Global Journal of Pharmacology 6 (3): 216-221, 2012
ISSN 1992-0075

DOI: 10.5829/idosi.gjp.2012.6.3.6624

An Enlarged Vision on Various Types of Study Design in Human Subjects

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Abstract: Clinical trials are utilized in many clinical specialties to test the efficacy of a specific treatment or intervention in a group of patients/subjects and inferences are then drawn about the use of the treatment in the general population. Just as in any other field of scientific and medical research, the choice of an appropriate design for a clinical trial is a vital element. In various study designs, the randomized clinical trial is the gold standard or reference, it is the design against which others are judged because it provides the greatest justification for concluding causality and is subject to the least number of problems or biases. Bias occurs when the way a study is designed or carried out causes an error in the results and conclusions. Both allocation concealment and masking add to the elimination of bias in randomized controlled trials. Clinical trials without controls are difficult to interpret and do not provide strong evidence.

Key words: Clinical Trials · Randomized Trial · Bias · Cross Sectional Trial · Case Control · Case Report

INTRODUCTION

Clinical trials are used to evaluate various types of medical interventions. New tests and procedures are used to find out whether those are safe and effective for diagnosing disease. New drugs, treatment schedules and surgical procedures are tested to determine if they are safe and effective treatments for specific diseases [1]. Dietary regimens, nutritional supplements, exercise programs and other interventions are tested to discover if they are able to prevent disease safely and effectively. There are two distinct study designs used in health research: observational and experimental (Fig. 1). Observational studies do not intentionally involve intervening in the way individuals live their lives or how they are treated. However, clinical trials are specifically designed to intervene and then to evaluate some health-related outcome. Some trials evaluate new drugs or medical devices that will later require a license (or marketing authorization) for human use from a regulatory authority, if a benefit is shown. This allows the treatment to be marketed and routinely available to the public [2]. Other trials are based on therapies that are already licensed, but will be used in different ways, such as a different disease group or in combination with other treatments. Case series studies frequently lead to the generation of hypotheses that are subsequently investigated in a case control, cross-sectional or cohort study. These three types of studies are defined by the period of time the study covers and by the direction or focus of the research question. Cohort and case control studies generally involve an extended period of time defined by the point when the study begins and the point when it ends; some process occurs and a certain amount of time is required to assess it. For this reason, both cohort and case control studies are sometimes also called longitudinal studies. The main objective of a clinical trial is to determine the differences between groups in outcomes of interest. However, these differences could be due to bias or to chance alone [3]. The final report translates the clinical research carried out into a document which should present the important findings to the

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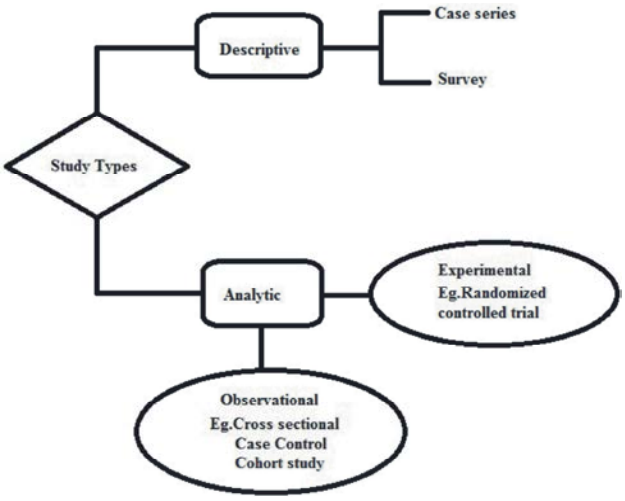

Fig. 1: Different types of clinical studies

reading audience. This report should cover the entire process of the development of the protocol to the statistical analysis. The purpose of this article is to present a comprehensive review on different types of clinical study designs in human subjects.

Case Report (Or) Case Series Study: A case report is a descriptive study of a single individual (case report) or small group (case series) in which the possibility of an association between an observed effect and a specific environmental exposure is based on detailed clinical evaluations and histories of the individual [4]. Case-series reports generally involve patients seen over a relatively short time. Generally case-series studies do not include control subjects, persons who do not have the disease or condition being described [5]. Case series reports have two advantages: They are easy to write and the observations may be extremely useful to investigators designing a study to evaluate causes or explanations of the observations but case series studies are susceptible to many possible biases related to subject selection and characteristics observed. In general, we should view them as hypothesis-generating and not as conclusive.

