ISSN: 0976-3031

Available Online at http://www.recentscientific.com

CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 14, Issue, 12, pp.4386-4391, December, 2023

International Journal of Recent Scientific Research

DOI: 10.24327/IJRSR

Research Article

HUMAN CLINICAL TRIALS MAGNIFY THE BALLOONING OF CLINICAL RESEARCH

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DOI: http://dx.doi.org/10.24327/ijrsr.20231412.0824

ARTICLE INFO

Article History:

Received 15th October, 2023
Received in revised form 22nd October, 2023
Accepted 15th November, 2023
Published online 28th December, 2023

Keywords:

Clinical trials, Public health, Drug Standard Control Organization (CDSCO), "vaccine efficacy", Therapeutic Efficacy

ABSTRACT

Clinical research has undergone a lengthy and fascinating history. Humans are used as test subjects in human clinical trials research, which is a form of scientific investigation. Human clinical trials are used to test new procedures and medications and determine how they affect patient outcomes. Clinical research informs clinical practice and evidence-based medicine. When novel drugs are tested on humans, there are various potential ethical problems. In highly developed countries like the USA and UK, clinical trials are subject to strict regulations, extensive safety measures, and compensation responsibilities. Finding volunteers is a time-consuming and expensive process in western countries. Clinical investigations are currently expanding, particularly in China, India, and other nations. Due to its strong regulatory environment, illiteracy, poverty, lack of awareness about clinical trials, and broken healthcare system, India was a suitable destination to outsource human clinical studies. India has been deemed one of the most promising centers of activity for clinical trials due to the large number of available patients who are treatment-naive, the low cost, and the large number of qualified professionals. Clinical trials are reliable, practical, and available in India.

INTRODUCTION

Concern over the growing outsourcing of clinical trials to India, which is of little service to the nation's public health requirements, has persisted. (1) The necessity for regulatory change and strict ethical measures has once again come under the spotlight as a result of allegations of unethical behavior in clinical trials. (2, 3). The most recent reports on contentious medication trials being carried out by government medical college doctors. (4) With a growth rate of 12%, the number of clinical studies performed in Latin America has greatly expanded. (5) Internationalization of clinical trials increases the research's external validity. (6) Clinical trials have an effect on society as a whole as well as on the individuals who participate in them.(7) Chagas disease, dengue, rabies, and schistosomiasis are a few of the so-called neglected illnesses that have the greatest impact in Latin America and the Caribbean. (8) High-income nations are where the majority of new drugs and vaccines are evaluated. (9) Due to tight laws and thorough safety, subject recruiting is expensive and time-consuming in western nations. (10, 11). India was a desirable location to outsource clinical trials because of its good regulatory environment, illiteracy, poverty, and lack of knowledge about clinical trials (12). Clinical trials in India that violated ethical standards occurred as a result of stakeholders' lack of GCP training and a lax regulatory system (13). The Central Drug Standard Control Organization (CDSCO) works on creating the standards and rules for pharmaceuticals in an effort to standardize clinical research in India. In 2005, Schedule Y of the Drug and Cosmetic Rules of 1945 was revised by the CDSCO, which outlined the obligations of sponsors and investigators. Currently, there are more than 3,000 clinical research organizations (CROs) operating globally, with more than $21 billion in combined market revenues (16, 17). We intended to measure the global distribution and migration of clinical research (18, 19, 20). Researchers, including CROs, leverage global networks to speed up patient recruitment and cut expenses.

HISTORY

In exchange for their lives, seven inmates who had been given the death penalty underwent variolation to avert smallpox at the

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request of Lady Mary Wortley Montagu. James Lind, who is regarded as the founder of clinical trials in the contemporary age, carried out a Scurvy clinical experiment in 1747.The James Lind Library was created to improve public and professional general knowledge about fair tests of treatments in healthcare and their history (21). The smallpox vaccine was subjected to similar clinical trials by Edward Jenner. The placebo was yet another significant development in the background of contemporary clinical trials. Clinical trials have evolved as a result of a protracted and fascinating experience.

