Study design made easy

Diogo Bruno
Arteriae, Lisbon, Portugal

Correspondence:
Diogo Bruno, Arteriae Unip. Lda.
R. Cid. Cádiz 14 4.º Dto-A, 1500-157
Lisboa, Portugal
diogobruno@arteriae.net
+351 966 625 510

Abstract
Analysis of statistical data is an important part of any medical writer's skill set, especially those professionals working in publication and regulatory areas. Understanding the various study designs is key to a thorough understanding of study methodology. Nevertheless, many medical writers come from a non-clinical background and have a knowledge gap when it comes to study design options. This article describes the main types of study design. Case report, cross-sectional, case control, cohort, quasi-experimental, randomised controlled trials, and systematic reviews and meta-analyses studies are explained and their uses, advantages, and limitations discussed.

The naked truth is that mankind still lacks time machines. If we had them, there would be no need for epidemiology as one could, for example, easily observe a group of individuals exposed to smoking over the course of their lives and, then, travel back in time and reobserve them after persuading them to stop smoking. Epidemiologists try to determine whether an exposure (i.e. risk factor) is associated with an outcome (i.e. disease), such as smoking and lung cancer in this example.[1]

The first step in a study is to define the hypothesis to be tested. After this, one must determine which study design is the most appropriate and/or feasible to test this hypothesis.

Overview of study designs
Broadly-speaking there are two approaches to study the association between an

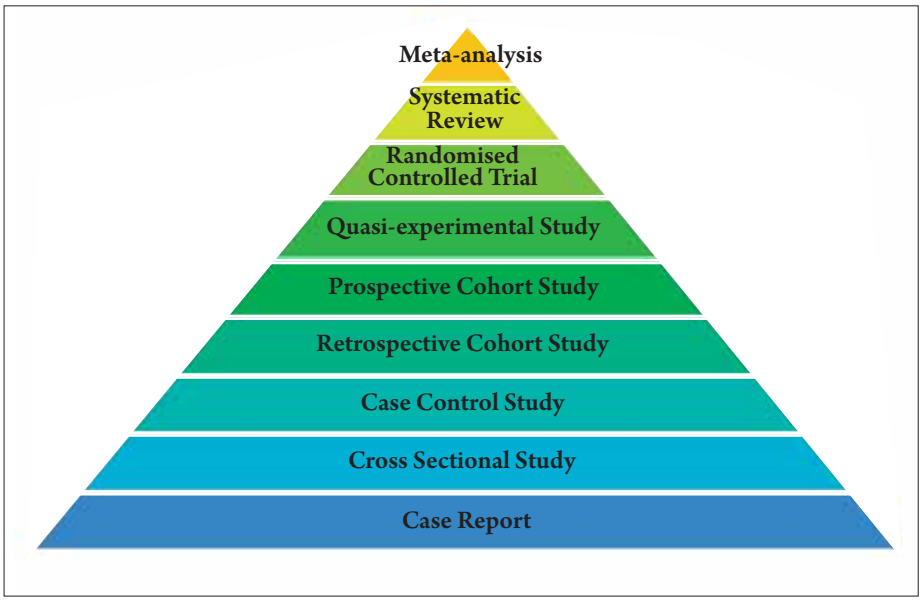

Figure 1: Main types of study design.
Study designs organised in order of statistical validity from the highest validity on the top of the pyramid to the lowest validity in the bottom of the pyramid.

exposure and an outcome: 1. **interventional or experimental** and 2. **observational or non-experimental** studies.[2] When analysing their scientific validity, experimental studies are of higher quality when compared to observational studies. They usually involve the study of a factor that can be controlled by the investigator and enrolled individuals are randomly assigned to being exposed or not to that factor. Observational studies, on the other hand, lack randomisation and, as such, various other factors might be unevenly distributed between the studied groups; as a consequence of these **confounding factors**, a true association is more difficult to ascertain.[2]

In addition, studies can be characterised as **retrospective** or **prospective** based on when the subjects are enrolled into the study.[3] These differences will be further explained when we explore cohort studies. As a consequence of these differences, study designs are often organised as a pyramid in order of validity (Figure 1).[4] Unfortunately, the most valid studies are often more expensive, more time-consuming, and more difficult to manage.

