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Understanding the Basics of Research as a Beginner: A Highlighter

Ravishankar M.V,[1] Vidya C.S. [2]

[1]Assistant Professor, [2]Associate Professor Dept. of Anatomy JSS Medical College JSS Academy of Higher Education & Research, Mysuru

Abstract

Research has grown beyond leaps and bounds; scientific progress solely depends on inquisitiveness and tireless coordination of teamwork. The word research is so attractive for a beginner, the student fraternity is overwhelmed about this process. Irrespective of any field, now the research is becoming an indispensable part of the educational system. This article is intended to create basic awareness about research and its components, especially for the research-oriented students in the field of medical, paramedical, allied health sciences, etc.

Key words: *Research, bioethics, clinical trials, good clinical practice*

Introduction

Biomedical research is based on fundamental biological scientific principles, which will focus on personal healthcare and public health. Basic research is also called as bench side research; it deals with in-vitro and in vivo experimental models involving the organisms or animals to obtain a valid outcome to further try on the humans. When the basic research results are tried on clinical patients it is called translational research, which is solely intended to trial the results of basic research from bench side to bedside, clinically by using patients virtually[1].

Research is practiced by humans since the time of evolution on earth. In history, the ancient practice of folklore medicine stands as the best example for the oldest model for clinical research; with the time it has gradually evolved through trial and error method. India is at the forefront of contributing to the field of clinical research; medical science like Ayurveda, Siddha, Unani; their medical literature has mentioned the use of medications for several human ailments for thousands of years. Based on its principles, Ayurveda has mentioned therapeutic interventions, and a number of herbs and mineral formulations applied directly to the human subjects with the sole purpose of alleviating human sufferings[2,3].

Corresponding author:
Dr. Vidya C.S
Associate Professor, Department of Anatomy
JSS Medical College, JSS Academy of Higher Education & Research, Mysuru-570015
Mob: 9449679386, E-mail: vidyacs@jssuni.edu.in

Classification of type of study:

Basic research: the basic medical research deals with understanding the functional, cellular or molecular mechanisms in primates through in vivo or invitro studies.

Preclinical research: preclinical research deals with the study on humans, which further supports the clinical trials on patients.

Clinical research: it is conducted on patients in the hospital or on the selected population; it is supervised by physicians.

What is the research question...?

It is the main inquiry of the issue which needs to be addressed through research. The research question should be clear, targeted and simple.

What is a pilot study...?

It is the study performed on a small scale by using a minimum number of participants/subjects.

This study gives every opportunity to the researcher/ investigator to understand all aspects of the main study including its feasibility, sample size, time duration, troubleshooters, etc.

What are the study parameters...?

Parameters are study exponents in the research; which are later subjected to analysis.

Bioethics

Bioethics deals with the study of ethical dimensions of medicine and biological sciences.

Important principles of bioethics are including Autonomy (respect to self-governing), Beneficence (best interest of the subject), Non-maleficence (causing no harm) and Justice (fair treatment)4

Basic research in non-human primates:

Research on non-human primates is a prerequisite for conducting trials on subsequent levels. Animal experiments mean, the use of animals preferably mammals in the experiments for education and research. The basic experiments use nonhuman primates like rats, mice, rabbits, hamsters, guinea pig, monkey, chimpanzee, dog. It can also be done by using fruit flies, cell lines, fish, etc. There are millions of animals that will be sacrificed worldwide for the sake of research every year. Experiments performed by using both vertebrates and non-vertebrates, but using the vertebrates will be taken into account as they are under more strict ethical vigilance. For research, all these animals should be procured from the authorized breeders who are registered under CPCSEA (committee for control and supervision of experiments on the animal) guidelines or from the recognized higher research centres.

Importance of animal testing in biomedical research

In the field of biomedical research, the use of the animal model experiments stands as "**Hall Mark**" of an interventional research study. The great scientists like Aristotle, Erasistratus Galen, etc. have tried their initial experiments on the animals for scientific purposes[5]. Age back, the use of animals got much attention, particularly to test the surgical procedures or use of drugs or devises before applying them clinically to humans. In spite of heavy criticism by the public and the animal protection activists there is a rise in several basic research experiments on animals; because in history, we have learned about the adverse effects of drugs that were used directly on patients. Causing harm to the animals can't justify the human benefit. But still, animal-based research outcome retains its importance in several aspects including, toxicological studies, where the animal experiment model stands as an inevitable tool in supporting the increasing hierarchy of evidence.

