essential documents, like an investigator's brochure, required for the research. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has developed Good Clinical Practice Guidance outlining the format and content of clinical trial protocols sponsored by pharmaceutical, biotechnology, or medical device companies in the US, EU, or Japan. Regulatory bodies in Australia and Canada also follow the ICH regulations [18]. To promote transparency and ensure the study's ethical and safe conduct, researchers are encouraged to publish their methods in journals. Overall, clinical trial protocols play a critical role in the development of new medical treatments and are essential for ensuring the integrity and success of a research study.

1.17 Seamless Clinical Trials:

A smooth and uninterrupted path can be achieved through a simple idea known as combined-phase research. It is better to conduct a trial with interim assessments dividing the phases rather than carrying out multiple phases of the trial. This approach results in fewer patient visits and typically saves time. [19].

1.17.1 Varieties of Seamless Trials:

Two main types of seamless trails apply to the majority of cases. When a seamless trail uses part of the data from before an intermediate look to make inferences after the intermediate glance, it is called an inferential seamless trail. Please review the combined phase 2/3 ADVENT trace once again. The goal of the four-arm experiment conducted before the intermediate review was to establish safety. Therefore, the information from the arm that made it to the trial's confirmatory phase served two purposes. The data helped establish safety before the intermediate glance, and it also helped determine efficacy following the interim look. As a result, there was inferential continuity in the two-look trail. Conversely, an operationally smooth trail preserves the information that distinguishes the data evaluated before and after the break. Every data gathering has a purpose.

1.17.2 Advantages of Seamless Clinical Trials:

Clinical trials that are smooth in their execution offer many benefits over traditional techniques. For one, by doing away with the need for distinct stages, they can significantly reduce the time and money required to bring a medication to market. In addition, they can help scientists generate clinical data for a drug's safety and efficacy more quickly by ensuring a seamless transition from early-phase dose-finding studies to confirmatory trials. Furthermore, seamless trials can provide a

more thorough and patient-centered trial experience, which can improve patient recruitment and retention. By avoiding protocol revisions and lessening the strain of several study visits, successful trials can boost patient compliance and engagement. As a result, data gathering and analysis can be more extensive. Lastly, seamless trials make adaptive trial design possible, as they utilize real-time data collection.

1.17.3 Traditional Clinical Trials vs Adaptive Clinical Trials:

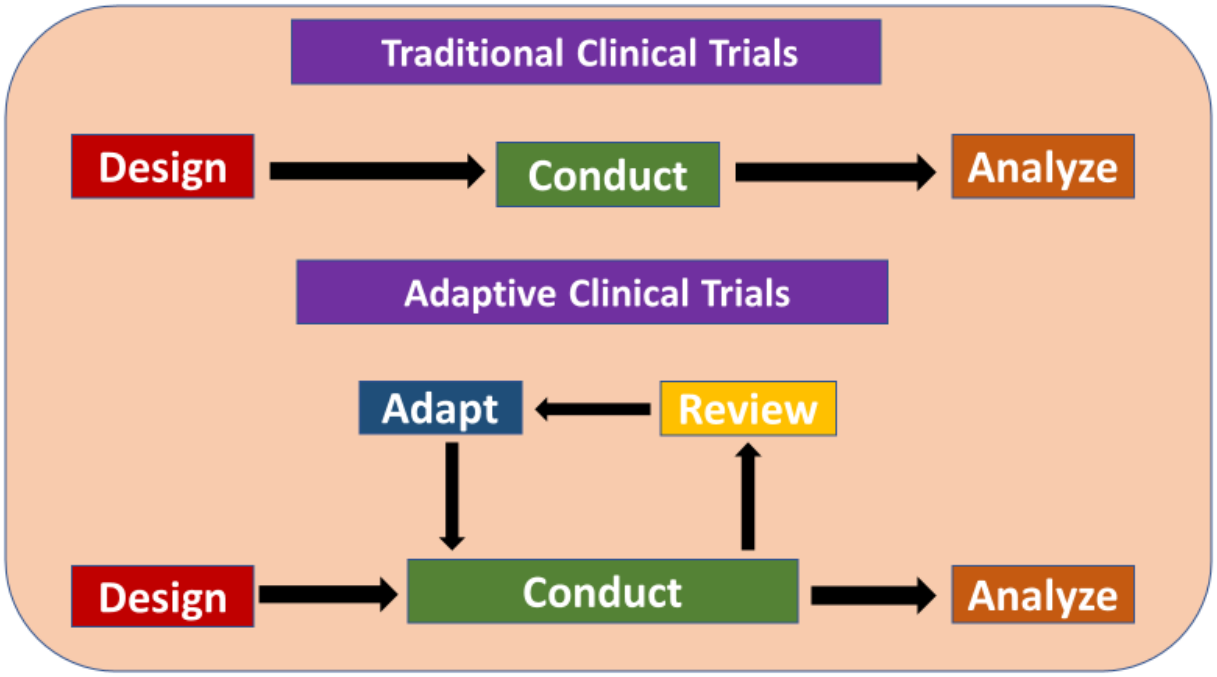

Figure: 7 Differences between Traditional and Adaptive Clinical Trials [19].

Adaptive designs can make clinical trials more flexible by using the trial's cumulative data to change its direction according to pre-established guidelines. These designs frequently make better use of resources such as time and money, and they may require fewer participants, making them more effective, educational, and ethical than trials with a typical fixed design. Adaptive designs can be used in all phases of clinical research, including confirmatory trials and early-phase dosage escalation. Although adaptive designs have been used in clinical research, their adoption has been slower than new approaches, and their potential benefits have been introduced in the statistical literature. This may be because many members of the clinical community are still unaware of the entire spectrum of trial design adjustments available, along with their advantages, disadvantages, and aims. Moreover, the phrase "adaptive design" has been misused as a catch-all to describe some approaches that may be viewed as contentious or that have been carried out insufficiently [19].