View on Cross Sectional Studies: Epidemiological strategy in which observations of numerous factors at the same time are recorded and then a comparison is made between them. Subjects are selected and information is obtained in a short period of time. Because they focus on a point in time, they are sometimes also called prevalence studies (Fig. 2). Surveys and polls are generally cross-sectional studies, although surveys can be part of a cohort or case control study [5, 6]. Cross-sectional

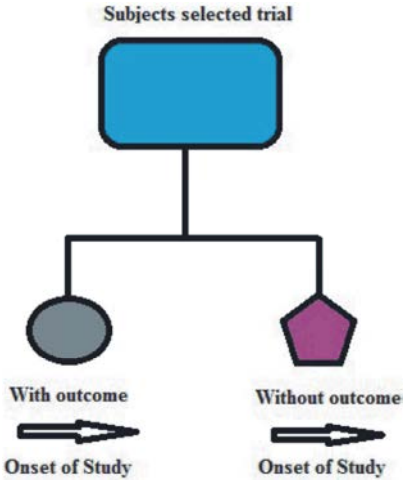

Fig. 2: Schematic diagram of cross-sectional study design

studies may be designed to address research questions raised by a case series, or they may be done without a previous descriptive study. Other applications of cross sectional surveys lie in planning health care. For example, an occupational physician planning a coronary prevention programme might wish to know the prevalence of different risk factors in the workforce under his care so that he could tailor his intervention accordingly [7].

Most of the voter polls done prior to an election are one-time samplings of a group of citizens and different results from week to week are based on different groups of people; that is, the same group of citizens is not followed to determine voting preferences through time. Similarly, consumer-oriented studies on customer satisfaction with automobiles, appliances, health care and so on are cross-sectional.

Case Control Studies- A Outlook: Case control studies are an efficient way to study rare diseases, examine conditions that take a long time to develop, or investigate a preliminary hypothesis. They are the quickest and generally the least expensive studies to design and carry out. Case control studies also are the most vulnerable to possible biases, however and they depend entirely on high-quality existing records [7, 8]. A major issue in case control studies is the selection of an appropriate control group. Some statisticians have recommended the use of two control groups: one similar in some ways to the cases and another made up of healthy subjects. A study that compares patients who have a disease or outcome of interest with patients who do not have the disease or outcome and looks back retrospectively to compare how frequently the exposure to a risk factor is present in each group to determine the relationship between the risk factor and the disease [9]. Fig. 3 illustrates that subjects in the study are chosen at the onset of the study after they are known to be either cases with the disease or outcome or controls without the disease or outcome. The histories of cases and controls are examined over a previous period to detect the presence (black shaded areas) or absence (blue shaded areas) of predisposing characteristics or risk factors, or, if the disease is infectious, whether the subject has been exposed to the presumed infectious agent. Case control studies are observational because no intervention is attempted and no attempt is made to alter the course of the disease. The goal is to retrospectively determine the exposure to the risk factor of interest from each of the two groups of individuals: cases and controls. Case control studies are also known as "retrospective studies" and "case-referent studies."

Main advantage is less time needed to conduct the study because the condition or disease has already occurred but it can be difficult to find a suitable control group.

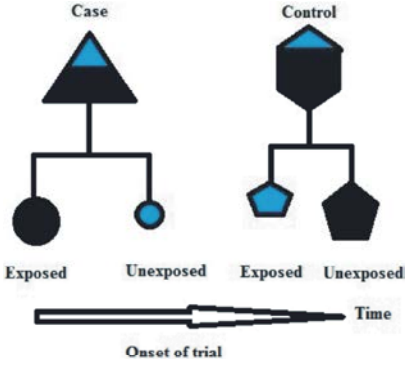

Fig. 3: Schematic diagram of case control study design

Cohort Studies: Cohort studies are the best observational study design for investigating the causes of a condition, the course of a disease, or risk factors. Causation cannot be proved with cohort studies, because they do not involve interventions [10]. Because they are longitudinal studies, however, they incorporate the correct time sequence to provide strong evidence for possible causes and effects. In addition, in cohort studies that are prospective, as opposed to historical, investigators can control many sources of bias. Cohort studies have disadvantages, of course. If they take a long time to complete, they are frequently weakened by patient attrition [11]. They are also expensive to carry out if the disease or outcome is rare or requires a long time to develop. A cohort is a group of people who have something in common and who remain part of a group over an extended time. In medicine, the subjects in cohort studies are selected by some defining characteristics suspected of being a precursor to or risk factor for a disease or health effect. Cohort studies, although difficult to organize and usually time consuming, can also be used to investigate the association between a certain risk factor and a particular disease. The length of time required in a cohort study depends on the problem studied. With diseases that develop over a long period of time or with conditions that occur as a result of long-term exposure to some causative agent, many years are needed for study [12, 13]. Extended time periods make such studies costly. Theoretically, they are better suited for this propose than case- control studies which, inspite of their many practical advantages, are often exposed to several kinds of bias that may occur in selection, misclassification, etc. and which require comparatively sophisticated analysis and in which the choice of appropriate controls is not always easy.