Clinical trial on human volunteers

Clinical trials are research studies that test a medical, surgical, or behavioral intervention in people. Aims of clinical research include:

1. New drug development or new therapeutic strategies
2. Testing ways to diagnose a disease early, sometimes before there are symptoms
3. Finding approaches to prevent a health problem, including in people who are healthy but at increased risk of developing a disease
4. Improving quality of life for people living with a life-threatening disease or chronic health problem
5. Studying the role of caregivers or support groups

Reasons for participation:

Volunteers are an integral part of the research process. People volunteer for clinical studies for many reasons.
They may have:

1. Desire to improve medical care for future generations
2. The treatments they have tried for their health problem did not work or there is no treatment for their health problem
3. Connection to a certain disease or illness, whether through personal experience or through friends or family
4. Personal interest in science

Many effective treatments that are used today, such as chemotherapy, anti cancer drugs, cholesterol-lowering drugs, vaccines, and cognitive-behavioral therapy, would not exist without research participants. Volunteers can be healthy or diseased and can be of all ages and backgrounds in clinical trials.

PROCEDURE

Before a clinical trial is designed and launched, scientists perform laboratory tests and often conduct studies in animals to test a potential intervention's safety and effectiveness. These are preclinical studies and are done to evaluate the safety and efficacy of any new treatment modality or intervention. If these studies show favorable results, the U.S. Food and Drug Administration (FDA) approves the intervention to be tested in humans.

Risks

1. The new treatment may cause serious side effects
2. The new treatment may not work, or it may not be better than the standard treatment.
3. The clinical trial could inconvenience you. For example, medical appointments could take a lot of time. You might need to travel to the study site several times or stay in the hospital.

Safety precautions

An Institutional Review Board, or IRB, at each study site must approve every clinical trial in the United States. The IRB is made up of doctors, scientists, and lay people who are dedicated to making sure that the study participants are not exposed to unnecessary risks. The people on the IRB regularly review the study and its results. They make sure that risks (or potential harm) to participants are as low as possible. Along with the IRB, many clinical trials are closely supervised by a Data and Safety Monitoring Committee. The Committee is made up of experts in your condition who periodically look at the results of the study as it is in progress. If they find that the experimental treatment is not working or is harming participants, they will stop the trial right away.

Informed consent

Before deciding to participate in a study, you will be asked to review an informational document called an informed consent form. This form will provide key facts about the study so that you can decide if participating is right for you. You must sign the informed consent form in order to participate in the study, though it is not a contract — you may still choose to leave the study at any time.

Risks and benefits

All medical research involves some level of risk to participants. Risks and benefits vary depending on the particular study. To help you make an informed decision, the study team is required to tell you about all known risks, benefits and available alternative health care options.

Ask questions

If you have questions when deciding to join a research study or at any time during it, ask a member of the study team. If your questions or concerns are not satisfactorily addressed, contact the study's principal investigator.

What happens when the trial ends?

Once a clinical trial or study ends, the researchers analyze the data to determine what the findings mean and to plan the next steps. As a participant, you should be provided information before the study starts about how long it will last, whether you will continue receiving the treatment after the trial ends (if applicable), and how the results of the research will be shared. If you have specific questions about what will happen when the trial or study ends, ask the research coordinator or staff.

Phases of clinical trials

Each phase has a different purpose

Phase 0/ Pre Phase 1

Volunteers in this phase are administered sub therapeutic
(micro dose) but pharmacologically active doses of drug. The end point is not to elicit a toxicity or safety profile. They help study the pharmacokinetics and drug targets effects in humans and can be conducted in either healthy or diseased volunteers. The data (pharmacokinetic and pharmacodynamic) generated can contribute to the phase 1 trial subsequently.

A **Phase 1** trial tests an experimental drug (also known as investigational new drug/IND) or device on a small group of healthy volunteers (around 20 to 80) to judge its safety, including any side effects, and to test the amount

(dosage).They include dose ranging and are also called dose escalation studies.

- Phase 1a- Single ascending dose - It helps to find out the maximum tolerated dose (MTD).
- Phase 1b- Multiple ascending dose -multiple ascending doses of the investigational new drug (IND) help elicit the pharmacokinetic and pharmacodynamic properties of multiple doses of the drug.

A **Phase 2** trial includes more people (around 100 to 300) to help determine whether a drug is effective. This phase aims to obtain preliminary data on whether the drug or device works in people who have a certain disease or condition. These trials also continue to examine safety, including short-term side effects.