1.17.4 Seamless Clinical Trials over Traditional Clinical Trials:

1. Efficiency: Trials that are conducted smoothly cut down on unnecessary steps and administrative work, which expedites trial completion. Time and resources can be saved by researchers by smoothly moving from one phase to the next.

2. Faster Decision Making: Data from previous stages may be swiftly examined and utilized to decide whether to go on to the next step or alter the trial protocol in seamless trials. This speeds up the duration of the experiment overall by enabling researchers to adjust in real time.
3. Reduced Costs: Seamless trials can result in reduced overall costs by shortening trial durations and removing effort duplication. Seamless studies may also need fewer people overall since results from one phase can more effectively guide succeeding stages.
4. Better Patient Experience: Participants in seamless trials may have a more unified experience with less interruption to their treatment plans and easier phase transitions. Higher patient retention rates and more general compliance may result from this.
5. Optimised Data Integration: Modern methods of data collecting and integration, such as real-time data monitoring and EHRs, are frequently used in seamless trials. This facilitates better data analysis and interpretation throughout the trial's various stages by researchers.
6. Improved Collaboration: Coordinating studies among many stakeholders, such as patients, researchers, physicians, and regulators, is encouraged. This cooperative strategy can promote creativity and enhance the overall planning, preparation, and conduct of trials.
7. Greater Flexibility: Trial design and execution can be more flexible with seamless trials, giving researchers the ability to adjust when conditions change or new information comes to light throughout the trial.

All things considered, smooth clinical trials present a more effective, economical, and patient-focused method of doing clinical research, which may hasten the creation of novel cures and treatments.

1.17.5 Adaptive Design:

Seamless Phase II/Phase III Design:

A "combination test" or seamless Phase II/Phase III design is often used for rare disorders. In Phase IIb of this design, patients are randomly assigned to three treatment arms. Patients in the first treatment arm receive standard care therapy and serve as the control group. Patients in the second and third treatment arms receive different therapies, Treatment 1 and Treatment 2, respectively. At the end of Phase IIb, the most successful treatment (based on progression-free survival or PFS) is selected between Treatment 1 and Treatment 2. The least successful treatment arm is then

eliminated. In the second stage (Phase III), the remaining treatment arm is continued, and its effectiveness is compared against the standard of care therapy. [20].

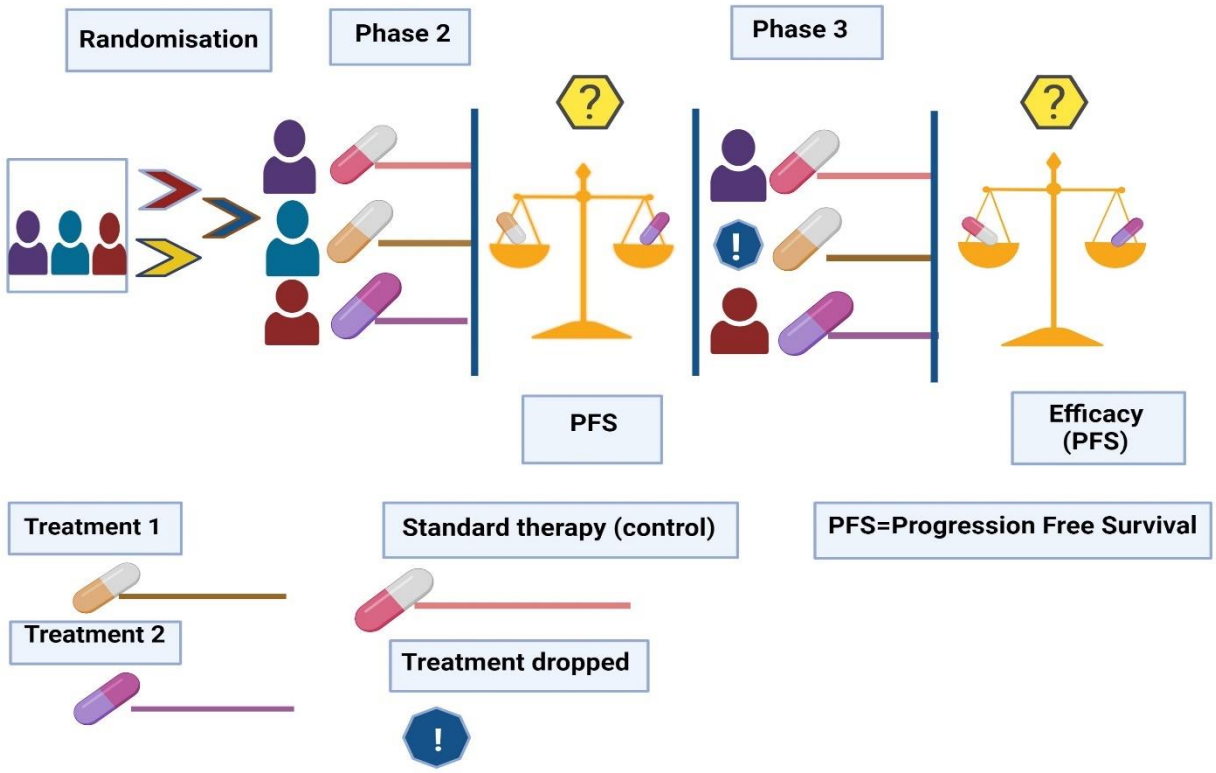

Figure: 8 Seamless Phase II/Phase III Design [26].

If the scientists knew which vaccines were real and which were not, they might unintentionally inform the participants, impacting their actions and the results unknowingly. This could even have an immediate effect on the outcome. For instance, researchers could mistakenly measure flu symptoms if they expect that the vaccine would lead to lower levels of symptoms, making the vaccine appear more effective than it is. To avoid this, double-blind trials conceal group allocations from both the volunteers and the researchers giving the vaccinations [51].

