EXPERIMENTAL STUDIES IN MEDICAL RESEARCH

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ABSTRACT

Research can be defined as the systematic collection, description, analysis and interpretation of data to answer certain question or solve a problem. Health research can also be defined as the process of research that can be used to improve the health of individuals or groups. The most commonly encountered experiment in health science research, and the research strategy by which evidence of effectiveness is measured, is the randomized controlled double-blind clinical trial, commonly known as an RCT.

KEYWORDS: Health research, Experimental studies, RCT, Clinical trials.

INTRODUCTION

An experiment is the best epidemiological study design to prove causation. It can be viewed as the final or definitive steps in the research process, a mechanism for confirming and rejecting the validity of ideas, assumptions, postulates and hypothesis about the behavior of objects or effects up on them which results from interventions under defined set of conditions, in observational strategies the investigator is just an observer only reporting the events in a defined population or sample under investigation, where as in experimental designs, the investigator is the experimenter and the master who is having the total control over the study. He may be able to manipulate the selection of participants, the intervention, outcome measurements, and the conditions of the experiment, therefore all experiments involve manipulation of one or more independent variable, and observing the effect on some outcome (dependent variable). Experiments can be done in the field or in a laboratory; they
may involve human or animal subjects. There are three types of experiments; True experiments, Quasi experiments and Single subject experiments.\[1\]

1. True Experiments

True experiments are characterized by prospective assignment of subjects in to one or more study groups and control groups by randomization it is a highly formal experiments. The single most examples for a true experiment is Randomized controlled clinical trial.

2. Quasi Experiments

Is one that looks a bit like an experimental design but lacks the key ingredient – random assignment. The random assignment to various groups is not employed because of either ethical or practical reasons. Quasi-experiments are sometimes called natural experiments because membership in the treatment level is determined by conditions beyond the control of the experimenter.\[1\] (Example, comparing achievements level of first-born children with that of later-born children).

3. Single-subject experiments

Instead of comparing behavior or performance of groups of people at a single point in time, a single subject experiment involves a single case studies over a longer period of time in this method, one individual or situation is exposed to the varying levels of the independent variable.

Randomized Controlled Trials

A randomized controlled trial is an epidemiological experiment designed to study the effects of a particular intervention, usually a treatment for a specific disease (clinical trial). Subjects in the study population are randomly allocated to intervention and control groups, and the results are assessed by comparing outcomes.

To ensure hat the groups being compared are equivalent, patients are allocated to them randomly, that is by chance. If the initial selection and randomization is done properly, the control and treatment groups will be comparable at the start of the investigation; any differences between groups are chance occurrences unaffected by the conscious or unconscious biases of the investigators.
Randomized controlled trials are the most rigorous way of determining whether a cause-effect relation exists between treatment and outcome and for assessing the cost effectiveness of a treatment.

The most commonly encountered experiment in health science research, and the research strategy by which evidence of effectiveness is measured, is the randomized, controlled, double-blind clinical trial, commonly known as an RCT.

In analytical study, no randomization, because a differentiation into diseased and non-diseased (exposed or non-exposed); groups has already taken place. The only option left to ensure comparability in analytical study is by matching.[3]

**Historical perspective of Randomized controlled Trails.**

I raised myself very early to visit them when beyond my hope I found those to whom I had applied the digestive medicament, feeling but little pain, their wounds neither swollen nor inflamed, and having slept through the night. The others to whom I had applied the boiling oil were feverish with much pain and swelling about their wounds. Then I determined never again to burn thus so cruelly the poor wounded by arquebuses.

Ambroise Pare (1510 -1590) Ambrose praise as French Surgoen. He is considered as one of the fathers of surgery and modern forensic pathology.

Studies that were conducted as comparison between two groups were conducted from the ancient times. The evolution of the modern methodology of randomized controlled trials was as procedure which took a long time and still it is undergoing changes.

**Some important dates in the history of Randomized Controlled Trials are as follows.**

- 1947 Lind's Scurvy experiment
- 1800 Waterhouse's smallpox experiments
- 1863 Gull's use of placebo Treatment
- 1923 Fisher's I application of randomization
- 1931 1\textsuperscript{st} use of randomization (and blindness)in a clinical trial
- 1946 Nuremberg Code for Human Experimentation
- 1962 Hill AB Statistical Methods of Clinical and Preventive Medicine
- 1979 Society for Clinical Trials
Randomized controlled trials when appropriately designed, conducted and reported represent the gold standard in evaluating healthcare interventions. Therapeutic trials may be conducted. To test efficacy – does a therapeutic agent work in an ideal, controlled situation etc.