In cohort studies, a sample of individuals, some exposed to the risk factor under study and some not so exposed, is followed up for an appropriate length of time and the incidence of a disease in the two groups during this period furnishes the basis for making a comparison and drawing conclusion regarding the strength of association between the risk factor and the disease [14] (Fig. 4). As this illustration shows, a cohort study starts with a risk factor or exposure and looks at consequences; a case control study takes the outcome as the starting point of the inquiry and looks for precursors or risk factors. Both case control and cohort studies evaluate risks and causes of disease and the design an investigator selects depends in part on the research question.

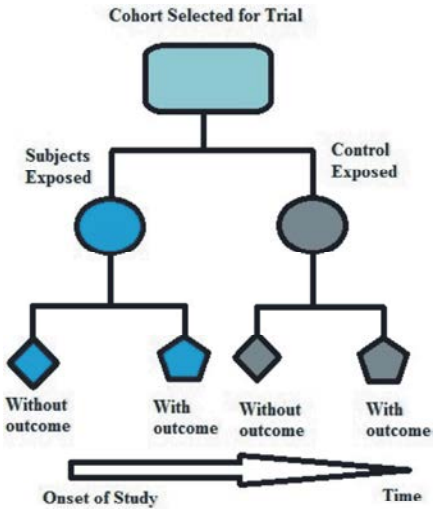

Fig. 4: Schematic diagram of cohort study design

Randomized Controlled Trial - General Principles: The randomized controlled trial (RCT) is one of the simplest but most powerful tools of research. In essence, RCT is a study in which people are allocated at random to receive one of several clinical interventions [15]. The prospective, randomized, controlled, blinded (if possible), sample-size calculated study with a pre-planned statistical analysis and trial monitoring is undoubtedly the gold standard for a therapeutic or interventional clinical study. RCTs are used to examine the effect of interventions on particular outcomes such as death or the recurrence of disease. Some consider randomized controlled trials to be the best of all research designs [16], mainly because the act of randomizing patients to receive or not receive the intervention ensures that, on average, all other possible causes are equal between the two groups. Thus, any significant differences between groups in the outcome event can be attributed to the intervention and not to some other unidentified factor. RCTs are not appropriate for cancer screening, a situation in which the outcome is rare and frequently occurs only after a long delay. Thus, the test for appraising the ultimate value of a diagnostic test may be a large well-designed randomized controlled trial that has patient outcomes as the end point [17] (Table 1). RCT may not be appropriate for the assessment of interventions that have rare outcomes or effects that take a long time to develop. In such instances, other study designs such as case-control studies or cohort studies are more appropriate.

Allocation of Subjects to Intervention and Control Groups: The process of randomization aims to ensure similar levels of all risk factors in each group; not only known, but also unknown, characteristics are rendered comparable, resulting in similar numbers or levels of outcomes in each group, except for either the play of chance or a real effect of the intervention. Simple randomization is usually achieved using a sequence of random numbers from a statistical textbook, or a computer-generated sequence. Block randomization is a method used to ensure that the numbers of participants assigned to each group is equally distributed and is commonly used in smaller trials [18, 19]. Stratified block randomization can further restrict chance imbalances to ensure the treatment groups are as alike as possible for selected prognostic variables or other patient factors. A set of permuted blocks is generated for each combination of prognostic factors. For example, in a trial of chemotherapy for breast cancer, suitable stratification factors might be menopausal status and estrogen-receptor status. A set of permuted blocks is generated for those women who are premenopausal and estrogen-receptor negative, another set for those who are premenopausal and estrogen-receptor positive and so on. Stratification can add to the credibility of a trial, as it ensures treatment balance on these known prognostic factors, allowing easy interpretation of outcomes without adjustment [20]. Minimized randomization may be used when the study is sufficiently small and simple randomization will not result in balanced groups. The randomization procedure gives the randomized controlled trial its strength (Fig. 5). Random allocation means all participants have the same chance of being assigned to each of the study groups.