1.18 Regulatory Approval for Traditional Drugs:

Coronaviruses are viruses with a long RNA genome. This genome is surrounded by a helical nucleocapsid and an outer envelope made up of different proteins, including the spike protein. The spike protein is responsible for binding onto a receptor in human cells called ACE2. The S protein is an important target antigen for vaccine development as it produces neutralizing antibodies against the virus. However, developing coronavirus vaccines has been challenging. While vaccines in animals have produced immune responses, they have not effectively prevented the disease. There is also concern that vaccination may not produce long-term immunity and that re-infection could happen. Previous studies of coronavirus vaccines in animals have raised safety concerns. Some studies have shown that vaccination can cause lung inflammation when challenged with the virus. Vaccine-associated disease enhancement may be more of a concern with certain vaccine types. Enhanced disease caused by viral challenge has been notable for some vaccines, including measles and RSV vaccines [170].

Clinical research is used in COVID-19 vaccine clinical research to determine the vaccine's properties. These qualities consist of safety, efficacy, and effectiveness. Forty vaccinations are approved for use in the general population as of November 2022 by at least one national regulatory body [82,83].

Vaccine Type	Vaccine Name
DNA vaccine	ZyCoV-D
RNA vaccines	Pfizer–BioNTech, Moderna, Walvax, and Gemcovac
Inactivated vaccines	Covaxin, CoviVac, COVIran Barekat, FAKHRAVAC, Minhai-Kangtai, QazVac, Sinopharm BIBP, WIBP, Turkovac, and VLA2001
Inactivated vaccines	Sputnik Light, Sputnik V, Oxford–AstraZeneca, Convidecia, Janssen, and iNCOVACC
Subunit vaccines	Abdala, Corbevax, COVAX-19, EpiVacCorona, IndoVac, MVC-COV1901, Noora, Novavax, Razi Cov Pars, Sanofi–GSK, Sinopharm CNBG, Skycovione, Soberana 02, Soberana Plus, V-01, and ZF2001.
Virus-like particle vaccine	CoVLP.

Table: 3 Traditional Drugs for COVID-19 [84-87].

1.19 Formulation:

Vaccines to combat COVID-19 are being created using various technologies. The development and implementation of mRNA and viral vector vaccines are considered groundbreaking due to their exceptional speed. However, there is still a lack of global equality when it comes to the distribution of COVID-19 vaccines. Using conventional vaccine production methods such as WIV, protein-based subunit vaccines, and VLPs may be beneficial for creating vaccines to be used in low- and middle-income countries and for filling gaps in vaccine access.
[87].

1.20 Vaccine Candidates in Human Trials:

The vaccine candidates and the phases they have completed, according to the sources, are displayed in the table below. Other information is displayed along with the current phases. In Phase I–III studies, COVID-19 candidate vaccines.

1.20.1 Homologous Prime-Boost Vaccination:

In July 2021, the CDC and the FDA jointly issued a statement stating that individuals who have received all recommended vaccinations do not need a booster dose [88]. However, those with weakened immune systems may receive an additional dose of the mRNA vaccine, as approved by the FDA and CDC in August 2021 [90-93]. In September 2021, these restrictions were expanded to include additional categories. The use of booster doses of homologous or heterologous vaccines was authorized by the FDA and CDC in October 2021 [94,95].

1.20.2 Heterologous Prime-Boost Vaccination:

First Dose	Second Dose	Schedules	The Current Phases (Participants, Period & Location)
Oxford–AstraZeneca Pfizer-BioNTech	Oxford–AstraZeneca Pfizer-BioNTech	Days 0 & 28- 84	Phase II (820) [100] Feb- Jun 2021, United Kingdom
Oxford–AstraZeneca Pfizer-BioNTech Novavax	Moderna Novavax	Days 0 & 56-84	Phase II (1050) [104] Mar 2021- Sep 2022, United Kingdom
Oxford–AstraZeneca	Pfizer-BioNTech	Days 0 & 28	Phase II (676) [102] Arp 2021- ARP 2022, UK
Oxford–AstraZeneca Pfizer-BioNTech Moderna	Pfizer-BioNTech Moderna	Days 0 & 28 Days 0 & 112	Phase II (1200) [103] May 2021- Mar 2023,Canada
Pfizer-BioNTech Moderna	Pfizer-BioNTech Moderna	Days 0 & 42	Phase II (400) [105] May 2021- Jan 2022,France
Janssen	Pfizer-BioNTech Janseen , Moderna	Days 0 & 84	Phase II (432) [110] Jun 2021- Sep 2022,Netherlands

Table: 4 Heterologous Prime-Boost Vaccination [94,95].

1.20.3 Heterologous Second Dose Regimes in Clinical Trials:

First Dose	Second Dose	Schedules	The Current Phases (Participants, Period & Location)
Oxford–AstraZeneca Pfizer-BioNTech	Oxford–AstraZeneca Pfizer-BioNTech	Days 0 & 28 Days 0 & 84	Phase II (820) [102] Feb- Aug 2021, United Kingdom
Oxford–AstraZeneca Pfizer-BioNTech	Oxford–AstraZeneca Pfizer-BioNTech Moderna Novavax	Days 0 & 56-84	Phase II (1050) [104] Mar 2021- Sep 2022, United Kingdom
Oxford–AstraZeneca	Pfizer-BioNTech	Days 0 & 28	Phase II (676) [107] Arp 2021- ARP 2022 Spain
Oxford–AstraZeneca Pfizer-BioNTech Moderna	Pfizer-BioNTech Moderna	Days 0 & 28 Days 0 & 112	Phase II (1200) [108] May 2021- Mar 2023,Canada
Pfizer-BioNTech Moderna	Pfizer-BioNTech Moderna	Days 0 & 42	Phase II (400) [109] May 2021- Jan 2022,France

Table: 5 Heterologous Second Dose Regimes in Clinical Trials [96].

