Study designs in healthcare research

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Study designs in clinical research are classified into 2 major categories.[1,2] The first category is the observational studies, in which the study subjects are merely observed and the characteristics of the patients are recorded. The second category is the experimental studies, in which an intervention such as a drug or procedure is introduced to test its effect on the study subjects.

Observational studies. There are 4 types of observational studies: care-series, case-control, cross-sectional, and cohort studies.[1-3]

A. Case-series study. Case-series studies include a simple description of interesting observations in a small number of subjects. These studies are not planned before and do not involve any hypothesis.[4,5] They do not include control subjects. For all these reasons, care series are often not considered by many authorities to be research studies.

As an example, Wong et al[6] described 4 dialysis patients who developed a severe acute respiratory syndrome (SARS) in Hong Kong. All the 4 cases were diagnosed using the standard World Health Organization (WHO) definition criteria of SARS. The authors individually described the cases including their clinical presentation and the possible way by which they encountered the disease.

Advantages and disadvantages of case-series study. They are easy to write and can be useful in new observations or disease. However, they are subjected to many bias related to subject selection.[1-5]

B. Case-control studies. Case-control studies start with the presence or absence outcome, then they look back into the past to detect possible causes or risk factors.[7] The researcher then selects a control group of subjects who do not have the outcome but are similar the cases in age, gender and other features. The researcher compares the cases (the individuals with the disease) with the control group. The histories of previous events of the 2 groups are compared to identify whether certain risk factors are present in the cases but not in the controls.

As an example, Mutsch et al[8] examined whether cases of Bell's palsy were related to the use of inactivated intranasal influenza vaccine in Switzerland. The matched 250 cases of Bell's palsy with 722 control patients (without Bell's palsy). The controls were matched with the case patients according to age, date of clinic visits and physician. They reviewed the history of exposure to the influenza vaccine. They found that 27% of the patients with Bell's palsy and 1% of the controls had received the intranasal vaccine ($p<0.001$). Therefore, they concluded that the use of the intranasal influenza vaccine significantly increased the risk of Bell's palsy.

Advantages of case-control studies. 1. They can be performed fairly quickly and cheaply.[1,7] 2. They are particularly useful for rare diseases.[1-2] 3. They require a small number of subjects. 4. They allow the investigation of multiple causes of disease.

Disadvantages of case-control studies. 1. Case-control studies are subject to recall-bias. Recall of prior exposures may be biased by the fact of having the disease now.[2] 2. Because they start with patients who already have the outcome, asymptomatic cases are missed.[1] 3. Selection of the control group is also subject to bias.[2] 4. They cannot establish a cause-effect relationship.

C. Cross-sectional studies. Cross-sectional studies are observational studies in which all the measurements are performed on a single occasion, with no follow-up period.[3]

Cross-sectional studies are used to describe the distribution of variables. For that reason, they are also called prevalence studies. Prevalence is defined as the proportion of the population who has a disease at one period of time. Cross-sectional

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studies are also used to examine associations. Surveys are special type of cross-sectional studies because they are performed at a given period of time.[2-3]

As an example, to examine whether the use of inhaled corticosteroids is a risk factor for the development of posterior subcapsular cataracts, Cumming et al[9] conducted a cross-sectional study of vision in 3654 people in Australia. The investigators collected the information by questionnaire on potential risk factors for cataracts, including the current or prior use of inhaled corticosteroids (beclomethasone or budesonide). They examined photographs of the subjects' lenses to determine the presence and severity of cataracts. They found higher prevalence of nuclear and subcapsular cataracts but not cortical cataracts among the patients who received inhaled corticosteroids. Higher cumulative lifetime doses of beclomethasone were associated with higher risks of posterior subcapsular cataracts; the highest prevalence was found in subjects whose lifetime dose was over 2000 mg. The authors conclude that the use of inhaled corticosteroids was associated with the development of posterior subcapsular and nuclear cataracts.

