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AN OVERVIEW OF RESEARCH STUDY DESIGNS

Ramalingam Sitharthan and Deepthi Gilla

Principal & Professor, Department of Practice of Medicine, National Homoeopathy Research Institute in Mental Health, Kottayam, Kerala

Assistant Professor, Department of Psychiatry, National Homoeopathy Research Institute in Mental Health (NHRIMH), Kottayam

Corresponding Author's Email ID: sitharthan.r@gmail.com

ABSTRACT

The choice of the study design is a major determinant of scientific quality and clinical value of a research study. To select an appropriate study design is a perplex task for novice as well as veterans in research. AYUSH systems of medicines have evidence database showing the effectiveness in a wide range of clinical conditions, yet improving the quality of trials by well- designed studies is indispensable to demonstrate widespread utility on more scientific grounds. This article describes the structured classification of research designs done on the basis of a selective literature search concerning medical research. The study design and type that can best answer the particular research question at hand must be determined not only on a scientific basis, but also in view of the available resources, ethical issues and practical feasibility of study.

Keywords: Study design, Clinical trial phases, Observational studies, Experimental studies. Randomized Controlled Trial (RCT).

INTRODUCTION

Research study design is a framework, or the set of methods and procedures used to collect and analyze data on variables specified in a particular research problem. There are several types of research study designs, each with its inherent strengths and flaws. [1] Clinical trial design is an important aspect of interventional trials that serves to optimize ergonomise and economize the clinical trial conduct. [2] A study design is in fact, the researcher's general plan to acquire the answer (s) to the hypothesis being tested.

Selection of an appropriate study design is an onerous task for beginners in research. Post graduate students find perplexity in selection of study design for their dissertation work to be done as a part of their curriculum. Evidence of clinical trials in Homoeopathy is positive but, in analysis of most studies, concerns about study quality are expressed. Homoeopathy is the latest and developing system of medicine, which has witnessed proven efficacy and burgeoning evidence base in the new millennium. Yet, controversies and skepticism revolve around the system making enhancement of the quality of studies indispensable to demonstrate authenticity of its widespread utility. So, researchers of homoeopathy should get themselves well acquainted with the concepts of designing research and methodology of conducting clinical trials as trial designs are being revisited in both conventional system and alternative systems like Homoeopathy. [4]

The aim of clinical research to design a study, which would be able to derive a valid and meaningful scientific conclusion using appropriate statistical methods that can be translated to the "real world" setting. [5] Before choosing a study design, one must establish aims and objectives of the study, and choose an appropriate target population that is most representative of the population being studied. The conclusions derived from a research study can either improve health care or result in inadvertent harm to patients. Hence, this requires a well-designed clinical research study that rests on a strong foundation of a detailed methodology and is governed by ethical principles. [6]

TYPES OF MEDICAL RESEARCH

The type of research that one wants to conduct is a primary determinant for choice of the study design. Medical research, also known as experimental medicine, encompasses a wide array of research, extending from "basic research", involving fundamental scientific principles that may apply to a preclinical understanding to clinical research, which involves studies of people who may be subjects in clinical trials.

Medical research is classified into primary and secondary research. Three main areas in **Primary research** are basic medical research, clinical research and epidemiological research. Clinical/experimental studies are performed in Primary research, whereas **Secondary research** consolidates available studies as reviews, systematic reviews and meta-analyses. [7]

In the view point of timing of the research in relation to the development of the outcome, research studies are of two basic types: Retrospective and Prospective. In **Retrospective studies**, the outcome of interest has already occurred (or not occurred – e.g., in controls) in each individual by the time she/he is enrolled, and the data are collected either from records or by asking participants to recall exposures. There is no follow-up of participants. By contrast, in **Prospective studies**, the outcome (and sometimes even the exposure or intervention) has not occurred when the study starts and participants are followed up over a period of time to determine the occurrence of outcomes. [8]

Study designs are different for qualitative and quantitative research. The quantitative research study designs are broadly classified either as descriptive versus analytical study designs or as observational versus interventional. **Descriptive study designs** are useful for simply describing the desired characteristics of the sample that is being studied, e.g., an abnormal presentation of a disease in a case report or a case series which includes a collection of cases with the same disease/condition. A descriptive study may also try to generalize the findings from a representative sample to a larger target population as in a cross-sectional survey. [9] As compared to descriptive studies which merely describe one or more variables in a sample (or occasionally population), **analytical studies** attempt to quantify a relationship or association between two variables – an exposure and an outcome. [10]