In the next sections, I will describe each study design further with a special emphasis on the most important study design for medical writers, the randomised controlled trial (RCT).

Unfortunately, the most valid studies are often more expensive, more time-consuming, and more difficult to manage.

Case report

Case report articles are considered the lowest level of evidence and findings usually require formal verification through robust epidemiological studies. However, they can represent the emergence of new issues and key ideas. Namely, they can provide important information for patient care that is not detected in clinical trials or other studies seen as more robust in design. They usually describe in detail an individual clinical case that shows: 1. a rare variation of a condition, 2. an unexpected drug adverse event, 3. clues on the pathogenesis of a disease, 4. an unexpected association between factors, 5. a unique therapy, or 6. a unique anatomical variation.

Cross-sectional study

Cross-sectional studies analyse data taken from a sample at a specific point in time. They are usually applied for public health purposes as they give a snapshot of the rate of an outcome of interest (i.e. prevalence of a condition) in a population. Moreover, researchers also describe patient characterstics and important risk factors thought to be associated with the outcome. Another use for this design is in the case of descriptive survey studies when the main aim is to describe a population in a given time period.[5]

Cross-sectional design lends itself well to **descriptive statistics**, where no association between exposure and outcome or causal relationship is sought, and the intention is solely to describe the properties of the observed data. On the other hand, **inferential statistics** aims to drive an association between exposures and outcomes through hypotheses and estimates. The designs described in the next sections are better approaches to describe these associations as cross-sectional studies give no indication of the sequence of events and are prone to prevalence-incidence bias (e.g. high mortality conditions will be under-represented as they will have low prevalence even in the case of high incidence).

Case control study

Contrary to the cross-sectional studies, the case control design aims to establish an association between risk factors and disease (i.e. uses inferential statistics). A group of patients with the study disease (**cases**) is selected and compared to a group of healthy individuals similar to the group of cases in every other aspect (**controls**). Information about risk factors is then collected retrospectively and is used to compare both groups and to find measures of association.[6]

Consequently, this design is often used to study infrequent or rare diseases in which prospective studies would be difficult to perform. To study rare diseases in prospective designs, a great number of patients would have to be enrolled, rendering them unfeasible.[7] Additionally, case control studies may have more power than cohort studies as it is easier to have larger samples.

Finally, instead of measuring the risk of disease based on exposure, we measure the odds of exposure based on disease. Therefore, relative risk is not applicable as a measure of association. It is the disease that is selected at the study onset, so the odds ratio is used.

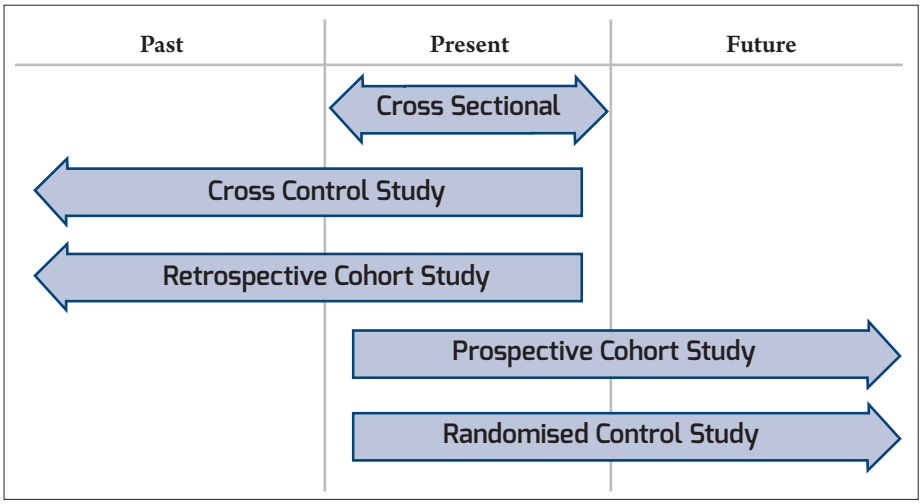

Figure 2: Retrospective and prospective study designs.
Main types of study design and their relation to the studied time-points.