1.20.4 Heterologous Booster Dose Regimens in Clinical Trials:

Initial Course	Booster Dose	Interval	The Current Phase
Corona Vac (2 doses)	Corona Vac Pfizer-BioNTech Oxford–AstraZeneca	19 weeks or more	Phase IV 92,017,878) [111,112] Aug – Nov 2021

Table: 6 Heterologous Booster Dose Regimens in Clinical Trials [97].

1.21 Treatment Strategies:

1.21.1 Antiviral Treatments:

Drugs	Catalyst	Participants	Result
Combination of Lopinavir and Ritonavir	Cytochrome P450 enzyme catabolizes quickly	150	Positive

Table: 7 Antiviral Treatments [97].

1.21.2 Antimalarial Treatments:

Drug	Participants	Period	Result
Chloroquine or, Hydroxychloroquine	100	Six days after inclusion	Positive
Azithromycin	16	Six days after inclusion	Negative

Table: 8 Antimalarial Treatments [97].

1.21.3 Cell and Plasma-Based Therapy

Therapies	Participants	Result	Improvement
Convalescent plasma or Whole-blood therapies	120	Positive	Clinical and Inflammatory Outcomes

Table: 9 Cell and Plasma-based Therapy [98].

1.21.4 Vaccines:

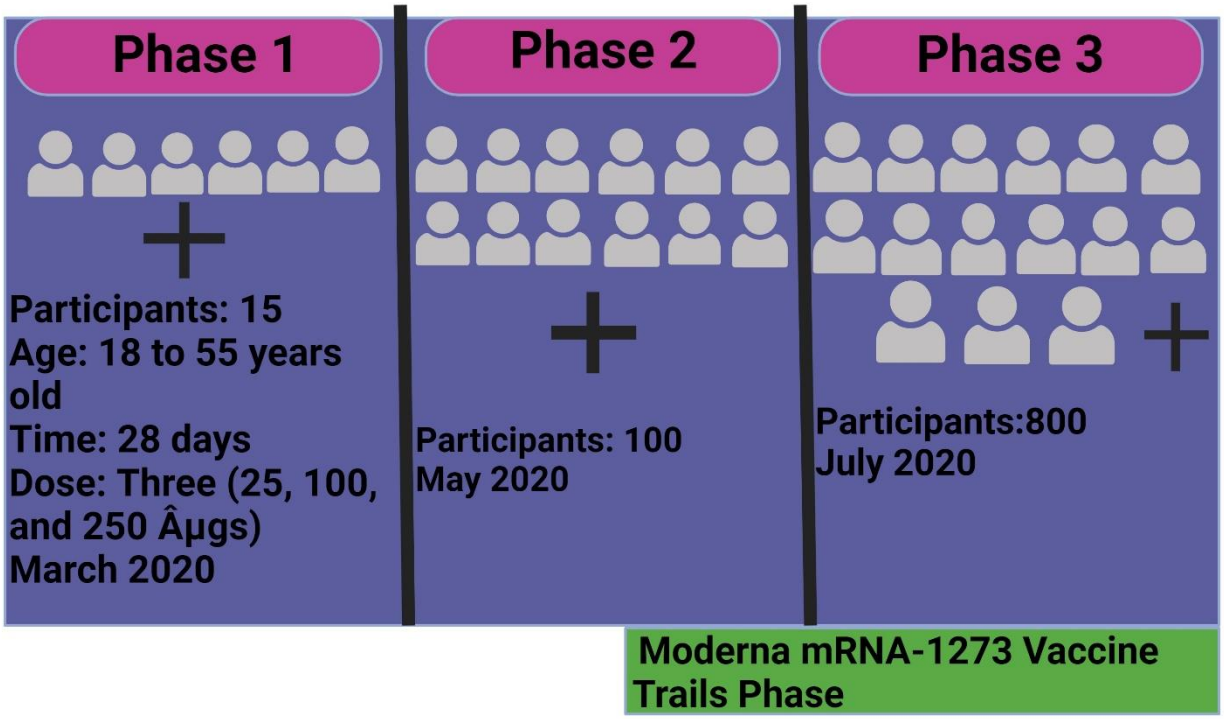

Figure: 9 Vaccines [100].

1.22 Global Response:

Coronavirus Prevalence and Treatment in China and Europe

• All TCM and over 85% of clinical preliminaries for coronavirus prevention and treatment have been enlisted in China.
• The country's coronavirus case rate has dropped due to general health measures.
• New clinical preliminaries are fewer due to a smaller pool of potential workers.
• Responses have been deferred by the global local area.
• Europe has been declared the new disease focal point by the WHO, with a 40% increase in total cases.
• Despite the rapid increase in preliminaries in China, Europe has not seen the same increase due to increasing disease frequency.
• The European Association is supporting efforts for larger patient studies compared to smaller ones in China and the USA.

• An increase in clinical preliminaries in the USA has been observed due to rising coronavirus cases in North America.