From an epidemiological standpoint, there are two major types of clinical study designs, Observational and Experimental. **Observational studies** also called epidemiologic study designs, are often retrospective and are used to assess potential causation in exposure-outcome relationships and therefore influence preventive methods. They are hypothesis-generating studies, and they can be further divided into Descriptive and Inferential. *Descriptive or Non-analytical observational studies* provide a description of the exposure and/or the outcome, and *Inferential or analytical observational studies* provide a measurement of the association between the exposure and the outcome. Observational study designs include ecological designs, cross sectional, case-control, case-crossover, retrospective and prospective cohorts. **Experimental studies**, on the other hand, are hypothesis testing studies. It involves an intervention that tests the association between the exposure and outcome, hence called as ***Interventional studies***. They are often prospective and are specifically tailored to evaluate direct impacts of treatment or preventive measures on disease. [1] [10] A kind of experimental study include **Field trials**, also known as preventive or prophylactic trials, in which the subjects without the disease are placed in different preventive intervention groups. One of the hypothetical examples for a field trial would be to randomly assign to groups of a healthy population and to provide an intervention to a group such as AYUSH medications and following through to measure certain outcomes like morbidity in Covid-19. [11]

According to WHO, **Clinical trials** are a type of research that studies new tests and treatments and evaluates their effects on human health outcomes. People volunteer to take part in clinical trials to test medical interventions including drugs, cells and other biological products, surgical procedures, radiological procedures, devices, behavioral treatments and preventive care.[2] Clinical trials are carefully designed, reviewed and completed, and need to be approved by competent authority before they can start. For example, Clinical Trials Registry – India (CTRI) established by Indian Council of Medical Research on 20 July 2007 is the government of India's official clinical trial registry platform. The appropriate choice in study design is essential for the successful execution of any clinical trial. [10] Studies on drugs/devices are subject to legal and ethical requirements including the Drug Controller General India (DCGI) directives. They require the approval of DCGI recognized Ethics Committee and must be performed in accordance with the rules of 'Good Clinical Practice'. [7]

The purpose of the clinical trial is assessment of efficacy, safety, or risk benefit ratio. Goal may be superiority, non-inferiority, or equivalence. No trial design is perfect, and no design provides optimum answer to all research questions, the researchers must be guided to study the most optimum design among a clutch of options and they must incorporate biostatistician in initial trial design and post-trial analysis. [2] The type of study design used to answer a particular research question is determined by the nature of question, the goal of research, and the availability of resources. Since the design of a study can affect the validity of its results, it is important to understand the different types of study designs and their strengths and limitations. [1]

The appropriate study design for answering the research question in hand also depends on the stage/ phase of the clinical trial. Clinical trials are classified into phases based on the objectives of the trial. There are different stages of drug development and approval by Food and Drug Administration (FDA)**.**

1. **Phase '0' or Pre-clinical investigations** include animal studies and evaluation of drug production and purity. Animal studies explore: 1) *Drug's safety* in doses equivalent to approximated human exposures, 2) *Pharmacodynamics* (i.e, mechanisms of action, and the relationship between drug levels and clinical response), and 3) *Pharmacokinetics* (ie, drug absorption, distribution, metabolism, excretion, and potential drug–drug interactions). [12]
2. **Phase I Trials -** These are the first studies of an intervention conducted in humans. Phase I trials have small sample sizes (e.g., <20), may enroll healthy human participants, and are used to investigate pharmacokinetics, pharmacodynamics, and toxicity.
3. **Phase II Trials-** These are typically conducted to investigate a dose response relationship, identify an optimal dose, and to investigate safety issues. Phase II trials are done in larger groups of patients compared to Phase I trials.
4. **Phase III Trials -** These are generally large trials (i.e., many study participants) designed to "confirm" efficacy of an intervention. They are sometimes called "confirmatory trials" or "registration trials" in the context of pharmaceutical development.
5. **Phase IV Trials-** These trials are conducted after registration of an intervention. They are generally very large and are typically conducted by pharmaceutical

companies for marketing purposes and to gain broader experience with the intervention. [11]

Phase III trials often require large sample sizes, leading to high costs and delays in clinical decision-making. Group sequential designs can improve trial efficiency by allowing for early stopping for efficacy and/or futility and thus may decrease the sample size, trial duration and associated costs. [12] Bayesian adaptive designs can improve the efficiency of trials, and lead to trials that can produce high quality evidence more quickly, with fewer patients and lower costs than traditional methods. [13]

INTERVENTIONAL STUDY DESIGNS

Interventional study designs, also called Experimental study designs, are those where the researcher intervenes at some point throughout the study. There are different kinds of interventional study design like pre-post study design, non-randomized controlled trials, quasi-experiments, randomized controlled trial etc.