To test effectiveness after having established efficacy, if the therapy is introduced to the population a large, will bit be effective when having to deal with other co-interventions, confounding and Contamination etc.

The intervention in a clinical trial may include.
A. Drugs for prevention, treatment or palliation;
B. Clinical devices, such as intrauterine devices;
C. Surgical procedures, rehabilitation procedures;
D. Medical counseling;
E. Diet, exercise, change of other lifestyle.
F. Hospital services, e.g. integrated versus non-integrated, acute versus chronic care
G. Risk factors;
H. Communication approaches, e.g. face to face communication versus pamphlets;
I. Different categories of health personnel, e.g. doctors versus nurses;
J. Treatment regimens, e.g. once-a –day dispensation versus three times a day.

Traditionally, clinical trials of new therapies or devices pass through four phases.

a. Phase I clinical trial
The first phase in humans is preceded by considerable research, including pharmacological and toxicological studies in experimental animals to establish that the new agent is effective and may be suitable for human use and to estimate roughly the dose to be used in man. Phase I trials include studies of healthy volunteers who receive, initially, a fraction of what the anticipated does is likely to ban and are monitored for effects on body functions, such as hepatic, cardiovascular, renal, gastrointestinal and endocrinal functions. The metabolism of the drug may also be investigated at this stage. These studies are normally done on volunteers, who are usually institutionalized, and occupy what are called 'research beds’ they require close supervision. This phase, which is of short duration (usually one or two months), requires high technology and varied medical expertise. It also requires access to highly developed laboratory facilities. This trial estimates the maximum tolerated dose (MTD) and also the does response models.[2]
b. Phase II clinical trial
The phase tests the biological activity or effect of the drug. It is also carried out on volunteers selected according to strict criteria. The purpose of Phase II is to assess the effectiveness of the drug or device, to determine the appropriate dosage and to investigate its safety. Further information on the pharmacology, especially the dose-response relationship of the drug, is collected. In the case of a device its effectiveness is assessed and its configuration is tested and, if needed improved. It can be done with or without comparison group. It estimates the rates of adverse events.

C. Phase III clinical trial
This is the classical phase (the one usually referred to as a 'clinical trial' and reported in health research journals). It is performed on patients, who should consent to being in a clinical trial. Strict criteria for inclusion in and exclusion out from the trial are followed, the purpose of this phase is to assess the effectiveness (one could argue that it is still only an efficacy trial, because of the strict conditions under which the study is conducted) and to assess safety in continued use of the drug or device in a large and more heterogeneous population than in Phase-II.

It includes more detailed studies and monitoring than those given in a normal service situation. This phase is usually carried out on hospital inpatients, but may be performed on outpatients with intensive monitoring and follow-up, it required superior clinical and epidemiological skills, in addition to the required laboratory technology, it also requires proper planning, organization and strict adherence to per formulated protocols and instructions, especially in multi-centre collaborative trials. Emphasis is also given to proper record keeping, follow-up and supervision.

Results from Phase III trials are used by regulatory agencies to evaluate whether a new product or device should be licensed for general public use. Initial Phase III trials therefore, have strict guidelines on the type and amount of data to be collected, the way the data are analyzed and presented, and their dissemination to the users (Patients and health care workers).

d. Phase IV trial
Although it has been customary to approve drugs or devices for general use following successful Phase III trials, increasing interest has been shown by governments, and by WHO and other agencies, in subjecting drugs and devices to yet another phase, i.e. a trial in normal
field conditions. The purpose of the Phase IV trials is to re-assess the effectiveness, safety, acceptability and continue use of the drugs or devices under these conditions. Note that Phase III trials are often time limited and any adverse effects may not become apparent in such a short time Phase IV trials add to the evidence of safety from this perspective. They also encompass a formulations of the service requirements of the new method of the service requirements of the new method, including facilities, training, logistics of supply and transportation, supervision and other programme aspects. Although this phase is carried out under conditions that are as close to normal as possible, phase IV required additional epidemiological and biostatistician skills, as well as research requirements, including record-keeping and computer facilities. It is often non randomized and it looks and rare side effects.