1.23 Seamless Clinical Trials During Pandemic:

Effective vaccines are urgently needed to protect people from the COVID-19 virus. Leading manufacturers such as Moderna, Pfizer, and BioNTech have quickly responded to this need. However, there are concerns about the safety and efficacy of vaccines developed so quickly. To address these concerns, clinical trials must be carried out by acceptable standards. Some manufacturers have skipped Phase II dosage-ranging trials in their rush to develop a vaccine. These trials determine the optimal vaccination schedule and dosage. Ignoring them could result in an insufficient dose selection for the Phase III trial. It is crucial to carry out these investigations thoroughly to ensure the vaccine's safety and effectiveness. One approach is to combine Phase II (proof-of-concept and/or dose-ranging) and Phase III (confirmatory) objectives into a single study, known as a seamless Phase II/III design. This can shorten the study's duration while collecting more data, making it more efficient. Platform trials differ from traditional clinical trials in several ways. In platform trials, researchers can test multiple investigational agents in a single trial. These agents cycle in and out of the trial as required. In traditional clinical trials, a single agent is tested in a single trial. Another important component of platform studies is the seamless integration of many research stages and their objectives into a single study for the same investigational drug. Platform trials offer numerous advantages for drug development. One of these benefits is the elimination of the development phase time gap, which can be a significant bottleneck in the drug development process. By testing multiple agents simultaneously in a single trial, researchers can reduce the time taken to move a drug from the lab to the clinic. Another benefit of platform trials is the reduction of overall sample sizes through the utilization of all available data from all study components while preserving sufficient scientific rigor. This means that researchers can gather more data from a single trial, which can help to reduce the total number of patients needed to achieve statistical significance. Overall, platform trials are a cutting-edge method of drug development that may expedite the process and reduce costs without sacrificing scientific integrity. One of the adaptive techniques used during clinical trials is re-estimating the sample size. This involves starting with a smaller trial and then expanding it only as necessary based on the analysis of data results. The rationale behind this approach is that many treatments tend to be ineffective due to a lack of study participant enrollment. This issue may arise in rare cases such as during a pandemic, where there is insufficient evidence to make solid assumptions about the size and/or variability of the therapeutic impact. In such circumstances, it becomes necessary to use adaptive strategies to maximize the clinical trial's design and improve the chances of obtaining positive results. Despite careful planning, unexpected research findings can still occur. The efficacy may be surprisingly lower than anticipated, even after previously successful trials. Additionally, the sample size calculation may have been based on incorrect assumptions, leading to an inadequate

study size. Fortunately, there are strategies to deal with treatment effect uncertainty, such as the Group Sequential Design Accepted Manuscript. This design helps researchers better handle situations where the observed efficacy differs from what was predicted at the beginning of the trial. This approach is useful when there is treatment impact uncertainty, particularly in a rapidly evolving pandemic involving a novel infectious agent. In such circumstances, the behavior of microbiology and clinical manifestations of the disease remain poorly understood. Simplifying the sample sizes of these trials can also be a helpful solution to the issue of large-scale trials. Large-scale trials are expensive, increase the cost of resulting therapies, take longer to obtain definitive results, and waste resources that could be used for other types of research. Therefore, a simplified sample size design can help save resources and expedite the clinical trial process, leading to faster and more definitive results. Many patients are currently awaiting the development of effective treatments, and it is crucial to make the clinical trial process as efficient as possible to provide them with the care they need [168].

1.24 Concluding Remarks:

The COVID-19 pandemic is a significant global health crisis that poses a severe threat to public health worldwide. Clinical trials play a vital role in gathering high-quality data to develop potential solutions for treating and preventing this widespread calamity. It is crucial to allocate international funding to clinical trials that have solid scientific reasoning and statistical support. In the future, globalizing clinical trials with large patient populations and international cooperation will become necessary to achieve significant and definitive results. In December 2019, pneumonia with an unclear cause was detected in Wuhan, China, leading to the discovery of SARS-CoV-2. By February 17, 2020, the pandemic had affected every province in mainland China and 27 other countries and territories, with over 70,000 confirmed cases. To address this persistent public health concern, the Johns Hopkins University CSSE created an online interactive dashboard to track and visualize COVID-19 instances in real time. The dashboard's feature layers and data are available on the GitHub repository, and it is currently included in the Esri Living Atlas. From January 22 to January 31, data collection and processing were done manually, but the manual reporting process became unfeasible as the disease spread. Therefore, starting from February 1, a semi-automated live data stream strategy was implemented through DXY, an online resource run by Chinese medical experts. DXY collects official data and local media to generate cumulative totals of COVID-19 cases at the provincial and national levels. Case numbers are verified with regional and local health departments, state and local health authorities, the Hong Kong Department of Health, the Macau Government, the respective CDC of China, Taiwan, and Europe, as well as city-level and state-level health authorities. The dashboard is particularly useful in pinpointing the moment of the first COVID-19 case to be reported in new nations or areas. The CSSE at Johns Hopkins University has reported newly infected countries ahead of the WHO, except for Australia, Hong

Kong, and Italy. Due to its popularity and impact, the CSSE at Johns Hopkins University intends to continue hosting and maintaining the dashboard for the duration of the COVID-19 epidemic. [142].

Chapter 2

LITERATURE REVIEW

2. Literature Review:

During the pandemic era, there has been an increasing belief that seamless clinical trials are the most effective approach in such situations. However, the topic of seamless trials has been largely neglected in academic research, despite recent studies indicating that the clinical trials process has changed. This paper aims to explore the reasons behind the use of seamless clinical trials by analyzing these studies. The analysis will draw on research conducted on seamless clinical trials between 2020 to 2023, and provide a summary along with statistical analysis of data related to clinical trial patterns. These findings will contribute to a better understanding of how to save time and money during clinical trials. In recent years, adaptive clinical trials which allow companies to adapt a design after seeing interim analysis have emerged as a way to expedite drug development. Within adaptive trials, the approach of combining two phases into one a "seamless" design has also gained steam. In 1747, Naval surgeon James Lind conducted the first controlled clinical trial to find a remedy for scurvy in a group of sailors. He divided the 12 sick sailors into six pairs and gave each pair a different dietary supplement such as cider, vinegar, seawater, sulfuric acid, oranges, and lemon. In 2018, the FDA approved adaptive trials, which help modernize drug development and approvals. To save time and money, seamless clinical trials have become more popular, especially in the oncology field. Seamless trials accelerate drug development by transitioning efficiently from early-phase trials to later-phase trials. This reduces the time to bring new therapies to market, which is crucial for treating life-threatening conditions. However, there may be some issues with running two phases of trials simultaneously, as the approach can sometimes complicate protocols. While seamless trials work well for certain development programs and disease states, they may not be appropriate in all cases. Further research is needed to better understand some of the reasons behind these issues.

2.1 Shahapur, P. R., Vadakedath, S., Bharadwaj, V. G., Kumar, P., Pinnelli, V. B., Godishala, V., & Kandi, V. (2022). Research question, objectives, and endpoints in clinical and oncological research: a comprehensive review. *Cureus*, *14*(9).

