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A REVIEW ON TYPES OF CLINICAL TRIAL STUDIES, CLINICAL TRIALS ETHICS, AND ITS IMPACT ON HEALTH CARE RESEARCH

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ABSTRACT

A clinical trial is an experimental study that evaluate new medical treatment effectiveness is compared to an existing treatment. Initially all the new drugs must pass into preclinical studies. A preclinical study involves in-vitro studies. Clinical trials consist of four phases that includes Phase I, II,III,IV. Phase I clinical trials studied in a small number of healthy volunteers. The dose level toxicity determined use of multiple statistical designs. Phase II trials conducted in a small number of volunteers who have the illness. The drug level dose, toxicity, dose frequencies, administration, safety, efficacy, and the study endpoint will be determined to start phase III trials. Phase III study is conducted in larger patients to confirm efficacy and to identify the incidence of common adverse reactions. In this phase a sponsor to conduct a phase IV trial as a stipulation for drug approval. Phase IV trials referred to observational studies performed for FDA-approved drugs. There are various types of clinical trials includes experiments and comparative analyses, observational studies, surveys etc. Clinical trials aim to prove the therapeutic effectiveness of a new drug by conducting biological assays, toxicity studies, and pharmacokinetics studies will enhance the drug efficacy. Clinical trials are designed to monitor the new drug outcomes in human subjects. Randomization is commonly followed in the clinical trials to remove the occurrence of bias of study results. Clinical trials professionals strive to provide advanced patient services could enhance the patient's health outcomes and minimize the treatment related harmful effects.

KEYWORDS: Clinical trials, biological assays, FDA, pharmacokinetics, randomization, safety, and efficacy.

INTRODUCTION

Clinical trials are used to test the novel methods of diagnosis, treatment, and prevention of health conditions. The major objective is to identify the safe and effectiveness of new medication.

Phase I clinical trials

Phase I clinical trials done in human patients to identify the safety of the medication. This Phase require small sample size approximately 20 to 100 volunteers. Phase I clinical trials is design to prove the safety and effectiveness of the drug. This trial can be done from several months to years. Clinicians can start the trial by prescribing a small dose of drug to the study population and measure the pharmacokinetics of the prescribed drug. This phase if the research investigators found drug is to be safe, then the study forwarded to phase II trials.[1-2]

Phase II clinical trials

Phase II trials are performed to test the safety and effectiveness of the drug. This trials are performed from several months to few years and recruit the patients from 100-300. Phase II clinical trials are randomized controlled trials in which one group receive investigation drug and another group receive placebo drug. This phase if the drug has found safe and effective, then the drug will be forwarded to phase III trials.

Phase III clinical trials

Phase III trials are performed in more group of patients. This trial will be done in 3000-5000 study patients. This study was done to detect the efficacy and side effects of the drug. A pharmaceutical company approves marketing of new drug. The study investigator or company can submit New Drug Application to the FDA. The FDA will review the all stages of the clinical trials to determine the drug whether it is safe or not. If any additional studies are required it will be done by the pharmaceutical company and study reports were documented and submitted to the drug regulatory authorities.[3]

Phase IV clinical trials

This Phase is known as Post marketing surveillance. The Pharmaceutical companies can monitor the chronic impact of drugs on humans. It may take few years for

monitoring side effects of drugs. Phase IV trials monitor the safety surveillance of the marketed drug. Phase IV trials need regulatory authorities approval for marketing and distribution of drugs. The safety surveillance is used to detect the long-term adverse effects of drugs.

History of clinical trials

Many clinical trials has began at the dawn of Great Depression (1929) and continued through the end of World War II (1945).

