Overview of Clinical study design

Running title: Clinical Study Designs

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ABSTRACT

The goal of clinical study is to examine the associated factors to the disease and to assess the efficacy and safety of an investigational drug or procedure or device. Since the clinical study design is different according to the own characteristics of each type of the study, it is aimed to help researchers understand the design of each type of the clinical study, select the optimal type of study within the given research circumstances. Clinical studies are classified into the two main types, observational study and clinical trial, according to presence or absence of intervention applied to human for the study. Designs for case-control study, cohort study involving prospective study and retrospective study, case-control study within a cohort including nested case-control study, case cohort study, and cross-sectional study in observational study are explained. Also, controlled/non-controlled trial, randomized/non-randomized trial, open-label/blind trial, parallel/cross-over/factorial design trials and pragmatic trial are reviewed. Each type of clinical study has both advantages and disadvantages. Therefore, in consideration of the characteristics of designs of the study, the researcher must plan and proceed his or her study by choosing the type of the clinical study that can most scientifically achieve the study objective within the given study circumstances.

Key words: Clinical study, Observational study, Clinical trial, Study design, Bias
Introduction

Clinical study is medical study involving people. The goal of clinical study is to examine the associated factors to the disease and to assess the efficacy and safety of an investigational drug or procedure or device, for preventing, diagnosing, and treating disease. It can also be to investigate long-term effects or cost-effectiveness of the investigational treatment. There are two main types of clinical study, observational study, and clinical trial. In observational studies, investigators gather information according to broad characteristics. For example, investigators may collect data through medical exams or questionnaires about a group of older adults over time to learn more about the effects of different lifestyles on cognitive health. As well as the values of these observational studies in themselves, these studies may help identify new possibilities for clinical trials. In clinical trials, the studies are performed in people that are aimed at evaluating a medical, surgical, or behavioral intervention. They are the primary way that investigators find out if a new treatment is safe and effective in people. Clinical study results have clinical, public, and economic impacts, and therefore, well-planned clinical study is required to provide valid study results.

Since each study design is different according to the own characteristics of each study type, it is important to choose the optimal study type for the study objective given the study environment. In this article, by introducing the design of each type of clinical study, it is aimed to help researchers understand the design of each type of the clinical study, select the optimal type of study within the given research circumstances.

Observational study designs

A type of study in which certain individuals are observed or certain outcomes measured without manipulation or intervention to affect the outcome. The analytical study designs include case-control study, cohort study, and cross-section study.
**Case-control study**

Case-control studies are study designs that compare two groups, such as the subjects with disease or condition under study (cases) to the subject without disease or condition (controls). Investigators study the medical or lifestyle histories of the people in each group to learn what exposure may be associated with the disease or condition (fig. 1). If an exposure is found more commonly in the cases than in the controls, the investigator can hypothesize that the exposure may be linked to the disease. For example, to investigate risk factors of depression in intensive care unit (ICU) patients, the patients with depression were defined as cases, and gender, age (years), length of ICU stay (days), and medicated drug were considered as risk factors associated the depression [1].

Advantages and disadvantages

Main advantage of case control study is less expensive and less time-consuming than cohort study. The case-control approach allows for the study of rare disease that takes too long to develop. The case-control study design also makes it possible to look at multiple risk factors at once. This is because, after setting the cases and controls, data can be obtained from the various source of data such as past medical records of the cases and controls without newly investigating factors that may be related to the disease of the study.

Bias is inherent in case-control studies. Case control studies have the potential for recall bias. Recall bias in a case-control study is the increased likelihood that those with the outcome will recall and report exposures compared to those without the outcome. Recall bias may lead to concluding that there are associations between exposure and disease that do not, in fact, exist. One of the aspects that is often overlooked is the selection of cases and controls. It is important to select the cases and controls appropriately to obtain a meaningful and scientifically sound conclusion and this can be achieved by implementing matching. This would help identify risk factors or probable etiologies that are not due to differences between the cases and the controls. Thus, the investigator must put a great deal of effort into creating a proper control group to bolster the strength of the case-control study as well as enhance their
ability to find true and valid potential correlations between exposures and disease states. The investigator also must recognize the potential for failing to identify confounding factors, introducing the possibility of confounding bias, which occurs when a variable that is not being accounted for that has a relationship with both the exposure and the outcome.