1. Drawing of a protocol; or study design

A strict and detailed protocol should be drawn up which describes the exact features of the trail, the aims and the objectives of the study, questions to be answered, criteria for the selection of the study, questions to be answered, criteria for the selections of the study and control groups the outcomes to be recoded, the treatment to be used, how these will be used and what recodes will be kept as well as responsibilities of the parties involved in the trial. A protocol is essential especially when a number of centers are participating in a trial (multi centered trial). Once a protocol has been evolved it should be strictly adhered to through out the study.[3]

Ethical issues should be carefully considered at the planning stage. Women, children, the elderly and those with common medical condition are frequently excluded from RCTs due to ethical consideration. Subject should not be exposed to known or potential hazards. It may be unacceptable to withhold treatment from subjects in a control group (e.g. it is obviously unethical not to treat patients who have been diagnosed with Cancer). Codes of practice such as those set out in the treaty of Helsinki and others published by various organization provide guidelines for dealing with ethical issues. It will almost certainly be necessary to be seek approval from one or more Local Research Ethics Committees (LRECs) before commencing trial. A decision should also be made as to what will constitute the end of the trial (e.g. changes in subject’s condition, death or other physical status). It is likely that an RCT will need a large sample of subjects. The actual sample size required should be calculated. It is important that the final version of the protocol should be agreed upon by all concerned before the trial begins.
2. Selecting reference and experimental populations

a. Reference or target population

It is the population to which the findings of the trial, if found successful, are expected to be applicable (example: a drug, vaccine or other procedure). They may be Geographically limited or limited to persons in specific age, sex, occupational or social group. They may compromise the population of a whole city, or a population of school children, industrial workers, and obstetric population and so on according to nature of the study.

b. Experimental or study population derived from the reference population and should be randomly chosen it has the same characteristics of reference population that participates in the experimental study. It is important to choose stable population a stable population whose co-operation is assured to avoid loses to follow up.

Participants or volunteers must fulfill the following three criteria

I. Must give informed consent.

II. Should be representative of the population to which they belong.

III. They be qualified or legible for the trial.

3. Randomization

It is a statistical procedure by which the participated are allocated into groups usually called study or control groups or receive not to receive and experimental, preventive, or therapeutic, procedure, manœuvre or intervention. It is an attempt to eliminate bias and allow comparability.

Manipulation

The next step is to intervene or manipulate the study (experimental) group by the deliberate application or withdraw or reduction of the suspected causal factors. (E.g. This may be a drug, vaccine, dietary component, a habit etc) as laid down in the protocol. This manipulation creates in independent variable (e.g. drug, vaccine a new procedure) whose affect is then determined by the measurement of the final outcome which constitute the depend variable (e.g. incidence of disease survival time, recovery period etc.)

4. Follow-up

Implies examination of the experimental and control group subject at defined interval of time, in a standard manner along with equal intensity, under the same given circumstances in the same frame till final assessment of outcome. The duration of the trial is usually based on the
expectation that a significant deference will be demonstrable at a given point in time after the start of the trial. It may be short or may require many years depending on the study undertaken. It may be mentioned that some losses of follow-up are inevitable due to factors such a death, migration and loss of interest. This is known as attrition. If attrition is substantial, it may be difficult to be generalize the results of the study to the reference population. Every effort should be made to minimize loses to follow up.

5. Assessment
Final step assessment of outcome of the trial in terms of.

a. Positive results.
That is benefits of the experimental measure such as reduced incidence of severity of the disease, cost to the health services or other appropriate outcome in the study and control group.

b. Negative results
That is severely and frequently of side effects and complications, if anything including death. Adverse effects may be missed if they are not sought. Incidence of positive or negative results is rigorously compared in both the groups and the differences, if any are tested for statistical significance. Techniques are available for the analysis of the data as they are collected (sequential analysis). But it is useful to analyze the data at the end of the trials.

Meta analysis
Unless it is very large, it is unlikely that a single randomized controlled trial will be able to demonstrate the efficacy adequately. The evidence will be stronger if more one RCT obtains similar results. Meta-analysis can be performed in order to summaries the results of several trials. These aim to pool together' the results of trials (provided that it is appropriate to do so). As the results of all of the included trails are taken into account a better over all picture of an intervention's efficacy is obtained and important draw back of meta-analyses is that no efforts has necessary has been made to end every study on the intervention of interest, resulting in bias. For instance, if journals are more likely to publish trials of negative trials will be overlooked, resulting in a misleading impression of true efficacy (this is an example of a bias called publication bias). Furthermore, important elements such as the quality of studies, quality of life and cost effectiveness are not normally evaluated. Systematic reviews attempt to overcome these problems by systematically seeking out all studies (published,
unpublished, abandoned and in progress). As well as summarizing results, systematic reviews usually evaluate the quality of studies together with quality of life and cost effectiveness. For this reason, systematic reviews are currently considered to be the 'gold standard' of clinical evidence.[4]

**Blinding or masking in R.C.T**

R.C.T cannot guard against many of biases in an experiment. In order to reduce these problems a technique known as blinding is adapted which will ensure that the outcome is assessed objectively.