1932: The "Tuskegee Study of Untreated Syphilis in the Negro Male" begins. The "Tuskegee Study of Untreated Syphilis in the Negro Male" was a started between the U.S. Public Health Service and Tuskegee Institute to follow the effects of untreated syphilis in black men in Alabama. During that time 35% of the black, reproductive aged patients were suffered from syphilis and there was no effective cure for the same disease.[4]

1937: Sulfa craze

1937: Sulfonamide drugs were the first systemic antibiotics. It is used to treat bacterial infections and it was very effective against infections caused by streptococci. The active molecule was called sulfanilamide and frequently used in dye-making industry and no testing was done at that time. These results in 107 people died from diethylene glycol poisoning from an improperly prepared batch of sulfa medicine in 1937.

1938: Federal Food, Drug, & Cosmetic Act

The federal food, drug, and cosmetic act was created in response to the sulfa drug incident. It is replaced by Pure Food and Drug Act of 1906. The Federal Food, Drug, and Cosmetic Act need new drugs to be checked for safety and efficacy before they were marketed into the market.[5]

1946: Nuremburg trials

From the year of 1939 to 1945, the Nazi's performed experiments on camp prisoners to create new weapons aid in the recovery of injured military members.[6]

1947: Nuremburg Code

In the year of 1947, Dr. Leo Alexander submitted six point that defined legitimate medical research to the Counsel for War Crimes. The ten points of the Nuremberg Code include such principals as informed consent, absence of coercion, and beneficence toward study participants.[7]

1948: First randomized controlled clinical trial

The randomized treatment and control groups were executed in 1948 by the Medical Research Council. This study involves streptomycin used as a treatment for pulmonary tuberculosis. This trial also used the blind assessment method, the patients nor researchers know which treatment group each patient was in at the time of the study.

562 BC - 1537: Pre-James Lind Era

Avicenna suggested that in the clinical trial is a remedy should be used in its natural state in disease without having any complications. These rules suggest a contemporary approach for conducting clinical trials in the community settings. The first clinical trial of a novel therapy was conducted by the famous surgeon Ambroise Pare in 1537. In the year 1537 Mareschal de Motegni was responsible for the treatment of the battlefield wounded soldiers. James Lind is considered the first physician to conduct conducted controlled clinical trial of the modern era.[8-11]

Dr Lind (1716-94): working as a surgeon on a ship, was appalled by the high mortality of scurvy amongst the sailors. He conducted a study on scurvy. His vivid description of the trial covers the essential elements of a controlled trial. The word placebo was first appeared in medical literature in the early 1800s. He treated 13 patients suffering from rheumatism with an herbal extract which was advised instead of an established remedy. The Medical Research Council carried out a trial in 1943-1944 to investigate patulin treatment for an extract of Penicillium patulinum used for the treatment of common cold.

1946 First Randomized Curative Trial: The Randomized controlled trial of Streptomycin.

1946: The randomization was introduced in 1923. The first randomized controlled trial of streptomycin in pulmonary tuberculosis was performed in 1946 by medical research council in UK. The first International Guidance on the ethics of medical research involving subjects the Nuremberg Code was designed in 1947. The informed consent for participation in research study was described in 1900, and Nuremberg Code was highlighted the essentiality of informed consent in research process.

1948: Universal Declaration of Human Rights concern about rights of human beings being subjected to involuntary maltreatment. In the year 1964 at Helsinki, the World Medical Association framed general principles and specific guidelines on use of human subjects in medical research which is called as Helsinki Declaration.[12]

1966: The International Covenant on Civil and Political Rights was designed.

1970s: The US National Research Act of 1974 and Belmont Report of 1979 were major efforts in re shaping of human ethics. In 1996, International Conference on Harmonization published Good Clinical Practice which was universal standard for ethical conduct of clinical trials.