Cohort study

Cohort studies are a type of longitudinal study, an approach that follows study participants over a period of time. Specifically, cohort studies recruit and follow study participants who share common characteristics. When people join a cohort study, the investigators gather data about them to get a more detailed picture of the group they are studying such as biological, social psychological, medical, environmental, genetic etc. This information forms the baseline for the study. Later, investigators collect data from different points in the participants’ lives. Investigators compare the development of disease between the two groups, the exposed group and the non-exposed group by the baseline data of participants who did not initially have a disease. Also, by comparing data from the follow-up points to the baseline, investigators can see how change of the factors have affected the group members’ health.

Prospective cohort study and retrospective cohort study

Cohort studies can be classified as prospective cohort studies and retrospective cohort studies. A forward-looking cohort study is known as a prospective cohort study, and a backward-looking cohort study is called a retrospective cohort study (fig. 1).

Prospective cohort studies involve recruiting a group of participants and following them over time to gather new data. Investigators follow the participants from presence of exposure to development of disease for the investigation between exposure and disease. As a prospective cohort study for syncope prognosis based on emergency department diagnosis, a cohort was a group of the adult patients with emergency department (ED) visits for syncope. The patients were follow up to investigate the frequency of occurrence of the serious outcomes at 30 days and the associated factors with the outcome [2].
Retrospective cohort studies involve using preexisting data. For investigation between exposure and disease, retrospective cohort studies identify a population with and without the risk exposure based on past records and then assess if they had developed the disease at the time of study. For example, to determine the effects of three aspects of care provided by primary physicians (physician specialty, continuity of care and comprehensiveness of care) on their patients’ use of the ED, investigators created a retrospective cohort of adults aged 18 years and older using provincial administrative databases covering a three years period. Primary care variable and covariables were measured during an initial baseline period (the first two years of the study); visits to ED of the primary outcome were measured during the last year of the study [3].

Advantages and disadvantages

Cohort studies are an effective method of establishing cause and effect. As they are usually large in size, investigators are able to draw confident conclusions regarding the link between risk factors and disease. In many cases, because participants are often free of disease at the commencement of the study, cohort studies are particularly useful at identifying the timelines over which certain behaviors can contribute to disease. Another advantage is that cohort studies can collect a wide variety of data that investigators can use in many ways. A study on the impact of smoking, for example, might reveal links with multiple types of diseases. Investigators can also assess how risky a factor is in comparison with others.

Some of the biases observed with cohort studies include selection bias and information bias. Some individuals who have the exposure may refuse to participate in the study or would be lost to follow-up, and in those instances, it becomes difficult to interpret the association between and exposure and outcome. Also, if the information is inaccurate when past records are used to evaluate for exposure status, then again, the association between the exposure and outcome becomes difficult to interpret. Study participants are aware that they are part of a study cohort, it may influence on their behavior during follow-up, thus on causal inference.

Prospective cohort study is time-consuming and often more expensive than case-control studies.
Retrospective cohort study is a more pragmatic approach, as it can be completed more quickly using historical data. However, this retrospective approach increases the risk of bias in the sampling of the cohort, with greater likelihood of missing data. Retrospective cohort studies are also weakened by the fact that the data fields available are not designed with the study in mind instead.

**Case-control studies based within a defined cohort**

This type of study has a form of study design that combines some of the features of a cohort study design and a case-control study design. When a defined cohort is embedded in a case-control study design, all the baseline information collected before the onset of disease, then the cohort is followed onset of disease. One of the advantages of following the above design is that it eliminates recall bias as the information regarding risk factors is collected before onset of disease. Case-control studies based within a defined cohort can be further classified into two types: Nested case-control study and Case-cohort study.