A pre-post study measures the occurrence of an outcome before and again after a particular intervention is implemented.

Non-randomized trials are interventional study designs that compare a group where an intervention was performed with a group where there was no intervention. These are convenient study designs that are most often performed prospectively and can suggest possible relationships between the intervention and the outcome. However, these study designs are often subject to many types of bias and error and are not considered a strong study design. [14]

Quasi-experimental studies evaluate the association between an intervention and an outcome using experiments in which the intervention is not randomly assigned. Quasi-experimental studies are often used to evaluate rapid responses to outbreaks or other patient safety problems requiring prompt non-randomized interventions. Quasi-experimental studies can be categorized into three major types: interrupted time series designs, designs with control groups, and designs without control groups. Quasi-experimental studies are appropriate when randomization is deemed unethical. [15]

Uncontrolled trial design incorporates no control arm. This design is usually utilized to determine pharmacokinetic properties of a new drug (Phase 1 trials). Uncontrolled trials are known to produce greater mean effect estimates than a

controlled trial, thereby inflating the expectations from the intervention. As there is a threat of inherent bias, results are considered less valid than RCT.

Randomized Control Trial (RCT) design, In RCTs, trial participants are randomly assigned to either treatment or control arms. The process of randomly assigning a trial participant to treatment or control arms is called "Randomization". Different tools can be used to randomize (closed envelopes, computer generated sequences, random numbers). There are two components to randomization: the generation of a random sequence and the implementation of that random sequence, ideally in a way that keeps participants unaware of the sequence (allocation concealment). Randomization removes potential for systematic error or bias. [2]

Randomized controlled trials (RCTs) are considered as "Gold standard" for research. Most often the aim of an RCT is to show that a new therapy is superior to an established therapy or placebo, i.e. they are planned and performed as **Superiority trials**. Sometimes the aim of an RCT is just to show that a new therapy is not superior but equivalent to or not inferior to an established therapy, i.e. they are planned and performed as **Equivalence trials** or **Non-inferiority trials**. [16] RCTs can have many modifications like parallel group trial design, cross over design, factorial design, randomized withdrawal design etc.

a. ***Parallel group trial design*** is the most commonly used study design. In this design, subjects are randomized to one or more study arms and each study arm will be allocated a different intervention. After randomization each participant will stay in their assigned treatment arm for the duration of the study. The randomized patients in parallel groups should not inadvertently contaminate the other group by unplanned co-interventions or cross-overs. [2]

b. ***Cross over trial*** is a design in which participants receive two or more sequential interventions in a random order in separate treatment periods, often separated by a washout period to avoid a 'carry-over' intervention effect from one treatment period into the next. Each person serves as his/her own control results in balancing the covariates in treatment and control arms. The ethical limitations of a placebo control are partially overcome by a cross over design. Another advantage is requirement of a smaller sample size. There are two requirements for conducting cross over design. They are (1) The disease must be chronic, stable, and incurable and characteristics

must not vary for the duration of the two study periods and the interim wash out period and (2) the effect of each drug must not be irreversible. There are variations of crossover designs like (i) Switch back design (ABA vs BAB arms) (ii) N of 1 design – N of 1 trials or "single-subject", used to evaluate all interventions in a single patient. Data from many N-of 1 subject can be even combined to derive population effect sizes by meta-analysis or Bayesian methods. [17]