Evolution of Clinical Trials in India

India has been recognized for attractive country for conducting clinical trials. India has a rich heritage of

traditional medicine Ayurveda. The ayurvedic texts contain detailed observations on diseases and in-depth guidance on ayurvedic remedies. The first meeting of Governing Body of the Indian Research Fund Association was held on November 15, 1911 at the Plague Laboratory, Mumbai. The second clinical meeting was held on 1912 and a historic decision was taken to start a journal for Indian Medical research. In 1949 Indian Research Fund Association was redesignated as the Indian Council of Medical Research. In between 1918-1920 various projects on beriberi, malaria, kala azar and indigenous drugs studies was conducted. The Central Ethical Committee of ICMR on Human Research was held under the Chairmanship of Hon'ble Justice M.N. Venkatachaliah held its first meeting on September 10, 1996 to solve the ethical issues in the areas of Epidemiological Research; Clinical Evaluation of Products to be used on Humans; Organ Transplantation; Human Genetics. The committee was released ethical Guidelines for Biomedical Research on Human Participants in the year of 2000 and the revised guidelines was released in 2006. Schedule Y of Drugs and Cosmetics Act was forced in 1988 and control the conducting clinical trials in India. The revision of ethical guidelines was performed in 2005. The definitions and guidelines for clinical trial phases are broad and rational. Schedule Y rules was introduced in 2001 to monitor the clinical trials. It provides the information on responsibilities of sponsor, investigator, and design of clinical documents, clinical trial documents, informed consent form, and adverse drug reaction form for monitoring of clinical trials. The Schedule Y 2005 legalized Indian GCP guidelines were released in the year of 2001. The GCP guidelines explain the roles and responsibilities of ethics committee, investigator and sponsor and required formats for critical documents such as informed consent, patient data collection form, reporting drug related problems include adverse drug reactions, drug interactions etc. The strict adherence to SOP protocol, GCP, GMP protocol guidelines, ethics rules and regulations can prevent the harmful effects to the individual patients.[13-17]

Types of research studies in clinical trials

There are several types of scientific studies includes experiments and comparative analyses, observational studies, and surveys.

Clinical trial

Clinical trial studies are ethically designed and study participants are assigned to various modes of intervention to monitor the study subjects continuously. Random distribution method is used to select the samples to assess the study participant's response after the study participant's intervention. The clinical trial is more accurate epidemiological method for testing study hypotheses.

The main aim of clinical trials is designed to

- To find out its pharmacodynamic effects
- To establish its efficiency for a specific therapeutic indication
- To find out the profile of its adverse reactions and establish its safety.

Types of clinical trial studies

Feasibility studies are designed to check the feasibility of conducting main study. Pilot studies are small scale of the main study that help to answer the research question.

Prevention trials

Prevention trials are used to prevent the particular disease in the community.

Screening trials

These studies are performed to assess the early signs of disease before the patients suffering from disease symptoms. Screening trials can be done for the general population to identify the group of people who have a higher risk than normal risk of developing disease.[18-19]

Treatment trials

Treatment trials are done in various phases of clinical trials. The early treatment phases are aim to find out safety and side effects of a new treatments. It is used to know the reliable information about effectiveness of new treatment outcomes among patients.

Multi-arm multi-stage trials

A multi arm trial is a type of clinical trial that has several treatment groups which is known as arms as well as the standard treatment group. Multi-arm multi-stage (MAMS) trials have the same control group. This study is used to analyze the safety of new treatment pattern in clinical subjects.

Open clinical trial

It is used to indicate that a clinical trial does not have any specific methodological characteristics.

Single-blind clinical trial

In this trial the subject doesn't know which of the possible treatments he is receiving.

Double-blind clinical trial

It is a clinical trial in which the subject and observer don't know which treatment is being administered.

Triple-blind clinical trial

Clinical trial in which the participating subject, the observer-researcher do not know which treatment is being received.[20]

Crossover clinical trial

In this study each individual consecutively receives each of the treatments in the study.

Explanatory clinical trial

This study is used to identify the efficacy of the drug, The study was performed in a limited number of

participants. This study is performed to analyze the habitual practices of study patients.[21]

Unicenter clinical trial
This study was carried out by a single researcher in one study centre or sometimes various study centers.

Multicenter clinical trial
This study was carried out in two or more centers with the same protocol. Study coordinator is responsible for processing all the data and for analyzing the results.