**Nested case-control study**

This type of study design involves the selection of several controls for each case, typically from those still under observation at the time when the case developed the disease. A nested case-control study consists of defining a cohort with suspected risk factors and assigning a control within a cohort to the subject who develops the disease [4]. Over a period, cases and controls are identified and followed as per the investigator’s protocol. Hence, the case and control are matched on calendar time and length of follow-up (fig. 2A). When this study design is implemented, it is possible for the control that was selected early in the study to develop the disease and become a case in the latter part of the study. Sampling of the nested case control study is as follows. Select all those who become cases. Select controls randomly from those still at risk at time of the cases (called as riskset), usually select 5 controls per case since more than 5 controls only improves minor efficiency. Controls are time-matched to cases. Persons can be controls more than once, and a person selected as control may later become a case. In
the matching process, additional matching on confounders is often involved. To examine the association between incident injury after prescription opioid initiating and subsequent risk of opioid-related adverse events (ORAEs) and to assess whether the association differs by recency of injury among older patients, the nested case-control study was conducted within a cohort of individuals aged 65 years or older. ORAE cases were identified as patients who had an inpatient or outpatient encounter with diagnosis codes for opioid misuse, dependence, or poisoning. Using 1:4 matching, controls were randomly selected using incidence density sampling with matching criteria including the year of cohort entry date and a disease risk score [5].

However, nested case-control studies have some limitations. When there are more than one disease outcomes considered, a strict implementation of the nested case-control design requires the selection of a new set of controls for each distinct disease outcome. We cannot estimate rates or risks, since we do not know the underlying person-time at risk. If we know the size of risksets and sampling fractions in each riskset, then it is possible to estimate rates. But it is not trivial, especially if there are time-dependent effects.

Case-cohort study

Case-cohort study designs were proposed as an alternative to the nested case-control study design. It requires only the selection of a random sample, named a sub-cohort, and all cases. Cases are defined as those participants of the cohort who developed the disease of interest, but control are identified before the cases develop (fig. 2B). This means that controls are randomly chosen from all cohort participants regardless of whether they have the disease of interest or not, and that baseline data can be collected early in the study. Case-cohort studies are very similar to nested case-control studies. Thus, the main difference between the two studies is the way in which controls are chosen. A case-cohort study was conducted to examine the association between the following risk factors and hospitalization: infection, complicated injury, host-defense abnormality, number of previous evaluations for the injury, and anatomic location of the bite. The case-cohort design was chosen because cases could be identified in a well-defined administrative cohort, medical record review was required for each study patient, and
the risk ratio was the effect measure of interest. The cohort consisted of patients with ED visit evaluated for dog bite injuries. Cases were cohort members who were admitted as inpatients directly from the ED. From the cohort, a simple random sample was selected for the subcohort comparison group. Some patients were included into both of subcohort and cases [6].

Compared to the nested case-control studies, a major advantage of the case-cohort design is the ability to study several disease outcomes using the same subcohort. For example, suppose that investigators are interested in whether smoking is a risk factor for diabetes as well as lung cancer. Under this situation, two control groups need to be sampled under the nested case-control design while a case-cohort design only requires one subcohort which is sued to evaluate the effect of smoking for both diabetes and lung cancer. Unlike nested case-control study, case-cohort study can estimate rate or risk, since the measurement in subcohort can be observed at any time up to t (e.g. elapsed time from a variable event, such as menopause, birth) and person-time risk can be calculated. Case-cohort study has some limitations. Information bias can be increased because subcohort may have been established after baseline. If there are many censoring, the subcohort will be “thin” in the end and not be the representative of the cohort. Analysis is rather complicated than nested case-control study.

**Cross-sectional study**

A cross-sectional study is a type of observational study that analyzes data from a population, or a representative subset, at a specific point in time. It involves data collected at a defined time. They are often used to assess the prevalence of acute or chronic condition, but cannot be used to answer questions about the causes of disease or the results of intervention. That is, cross-sectional data cannot be used to infer causality because temporality is not known. Cross-sectional studies may involve special data collection, including questions about the past, but they often rely on data originally collected for other purposes.