- Phase 2a- proof of concept study
- Phase 2b - definite dose finding study

A **Phase 3** trial gathers additional information from several hundred to a few thousand people about safety and effectiveness, studying different populations and different dosages, and comparing the intervention with other drugs or treatment approaches. If the FDA agrees that the trial results support the intervention's use for a particular health condition, it will approve the experimental drug or device.

Phase 4 trial takes place after the FDA approves the drug or device. The treatment's effectiveness and safety are monitored in large, diverse populations. Sometimes, side effects may not become clear until more people have used the drug or device over a longer period of time. Choosing to participate in research is an important personal decision. If you are considering joining a trial or study, get answers to your questions and know your options before you decide.

How will the study affect during COVID time?

Thousands of clinical trials will be stopped during the epidemic. Universities and research facilities were shut down. Curfew and police restrictions caused individual visits with volunteers to be delayed or blocked. Face-to-face communication was always dangerous.

Clinical Trials Are Moving out of the Lab and into People's Homes

After the pandemic shut down thousands of trials, researchers devised creative techniques to conduct human studies remotely, which allowed them to swiftly and cheaply reach a larger population. Researchers carried out clinical studies in a particular way. They mailed drugs, gave patients instructions on how to monitor their own vital signs from home, and conducted video chat examinations. Researchers are moving towards virtual research using the technology that has been built.(22) The rapid approval of COVID-19 vaccinations during the SARS-CoV-2 pandemic demonstrated the importance of clinical trials. Previously only employed in the context of medical research, terms like "vaccine efficacy" and "clinical trial" have become commonplace. COVID-19 has no proven effective treatment. A novel therapy cannot be used in clinical practice unless its efficacy has been proven in clinical trials. As seen by past outbreaks like the Ebola virus, designing clinical trials in patients with hazardous diseases involves both scientific and ethical challenges. There is no time for the development of novel therapeutics during a pandemic; instead, therapies that have already been approved by regulatory bodies and have a well-established safety profile are studied. These could be investigated if there is scientific evidence of their potential utility, based on biological systems tested in laboratory or animal studies. However, it may not be thought of as potent to use the recommended standard doses of medication. If higher doses are being investigated, there must be a compelling argument supported by laboratory, animal, and human studies. However, there would also be more likelihood of unfavorable results.

What are the problems with India's clinical trials registry?

-Despite their success, the hastiness with which the COVID vaccines were approved in India raised several questions regarding the transparency of the clinical trials and the safety and efficacy of the vaccines themselves. The speedy approval of Covid-19 vaccines during the SARS-CoV-2 pandemic spotlighted the importance of clinical trials. Terms like "vaccine efficacy" and "clinical trial", previously restricted to medical research circles, became a part of everyday language. (23)

Patients suffer as new norms impede clinical trials in India

Doctors have said the decline in the number of clinical trials is a loss to patients, who are being deprived of cutting edge drugs that clinical trials can offer. Indian Society for Clinical Research (ICSR) and academic researchers have said India has now fallen behind smaller countries like Korea, Taiwan and Japan because of the new regulations were framed following a public interest litigation (PIL) in the Supreme Court. The regulations were enforced based on the recommendations of the Professor Ranjit Roy Choudhury expert committee appointed by the ministry of health and family welfare. (24)

Benefits of clinical trials

Clinical research can help scientists develop new medications and other strategies to treat and prevent disease. Many effective treatments that are used today, such as antimicrobial chemotherapy, cancer chemotherapy, cholesterol-lowering drugs, vaccines, and cognitive- behavioural therapy, treatments are available now. They would not have existed without clinical trials and participation of volunteers. Whether you're healthy or have a medical condition, people of all ages and backgrounds can participate in clinical trials.