Cohort study

By definition, in cohort studies a group of subjects comprising a sample deemed to represent the population of interested is followed over time whilst collecting data on risk factors and outcomes. It differs from cross-sectional studies in the sense that, although risk factors and outcomes are studied, subjects are studied over time. Moreover, unlike case control studies, individuals are disease-free at the outset of the study and the risk of development of the disease (outcome) is the measure of interest.

As discussed previously, cohort studies can either be retrospective or prospective when relating to time of subject enrolment (Figure 2). **Retrospective** studies are also called **historical cohort studies** and study events from the past up until the present time. The obvious advantage is that the information is readily available, however tracing subjects might prove difficult and investigators have to rely on the quality of the recorded information (e.g. electronic health records, patient recollection) which is often low.[3]

On the other hand, prospective cohort studies are those studying events from the present time until a time in the future. The study design allows investigators to incorporate any exposure or baseline characteristics to be studied so the study is more complete; however, the follow-up time can be long, especially for infrequent outcomes, and such studies can have a high loss to follow-up (dropout) rate.

Less often, **ambispective** or **ambidirectional cohort studies** are performed that, as the name implies, combine retrospective and prospective information including past, present, and future timepoints.[8]

Regarding the data analysis, unlike case control studies, the most usual measure is the risk ratio of the outcome of interest, calculated by the risk of the outcome in exposed subjects relative to those not exposed to the risk factor.

Quasi-experimental study

Quasi-experimental studies are sometimes also called **nonrandomised** or **pre-post intervention studies** and are used to evaluate the effects of specific interventions or policy changes. It is a design chosen when it is not logistically feasible or ethical to conduct a RCT. By definition, these studies lack randomisation and are conducted after a policy change comes into effect. As policy changes can inadvertently be non-beneficial, investigators compare specific outcomes before and after a policy change to determine if it was of benefit.[9]

Unlike previous designs, these studies include an intervention chosen by the researchers (policy change at a given time-point). However, they lack randomisation and, consequently, are sensitive to confounding effects and causal relationships, and are, therefore, less valid than RCTs.[9]

Randomised controlled trial (RCT)

RCTs are the only studies truly experimental in nature as the effect of an investigator-chosen intervention is studied in randomly assigned subjects from a study sample deemed to be representative of a population. Frequently, a study group is exposed to an intervention (e.g. a novel treatment) and its effects on one or more outcomes of interest are studied by comparing the exposed group to a control group not exposed to the intervention (e.g. placebo) or exposed to a standard intervention (e.g. already established therapy or standard of care).[10] Figure 3 gives a representation of this study design.

The RCT's inherent characteristics make it a robust study design. **Randomisation** of intervention allocation is used to decrease confounding effects and allocation bias. The characteristics that might affect the relationship between intervention and outcome measures will be roughly equal between study and control groups. **Blinding** or **masking** is also frequently used to decrease study bias. In single-blinded studies, subjects are unaware of their group assignment, decreasing the performance bias that could occur as this knowledge can affect the subjects' response to the intervention. In double-blinded studies, group allocation is not known to both study subjects and investigators. This further decreases bias by avoiding differences in treatment administration between treatment arms (performance bias) or the over- or under-estimation of the effects of an intervention (assessment bias).[11] Studies that have no blinding are characterised as **open-label**.

The RCT allows investigators to control the intervention and establish causality with a good degree of certainty providing the strongest evidence of an association (efficacy or safety data). However, to calculate the sample size, researchers must have prior knowledge about the expected effect size and sometimes ethical issues prevent the comparison of an intervention with a **placebo** (an inert treatment in blinded

RCTs frequently give rise to higher quality evidence, however researchers and medical writers have to be aware of the limitations of RCTs when analysing the results