Table 1: Study design for randomized controlled trial

Stage 1. Scheme of the study
i. Setting up the protocol
ii. Defining primary and secondary outcomes
iii. Study population, inclusion and exclusion criteria
iv. Sample size and statistical plan
v. Design of Case record forms
vi. Logistical issues for conduct
Stage 2. Conduct of the study
i. Monitoring of the study
ii. Data capture, database design and data entry
Stage 3. Statistical analysis & reporting of trial

Blinding in Randomized Trial: This means the successful masking of treatment allocation, with 'matching' active and placebo. In a single blind design, because the patients are usually not aware of the allocated treatment, bias in reporting of symptoms or events will be controlled. The double blind design, where neither clinician nor patient knows which treatment is given,

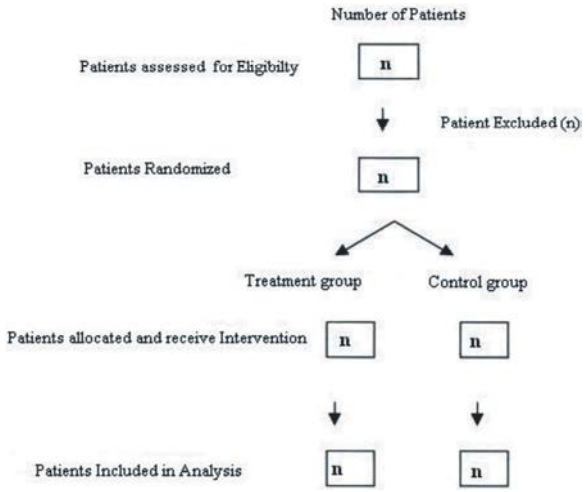

Fig. 5: Randomization and allocation of Patients for RCT

has the advantage of controlling both reporting and assessment bias [21]. In this case, emergency unblinding procedures must be always promptly available. For double blind studies, a proper procedure for packaging of the matching placebos and actives, according to the randomization codes, must be drawn up by the packaging company and this should be witnessed by the sponsor or the independent monitor [22]. If more than one bottle of medications is to be given at various times, the trial/nurse co-ordinator despatching the medications must keep an accurate account.

Bias in Randomized Controlled Study Design: The main appeal of the RCT in health care derives from its potential for reducing allocation bias. No other study design allows researchers to balance unknown prognostic factors at baseline. Random allocation does not, however, protect randomized controlled trials against other types of bias [23, 24]. The existence of most biases related to RCTs is supported mainly by common sense. In recent years, however, important research efforts have used RCTs as the subject rather than the tool of research. These studies are usually designed to generate empirical evidence to improve the design, reporting, dissemination and use of RCTs in health care. They have confirmed that RCTs are vulnerable to many types of bias throughout their entire life span. Random allocation of the participants to different study groups increases the potential of a study to be free of allocation bias, but has no effect on other important biases. Randomization is essential, as it aims to remove bias introduced by patient's individual characteristics. This makes it more likely that only the effect of the treatment will influence the results [25-27]. The process also helps to reduce allocation bias in the selection of subjects (e.g. preventing a clinician from selecting only healthier patients to receive a new treatment). Randomization controls for known and, more importantly, unknown confounders if the sample size is large enough.

Non-Randomized Trials: Subjects are not always randomized to treatment options. Studies that do not use randomized assignment are generally referred to as non-randomized trials or simply as clinical trials or comparative studies, with no mention about randomization [28]. Many investigators believe that, studies with non-randomized controls are open to so many sources of bias that, their conclusions are highly questionable [29]. Studies using non-randomized controls are considered to be much weaker because they do nothing to prevent bias in patient assignment.

Reporting Clinical Trials: The first rule after completing a clinical trial is to report the results, whether they are positive, negative or equivocal. Selective reporting whereby results of positive studies tend to be published and negative studies tend not to be published presents a distorted view of the true situation [30]. This approach of reporting is, particularly important for clinical trial overviews and meta-analysis where it is clearly important to be able to include all relevant studies (not just the published ones) in the overall synthesis.

CONCLUSION

Clinical trials provide the strongest evidence for causation because they are experiments and as such, are subject to the least number of problems or biases. To prevent selection bias, investigators should anticipate and analyze all the confounders important for the outcome studied. They should use an adequate method of randomization and allocation concealment and they should report these methods in their trial. Trials with randomized controls are the study type of choice when the objective is to evaluate the effectiveness of a treatment or a procedure.