Advantages of cross-sectional studies. 1. Fast and relatively inexpensive.[1-2,8] 2. No loss to follow-up.

Disadvantages of cross-sectional studies. 1. Cross-sectional studies do not establish causal relationship.[1] 2. They are impractical for rare disease.[2]

D. Cohort studies. A cohort is a group of subjects who have something in common and followed overtime.[1] Typically, cohort studies are prospective but they can also be retrospective.[1,2]

Prospective cohort studies. In the prospective cohort study, the investigator defines a sample of subjects and identifies certain risk factors, such as hypertension or diabetes that may predict the subsequent outcomes. The investigators follow these patients overtime to measure the outcome.[10]

Framingham study is a typical prospective cohort study.[2] The study started in 1948 to study factors associated with the development of cardiovascular disease. The basic steps in performing the study were to: 1. Assemble the cohort - the investigators recruited more than 6,000 subjects in Framingham, Massachusetts, USA in 1948. 2. Measure potential risk factors - the investigators defined the presence of absence of potential risk factors such as diabetes, hypertension, smoking, and hypercholesterolemia. 3. Follow-up and measure outcomes - the subjects in the cohort were followed for long period to determine the occurrence of coronary artery disease.

Advantages of cohort studies. 1. Prospective cohort studies are very useful when an experimental study cannot be conducted for ethical or practical reasons.[2] 2. Prospective cohort study provides information about the risk of contracting a disease (incidence).[10] 3. Because of the prospective nature, important variables can be measured completely and accurately.[2] 4. Unlike case-control, the assessment of risk factors is unbiased by the outcome. For example, the subjects recollection of dietary habits can be affected in case- control designs (but not in cohort studies) by the fact that they already have coronary artery disease. This is called recall bias.[1-3]

Disadvantages of cohort studies. 1. Prospective cohort studies are expensive and resource consuming. For example, to study the risk factors for lung cancer, a large cohort needs to be followed for long period of time to observe enough cases of lung cancer to provide meaningful results.[3] 2. Prospective cohort studies may be impractical for rare diseases. If a disease has an incidence of 1/100,000 of the population, then cohort needed to study this disease will be extremely large. Prospective cohort designs become more efficient as the outcomes become more common.[2]

Retrospective cohort studies. The design of retrospective cohort studies is essentially the same as that of the prospective cohort study.[1,2] It starts with identifying the cohort, followed by collecting data about predictor variables and follow the subjects to determine the occurrence of outcome. The difference is that the events being evaluated occurred in the past. The direction of inquiry is still forwarded in time such as the prospective cohort studies.

Choi et al[11] studied retrospectively 267 patients hospitalized with probable or confirmed diagnosis of SARS. They examined certain prognostic factors, such as respiratory failure and renal failure. They collected information about their outcome (mortality). They found that respiratory and renal failure were associated with increased mortality. They found that age older than 60 years and elevated lactate dehydrogenase level were independent predictors of mortality.

Advantages of retrospective cohort studies. 1. Retrospective cohort studies have some of the advantages of prospective cohort studies. They provide information about incidence, and they are useful when an experimental study is not possible. Also, because the measurements are collected before the outcomes are known, the measurement of predictors cannot be biased by the knowledge of the outcome (recall bias).[1,3] 2. Retrospective cohort studies have the following, advantages over prospective studies: a. They are useful particularly for rare diseases.[1] b. They are less costly and time-consuming. c) The subjects are already assembled, measurements are already made and the follow-up is already completed.[2]

Disadvantages of retrospective cohort studies. 1. The already documented data may not answer the

study question. 2. Even if the needed data exist, it may be inaccurate or incomplete.

Experimental studies. In experimental studies, the researchers apply an intervention (therapy or procedure) and observe the effect on an outcome. Experimental studies that involve humans are called clinical trials.