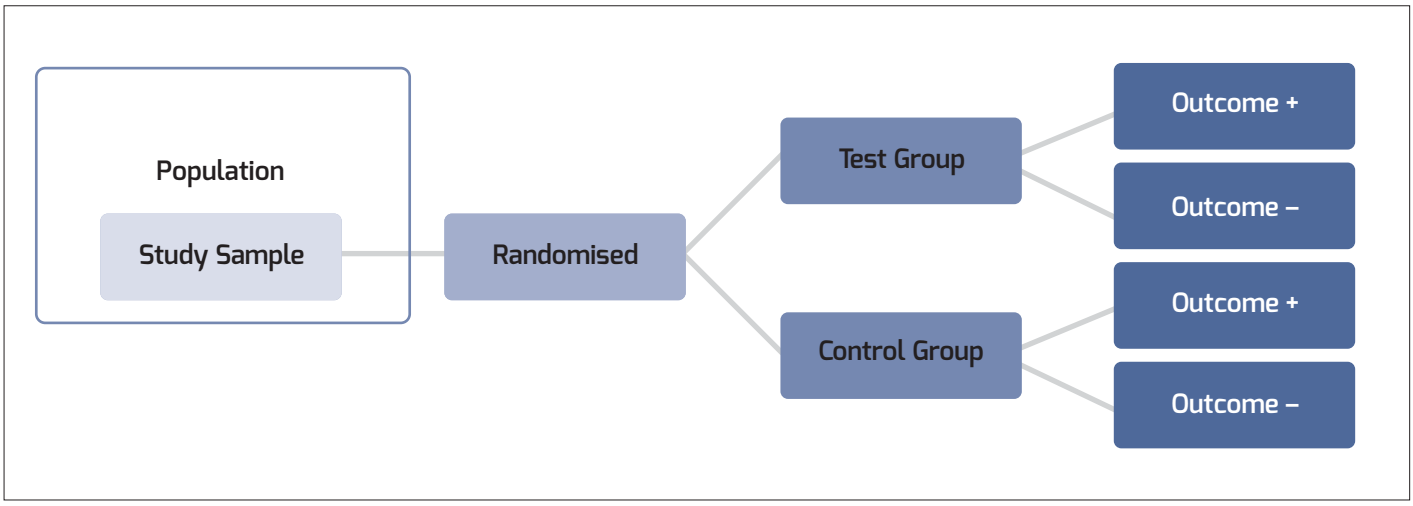

Figure 3: Schematic representation of a randomised controlled trial.
Subjects in a sample are randomly assigned to different interventions (test and control groups) and then followed to compare the risk of the outcome between groups.

studies) or no intervention (in open-label studies).[12]

RCTs of new drugs are often classified in **phases**. Phase I trials involve testing in healthy volunteers (except for novel oncology drugs) with dose escalation to assess safety (i.e. side effects and toxicity) and to determine if it is appropriate to check for efficacy. Phase II trials involve a small group of patients to assess safety and efficacy. Phase III trials involve a large group of patients to further assess and establish safety, efficacy, and effectiveness. Phase IV trials are those performed during post-marketing surveillance.[13]

Systematic review and meta-analysis

Systematic reviews are studies that try to collect all available evidence about a subject of interest and critically appraise it. Systematic reviews of RCTs are often used to guide guidelines and other aspects of evidence-based medicine. They usually involve a thorough search on a research question in multiple article databases and indexes, such as Web of Science, Embase, and PubMed.[14]

Meta-analyses not only try to collect all available evidence but also combine the results of similar papers to give an approximate pooled measure of association (e.g. odds ratio or risk ratio) using specific statistical methodology. In summary, systematic reviews give a qualitative evaluation, whilst meta-analyses aim at a quantitative appraisal.[14] While meta-analyses virtually always include systematic reviews of the literature, this is not always true for systematic reviews.

Discussion and conclusion

It is true that observational studies are more prone to bias and confounding effects than RCTs and that RCTs frequently give rise to higher quality evidence, however researchers and medical writers have to be aware of the limitations of RCTs when analysing the results. They have more **internal validity** when compared to prospective cohort studies; that is, the causal inference or relation is properly demonstrated in the study sample, as bias and confounding factors are often adequately controlled. However, the strategies aimed at increasing internal validity, such as controlling the intervention and the strict inclusion and exclusion criteria, may undermine the **external validity** or **generalisability** of the study findings. One pivotal example is the finding of increased rates of coronary heart disease (CHD) in postmenopausal women taking hormone replacement therapy in the Women's Health Initiative (WHI) RCT.[15] Contrary to the WHI, two previous prospective cohort studies based on the Nurses' Health Study Cohort suggested a reduced CHD risk.[16,17] At first glance, differences were attributed to a lack of randomisation in the observational studies. As a consequence of the WHI study, millions of women worldwide stopped taking hormone replacement therapy. More recent studies, however, attribute the differences to a lack of external validity of the WHI study that had an older study population (average age of 63 vs. 57-59 years) and a higher percentage of users who had gone through menopause more than 10 years previously.[18]

