CHAPTER 1

Introduction

'I mean, shit, we learn by climbing over the bodies of humans.'
Murray Gardner, MD, University of California HIV Researcher

After reading this chapter, you should be able to understand:

- Clinical research – what and why? ;
- Different types of clinical research; and
- Prospects and Issues associated with clinical research.

Research is a quest for knowledge aimed at the discovery and interpretation of new knowledge. Clinical research, in simplest and broadest sense, is the research conducted on human beings leading to discovery of fact or information which increases the understanding of human health and disease. Clinical Research plays an important role in our efforts to maintain or promote health and combating diseases.

What is Clinical Research?

Clinical research, a branch of health sciences, is defined as a well-planned, designed, executed, managed, and analysed study involving human beings (including materials of human origin such as tissues or behaviour) for testing the safety and efficacy of new drugs, devices or procedures in an attempt to use them for the

benefit of mankind. It covers clinical trials, research in epidemiology, physiology, pathology, health education, outcomes and mental health. The ultimate objectives of the clinical research are to develop interventions to prevent, diagnose, treat illness and promote health.

People are often confused between the term 'clinical research' and 'medical care'. In medical care, the doctor develops a care plan for the patient (often in consultation with the patient) and the individual needs to follow. On the other hand, in clinical research, doctor and the individual need to follow a study protocol specifically designed for the purpose. It cannot be changed at doctor's or patient's wish.

Similarly, there are confusions between clinical research and clinical trials. Clinical trials are one type, perhaps most important type, of clinical research. Clinical research is a bigger domain and clinical trial is a subset of clinical research.

James Lind, Scottish doctor is credited to be the first scientist who performed clinical trial in 1747. Lind divided the 12 soldiers in the ship suffering from scurvy (symptoms are loose teeth, bleeding gums, and haemorrhage) into six pairs and gave different supplement to different group along with usual diet. Each pair's diet was supplemented by cider; sulphuric acid (elixir vitriol); vinegar; sea water; a mixture of nutmeg, garlic, mustard and tamarind in barley water; two oranges and one lemon daily. The pair receiving the oranges and lemon recovered within a week and back on duty. This led to the discovery of remedy of scurvy and Dr. Lind is recognized as father of clinical trial.

The clinical research has moved much beyond the general understanding of experiments or studies on living human beings. There are reports of experiments on 'living cadaver' or brain dead patients. The world's first clinical trial on the revival of brain dead patients in Uttarakhand town was reported recently.

Why do we need Clinical Research?

Throughout the history of mankind, animal experimentations contributed immensely in our understanding of anatomy, physiology, pathology, microbiology, immunology, genetics etc. Scientists used animals in quest for knowledge. While animal experimentations are easy to perform, it is not possible to accurately predict or extrapolate the data from animals to humans. Besides, all human diseases cannot be reproduced in animals. World Health Organization's testing of typhoid vaccine in 1950s in Yugoslavia clearly demonstrates the difficulty of projection from animal experiment results to humans. Animal experiments showed that the alcohol killed and preserved vaccine was more effective than the heat killed phenol preserved vaccine. But the randomised controlled trials in humans showed the contrary results: Alcohol preserved vaccine effectiveness was found to be less than half of that of phenol preserved vaccine in preventing typhoid fever.

Hence, it is mandatory to do clinical research before a new drug or new treatment option is approved for mass use. Research in humans is our quest or aspiration to know and to advance our society. The purpose of clinical research is to find (list not exhaustive):

- New techniques for screening and diagnosing a disease;
- New drugs to introduce into market;
- New methods for surgery;
- New approach for therapy;
- New combinations of standard treatment;
- New techniques such as stem or gene therapy;
- Causes of illness.

Types of Clinical Research

The common types of clinical research include:

I. Patient oriented research – Examples are: Mechanism(s) of human disease; Therapeutic intervention; Clinical trials; Development of new techniques.

II. Epidemiological and Behavioural research – Examples are: Distribution of diseases: Factors that affect health; How people make health related decision.

III. Outcome and Health Services research – Examples are: Identifying the most effective, and most efficient intervention, treatment and services.

The clinical research may be divided into two broad types: observational research and interventional research (or, experimental research). In observational research, researcher allows the nature to take its own course. The researcher just observes the natural course of events or outcomes and reports. On the other hand, in interventional or experimental research the researcher involves in active attempt to change a disease determinant or progress of the disease. The experiments are attempted to discover something unknown, or to test a hypothesis, or principle, but one cannot be sure of outcomes.

Clinical Research Vs Clinical Trial

Clinical research is a research conducted with human subjects or materials of human origin. Clinical research is a broader term which includes both observational and experimental studies. But the clinical trials are one type of experimental clinical research. The clinical trial is a systematic study of pharmaceutical product or medical device in human subjects in order to assess their safety and / or efficacy. Clinical trials are done for various purposes and the most common types are (based on purpose):

(a) Prophylactic – Examples: testing of vaccines, contraceptives.