Advantages and disadvantages
The use of routinely collected data allows large cross-sectional studies to be made at little or no expense. A natural progression has been suggested from cheap cross-sectional studies of routinely collected data (e.g. National Health Examination and Nutrition Survey) which suggest hypotheses, to case-control studies testing them more specifically, then to cohort studies and trials which cost much more and take much longer, but may give stronger evidence.

Temporal association cannot be established as the information is collected at the same point of time. If a study involves a questionnaire, then the investigator can ask questions to onset of symptoms or risk factors in relation to onset of disease. The incidence, but not prevalence, cannot be measured. Cross-sectional study is not good for studying rare disease, and is susceptible to biases such as nonresponse bias and recall bias.

Advantages and disadvantages of each type of study in observational studies are listed in Table 1.

**Clinical trial**

A clinical trial is a prospective study of the effects of intervention or manipulations of interest in humans. Since this type of study can provide the most convincing demonstration of evidence of causality, the design of the study requires meticulous planning and resources to provide an accurate result.

**General considerations**

While designing a clinical trial, it is important to select the population that is best representative of the target population of intervention of the study, to be able to generalize the results obtained from the study to the target population. It is also important to select appropriate endpoints while designing a trial. Endpoints need to be well-defined, reproducible, clinically relevant and achievable. The types of endpoints include continuous, ordinal, nominal and time-to-event, and it is typically classified as primary, secondary or tertiary. An ideal endpoint is a purely clinical outcome, for example, cure/survival, and thus, the clinical trials will become very long and expensive trials. Therefore, surrogate endpoints
may be used that are biologically related to the ideal endpoint. Surrogate endpoints also need to be reproducible, easily measured, related to the clinical outcome, affected by treatment and occurring earlier than clinical outcome.

**Controlled vs non-controlled trials**

Regarding the presence (or absence) of a control group as comparator to the investigational treatment, clinical trials are divided into controlled clinical trial versus non-controlled clinical trial.

Uncontrolled trials

Uncontrolled trials are often used in the early phases of drug research, phase I and II, to determine pharmacokinetic properties or to investigate tolerated dose ranges. They can also be useful to study side effects, biochemical changes in long-term therapies, tolerance, interaction or efficacy of drugs. It is known that uncontrolled trials produce higher estimates of the mean effect than those obtained in a controlled trial, since by not having a control group acting as a reference, they can induce erroneous impressions about the results of the investigated drug [7]. As they can generate a certain bias, the results of uncontrolled trials are considered less valid than those of controlled trials.

Controlled trials

The design of these trials includes at least one treatment group that is compared with a control group. The control group receive placebo or another effective treatment. Both groups are studied simultaneously, except when historical data are used as a control or some adaptive designs are used. These types of trials are the most common in phase III trial. Controlled trials allow the participant’s outcome to be discriminated from an outcome caused by other factors, such as the natural history of the disease or the expectations of the participant or the investigator.

The controls that are usually used are placebo control, active treatment control, control with dose comparison, and historical control, and particular care must be considered when attempting to use
placebo control and historical control.

Placebo control

Placebo is defined as ‘an inert or innocuous substance used especially in controlled experiment testing the efficacy of another substance (such as a drug) (Placebo. Merriam-Webster Dictionary. Accessed 21/03/2023). This is especially useful if the outcome measured is subjective, and should only be used if no permanent harm (death or irreversible morbidity) occurs by delaying available active treatment for the duration of the trial. The ethics of placebo-controlled studies is complex and remains a debate in the medical research community. According to the Declaration of Helsinki on the use of placebo released in October 2013, “The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances: Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the participants who receive any intervention less effective than the best proved one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option [8]. Hence, while designing a research study, both the scientific validity and ethical aspects of the study will need to be thoroughly evaluated.

Active treatment control

This design involves comparing a new drug with a standard drug or comparing the combination of new and standard therapies versus standard therapy alone. This design is more ethical, provided that approved drugs are available for the disease under study.

Control with dose comparison

Different doses or regimens of the same treatment are used as active arm and control arm. The purpose is to establish a relationship between the dose and the efficacy/safety of the intervention. This design
can include active and placebo groups in addition to the different dose groups. The design may be ineffective if the therapeutic range of the drug is not known.