**A. Single blind trial**

Trail is so planned hat the participant is not aware whether he belongs to the study group or control group.

**B. Double-blind trial**

Trial is so planned that neither the doctor nor the participant is aware of the group allocation and the treatment received. The most commonly encountered experiment in health science research, and the research strategy by which evidence of effectiveness is measured, is the randomized, controlled, double-blind clinical trial.

**c. Triple blind trial**

The participant, investigator and the person analyzing the data are all blind. Ideally of course, triple blinding should be used. Blinding is not so essential in measuring outcome such as death.

**Some study designs**

**a. Concurrent parallel study design**

In this type of study design, each patient serves as his own control. As before, the patients are randomly assigned to a study group and control group. The study group receives the treatment under consideration. The controllee group receives an alternate form of active treatment or placebo. The two groups are observed over time. Then the patients in each group are taken off their medication or placebo to allow the eliminating of the medication from the body and for the possibility of any carry over effects. After this period of medication the two groups are switched. The length of the interval is determined by the pharmacologic properties
of the drug being tested. Those who received the treatment under study are changed to the control groups therapy or placebo, and vice versa.

b. Cross over type of study design
Cross over studies offer a number of advantages. With such a design, all patients can be assured that sometime during the course of investigation, they will receive the new therapy. Such studies generally economize on the total number of patients required at the expense of the time necessary to complete the study. This method is not suitable if the drug of interest cures the disease, if the drug is effective only during a certain stage of the disease or if disease changes radically during a certain stage of the disease or if disease changes radically during the period of time required for the study.\[3\]

c. Factorial designs
Each participant is randomly assigned to be group that receives a particular combination of interventions or non-interventions.

**Advantages**
- Two trials can be done for almost the price of one.
- Design is best if the two interventions have different mechanism of acting or different outcomes.

**Disadvantages**
- Need to test for possibility of interactions (e.g. A differs based on the presence or absence of B).
- Need to consider gain in cost Vs. increased complexity, recruitment and adherence issues and potential for adverse events.

d. Cluster designs
Pre-existing group of the participant (e.g. villages, schools) are randomly selected to receive (or not receive) an intervention. It is also called group randomization. Sample size will be based on the number of group and not individuals.

e. Large sample trials
These are needed to uncover smaller treatment effects that are important in some common conditions. It increases the generalizability of the results. There will be decreased cost by
simplifying design and management. But strong randomization procedures and reliable outcomes assessment are needed for the study.

Types of randomized controlled trials\(^2\)

1. **Clinical trials**
   It Concerned along with evaluating therapeutic agents mainly drugs. Some recent examples include:
   - Randomized controlled trial of coronary bypass surgery for the prevention of myocardial infection.
   - Evaluation of beta blockers in reducing cardiovascular mortality in patients surviving the acute phase of myocardial infarction.

2. **Preventive trial**
   Prevention is synonymous along with primary prevention and the term preventive trials implies of primary preventive measures. These trials are purported to prevent or eliminate disease on an experimental basis. The most frequently occurring type of preventive trials is the trials of vaccines and chemo-prophylactic drugs. It may be necessary to apply the trials to group of subjects instead of 4individual subjects.

In 1946 the medical research council of uk conducted an extensive trial to test whooping cough vaccine from three manufacturers in ten separate field trials. Those children between 6 to 10 months who were entered into the trials were randomly allocated in study and control groups. The vaccine was given in three , monthly injections, and the children were followed up at monthly intervals to detect the occurrence of whooping cough. The study groups comprised of 3801 children who were vaccinated, and 149 developed whooping cough. The control groups consisted of 3757 unvaccinated children and 687 of them developed the infection. this gave an attack rate of 1.45 per 1000 child in the vaccinated groups and 6.72 per 1000 child in the control groups. the difference was significant. Analysis of a preventive trial must result in a clear statement about:
   a. The benefit that the community will derive from the measure.
   b. The risk involved
   c. Costs to the health services in terms of money, men, and material sources.
Preventive trials involve larger number of subjects and sometimes a longer time span to obtain results, there may be greater number of practical problems in their organization and execution.