REFERENCES

1. John, G., 2007. Case study research: Principles and Practices.

2. Gillham, B., 2000. Case Study Research Methods.
3. Rebecca, D.S and L. Nan, 1986. Meta-analysis in clinical trials. Controlled Clinical Trials, 7: 177-188.
4. Pocock, S.J., 1983. Clinical Trials: a practical approach. Chichester: John Wiley and Son.
5. Fowkes, F. and P. Fulton, 1991. Critical appraisal of published research: introductory guidelines. BMJ, 302: 1136-40.
6. Hajiro, T., K. Nishimura, M. Tsukino, A. Ikeda, H. Koyama and T. Izumi, 1998. Analysis of Clinical Methods Used to Evaluate Dyspnea in Patients with Chronic Obstructive Pulmonary Disease. Am. J. Resp. Crit. Care Med., 158: 1185-1189.
7. Winston, T., 1997. Introduction to Case Study. The Qualitative Report.
8. Cramer, J.A., R. Fisher, E. Ben-Menachem, J. French and R.H. Mattson, 1999. New Antiepileptic Drugs: Comparison of Key Clinical Trials. Epilepsia., 40: 590-600.
9. Robert, K.Y., 1981. The Case Study Crisis: Some Answers. Administrative Science Quarterly, 26: 58-65.
10. Nicolaj, S., 2007. Persuasion with case studies. Academy of Management Journal, 50: 120-24.
11. Winston, T., 1997. Application of a Case Study Methodology. The Qualitative Report.
12. David, A.G. and F.S. Kennath, 2002. Descriptive studies: what they can and cannot do. Lancet., 359: 145-149.
13. Catherine, C. and S. Gillian, 2004. Essential Guide to Qualitative Methods in Organizational Research.
14. Harald, O.S., N. Geoffrey and T. Isabelle, 2004. Fundamentals of Clinical Research for Radiologists. AJR., 183: 1539-44.
15. Jadad, A.R., 1998. Randomised controlled trials: a user's guide London, England: BMJ Books.
16. Food and Drug Administration. Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees. Available at:http:// www.fda.gov/ cber/ gdlns/ clindatmon.htm, Accessed December 12, 2011.
17. Nystrom, L., L.E. Rutqvist and S. Wall, 1993. Breast cancer screening with mammography: overview of Swedish Randomized Trials. Lancet, 341: 973-978.
18. Louis, T.A., P.W. Lavori, J.C. Bailar and M. Polansky, 1992. Crossover and self-controlleddesigns in clinical research. In: J.C. Bailar, III, F. Mosteller, eds. Medical uses of statistics, 2nd ed. Boston, MA: New England Medical Journal Publications, pp: 83-104.
19. Begg, C., M. Cho, S. Eastwood, R. Horton, D. Moher, I. Olkin, R. Pitkin, D. Rennie, K.F. Schulz, D. Simel and D.F. Stroup, 1996. Improving the quality of reporting of randomized controlled trials. The CONSORT statement, JAMA, 276: 637-9.
20. Piantadosi, S.,1997. Clinical Trials - A Methodologic Perspective. John Wiley and Sons, INC.
21. Altman, D.G., 1991. Practical statistics for medical research. London, England: Chapman and Hall.
22. Chalmers, T.C., P. Celano, H.S. Sacks and H. Smith, 1983. Bias in treatment assignment in controlled clinical trials. New England Journal of Medicine, 309: 1359-1361.
23. Owen, R. Reader Bias, 1982. J. Amer. Med. Assoc., 247: 2533-2534.
24. Jadad, A.R. and D. Rennie, 1998. The randomized controlled trial gets a middle-aged checkup. Journal of American Medical Association, 279: 319-320.
25. Duffy, S.W., 2001. Interpretation of the breast screening trials: a commentary on the recent paper. Breast, 10: 209-212.
26. Sheila, M.G., 1981. Assessing clinical trials-simple randomization. BMJ, 282: 2026-39.
27. Koren, G. and N. Klein, 1991. Bias against negative studies in newspaper reports of medical research. JAMA, 266: 1824-1826.
28. McNutt, R.A., A.T. Evans, R.H. Fletcher and S.W. Fletcher, 1990. The effects of blinding on the quality of peer review. A randomized trial. JAMA, 263: 1371-1376.
29. Brewin, C.R. and C. Bradley, 1989. Patient preferences and randomized clinical trials. BMJ, 299: 684-685.
30. Altman, D.G., 1996. Better reporting of randomized controlled trials: the CONSORT Statement. BMJ, 313: 570-571.