Clinical research helps solve human health problems by diagnosing, treating, and preventing diseases. COVID-19 caused global unrest due to the lack of drugs and therapies to manage it. The disease has caused the death of more than 50 million people worldwide and has resulted in severe health problems. The pandemic became such a significant threat to human health because there were no drugs or therapies available to manage the disease. Cancer is the second leading cause of death worldwide. In this review, we discuss critical aspects of clinical research.

2.2 Van Spall, H. G., Toren, A., Kiss, A., & Fowler, R. A. (2007). Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. *Jama*, *297*(11), 1233-1240.

Clinical trials published in major medical journals often fail to report their exclusion criteria. This means that women, children, the elderly, and those with common medical conditions are frequently excluded from participating in these trials. Trials that involve multiple centers and those that test drug interventions are particularly likely to have extensive exclusions. The problem with such exclusions is that they may prevent the trial results from being generalizable to the broader population. Therefore, it is crucial for clinical trial researchers to carefully consider, transparently report, and justify their exclusion criteria to improve the accuracy and applicability of their findings.

2.3 Tregoning, J. S., Brown, E. S., Cheeseman, H. M., Flight, K. E., Higham, S. L., Lemm, N. M., ... & Pollock, K. M. (2020). Vaccines for COVID-19. *Clinical & Experimental Immunology*, *202*(2), 162-192.

COVID-19 is a sickness caused by a virus called SARS-CoV-2. It makes it hard to breathe and can make you feel sick in other ways too. It spreads from one person to another and can make people very sick. Elderly people are more likely to die from it. There is no vaccine for COVID-19 yet.

Chapter 3

PURPOSE of THE STUDY

3. Purpose of the Study:

- Seamless clinical trials can accelerate drug development by allowing for a more efficient transition from early-phase trials (Phase I and Phase II) to later-phase trials (Phase III). This helps to reduce the time it takes to bring new therapies to market, which can be crucial for treating life-threatening conditions where time is of the essence.
- Additionally, integrating phases or components of clinical trials, such as combining Phase II and Phase III trials or overlapping certain stages, can reduce the overall cost of drug development. This cost reduction benefits both pharmaceutical companies and healthcare systems, potentially leading to more affordable treatments for patients.
- Seamless trials can also enhance the patient experience by minimizing the time and effort required of participants. By avoiding separate enrollment processes for different phases of the trial, patients can experience improved retention rates and overall participant satisfaction, leading to more reliable data collection. Furthermore, integrating different phases of clinical trials allows for more seamless data collection and analysis. This continuity can provide researchers with a more comprehensive understanding of a drug's safety, efficacy, and dosing requirements across various stages of development. Seamless trials also enable researchers to make informed decisions about the continuation, modification, or termination of a trial based on interim data analysis. This flexibility can lead to quicker identification of promising treatments or early recognition of safety concerns, allowing for early decision-making.
- By providing a more cohesive and comprehensive dataset, seamless trials can also facilitate interactions with regulatory agencies, potentially expediting the regulatory approval process by reducing the need for additional studies or clarifications.
- Moreover, seamless trials enable more efficient allocation of resources such as personnel, funding, and infrastructure. This optimization can help ensure that resources are utilized effectively to maximize the likelihood of successful drug development outcomes.

Overall, the purpose of seamless clinical trials is to enhance the drug development process, from early research stages to market approval, by increasing efficiency, reducing costs, and improving patient outcomes.

Chapter 4

METHODOLOGY

4. Methodology:

I conducted a thorough search on several research databases, such as Google, Google Scholar, and PubMed, and retrieved about 20 documents comprising research and review papers. After reading the articles and relevant sources, I produced a paper. To ensure the accuracy of my essay, I only cited works published between 2010 and 2022. PubMed is a widely used biomedical literature resource that provides access to publications on clinical trials, medication development, and regulatory approval procedures. Researchers can access peer-reviewed papers, reviews, and meta-analyses on efficient clinical trials and their role in accelerating medication development. ClinicalTrials.gov is a comprehensive global registration and database of clinical trials that are supported by both public and commercial sources. Researchers can access information on ongoing or completed clinical trials, as well as those that employ seamless trial designs. This website provides valuable insights into the implementation and outcomes of efficient clinical trials across different therapeutic domains. JCO is a respected peer-reviewed journal that focuses primarily on clinical oncology research. It publishes original research, reviews, and clinical trial reports, including studies that evaluate the feasibility and effectiveness of seamless clinical trial designs in cancer. Researchers can find valuable information on how efficient trials can accelerate medication development and clearance from regulators through JCO's oncology-related articles. Regulatory frameworks, reports, and guidance materials for the approval and development of drugs can be accessed on the official websites of regulatory bodies, such as the FDA and EMA. Researchers interested in using seamless clinical trial designs to speed up drug development and regulatory approval in the post-pandemic environment can find information on recommendations, case studies, and regulatory activities on these websites. Pharmacies and research institutions often provide industry studies and whitepapers that offer insightful information about new developments, best practices, and emerging trends in drug development and clinical trial procedures. Those seeking insights from stakeholders in drug development, regulatory affairs, and clinical research can browse through corporate papers that focus on seamless clinical trials.