The first-in-human trial of an oral drug to treat radioactive contamination begins

At a facility in Plymouth, Michigan in the United States, an experimental drug called HOPO 14-1 is undergoing its first-ever human study to remove radioactive pollutants from the human body. The experiment (NCT05628961), funded by the National Institutes of Health (NIH), is examining the pharmacokinetics of this novel medication at increasing doses as well as its safety and tolerability. In comparison to DTPA (diethylenetriaminepentaacetate), HOPO 14-1 has been proven in preclinical trials to be 100 times more successful at removing radioactive pollutants such plutonium, neptunium, uranium, americium, and curium. Contrary to the pentetate calcium trisodium injection (Ca-DTPA) and pentetate zinc trisodium injection (Zn-DTPA), which have been approved by the FDA for treating radioactive contamination with plutonium, americium, or curium, HOPO 14-1 is made as an oral capsule. Zn-DTPA and Ca-DTPA are intravenously administered. The trial will enroll 42 healthy adults between the ages of 18 and

65. After that, they will be divided into seven groups of six each. The first group will be given 100 mg of HOPO 14-1, and the remaining groups will receive the medication in escalating levels, with the final group receiving 7500 mg. This would depend on the drug's safety at lesser levels, though. The main pharmacological component in this formulation is 3,4,3-LI(1,2-HOPO).With a follow-up of 14 days, all trial participants would be evaluated for safety while the study drug's absorption, distribution, and excretion were tracked. In the upcoming year, the study's findings are anticipated. (25,26)

A Review of Clinical Studies Assessing the Therapeutic Efficacy of Escitalopram: A Step towards Development

Based on the available clinical evidence and pharmacoeconomic data, it was concluded that escitalopram is an effective first-line therapeutic modality for MDD patients. (27)

Now an mRNA vaccine for influenza

In Durham, North Carolina, the Duke University has started the first phase of a study for an experimental universal influenza vaccine. The Vaccine Research Center (VRC) of the National Institute of Allergy and Infectious Diseases (NIAID) has created the vaccine candidate H1ssF-3928 mRNA-LNP using the messenger RNA (mRNA) platform. The safety and immunogenicity of the vaccine will be investigated in the trial (NCT05755620). An essential line of defense against the spread of a future flu pandemic could be a universal flu vaccine. The trial is anticipated to be finished by August of the following year. (28,29)

Modifying Treatments for Alzheimer Disease and Their Contribution in Recent Research

Drug-development research for AD is aimed to overcome these drawbacks. Preclinical and prodromal AD populations, as well as traditionally investigated populations representing all the clinical stages of AD, are included in recent trials. (30)

Major Causes Associated with Clinical Trials Failure

Other elements like the presence of a novel molecule, molecular size, and therapeutic efficacy are also linked to the success or failure of a trial. A failed trial has a negative impact on the subject's quality of life through physical and social repercussions and causes significant losses to pharmaceutical firms because medication research involves many lives and billions of dollars in investments.(31) While operational clinical trial sites, particularly for phase 3 studies, may be moving to low- and middle-income nations with growing economies, human clinical research is still primarily conducted in high-income countries.(32) Patients are frequently eager to agree to take part in a clinical study if they think they have the chance to obtain better care or if the outcomes can benefit others (33)

DISASTROUS CLINICAL TRIALS WITH TRAGIC OUTCOMES

BIA 10-2474 safety trial

One individual passed away and four developed illnesses after using BIA 10-2474, a medicine that affects the endocannabinoid system and was intended to treat a variety of disorders, in January 2016 during a drug safety trial carried out in France. The wounded group of eight patients was the first to get numerous large doses of the medicine even though the trial didn't start until June 2015 and there were no serious adverse effects reported among study participants. Four other people got sick in the interval, and the first person later had an MRI that revealed brain death. Bio trial finally found out about the passing and halted the investigation. (34)

Thalidomide

Drug thalidomide was created in the 1950s by Chemie Grünenthal GmbH, a pharmaceutical business in West Germany. Its primary usage was as a sedative or tranquilizer, but it was quickly shown to be effective for treating a variety of other ailments, such as colds, the flu, nausea, and morning sickness in pregnant women. Drug usage during pregnancy was not carefully regulated in the 1950s since scientists did not realize that a drug's effects could cross the placental barrier and harm an unborn child. Additionally, no tests involving pregnant women were conducted in the case of thalidomide.Eyesight, hearing, internal organs, including the brain, and limbs may all be impacted. Multiple birth abnormalities were caused by thalidomide treatment.