Historical control (external and non-concurrent)

In this design, the information from the controls is not obtained during the study, but is from subjects who were treated at an earlier time or in a different setting. The type of design has an advantage when studying rare conditions where it is difficult to generate a sample size, and is cost-effective and time saving. On the contrary, it has many disadvantages such as that randomization and blinding is not possible and that the comparability of the current intervention with the historical control is difficult due to the differences in the baseline characteristics of the subjects in the study group versus the historical group even if it can be solved to some extent by statistical methods. The information obtained may not be accurate, reliable, lack uniformity and/or completeness as well.

Randomized vs non-randomized clinical trials

According to the method used to allocate a participant to a treatment or control group, clinical trials are called as randomized clinical trials or non-randomized clinical trials.

Randomized clinical trials

A randomized clinical trial involves randomizing participants with similar characteristics to two group (or multiple groups): the group that receives the intervention/experimental therapy and the other group that received the placebo or standard of care. This is typically performed by suing a computer software. Hence, we can measure the outcomes and efficacy of the intervention/experimental therapy being studied without bias as participants have been randomized to their respective groups with similar baseline characteristics. This type of study design, randomized controlled trials, is considered gold standard for clinical study. However, this study design is generally not applicable to rare and serious disease process as it would unethical to treat that group with a placebo.
Non-randomized trials

A non-randomized trial involves an approach to selecting controls without randomization, usually allocate participants into the group by the investigator or selection of participants and controls on certain days of the week or certain clinician. This type of the selection of participants becomes predictable and therefore, there is bias with regards to selection of participants and controls that would question the validity of the results obtained.

Open-label vs blind trials

Clinical trials are divided into open-label trial versus blind trial based on participants’ or investigators’ awareness of the treatment group to which participants have been allocated.

Open-label trials

Certain treatments cannot be blinded such as surgeries or if the treatment group requires an assessment of the effect of intervention such as quitting exercise. In this case, open-label trials are planned in which both trial participants and investigators know which group the participants were assigned to.

Blind trials

This is a method used in clinical trials to reduce the risk of bias, which may be intentional or not, when trial participants and/or investigators are aware of which participants are receiving treatment (or control). There are 3 forms of blinding: single-blinded, double-blinded and triple-blinded. In single-blind study, the participants do not know to which group they have been assigned, but investigators do until the trial is over. In double-blinded studies, both the study participants and the investigator are unaware of the group to which they were allocated to. Double-blinded studies are typically used in clinical trials to test the safety and efficacy of the drugs. In triple-blinded studies, participants, investigators, data analysts are aware of the group allocation. It is also recommended that those who will be directly or indirectly involved in the trial, such as caregivers and data recorders, are blinded to the group allocation of the
trial participant in order to increase the effect of blinding.

**Parallel design, Cross-over design, and Factorial design trials**

Based on the treatment structure, clinical trial designs are classified into parallel, cross-over, factorial design.

**Parallel design trials**

A parallel design in clinical trial is a type of design in which two or more groups of participants receive different interventions. Participants are assigned to one of the treatment arms at the beginning of the trial and continue in that arm throughout the length of the trial (fig. 3). It is the most commonly used clinical trial design.

**Advantages and disadvantages**

Parallel design has two advantages over the cross-over design described later. All other conditions being the same, the duration of the study is shorter and the visits fewer, which results in a study less burdensome for the participant. The statistical analysis requires fewer assumptions, which, if not verified, would reduce the reliability of the conclusions. The weakness of the parallel design is that, under all other conditions being the same, it requires a larger sample size comparing to the cross-over design.

**Cross-over design trial**

Cross-over clinical trial is a type of clinical trial in which all participants receive the same two or more treatments, but the order in which they receive them depends on the groups to which they are randomly assigned. Hence, in this type of design, there are two groups who undergoes the same intervention/experiment at different time periods of the study. That is, each group serves as a control while the other group is undergoing the intervention/experiment. Depending on the intervention/experiment, a ‘washout’ period is recommended in order to eliminate residual effects of
the intervention/experiment (carryover effect) when the experiment group transitions to be the control
group vice versa (fig. 3).