4.1 Inclusion Criteria:

The following criteria will be adopted to ensure that only relevant publications, research papers, and reports are considered for inclusion in the analysis of seamless clinical trials. The focus of the papers should primarily be on the methods aimed at accelerating drug development as well as streamlining regulatory approval procedures. To be eligible, the studies should address the concept of smooth clinical trials across the entire drug development process, starting from preclinical research to post-marketing surveillance. Priority will be given to research that examines how seamless clinical trials affect the regulatory approval procedures, including communication with regulatory organizations such as the FDA, EMA, or other relevant authorities. Interdisciplinary studies that integrate clinical research, regulatory science, data analytics, and technology

viewpoints will be included. To promote comprehensiveness and rigor, peer-reviewed journal articles, conference proceedings, government reports, and industry white papers will be considered for inclusion. The studies included in the analysis should provide information on the effectiveness, safety, affordability, and/or efficiency of smooth clinical trial procedures in accelerating the development of new drugs and obtaining regulatory clearance. Research that meets the eligibility criteria may use various approaches, such as case studies, observational studies, qualitative analyses, systematic reviews, and meta-analyses. There will be no geographical limitations, and research from different regions and countries will be included to represent a range of perspectives and methods for implementing seamless clinical trials. To summarize, only publications, research papers, and reports generated after the COVID-19 pandemic will be considered for inclusion. The primary focus of the papers included should be on seamless clinical trials, which involve methods aimed at accelerating drug development and streamlining regulatory approval procedures. Interdisciplinary studies that integrate clinical research, regulatory science, data analytics, and technology viewpoints will be prioritized. Studies should provide information on the effectiveness, safety, affordability, and/or efficiency of smooth clinical trial procedures in accelerating the development of new drugs and obtaining regulatory clearance.

4.2 Study Design:

Studies with smooth phase 1/2 or phase 2/3 designs analyzing post-pandemic therapeutic fields.

4.3 Exclusion Criteria:

It's important to establish exclusion criteria and guidelines when conducting a review on "Seamless Clinical Trials: Accelerating Drug Development and Regulatory Approval in the Post-Pandemic Landscape." This will help focus on the most pertinent data. Consider excluding studies that do not directly address smooth clinical trials, medication development, and regulatory approval in the post-pandemic environment to ensure the review stays on topic. Outdated literature should be removed to include the most recent developments and ideas on the subject, depending on the review's scope and material availability. Unless they provide substantial contributions from non-English sources that justify their inclusion and translation, studies that have not been published in English should be excluded. Studies that do not use appropriate research designs, such as randomized controlled trials, cohort studies, or systematic reviews, or that do not employ the methodology for evaluating smooth clinical trials and drug development processes, should be excluded. Discard studies with insufficient data or methodological errors that could compromise the validity and reliability of their findings. To avoid repetition and ensure each study provides unique insights, exclude duplicate publications or reports on the same topic. Unless they offer valuable additional information not found in peer-reviewed publications, exclude sources that have not undergone peer review, such as conference abstracts, preprints, or gray literature. Remove studies with possible conflicts of interest that may skew their conclusions, unless their

contributions are critical and openly disclosed. Reject research with limited sample sizes or statistical power that cannot provide reliable information. Discard studies conducted in extremely narrow demographics or environments that restrict the applicability of their findings to wider contexts relevant to the smooth conduct of clinical trials and the development of new drugs.

Chapter 5

RESULT

5. Result:

Adaptive clinical trial designs are gaining popularity in drug development research. Among the most commonly used designs are seamless Phase II/III designs (57%), group sequential designs (21%), biomarker adaptive designs (20%), and adaptive dose-finding designs (16%). About 32% of trials had an independent Data Monitoring Committee (DMC), while 6% had blinded interim analysis. Our research indicates that 9% of adaptive trials were considered for FDA product approval, and 12% for EMA product approval.

5.1 FDA process of regulatory approval:

The FDA's Center for Drug Evaluation and Research is responsible for approving drugs in the US. Before any new medication can be sold in the country, the CDER conducts a thorough review to ensure that the drug is safe and effective and that its benefits outweigh its risks. This process takes around ten years from the initial discovery of the drug to final market approval. The regulatory process begins with the submission of an investigational new drug application (IND) to the FDA. The IND provides detailed information on the drug's chemistry, pharmacology, toxicology, and manufacturing processes, as well as outlining the human trials that the sponsor plans to conduct to demonstrate the drug's safety and efficacy. The FDA reviews the IND to determine whether the proposed human-subject drug testing is acceptable, to ensure that patients are not put at unnecessary risk, and to evaluate the scientific validity of the proposed research. Only after the FDA has given its approval and an ethical review board has approved the research design can a clinical trial begin. Clinical trials are typically divided into four phases: Phase 1, Phase 2, Phase 3, and Phase 4. Phase 4 trials are conducted following the drug's approval for sale in the US. Phase 1 studies are intended to evaluate the agent's metabolic and pharmacologic profiles in humans, detect potential side effects, and provide proof of the medicine's efficacy if feasible. Phase 1 trials are usually single-blind and conducted on a limited sample size of 20-80 individuals to reduce potential risks to future research participants while providing enough data to support the creation of Phase 2 studies with scientific validity. Phase 2 trials are extensive clinical investigations that assess a medication's efficacy in treating a specific ailment and determine the optimal dosage for a patient's benefit-risk ratio. Typically, several hundred participants are involved in Phase 2 studies. Phase 3 studies are conducted concurrently using the same research design and usually involve thousands of participants. The main goal of Phase 3 trials is to validate the safety and efficacy conclusions drawn from earlier studies. Phase 4 studies are conducted after a drug is approved and are typically required by the FDA to provide additional data on the safety, effectiveness, or manufacturing procedures of the product. To support drug development, the FDA provides sponsors with strategic advice at various stages of the process, either in writing or through meetings. Once all drug investigations are complete, the sponsor compiles all the information from manufacturing, preclinical, and clinical studies into a new drug marketing application NDA, which is then submitted to the FDA. If the FDA determines that the application is substantially complete, the NDA moves through five review areas: pharmaceutical, medicinal, chemistry,

biopharmaceutical, and statistical. Sponsors and the FDA frequently communicate throughout the NDA review process via phone calls, letters, and meetings. The agency's reviewers make every effort to verify and validate the sponsor's findings and conclusions on the drug's safety and efficacy for the intended purpose, as well as compliance with quality and manufacturing standards. The FDA has the authority to request independent opinions and recommendations on the approval of the NDA from an advisory committee made up of external experts. Although the FDA takes into account the advisory committee's suggestions, it is not required to adopt their conclusions. Once the NDA review is complete, an FDA Therapeutic Division Director and management assess the technical evaluations and determine what steps the division will take to approve the application. The FDA has recently updated its action letters, which are given to sponsors following the conclusion of an NDA evaluation. A letter of "approval" certifies that the research medication is permitted to be sold in the US. The previous "approvable" and "not approval" letters have been replaced by the "complete response letter," which states that the NDA is not approved in its current form. The action letter outlines the specific application flaws that were found.
[143].