ROCKET trial

The "ROCKET" trial, a Phase II clinical trial of JCAR015 in adult patients with relapsed or refractory B cell acute lymphoblastic leukemia, has been voluntarily suspended, according to Juno Therapeutics, Inc. (Nasdaq: JUNO), a biopharmaceutical company dedicated to reactivating the body's immune system to revolutionize the treatment of cancer. After two patients experienced cerebral edema earlier this week, the clinical hold was imposed. As of last night, one patient had passed away, while the other was not expected to survive. (35)

TGN1412 fiasco

A medicine is tested on healthy human volunteers for first-in-man trials after being found to be both safe and effective in preclinical investigations. Six human volunteers participated in a phase I clinical investigation in 2006 for the CD28 super agonist antibody TGN1412. All six human volunteers experienced multiorgan failure that was life-threatening after the initial infusion at a dose 500 times lower than that deemed safe in animal research. As a result, they were all transferred to an intensive care unit. Following this specific incidence, there have been significant changes to both how regulatory agencies approve first-in-man experiments and how clinical trials are carried out. (36)

CAFÉ study

It's interesting how this particular egregious case of a clinical trial went horribly wrong. The CAFÉ study was a double blinded study aimed at comparing three atypical antipsychotic drugs. On the advice of Stephen Olson, MD, a physician at the University of Minnesota, a judge ordered the involuntary confinementof Dan Markingson, age 26, in 2003. Markingson had psychosis and homicidal tendencies. The judge was eventually persuaded by Dr. Olson to release Markingson—but only if he joined his treatment program. Markingson was engaged in a clinical study of Quetiapine in which Dr. Olson was an investigator.Even more alarming, Dr. Olson assigned Jeanne Kenney, a social worker, to administer prescription medicines while simultaneously keeping an eye out for potentially fatal side effects including akathisia. Markingson's mother attempted to have him removed from the research after noticing that her son was decompensating. Dr. Olson and a

research co-investigator, however, declined to do so. Shortly after, Markingson committed suicide.

Recommendations of Ranjit Roy Committee on Clinical Trials

1. The committee suggested that only accredited centres should conduct clinical studies.
2. It was suggested that a central accreditation council be established, tasked with selecting the professionals who will examine new medication applications.
3. The lead investigator should be held accountable for any violations of the participant's rights.
4. Technical Review Committee is responsible to take the place of drug advisory committees and speed up the approval procedure for clinical trials.
5. Compensation - The committee advised that any negative impacts on the participant during the clinical trial be handled by the sponsor investigator.
6. Special Expert Committee that is separate from the Drug Technical Advisory Board will be established to examine the drug formulations currently on the market and find medicines that could be dangerous.

Summary

Patients have access to treatments or medications as a result of extensive research spanning few decades.Lucrative pharmaceutical developments come with a lot of risk and ethical considerations.First priority is to assess the risks before deciding whether or not to use the drug. The legal process for employing novel experimental medications to treat humans is governed by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), two important international health organizations in USA and Europe respectively. Clinical (human) tests for investigational medical devices are covered by the investigational device exemption regulations (IDE). The mandate of the U.S. Food and Drug Administration (FDA) includes the censorious duty of safeguarding clinical trial participants' welfare, safety, and morality. Federal law and good clinical practice (GCP) guidelines, which the FDA monitors or coordinates, must be followed in the planning, execution, examination, inspection, analysis, and reporting of clinical studies. All studies involving humans must be reviewed, evaluated, and approved by a Human Ethics research Committee.

CONCLUSION

Clinical research is an international field. Clinical studies are expensive, time-consuming, and frequently stressful for patients. Numerous factors might cause clinical studies to fail. Clinical trials explore cutting-edge methods for diagnosing, treating, or eliminating the underlying causes of diseases in order to advance healthcare. Prior to introduction of a new drug or medicine to patients as treatment, cure, or therapy, it must successfully complete the relevant preclinical and clinical trial stages, which is intended to test the investigational new drug (IND) or medicine for safety and efficacy.

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How to cite this article:

Raghavendra Rao M.V, N. Uday Goutham, M.M. Karindas, G. Pavani, SumanaSen, A. Neeraja, D. Srinivasa Rao, B. Aruna. (2023). Human Clinical Trials Magnify the Ballooning of Clinical Research. *Int J Recent Sci Res.* 14(12), pp.4386-4391.

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