(b) Therapeutic – Examples: testing of new drugs, surgical techniques for efficacy.

(c) Safety trials – Examples: side effects of contraceptives.

(d) Risk factors trials – Examples: proving the aetiology of a disease by withdrawing the agent (smoking) through cessation.

The clinical trials are conducted under strict regulatory supervision.

Scope of Clinical Research

As the clinical research including clinical trial aims to find out the suitability of a new drug, new drug product, or finding a new use of old drug, there would be continuing need of such research in the society. The pharmaceutical industries continue to invest on development of new drugs and so is the situation in medical device industries. New drugs are necessary not only for new diseases but also necessary for treatment of existing diseases like drug resistant tuberculosis. After laboratory investigation in experimental animals, it is necessary to conduct the safety and efficacy testing of a new treatment/drug through clinical trials before approval for mass use. Safety and efficacy are important criteria of any drug or drug products.

Persons qualified or trained in clinical research have good opportunities for employment in clinical trial industries or contract clinical research organizations as clinical research associates (CRAs) at different levels, clinical research monitor, clinical research manager, clinical research scientists, project manager, business development manager etc. As there are no fixed designations, the title of the posts may vary from industry to industry or from organization to organization. These clinical research professionals may be involved in all or some of these activities:

- Identifying and selecting investigator for the study;
- Coordinating with ethics committee for approval of the study;
- Coordinating with regulatory authority for seeking approval of the study;
- Visiting the investigation sites to assess their suitability to conduct the study;
- Organizing the investigators meeting and making presentations;
- Initiating, monitoring and closing of investigational sites;
- Training of site staff on Good Clinical Practice or other requirements of industry;

- Ensuring timely availability and distribution of investigational products;
- Developing protocol and case report forms;
- Preserving the study reports and all communications;
- Developing reports; and
- Preparing manuscript for publications.

Issues in Clinical Research

The clinical research/clinical trial data are necessary for submission to regulatory authority seeking approval for marketing a new drug or drug product. Being human experiments, there is a necessity of preventing exploitation of research participants who may be healthy volunteers or patients. In order to protect the interest of research participants, there are strict rules and ethics guidelines which need to be adhered. The pharmaceutical industries often look at the poor countries for these studies. There are reports of violation of regulatory and ethical guidelines not only in poor countries but also in developed countries. More details of these guidelines and their violations are described in other chapters. There are issues even with quality of data generated during clinical research.

Many of drug research are either conducted or supported by pharmaceutical industries. Many of the clinical trials are reported to be with flawed design, flaw in data analysis, and misleading results. The results are cooked into conclusion as useful for boosting sales. The industries are often accused that they can make exploitation appear a noble purpose.

Irrespective of whether it is industry sponsored or non-industry based, the clinical research must follow the same standards. The research must be scientifically sound, follow basic ethical principles and ensures data of high quality.

In addition to misleading results, it is also alleged that many of the clinical research findings are not useful. The key features of useful research are outlined in the table:

Feature	Questions to Ask
Problem base	Is there a health problem that is big /important enough to fix?
Context placement	Has prior evidence been systematically assessed to inform (the need for) new studies?

Table Contd….

Feature	Questions to Ask
Information gain	Is the proposed study large and long enough to be sufficiently informative?
Pragmatism	Does the research reflect real life? If it deviates, does this matter?
Patient centeredness	Does the research reflect top patient priorities?
Value for money	Is the research worth the money?
Feasibility	Can this research be done?
Transparency	Are methods, data, and analyses verifiable and unbiased?
Adopted from: Ioannidis JPA (2016) Why Most Clinical Research Is Not Useful. PLoS Med 13(6):e1002049. doi:10.1371/journal.pmed.1002049	

Though in broadest sense, the clinical research indicates that the research conducted on humans without involvement of any drug administration is also a type of clinical research (epidemiological research), the most important types of clinical research includes clinical trial and bioequivalence testing. The present text focuses on various aspects of clinical trial and bioequivalence. The Clinical Trials and Bioavailability & Bioequivalence fall under the domain of New Drugs and Clinical Trials Rules, 2019.

Key Points to Remember

- Clinical research is a well-planned, designed, executed, managed, and analysed study involving human beings (including materials of human origin such as tissues or behaviour) for testing the safety and efficacy of new drugs, devices or procedures in an attempt to use them for the benefit of mankind.
- Clinical trial is a type of clinical research aims to testing safety and efficacy of new drug/product/device.
- Clinical research needs to be conducted following regulatory and ethical standards to prevent exploitation of study participants and generate data of high quality.

James Lind was the scientist who had conducted the first clinical trial and is known as the father of clinical research.