In 2011, the FDA received $593 million in fees from the PDUFA. This amount helped fund the work of 3,877 full-time employees who evaluated drug applications [144]. The PDUFA fees constituted 18% of the FDA's $3.3 billion budget in 2011 [145]. The FDA projected the receipt of over $700 million in drug user fees in 2013, and the cost of submitting a New Drug Application (NDA) would be $1.96 million [146]. The PDUFA program has been effective, with the median approval time for novel molecular medications reduced from 19 months to 10 months [147]. The total cost of drug development is a major factor in the high cost of pharmaceuticals to consumers. The total capitalized cost of an approved medicine has been estimated by financial model studies to be between $868 million and $1,241 million [148]. Morgan et al. noted wide variations in costs in a review of drug development expenses, indicating a lack of openness in data sources and analytical techniques. Pronker et al. proposed that there is no standard approach to evaluating attrition rates and investment costs, which are critical in determining total expenses [149].

5.2 European Regulation of Drugs:

In 1965, the European Union accomplished the unification of medicine approval regulations across Europe with the adoption of EC Directive 65/65/EEC [150]. This directive defined a medical product as "any substance or combination of substances that may be administered to humans or animals to diagnose a medical condition or to restore, correct, or modify physiological functions in humans or animals [151]." It also required that any medical product advertised in a member state be authorized in the state of origin. The directive aimed to establish consistent guidelines for member states regarding the information required for approval, similar to those established by the FDA for investigational new drug submissions and new drug approval applications [152]. The pharmaceutical approval processes of the FDA and the EU are fundamentally similar. In Europe, an investigator obtains pre-authorization for a potential pharmaceutical to be used in clinical trials. All clinical trials in Europe are governed by the European Commission's Clinical Trials Directive (2001/20/EC) [153], which was later revoked, and the European Parliament's Regulation No. 536/2014 took its place in 2014 [154]. The drug approval process in Europe involves several stages. After small-scale Phase I trials involving healthy subjects to determine pharmacology and dose range, several hundred patients with the target condition participated in Phase II trials to explore the dose-response relationship. Phase III confirmatory trials, involving several hundred to several thousand patients, are then conducted to validate safety and efficacy. These investigations are similar to those conducted in the US. The EU, like the US, provides procedures for approving "orphan drugs," or drugs that treat conditions that affect so few people that it may not be feasible to conduct randomized controlled trials [155]. There are also ways to obtain conditional authorization, such as the right to use drugs in an emergency. The EMA was established in 1995 with funding from the pharmaceutical industry, member states, and the European Union [156]. The EMA was tasked with harmonizing procedures among member state regulatory agencies to reduce annual costs for pharmaceutical companies. These companies were constrained in their ability to compete by laws in sovereign nations and the requirement that they obtain separate permits in each state. However, unlike the FDA in the US, the EMA does not have the same level of control over all drug applications. In Europe, a drug can be licensed in one of four ways, depending on the class of drug and the manufacturer's preference [157]: decentralized procedures, mutual recognition, national processes, or centralized processes [158].

5.3 Drug Development Pandemic Era:

The ongoing COVID-19 pandemic has brought to the forefront the urgent need for effective medication to halt the spread of the virus. In response, numerous antiviral treatments are currently being investigated by medical researchers and pharmaceutical companies around the world. To expedite the drug approval process, regulatory bodies such as the European Medicines Agency and the FDA have formed special task forces. These groups are focused on identifying potential treatments that can be fast-tracked for approval and dissemination to patients in need. To facilitate this process, many clinical trials are being conducted to gather data on the efficacy and safety of

possible drugs for COVID-19. In addition, initiatives such as the CURE Drug Repurposing Collaboratory have been launched to collect real-world data that can inform drug development and approval. All of these efforts are playing a pivotal role in accelerating the drug approval process and ultimately saving lives. [160].

Chapter 6

CONCLUSION

6. Conclusion:

Seamless clinical trials are a revolutionary concept in drug development and regulatory approval processes. These trials offer the potential to accelerate innovation, enhance patient outcomes, and improve healthcare delivery, particularly in the post-pandemic era. The idea behind seamless trials is to eliminate the traditional barriers between clinical trial phases and integrate them into a single, continuous process. This approach can help to reduce the time and cost associated with drug development, making it more efficient and effective. However, to realize the full potential of seamless trials, stakeholders must overcome several key challenges. One of the most significant hurdles is regulatory harmonization. Different countries and regions have different regulatory frameworks and requirements for clinical trials, so it is crucial to ensure that the seamless trial methodologies comply with the regulations of the respective regions. Another significant challenge is ensuring data integrity. Seamless trials generate a vast amount of data, which must be managed efficiently. The data collected must be accurate, reliable, and secure to ensure that the results are reliable and can be used to make informed decisions. Operational complexities are also a significant challenge to seamless trials. These trials require significant collaboration between multiple parties, including researchers, sponsors, regulatory agencies, and clinical sites. Therefore, it is essential to have a streamlined and efficient process for managing the logistics and communication between these parties. To overcome these challenges, stakeholders must collaborate and work together. By optimizing seamless trial processes and maximizing their impact through collaboration, we can usher in a new era of innovation and efficiency in drug development and regulatory approval. This will help to improve patient outcomes, advance medical research, and ensure that safe and effective treatments are available to those who need them.