In the present situation to justify the rationality and inevitability of the use of animals in the experiments we need to follow principles of 4R.

Replacement: Use of alternate to animal model Ex: in silico i.e. use of computer modeling, in vitro cell line studies, etc.

Reduction: Method which minimizes the number of animals in experiments

Refinement: It deals with the reduced invasiveness, by adopting improved, non-invasive, non-painful procedures by using the most appropriate methods[6].

Rehabilitation: As a 4th component, the rehabilitation of animals will be done after its justified usage[6].

Toxicity study: it is a branch of science deals with the toxins and poisons and their effect and treatment. As per US food and drug administration (FDA), for the development of a new drug entity, it is essential to conduct toxicity tests in the biological subjects[7].

Trials before regulations

In the olden days, before formulating guidelines for clinical research activities, any individual or group of people would be a part of the research event; it was tried on the helpless community like war prisoners or people who convicted under crime, children, patients, aged people, etc. The direct use of drugs like thalidomide and Elixir Sulfanilamide on humans has resulted in the death of the study participants. Based on such consequences of unethical trials on humans, the present era has formulated a code that is mainly focused on obtaining voluntary consent. **By considering the above discrimination in the clinical research, a judgment formulated with a code known as "Nuremberg code" which has** streamlined the research at all levels with the sole intention to protect the safety and dignity of the participants to achieve more precise and valid outcome[8].

History of Clinical trials

The credit of clinical research goes to a Scottish physician Dr. James Lind, M.D. (1716–1794) has treated the disorder called scurvy in sailors, where patients were presented with the sign of bleeding through their gums. He has noticed that the administration of the orange and lemon has shown drastic improvement in their condition[9].

Regulations of clinical trials:

Good Clinical Practice (GCP): It is an international ethical and scientific standard protocol for conducting biomedical and behavioral research involving human participants; which protects participants' safety, rights and confidentiality at all levels[10].

International Conference on Harmonization (ICH): It is an international council that bringing together the regulatory authorities and pharmaceutical industry to discuss the technical aspects of drug registration. ICH's regulations are intended to achieve greater harmony worldwide to ensure safety, effectiveness, and quality of medicines; which are developed and registered in a hassle-free manner[11].

Institutional Ethics Committee (IEC): It plays a role in appointing members; it will review the protocol and informed consent forms (ICF), and periodic progress of the study[12]

World medical declaration of Helsinki: It is developed by the World Medical Association (WMA) in the year 1964; it is including ethical guidance for physicians and all other participants in the research team involving in clinical trials on human subjects. This rule binds all the research participants to the applicable law under its declaration[13]

Role of the investigator: all trial investigations are conducted by qualified and trained persons who are personally supervising the work.

Sponsor for trials:

The sponsor for a clinical trial may include an individual, an industry, an institution, etc. which takes the responsibility of initiation, management, financing, and auditing. They are also taking the responsibility of subjecting the study participants under sufficient insurance coverage, and compensating the subjects in any untoward incidence or reactions[14].

Role of statistics in research

Since the time of conception of the research protocol, the statistics play an important role to format different components of research like study design, conduct, sample size, data analysis, reporting, etc. they are essential to derive a valid and precise conclusion.

What is the placebo effect...?

Placebo is an inert substance without any therapeutic value; it is used to compare with standard control groups. The psychosomatic profile is an important factor to be considered in assessing the placebo drug response. The placebo effect can be better appreciated in the alleviation of symptoms of the pain rather than any other condition[15].

Clinical trials

Clinical trials are research study on human subjects, which is intended to evaluate the effect of biomedical interventions like vaccines, drugs, treatments, devices, new ways of using known drugs or to study drug interactions, etc. The study may also include the evaluation of behavioral interventions[16].

The ultimate goal of CT is to ascertain the drug safety of the subject, risk and benefit ratio before its final approval for marketing. There are many factors involved in research, out of which some are can be controlled, and some others are beyond one's control. Randomization means being nonselective to any application or intervention. Randomization in clinical trials is considered as the basis for the "Evidence-based Medicine"[17].