c. ***Factorial Design*** is suited for the study of two or more interventions in various combinations in one study setting and helps in the study of interactive effects resulting from combination of interventions. Factorial designs are highly efficient (permitting evaluation of multiple intervention components with good statistical power) and present the opportunity to detect interactions amongst intervention components. In a *2 × 2 factorial design* with placebo, patients are randomized into four groups: (i) to treatment A plus placebo; (ii) treatment B plus placebo; (iii) both treatments A and B; or (iv) neither of them, placebo only. Outcomes are analyzed using two-way analysis of variance (ANOVA) comparing all patients who receive treatment A (groups 1 and 3) with those not treated with A (groups 2 and 4), and all patients who receive treatment B (groups 2 and 3) with those not treated with B (groups 1 and 4). A prerequisite requirement is that there is no interaction between treatments A and B. If interaction exits, then loss of power is possible in case of separate analyses of the four different combinations. If an interaction is anticipated, then that has to be factored into the sample size in addition to estimated sample size. Incomplete factorial designs are used when it is deemed unethical to exercise a non-intervention option and here the placebo only arm is eliminated. [2]

d. ***Randomized withdrawal design [Enrichment enrolment randomized withdrawal (EERW)]***

In this design, after an initial open label period (enrichment period) during which all subjects are assigned to receive intervention, the non-responders are dropped from the trial and the responders (the enriched population) are randomized to receive intervention or placebo in the second phase of the trial. Thereby only responders are carried forward and randomized. Study analysis is conducted using only data from the withdrawal phase and outcome is usually relapsing of symptoms. The advantage is reduction in the time on placebo since only responders are randomized to placebo

thereby giving an ethical advantage. There are few disadvantages like missing data due to withdrawals and carry over effects from enrichment phase etc. [19]

There are different **Control arm options** in controlled trials. Choosing a right control at the right dose and right frequency is important for the success of a trial. The different types of controls which can be used in a research study such as *Placebo concurrent control*, "No treatment" concurrent control, Active treatment concurrent control, Dose-comparison concurrent control, Historical control etc.

Placebo is a form of inert substance, or an intervention designed to simulate medical therapy, without specificity for the condition being treated. The placebo must share the same appearance, frequency, and formulation as the active drug. Placebo control helps to discriminate outcomes due to intervention (new product) from outcomes due to other factors. This design is used to demonstrate superiority or equivalence. This design must be adopted only when no effective treatment exits, and it will be deemed unethical to use a placebo control if an effective standard of care exits. There are different **Variants of placebo-controlled trial designs** such as *Add-on design*, *Early escape design*, *Unbalanced assignment of patients to placebo and test treatment*, *Double-dummy design*, *Placebo run-in design* etc. [19]

OTHER STUDY DESIGNS:

There are other research study designs one should get acquainted with to identify the befitting ones for the study at hand. In a Group randomized trial (GRT) groups, rather than individuals, are randomized to each treatment arm with randomization potentially stratified by factors believed to affect the outcome variable. However, community leaders may object to randomization as some groups may be denied a potentially beneficial intervention. Under a Regression discontinuity design (RDD), individuals may be assigned to treatment based on the levels of a pretest measure, thereby allowing those most in need of the treatment to receive it. In the RDD, assignment of individual subjects or groups to treatment is determined by a quantitative score measured at baseline. A cut-point for the assignment score is established and those scoring on one-side of the cut-point are assigned to intervention and the others to control, hence, the general term "cut-off design" is used to refer to the RDD with and without randomization. [20]

There are other new study designs that are rarely used in special situations arising in research. These are designs like Adaptive randomization methods (play the winner, drop the loser designs), Internal pilot design, Matched pairs design, Delayed start design (DS), Randomized placebo phased design (RPPD), Stepped-wedge design (SWD), Three staged design (3S) etc. [21] ***The reader is encouraged to refer to these kinds of study designs as explaining all the types of study designs is not possible in a single article.***

CONCLUSION/ IMPLICATIONS

1. The study design that can best answer the particular research question in AYUSH Systems must be determined not only on the basis of scientific appropriateness and available financial resources but also on practical feasibility, Ethics, logistic concerns and philosophy of the system.
2. Updating knowledge about latest trends in research designing and methodology helps one to select the viable and befitting ones, so that the quality of individual trials and ultimately the authenticity of the systems can be demonstrated on more scientific grounds.
3. To offer patients the most effective and safest therapies possible, it is important to understand the key concepts involved in designing clinical trials. Through rigorous practices applied to AYUSH drug development and approval, physicians and patients can maintain confidence in the therapies prescribed.

Take a method and try it. If it fails, admit it frankly, and try another.

But by all means, try something. -Franklin D. Roosevelt

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