Advantages and disadvantages

Main advantage of the cross-over design is that each subject acts as a his or her own control, and that a
smaller number of subjects are required in comparison to parallel group studies because of removing
participant variation in this way. This type of trial can only be considered when the disease persists for
a longer period of time, hence, cross-over trials are mostly used in studying chronic diseases. Main
disadvantage is carryover effect may be aliased (confounded) with direct treatment effects, in the sense
that these effects cannot be estimated separately.

Factorial trial

In a factorial trial, two or more intervention comparisons are carried out simultaneously. For example,
participants may be randomized to receive aspirin or placebo, and also randomized to receive a
behavioral intervention or standard care. This factorial trial has two factors, each of which has two
levels; there are called 2x2 factorial trials (fig. 3). When designing a factorial trial, the main intention
of investigators is to achieve ‘two trials for the price of one’, and the assumption is made that the effects
of the different active interventions are independent, in other words, there should be no interaction (no
synergy or antagonism) between the treatments. No interaction effect between the two treatments can
be tested by a proper methodology. Since a 2x2 factorial trial can be seen as two trials addressing
different questions, it is important that both parts of the trial are reported as if they were just a two-arm
parallel group trial. Thus, we expect to see the results for aspirin versus placebo, including all
participants regardless of whether they had behavioral intervention or standard care, and likewise of the
behavioral intervention. We would also evaluate whether there may have been some interaction between
the treatments (i.e. effect of treatment A depends on whether treatment B or ‘not B’ was received) from
the factorial design.

Advantages and disadvantages
Factorial design allows investigators to obtain evidence about efficacy from fewer patients that would be needed if treatment A and treatment B were individually tested in the two separate trials. The main disadvantage is the difficulty of experimenting with more than one factors, or many levels. A factorial design has to be planned meticulously, as an error in one of the levels, or in the general operationalization, will jeopardize a great amount of work.

A summary of the advantages and disadvantages of each design are provided in Table 2.

**Pragmatic clinical trial design**

Classical clinical trial did not adequately inform practice because they were often strictly optimized to determine efficacy of intervention. Because such trials were also performed with relatively small size of participants at sites with experienced investigators and highly selected participants, they could be overestimating benefits and underestimating harm of intervention. These concerns lead more pragmatic trials, designed to show the real-world effectiveness of intervention in more generalized settings. Trial design can be more pragmatic considering four domains: the study population, the setting of the trial; operationalization of the intervention, and the outcome measures [9,10]. In order to provide the comprehensive evaluation of comparative clinical effects of 0.9% saline and balanced crystalloids across the full spectrum of diseases typical for hospitalized adults, a pragmatic trial was conducted among noncritically ill adults and were subsequently hospitalized outside an ICU. This trial was designed considering broad eligibility criteria, large sample size, study procedures including routine care, and execution of trial by clinical personnel [11,12].

**Conclusion**

The different types of clinical studies are used for different reasons. Selecting the best type for the study is critical to a successful outcome. In terms of the quality of evidence, clinical trial is superior to
observational study. But observational studies are conducted much more frequently than clinical trials. One of the main reasons the observational studies are used are when a clinical trial would be considered unethical, such as a life-saving medication used in a public health emergency. Another main reason is the lower cost for the observational study. Case-control study is still a good tool for exploring risk factors for rare diseases or when other types of study are not feasible. Investigators explore any possible association between exposure and disease through case-control study, and can then use the data from the case-control study to focus us a few of the most likely causative factors and develop additional hypotheses. Then through cohort studies or clinical trial, the investigator may be able to develop further support for the firm evidence of the association between exposure and disease. Cohort studies bring with it some important challenges, often related to their size, complexity and longevity. However, with careful planning and implementation, cohort studies can make valuable contributions to the development of evidence based in healthcare. To reduce cost and achieve the same goal as a cohort study, nested case-control and case-cohort study can be alternatives. These types of studies are based on some large size of cohort, and can be useful in analysis with big data [13]. Nested case-control and case-cohort study designs are efficient in terms of cost, and can be used to evaluate the relationship between exposure and disease. Compared to a nested case-control design, the case-cohort design is more efficient and allows an investigator to study several disease outcomes by using the same random sample [14]. While there are some advantages in observational studies, one should always pay attention to biases inherent in observational studies. In clinical trials, it is important to select the appropriate control group comparing with the investigational intervention group. Recently, as the studies using big data become possible, well-designed historical control studies have become possible. The clinical trial study should be planned so that people involved during the study as well as trial participants are blinded as much as possible. The classical trial designs are parallel, cross-over, and factorial designs. In addition, although it is not applicable to all types of diseases or all of clinical trials, the duration period for a clinical trial can be shortened as new methodologies such as adaptive designs develop. Investigators should also consider pragmatic clinical trials that are more efficient, patient-centered, and pragmatically
designed and conducted in order to provide more valuable information to clinical practice or policy decisions.
References