3. Risk factor trials
A type of preventive trial is the trial of risk factors in which the investigator intervenes to interrupt the usual sequence in the development of disease for those individuals who have risk factor for developing the disease, often this involve risk factor gave a new dimension to epidemiological research. It can be a single factor or multi factor. Both approaches are complementary and both are needed.

4. Cessation experiments
In his type of study of study and attempt is made to evaluate the termination of a habit (or removal of suspected agent) which is considered causally related to the disease. If such action is followed by a significant reduction in the disease the hypothesis of cause is greatly strengthened.

The familiar example is cigarette smoking and lung cancer. If in a Randomized Controlled Trial, one group of cigarette smokers continue to smoke and other group has given up the demonstration of a decrease in the incidence of lung cancer in the study group greatly strengthens the hypothesis of a causal relation ship.

5. Trial of etiological agents
One of the aims of experimental epidemiology is to confirm or refute an etiological hypothesis. The best known example of trial an etiological agent relates to Retrolental fibroplasias (RLF).RLF as a cause of blindness was non existent prior to 1938. It was originally observed and reported by T.L. Terry, a Boston ophthalmologist in 1942. RLF was recognized as a leading cause of blindness by descriptive studies which showed that beginning in about 1940-1941, the incidence of disease increased in an alarming rate and that this previously unknown disease was occurring only in premature babies. Analytical studies demonstrated its close association with administration of oxygen to premature babies. A large Randomized controlled trail was mounted involving 18 hospitals United states in which premature babies with birth weight of 1500g or less were allocated into experimental and control groups. In experimental groups all the babies received 50 percent oxygen therapy for 28 days while in he control group oxygen was used only for clinical emergency. It was later
found that all the babies who developed RLF had received some oxygen. There were no cases among who received none confirming the etiological hypothesis.

Since most diseases are fatal disabling or unpleasant human experiments to confirm an etiological hypothesis are rarely possible.

6. Evaluation of health services

RCT have been extended to assess the effectiveness and efficiency of health services. An excellent example of such an evaluation is the controlled trials in the chemotherapy of tuberculosis in India, which demonstrated that domiciliary treatment of pulmonary tuberculosis was as effective as the more costier hospital or sanatorium treatment. The results of the study have gained international acceptance and assured in a new era- the era of domiciliary treatment in the treatment of tuberculosis.

Some advantages and disadvantages of Randomized controlled trial[2]

Advantages

- Allows effectiveness of a new treatment to be evaluated.
- Provides strong evidence of effectiveness.
- Less prone to confounding than other study designs.

Disadvantages

1. Ethical issues

Although randomized control trials are powerful tools their use is limited by ethical and practical concerns. Exposing patients to an intervention believed to be inferior believed to be inferior to current treatment is often thought unethical. For example a non-random study suggested that multivitamin supplementation during pregnancy could prevent neural tube defects in children. Although the study was seriously flawed, ethics committees were unwilling to deprive patients of this potentially useful treatment making it difficult to carry out the trial which later showed that folic acid was the effective part of the multivitamin cocktail. On the other hand failure to perform trials may result in harmful treatments being used. For example neonates were widely traded with high concentrations of oxygen until randomized trials identified oxygen as a risk factor for retinopathy of prematurity.

2. Infeasibility

In other circumstances a randomized controlled trial may be ethical but infeasible. For example; because of difficulties with randomization or recruitment Indeed, Once an
intervention or recruitment. Indeed, once an intervention becomes widespread, it can prove impossible to recruit clinicians who are willing to “experiment” with alternatives. A recent attempt to conduct a trail of counseling in general practice failed when practitioners declined to recruit patients to be allocated at random. Strong patient preferences may also limit recruitment and bias outcomes if not accommodated within the study design.

3. Expensive and time consuming
A third limiting factor is that randomized controlled trials are generally more costly and time consuming than other studies. Careful consideration therefore needs to be given to their use and timing.

4. RCT cannot be conducted for interventions not enough developed to permit evaluation
   This can be especially difficult to decide when new interventions are heavily dependent on clinicians skills. Surgical procedures or talk therapies.

5. Patients may refuse treatment and non-compliance can affect results.

6. A large sample size is needed.

7. Informed patient consents is essential.

8. Absence of double blinding yield exaggerated estimates of treatment effects.

9. Disadvantages of RCTs to the health policy maker include lack of genera liability of the results, the difficulty of performing RCTs of surgical and diagnostic technologies due to the rapidity with which technology changes and the length of follow-up required in some RCTS.

REFERENCE