In the end, the pyramid shown in Figure 1 stands true for most study examples and studies higher in the pyramid have more valid and robust findings. However, medical writers have an increasingly active role as consultants and in literature review to properly counsel clients in strategies and evidence-based medicine. A sound knowledge of statistical methods is therefore essential for any contemporary medical writer, and understanding the key advantages and limitations of the several study designs presently at our disposal is another small step to achieve that goal.

References

1. Adami HO, Hunter D, Trichopoulos D, editors. Textbook of Cancer Epidemiology. 2nd ed. Oxford: Oxford University Press; 2009.
2. dos Santos Silva I. Cancer Epidemiology: Principles and Methods. 1st ed. Lyon: IARC Press; 1999.
3. Levin KA. Study design IV. Cohort studies. Evid Based Dent. 2003;7(2):51–2.

4. Haynes B. Of studies, syntheses, synopses, summaries, and systems: the "5S" evolution of information services for evidence-based healthcare decisions. Evid Based Nurs. 2007;10(1):6–7.
5. Levin KA. Study design III: Cross-sectional studies. Evid Based Dent. 2006;7(1):24–5.
6. Levin KA. Study design V. Case-control studies. Evid Based Dent. 2006;7(3):83–4.
7. Schulz KF, Grimes DA. Case-control studies: research in reverse. Lancet. 2002;359(9304):431–4.
8. Mortensen PB. Ambidirectional studies – an extension of longitudinal studies in psychiatry. Psychiatr Dev. 1988;6(2):173–81.
9. Harris AD, Bradham DD, Baumgarten M, Zuckerman IH, Fink JC, Perencevich EN. The use and interpretation of quasi-experimental studies in infectious diseases. Clin Infect Dis. 2004;38(11):1586–91.
10. Levin KA. Study design VII. Randomised controlled trials. Evid Based Dent. 2007;8(1):22–3.
11. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200–7.
12. Wechsler ME, Kelley JM, Boyd IO, Dutile S, Marigowda G, Kirsch I, et al. Active albuterol or placebo, sham acupuncture, or no intervention in asthma. N Engl J Med. 2011;365(2):119–26.
13. Friedman LM, Furberg CD, DeMets DL. Fundamentals of clinical trials. New York: Springer; 2010.
14. Higgins J, Churchill R, Cumpston M, Chandler J, editors. Cochrane Handbook for Systematic Reviews of Interventions. Ver. 5.0.2. New Jersey: Wiley-Blackwell; 2008.
15. Group TWHIS. Design of the Women's Health Initiative clinical trial and observational study. Control Clin Trials. 1998;19(1):61–109.
16. Grodstein F, Manson JE, Colditz GA, Willett WC, Speizer FE, Stampfer MJ. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. Ann Intern Med. 2000;133(12):933–41.
17. Grodstein F, Stampfer MJ, Manson JE, Colditz GA, Willett WC, Rosner B, *et al.* Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. N Engl J Med. 1996;335(7):453–61.
18. Hernán MA, Alonso A, Logan R, Grodstein F, Michels KB, Willett WC, et al. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. Epidemiology. 2008; 19(6):766–79.

Acknowledgements

The author would like to express gratitude to Joana Carlos for the proofreading of this article.

Conflicts of Interest and Disclaimers

The author declares no conflicts of interest.

Author information

Diogo Bruno, MD has been a medical writer, translator and proofreader for three years. He is a senior OB/GYN Specialty Registrar at *Hospital Prof. Dr. Fernando Fonseca*, Portugal, has a Harvard Medical School certificate in clinical research, and has presented works in obstetrics and gynaecology at several meetings.