Clinical trials can be classified based on the use of control to controlled trials and uncontrolled trials as follows:[1]

A. Controlled trials. ***1. Trials with concurrent controls.*** In this type of trials, there are 2 groups of patients: the experimental group, which is given the intervention under investigation and the control group, which is given exactly the same treatment except for the investigational intervention. Any difference that appears between the 2 groups can be attributed to the experimental intervention. There are 3 types of control groups used in medical research:[1-3] (i) No treatment control, in which the patients in the control group receives no treatment at all. The drawback of such design is that one cannot exclude the possibility that the effect seen with the intervention is not related to the properties of the intervention itself but rather to the placebo effect seen with any intervention or therapy. (ii) Placebo control. In this type of control, the patients in the control group are given an inert placebo treatment. (iii) Conventional therapy. In some medical conditions, in which a standard treatment already exists, new treatments should be compared with those already existing.

The assignment of study subjects to the experimental group versus the control group can be randomized or non-randomized. Randomization ensures that the 2 groups are equal in their characteristics.

Randomized control trials. Among all study designs, randomized control trials provide the strongest evidence for concluding causation and provide the best assurance that the observed effect was related to the intervention.

To further strengthen this design, double-blinding is used, in which neither subjects nor investigators know whether the subject is assigned to the experimental group or to the control group.[12]

Both randomization and blinding are aimed at eliminating the effects of confounding factors, but these 2 techniques work at different levels.[2] Randomization eliminates the influence on confounding factors present at the time of randomization but not during the follow-up period. Blinding eliminates the effect of confounding factors after randomization. In an unblinded study, the investigator may intentionally or non-intentionally give extra attention or therapy to the patients assisted to the experimental group; therefore, the observed result may be unrelated to the experimental investigation itself. Blinding will eliminate such an effect. The second important value of blinding is to prevent biased assessment of outcomes. In unblinded study, the investigator may look more carefully to outcomes he expects to be associated with the experimental intervention, again leading to be biased results.

Double-blinding may not be always possible and single-blinding is used.[12] In this case, the subject alone is unaware whether he is in experimental or the control groups. In some unusual circumstances, the investigator is blinded but not the subject. Blinding may not be possible at all in certain randomized control trials, especially in those involving procedures such as surgery. In such studies, the outcomes can be measured by "blinded" ratters, for example, if the outcomes involve a laboratory or radiological testing.

Examples of randomized control trials (i) Brenner et al[13] conducted a double-blinded randomized controlled trial to examine the effect of losartan, an angiotensin-II-receptor antagonist in halting the progression of diabetic nephropathy. The investigator enrolled 1513 patients with diabetic nephropathy who were randomized to receive losartan versus placebo in a double-blinded fashion. The primary outcomes were the composite of a doubling in the baseline creatinine, end-stage renal disease or death. They found that losartan reduced the incidence of doubling creatinine concentration and end-stage renal disease but had no effect on mortality. This is an example of a randomized double blinded trial. (ii) O'Dwyer et al[14] compared hernia repair performed under local anesthesia versus general anesthesia. Two hundred seventy-nine patients with hernia were enrolled and randomized to local or general anesthesia. The primary outcomes were pain, return to activity and costs. They found that return to normal activity was similar in both groups. However, pain and cost were less in the local anesthesia group. This is an example of a randomized unblinded trial.

Non-randomized trials. In this type of study, the investigator compares groups that have not been randomized. These are often called comparative studies. Non-randomized trials are subject to many sources of bias in patient assignment and in patient follow-up.