Parallel clinical trial
In this study each group of patients receives a single treatment simultaneously.

Sequential clinical trial
The clinical trial observations are evaluated by the total number of participants is not predetermined and depends on accumulated results.[22]

Community trial
In this study the treatment groups are randomly allocated to various study populations. This study is performed to assess the impact of a community interventions provided by health care professionals in the community.

Pilot study
The approved study protocol is used to perform research study in various study locations to determine the sample size, and to identify the bias results ti improve the future initiation of prospective study in same or other locations.[23]

Descriptive study
The information collected and summarized in statistics to estimate population parameters. It is a part of statistical analysis which will describe the sample size of the study population. The collected data will be analyzed for statistical analysis.

Observational study
The study will be categorized into case-control and cross-sectional study. In this study the researcher will allocate the study subjects to several groups and observe the study subjects treatment progress continuously as per the study protocol.

Observational descriptive study
The observational study is used to monitor the occurrence of disease and disease causative factors.

Observational analytical study
It is used to identify the disease risk factors and to predict the disease progression is associated with effective therapeutic interventions are provided by the study investigator. The subtypes of these studies include cohort studies, and case-controls studies.

Experimental study
The main aim of experimental studies is to assess the efficacy of a treatment intervention. The study groups are formed randomly to compare the effectiveness of intervention between treatment and control group.[24]

Cross-sectional studies
This study consists of data which shows the different degrees of a characteristic or disease. The study observations of several factors are noted and the association between the risk factors and disease will be compared and obtained results are recorded for future evaluations.

Longitudinal studies
It will help to establish the relation between different variables and the sequence time can be established between the variables. These studies can be descriptive and analytical type. A study which analyzes to find out the relationship between cause and effect relationship is considered as analytical.[25]

Feasibility study
This study will evaluate the effectiveness of study protocol that helps to calculate the sample size for a definite study.

Crossover study
It this type of clinical study the flow of subjects from the group subjects was seen in beginning of the observation to another group.

Analytical study
In clinical trials analytical studies are designed to evaluate the relationship between risk factors or specific interventions on health. The analytical studies are controlled clinical trials, cohort studies, case-control studies or cross-sectional studies.[26]

Prospective study
It is a continuous ongoing study which is used to include the study participants at the time of study initiation.

Retrospective study
The study patient's data were collected from previous years to measure the outcomes of particular disease.

Case-control study
This study evaluates the relationship between disease and non disease patients. The percentage of exposure group and risk factors between cases and control group is recoded. The percentage of exposure group is greater than control group, The link between cause and effect is known as odds ratio.

Cohort study
The cohort study is used to analyze the subjects with same clinical features and a group of characteristics who are monitored over a stipulated period of time. The cohort study will be depends on more number of study

subjects. The study patients are subjected to receive the treatment patients are compared with subjects who don't receive therapy.

IMPACT OF CLINICAL TRIALS IN HEALTH CARE RESEARCH

Ethics in biomedical research

The rapid development of biomedical Science field and inventive applications provoke new ethical problems in the society. There is a need for protecting human values and design of ethical guidelines is required[27]. The Word Ethics originated from the greek word Ethikos that states that moral principles of governing human character.

- Bio medical research promotes the aims of research and support the values required for collaborative work.
- Most of the research works are supported by funding, conflicts of interest and research involving humans or animals that are necessary to ensure that money is utilized properly.
- The research ethics will support human social and moral values to prevent the harm to others.

General principles of biomedical research or Clinical trials

Principles of essentiality

- The human participants are considered to be essential in research.
- It is necessary for the advancement of knowledge and benefit of humans.

Principles of voluntariness, informed consent and community agreement

- The research subjects are fully apprised of the research.
- The study participant have right to abstain from participation.
- The research subjects should informed about informed consent before initiation of the study.
- The ethical principles should be observed throughout the research study.
- Before initiation of research study ethics committee must explain research study risk to study participants.