Table 1. Advantages and disadvantages of case-control study, cohort study, case-control study within a defined cohort, cross-sectional study

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Case-control study</td>
<td>Less expensive, less time-consuming</td>
<td>Vulnerable to bias (recall bias, selection bias, confounding bias)</td>
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<td></td>
<td>Good for the study of rare disease</td>
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<td>Can assess multiple risk factors at once</td>
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<td>Cohort study</td>
<td>Effective to establish cause and effect</td>
<td>Possibility of selection bias, information bias</td>
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<td></td>
<td>Useful to identify the timelines over which certain exposures can contribute to outcome</td>
<td>More expensive, more time-consuming (Prospective cohort study)</td>
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<td>Can collect a wide variety of data</td>
<td>Risk bias in the sampling the cohort (Retrospective cohort study)</td>
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<td>Nested case-control study</td>
<td>Can reduce the cost to perform the study</td>
<td>Require the selection of a new set of controls for each distinct disease</td>
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<td>Confounders can be matched in matching process</td>
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<tr>
<td>Study Type</td>
<td>Advantages</td>
<td>Limitations</td>
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<tr>
<td>Case-cohort study</td>
<td>The ability to study several diseases using the same subcohort</td>
<td>Require a more complicated statistical analysis</td>
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<td>Cross-sectional study</td>
<td>Useful to assess the prevalence of disease</td>
<td>Cannot infer causality</td>
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<td></td>
<td>Can suggest a natural progression with less cost</td>
<td>Cannot estimate incidence rate</td>
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<td></td>
<td></td>
<td>Not good for studying rare disease</td>
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<td></td>
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<td>Susceptible to nonresponse bias and recall bias</td>
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Table 2. Advantages and disadvantages of parallel, cross-over, factorial design

<table>
<thead>
<tr>
<th></th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td>Parallel design</td>
<td>Shorter duration of the study and less burdensome for the participant</td>
<td>Require a larger sample size comparing to cross-over design</td>
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<td></td>
<td>Require fewer assumption for the statistical analysis</td>
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<tr>
<td>Cross-over design</td>
<td>A smaller sample size comparing to parallel design</td>
<td>Possibility of carryover effect</td>
</tr>
<tr>
<td>Factorial design</td>
<td>Efficiency from fewer participants than separately performed trials</td>
<td>Difficulty for experimenting with more than one factors, or many levels</td>
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Figure 1. Case-control study, Prospective cohort study, Retrospective cohort study
Figure 2. Case-control study based within a defined cohort

Fig. 2. Case-control study based within a defined cohort. (A) Nested case-control study: Controls are time-matched to cases (B) Case-cohort study: Subcohort is not time-matched to cases
Figure 3. Parallel design trial, Crossover design trial, Factorial design trial

Parallel

Crossover

Factorial

Washout

Red: Treatment A only; Dotted: No treatment A; Black: Treatment B only; Dashed: No treatment B

Both treatment A and treatment B; Blue: Neither treatment A nor treatment B

Fig. 3. Parallel design trial, Crossover design trial, Factorial design trial