Lundberg and Kristoffersson[15] compared laparoscopic and open cholecystectomy for gallbladder carcinoma patients with diagnosis of gallbladder cancer, 210 had open surgery and 60 had laparoscopic cholecystectomy. The primary outcome was the development of incisional metastasis, which the investigator found to occur more frequently in the laparoscopic group. One cannot exclude that the observed results are related to differences in the baseline characteristics of the 2

groups, since the assignments to one group or the other were decided by the treating teams. These studies are subjects to bias at different levels including the patient assignment, follow-up and outcome assessment. Therefore, the results of such studies are often questionable.[1]

Frequently, these studies are chosen occasionally because of the mistaken belief that they are more ethical than randomized controlled trials. However, the ethical basis for any trial is the uncertainty about the effectiveness of the experimental intervention. Ethical study is the one that try to answer the scientific question conclusively; in this regards randomized controlled trials are by far better than non- randomized trials.[2]

2. Trials with sequential controls. a) Trials with self-control. In these studies, also called time-series studies, the study subjects serve as their own controls.[1] The investigator selects his study sample and measures baseline and outcome variables before introducing the experimental intervention. Then after the intervention is introduced the researcher measures again the outcome variables.

Advantages of of self-controlled trials. Because each subject serves as his own control, certain characteristics such as age, gender and genetic factors are identical in the pre-and post intervention phases, therefore, they are eliminated from being confounding factors.

Disadvantages of self-controlled trials. 1. One of the major disadvantages of studies with self-control is that the effect seen with the intervention could be related to the learning effect, as the participant simply change certain practices because they learned from the first phase of the study.[1-2] 2. The apparent effect can also be related to cyclic changes in the whole population and has nothing to do with the intervention. For example, If the main outcome of a study with self- control is the incidence of upper respiratory infections, the changes seen can be simply related to the seasonal variations in upper respiratory tract infections.[1-2]

b) Cross-over studies. This design combines 2 types of controls: concurrent and self-control. In this design, the participants are divided into 2 groups: one assigned to the intervention and the other to the placebo. After a period of time, the outcomes are measured for the 2 groups and the intervention and placebo are both withdrawn. Both groups are left without receiving the intervention or placebo for a period called washout period. Then the groups are given the alternative therapies: the first group now is given the placebo and the other is given the intervention.[2]

Cromheecke et al[16] compared self-management of oral anticoagulant therapy using a portable coagulation monitoring device with conventional management by a specialist anticoagulation clinic. Fifty patients on long-term oral anticoagulant treatment were randomized to self-management or anticoagulation clinic management for a period of 3 months. After this period the alternative strategy was followed for each patient. International normalized ratio were measured at intervals of 1-2 weeks in both periods without knowledge of type of management. The primary endpoint was the number of measurements within the therapeutic range. The authors found no significant difference in the overall quality of control of anticoagulation between the 2 approaches.

Advantages of cross-over studies. 1. By having 2 different types of controls, many confounding factors are eliminated.[1] 2. The concern about the learning effect seen with studies with self-control is overcome by having a concurrent control group.[2]

Disadvantages of cross-over studies. Cross-over studies are not suitable for certain types of interventions or outcomes. For example, crossover studies cannot be performed to examine the effect of antibiotics on certain infections nor they can be used if the outcome is mortality or survival.

3. Trials with external controls. In these trials, the researcher uses control from previously performed studies when obtaining concurrent control is not possible. Also, the control can be obtained from previous patients with the same condition by reviewing medical records.[1]

When a difference is seen between the investigation group and the historical control group is seen, the main concern is that the difference is related to changes in other aspects of management and not necessary to the experimental intervention.[1] However, such studies can be useful for planning future studies and also for incurable diseases such as advanced cancer.

B. Uncontrolled studies. In these studies, the researcher describes the effect of the intervention on the study group without having a control group. Such studies are more common when investigating procedures more than when investigating medications.

Disadvantages of uncontrolled studies. In the absence of control group, it is impossible to know with certainty how much of the effect seen is related to the expected intervention and not to other confounding factors.[1]

With repeated studies like this, certain unproven procedures or treatment can become established. Attempting to subsequently perform a proper randomized controlled trial becomes a very difficult task.

In summary, this article illustrates the most commonly used study designs in the medical research. Each design has its own advantages and disadvantages. Randomized controlled trials provide the strongest evidence.[17] Well-conducted observational studies can provide useful data

regarding disease causation. Selecting the proper design to answer the research hypothesis is the key factor in conducting a successful study.

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