Principles of non-exploitation

The selected patients should demand remuneration for their participation in the research study.

Principles of privacy and confidentiality

The identity of patients records are kept confidential.

Principles of precaution and risk minimization

Proper care of patients is taken at all stages of trial.

Principles of maximization of the public interest

The benefit of all study participants and justice is followed to prevent the harm to study subjects.

Principles of institutional arrangements

All the study procedures required to be comply with and all institutional arrangements are required to construct in respect of the research.

Principles of compliance

All the persons are connected with research to ensure that following proper ethical norms and guidelines of ethical research.

Principles of public domain

The end of study, results is communicated to journals to publish their research work.

Principles of professional competence

The research is conducted at various study locations by qualified persons are responsible for monitoring of research protocol to meet the required outcomes.

Principles of totality of responsibility

Initiation of clinical study investigators look for funding, institutions where the research is conducted and the study groups, sponsor, benefit from the research, effect of the research is duly monitored and constantly subject to review at all stages of the research for future use.

Principles of accountability and transparency

The experiment will be conducted in honest, transparent manner after study disclosure is made by study investigator, any conflict of interest that may existed in study; and complete records of the research inclusive of data is retained for such reasonable period which is stored for future research.

Ethical committee roles

Ethical committee should ensure that the researcher has followed adequate measures for data security, confidentiality of information, and appropriate analysis of collected data. Ethical committee team contains a team of public health experts to verify the research protocol, and provide required suggestions to researchers to improve their research quality[28].

Review procedures of ethical committee in clinical trials

- Review of all research proposals
- The ethical report is forwarded to member-secretary to screen the proposals for study initiation and categorize them based on the risk involved into following divisions:
  - Exemption from review
  - Expedited review
  - Full review

Exemption from review

In this category the research proposals have minimal risk

- Research on educational practices such as instructional strategies
- Comparison of instructional techniques

Exceptions
Use of educational tests, survey or interview procedures, or observation of public behavior can identify the human participant directly or through identifiers,

- No more than minimal risk
- Revised proposal previously approved or continuing review of approved proposals where there is no additional risk
- Research involving clinical materials collected for non-research (clinical) purposes

Full Review

- Study protocol have vulnerable population and special groups
- Collection of blood samples by finger prick from healthy adults not more than 500 ml blood is drawn in an 8-week period frequency of collection is not more than 2 times per week

Decision making process
Reversing a decision or discontinuing a trial possible, if good & sufficient reasons exist. Consider any amendments to protocol, adverse events, new information likely to influence study etc. Investigator &/or patient /interested parties may be asked for inputs. Subject experts may be invited, and opinions recorded.

Records Keeping

- Research documents are filed & preserved for future reference.
- Constitution & composition of the ethical committee.
- National & International Guidelines Copies of protocols submitted to ethical committee.
- All correspondence with IEC members & investigators reg: application, decision and follow-up agenda of all IEC meetings.
- Minutes of all IEC meetings with chairperson's signature copies of decisions communicated to applicants.
- Record of notifications issued for premature termination of a study with reasons.
- Final Reports of studies with microfilms and video recordings of ethical committee.

Essential information for prospective research subjects
Before requesting an individual's consent to participate in research, the investigator must provide the individual with the following information in the language he or she is able to understand which should not only be scientifically accurate but should also be sensitive to their social and cultural context includes:

- The aims and methods of the research;
- The expected duration of the subject participation;
- The benefits that might reasonably be expected as an outcome of research to the subject
- Courses of treatment that might be as advantageous to the subject as the procedure
- Discomfort to the subject resulting from participation in the study;
- Right to prevent use of his / her biological sample at any time during research;
- The extent to which confidentiality of records could be maintained
- The identity of the research teams and contact persons with address and phone numbers

Selection of special groups as research subjects
Pregnant or nursing women: Pregnant or nursing women should in no circumstances be the subject of any research unless the research carries no more than minimal risk to the fetus or nursing infant and the object of the research is to obtain new knowledge about the foetus, pregnancy and lactation.

