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CLINICAL RESEARCH- INDIAN PERSPECTIVES: AN OVERVIEW

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ABSTRACT

Clinical study involves research using human volunteers that is intended to add to medical knowledge. In clinical trial, participants receive specific interventions according to the research plan or protocol created by the investigators. Clinical trials used in the drug development process, is described as four Phases. The present article briefly discusses the fundamentals of Clinical Research with reference to each Phase, Ethical guidelines, Consent form and its scope in India.

Keywords: Clinical trials, human ethics, Drug discovery, Consent form.

INTRODUCTION

Medical practice and clinical research are grounded in the beginnings of civilization. Egyptian medicine was dominant from approximately 2850 BC to 525 BC, showed the importance of clinical studies. There is also evidence that ancient Chinese medicine included clinical studies. Documents from early Judeo-Christian and Eastern civilizations provide examples of scientific approach to medicine and the origin of clinical research.

Although early examples of clinical research predate the Greeks, Hippocrates (460-370 BC) is considered the father of modern medicine, and he exhibited the strict discipline required of a clinical investigator. His emphasis on the art of clinical inspection, observation, and documentation established the science of medicine. Clinical research involves the study of human beings in a systematic investigation of human biology, health, or illness, designed to develop or contribute to generalizable knowledge.

Clinical research includes a set of activities meant to test a hypothesis, permit conclusions to be drawn, and thereby contribute to generalizable knowledge useful to others. Clinical Research or Clinical Trial is defined as a systematic study of pharmaceutical products on human subjects (patients or healthy volunteers) in order to discover or verify its role (in terms of efficacy and safety) as diagnostic, preventive or therapeutic agents. It also includes to a new surgical techniques or therapeutic interventions.

Phases of Clinical Research

Broadly, there are four phases, Phase-I, Phase-II, Phase-III and Phase-IV.

Phase-I is generally conducted on human healthy volunteers. The New Chemical Entity (NCE), i.e., the molecule after successful completion of *in vitro* and pre-clinical studies (animal experiments), is administered in human beings. Objective of Phase –I is to determine a safe dose of the NCE for subsequent studies and to evaluate its side effects in humans. On rare occasion, the Phase- I study is conducted on patients rather than healthy volunteers, e.g. Cancer drugs trials. The selection of volunteers is after thorough examination by detailed medical, drug, family history to overcome the jeopardize the safety study. From this study, dose is determined at which the risk of clinically significant toxicity becomes evident.

Phase-II is the state where the test drug is administered in patients with targeted diseases. The objective of Phase-II is the determination of efficacy of the NCE and to assess the toxicity that was not observed in Phase-I. In Phase-II, NCE is administered in small group of patients ie., in hundreds. This phase is called Decisive Phase as it proves the worth of NCE.

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Phase –III is the confirmatory phase of new drug development (safety and efficacy). Phase-III trial is carried out among large number of participants (ten thousand and more) in several centers and several different countries at the same time. Phase-III trial provides valuable information of drug behaviour on different ethnic groups.

After Phase-III, all the documents comprising of duly filled application form with complete experiment details of NCE are submitted to the Drug regulatory authorities, in India it is Drug Controller General (DCG), for getting the approval. On this stage, NCE is called as New Drug Application (NDA). After the approval from regulatory authorities, the drug will reach physicians for prescription.

Phase-IV is the research conducted on the marketed drug (post marketing research analysis). Objective of this phase is to obtain more data regarding the safety of the drug, finding new use of the drug, dose adjustments required for special populations like geriatric cases, pediatric cases, pregnant women and lactating mother. As obtaining information about these groups is critical, there are some countries do approval the NCA only after completion of the Phase –IV trial.

Clinical Research and Participants

Clinical Research contributes in following aspects

a. New Drug Development

b. New methods of surgery, Diagnostic and Drug administration

c. Disseminate scientific knowledge globally

All clinical trials are trying to answer following questions.

a. Is the investigational drug reasonably effective and safe?

b. If Yes, in which group of patients is the drug going to be most effective?

c. What will be the optimal dose and duration of treatment?

d. How does it compare with other available agents?

e. What and how much will be the short and long-term benefits of the agent?

f. What will be the side effects, of what severity and with what frequency do they occur?

In clinical research, healthy volunteers, patients of targeted disease, or any other group with the approval of the Principal Investigator, can participate in the research trials. The number of participants will be determined by the bio- statistician and screening and recruitment will be carried out as per the strict research study protocol which has been approved by the Ethical Committee. On whatever the case, the subject will be included in the research trial only after getting the consent from that person.

Informed Consent Form

It is defined as a procedure by which a subject voluntarily confirms his/her willingness to participate in a particular clinical trial, after having been informed of all aspects of the research that are relevant to the subject's decision to participate.