Blind experiments

Bias is the main concern of the clinical trials where blinding becomes essential to reduce the bias and increase the validity of the outcome. **Blinding is a process where one or the other participants in the study were deliberately kept unaware of intervention. Blinding is an important factor to ensure objectivity in the clinical trial by avoiding or preventing the conscious and unconscious bias in the study[18].**

Types of blind trials:

Open clinical trials: it is the trial where all the level of study participants in the research group will be knowing the intervention.

Single-blind study: where the subject alone in the research study is unaware of intervention.

Double-blind study: where the subject, as well as the researcher both, are unaware of the intervention

Triple-blind study: where the subject, researcher, and analyser are unaware of intervention.

At the end of the study result analysis, all masked or blinded interventions will be disclosed.

Protection of subjects

The protection of the clinical trial participants at all levels is an important issue. Concerned authorities should take care of all necessary precautions to address personal, social and legal issues during and after completion of trials. Any relevant issues should be addressed, and it should be properly compensated for the loss. It is essential to ensure proper compensation for all the study participants who are involved in the clinical trials.

Importance of Informed Consent (IC)

Clinical trial participants are strictly volunteer in its true sense without coercing them for any benefit.

Informed consent is an important prerequisite before allocating any human subject to the clinical trials. Privacy and confidentially of IC should be maintained in all the circumstances. It is very much essential to know whether the subject is a literate or illiterate, or whether he is fit to give valid consent. The investigator should explain and clarify all the doubts of participants regarding the research protocol before taking consent[19].

Types of clinical trials

Screening trial: screening for the possibility of occurrence of diseases in a healthy population

Prevention trail: it deals with the prevention of disease by using supplements, vaccines, devices, lifestyle modifications, etc.

Diagnostic trail: it deals with the accuracy of the disease

Treatment trail: it deals with the effectiveness of treatment in diseased

Conventionally the CT is having the following phases:

Phase 0: It is an Exploratory Investigational New Drug (IND) Study. It will be conducted first on humans; it is also known as human micro-dosing studies by using the sub-therapeutic dose. It is conducted by using 10-15 numbers of limited volunteer healthy human subjects to understand the pharmacokinetics, pharmacodynamic activity, and safety of a new drug or a molecule.

Phase I or Clinical pharmacology trial: It is also called "First in Man", done in small groups with 20-100 in number in healthy volunteers. It is to assess safety through pharmacovigilance and the details of the pharmacokinetic and pharmacodynamic effects of a drug. Dose escalation trial can give an idea about the appropriate maximum tolerable dose which can be used under subsequent trials.

Phase II or Exploratory Trial; the third phase of the clinical trial can be done in 200-300 number of larger healthy human volunteers. It is done in Phase I A is to assess the clinical efficacy or biological activity, and Phase II B is to assess and match the optimum dose, benefit with minimum side effects

Phase III trial or Confirmatory trial: It is a randomized control multicentric trials in a large number of volunteer patients in a group of 300-3000 or more. Such trials are more expensive, time-consuming and difficult to handle, especially while dealing with chronic disease conditions or disease with a long latency/ incubation period.

Phase IV or Post-marketing surveillance: Called post-marketing surveillance trial. It involves a pharmacovigilance study after receiving permission to market an approved drug. If the drug/treatment is found satisfactory in three phases, then it will be approved under the country's national regulatory authority for its use in the general population. Phase IV trials are invariably always under the research radar. [20,21]

Multicentric clinical trials

It includes a large number of participants from different parts of the world, including a wide range of populations; which will compare the results of different centers.

Accessibility of clinical trial reports

Accessing clinical trial data or information is an important prerequisite to tackle the challenges before considering them under policymaking. Archiving the

clinical trial documents is a must, which helps to analyze the data retrospectively in a systematic manner. Now online updates are available on the registered websites which are developed at the national institute of health under the national library of medicine. CT information is always accessible to any common man, through website clinicaltrials.gov and also through Cochrane Library, it is a collection of databases in medicine and other healthcare specialities22,23. The ultimate goal of accessing the clinical trial results is to introduce newer government policies and regulations to provide improvised health care facilities for the benefit of the population at large.

Conclusion

For a beginner, the present review will highlight the components of basic research, preclinical and clinical research. It has created basic awareness about the ethical factors involved in the research at different levels.

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