Children
Research involving children Before undertaking research involving children, the investigator must ensure that to obtain knowledge relevant to the health needs of children.

Permission of a parent or guardian:
The investigator must obtain the permission of a parent or guardian in accordance with local laws or established procedures. It may be assumed that children over the age of 12 or 13 years are usually capable of understanding what is necessary to give adequately informed consent, but their consent should normally be complemented by the permission of a parent or guardian, even when local law does not require such permission.

Vulnerable groups
Effort may be made to ensure that individuals or communities invited for research be selected in such a way that the burdens and benefits of the research are equally distributed. Rights and welfare of mentally challenged and mentally differently able persons who are incapable of giving informed consent or those with behavioral disorders must be protected.

ICH GCP guidelines
Ethical approval is necessary to conduct the clinical trials in health care settings. The clinical trials must consistent with good clinical practice; good manufacturing practices principles to enhance the standards of the clinical trials. Before initiation of clinical trial the study investigator check for patient's convenience, risk, benefits of the study. The safety, well being of the trial subjects are completely monitored by the study investigator. The study literatures must support the study protocol is necessary for initiation of study[29]. Clinical trials should be described in a detailed protocol to avoid the occurrence of error in trials. The medical care should be given to subjects by a qualified physician or health care team in study location. The ethical professionals must well qualified in research, trained well, to perform their duties conveniently. Informed consent should be received from study subjects prior to clinical trials. All

clinical trial information should be documented, recorded and preserved for future studies and data submitted to regulatory authorities for further approvals. The identify subjects should be protected in accordance with ethical principles. The pharmaceutical companies compete to lead the market. The FDA, European Union and Japan and representatives of the various pharmaceutical industries formed a organization in 1991 to address relevant regulatory issues related to drugs. This organization named as international conference on Harmonization of Pharmaceuticals for Human use. The ICH worked to brining regulatory requirements and frame of new standards for drug registration in individual countries. The effective implementation of ICH rules the false registered pharmaceuticals documents was removed and new drug approvals was made rapidly in worldwide. ICH standards focused on major areas includes quality, safety and efficacy. The quality of pharmaceutical products is evaluated for stability, analytical validation, impurities and safety of the drugs checked by continuous monitoring of patients in trials. The ICH guidelines will be incorporated in to domestic regulations. In the United states ICH guidelines published in the Federal Register as notices which help to pharmaceutical companies to get regulatory approval for marketing of pharmaceutical product.

Clinical pharmacist role in clinical trials

Clinical pharmacists have an essential role in clinical research and patient care research. Clinical pharmacists have an essential role in administration of medications to patients and monitoring of drug related problems during the clinical trials. Clinical pharmacists maintain the records of individual patients and counseling to study patients to monitor the proper supply of medications. Drug utilization evaluations are conducted by clinical pharmacists to provide rational use of medications in clinical practice to ensure the medication prescribing was appropriate. Clinical pharmacists perform observational research studies in clinical trials to identify the physician's attitude towards medications prescribing pattern. The results of the study will enhance the health care services in clinical trials.

CONCLUSION

Clinical trials are experimental studies conducted in animals and human volunteers to prove the effectiveness of new drug. Health care providers have an essential role advising, guiding, and the patients to enroll in clinical research. Clinical trials should follow the guidelines of ICH and standard operating procedures are implemented in the trial site to minimize the study bias during the clinical research. Successful completion of preclinical trials the investigational new drug should enter into several clinical phases such as phases I, II, III and IV. The clinical trial phases determine the pharmacokinetic, pharmacodynamic and side effects of medications data will be beneficial for monitoring post marketing surveillance of drugs[30]. The more advancement of biomedical research applications causes ethical problems in the society. The protection of human subject's ethical guidelines is required. Proper support from funding agencies in clinical trial studies will provide valuable information about the benefits of existing therapies to choose alternative therapy for prevention of disease in the health care settings.

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