The informed consent form also should be shown to the Ethical committee for its approval.

- Disclosure and comprehension
- Form should be in mother tongue. Very simple language.
- Easy to understand even by a primary educated level person

Informed consent for special category participants like Children, mentally challenged, geriatric, coma condition should be dealt as per the guidelines. The participants have the right to know the details on various aspects of the research trial, and all these should be addressed properly. They are free to ask any question related with study: E.g.

- What is the purpose of the study?
- Who is conducting it?
- What will be my role in the study?
- How long the study is going to last?
- If I am being denied of any existing treatment and if doing so may deteriorate my condition?
- What is the best treatment available for the condition?
- How many additional visits do I need to make to the hospital?
- How many blood samples will I need to provide?
- Can I inform to my family physician about my participation in research?
- How are the results going to help me or the society?
- Will I be compensated if anything happens? How?
- Can I opt out of the study?
- Can I take other medicines?
- Whom should I approach in case I require any help or information?
- What will happen to me when the study is over?
- Etc….etc…..

All these questions should be answered by the Principal Investigator properly till the participant understand them. At the end, the participant may agree and give his consent for the participation in trial or he may take time to give consent, or he may don't want to give his consent for participation in trial. In all the cases, the Principal Investigator should not pressurize or influence the subjects by forcing them to participate in clinical trials. It is to be noted that the participant has the full right to withdraw from the trial at any stage without assigning any reason.

Remuneration to Volunteers

The remuneration to volunteers is taking following issues.

- The amount should be pre-decided by the investigators and needs to be approved by an independent ethics committee.

- To be ensured the amount is not so high that acts as inducement and subjects ignore the risk involved.
- Fixation is based on the daily wages, no. of days the subject will be on leave, other expenditure including travelling, no. of blood samples collected
- High remuneration leads to encourage money minded persons to involve in research by concealing their personal, medical, and drug history

Clinical Research Indian perspectives

- India is at an advantageous position as far as the clinical research concerned.
- Good number of well-qualified physicians, dentists, surgeons
- Qualified scientific community
- Large number of patients / volunteers
- Economical (Expensive of $1/5^{th}$ of developed nations)

Table 1. Brief of Phase I Clinical Trial

S. No.	Details	No. of Cases and Specificity
1	Generally conduced in human healthy volunteers	Different Age groups. Each group less than 10 cases. Selection of volunteer is after thorough examination of detailed medical/drug/ family history.
2	First time New Chemical Entity (NCE) is administered in human beings.	
3	Objective is to determine a safe dose of the NCE for subsequent studies and to evaluate its side effects in humans.	
4	Occasionally it is done on patients. For example. Cancer Drugs.	
5	Centre should be adequate facility to deal any kind of emergency.	
6	Dose is determined at which the risk of clinically significance toxicity becomes evident.	

Table 2. Brief of Phase –II Clinical Trial

S. No.	Details	No. of Cases and Specificity
1	Drug is administered in Patients with Target disease	Number of cases is around hundreds. Selection of case is after thorough examination of detailed medical /drug/ family history.
2	Determination of Efficacy of NCE and to assess the toxicity that was not observed in Phase I	
3	NCE is given to small number or groups of patients	
4	This phase proves the worth of NCE. So it is a milestone phase / Decisive phase.	

Table 3. Brief of Phase –III of Clinical Trial

S. No.	Details	No. of Cases and Specificity
1	Phase III is the Confirmatory Phase of new drug development (Safety and Efficacy)	Number of cases is around ten thousands and more. Selection of case is after thorough examination of detailed medical /drug/ family history with relevance to ethnic background.
2	Trial is conducted in several centers and several different countries at the same time by uniform method.	
3	Provides information of drug behaviors on different ethnic groups.	
4	Expensive Phase as the major part of the total fund in Clinical Trial is spent during this phase.	
5	Submission of application with complete details of NCE to Drug Regulatory Authorities.	
6	From this phase onwards NCE is called as New Drug Application (NDA).	
7	After the approval from the authorities, the drug will reach Physicians for prescription.	

Table 4. Brief of Phase- IV Clinical Trial

S. No.	Details	No. of Cases and Specificity
1	Research on the marketed drug is carried out as long as the drug stays in the market.	No limit regarding number of cases. Selection of case is after thorough examination of detailed medical /drug/ family history.
2	Objective of this phase is to obtain more data regarding the Safety of the drug, Finding new uses of the drug, Dose adjustments for special populations like elderly, children, pregnant and lactating women.	
3	Obtaining information about these groups is critical. So, some countries (European and Western) do approve only after Phase –IV research.	

CONCLUSION

As there are lot of scope in all the above aspects, there is no doubt that India is going to be one of the top most countries for carrying out Clinical Research Trials on various ailments for the welfare of the mankind.

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