

# 5

## Evaluating clinical studies – step 1: what type of study is it?

### Learning objectives

#### Upon completion of this chapter, you should be able to:

- describe the main types of study designs
- describe the features, advantages and disadvantages of the observational study designs
- explain why the overall study design is important when evaluating studies and applying their findings to practice.

### Introduction

There are two broad types of published studies: descriptive (simply recording information from observing patients) and explanatory (using group comparisons as the basis for determining whether an exposure/treatment might cause or affect a condition or outcome). Descriptive studies include case reports (reporting observations in one or a small number of individual patients) and case series (reporting observations from a small group or series of patients). Since descriptive studies are generally not considered to be “studies” and are normally referred to as “reports,” we will focus on explanatory studies (consisting of experimental and observational studies).

### Experimental studies

Experimental studies (controlled or noncontrolled) involve *actual intervention* by the investigators (i.e., subjects are assigned and given the treatments by investigators). Controlled experimental designs are best (i.e., “gold standard”) since they use a treatment group(s) and a control (comparison) group(s). Types of control groups include placebo, active (use of another treatment with established efficacy for the condition studied), no treatment, or historical (comparison with a treatment previously studied; not commonly used and only when it is not possible to use a different type of control). The control group helps account for factors (other than the treatment) that might affect the study results. Investigators compare the effects seen in the control patients with those in the treatment patients to determine if there is a difference between them.

## Key Point

### Disadvantages of *n*-of-1 studies

- Inability to generalize results to others
- Difficult to impossible to perform statistical analyses
- Difficult to validate findings.

One unique type of experimental study has been called the “*n*-of-1” or single-subject research design. With this study, the researcher, often a primary care practitioner, identifies a specific patient to study. The researcher conducts a baseline assessment of the patient’s condition, followed by therapy initiation.

During/after therapy, the researcher measures changes in the condition. The researcher might decide, after stopping therapy and reassessing baseline measures, to repeat the therapy to determine if the same effects are again observed. If there is another therapy to study, after stopping the first therapy the researcher would reassess the baseline measures and then initiate the next treatment, repeating the same measurements during/after therapy. While the *n*-of-1 trial can be beneficial for studying individuals with rare conditions or those requiring unique, individualized therapy, its disadvantages do not allow it to replace other experimental designs. Readers should refer to a review by Janosky (2005) for more information about *n*-of-1 studies.

Since controlled experimental studies are critically important for determining therapy efficacy and in making clinical therapeutic decisions, this type of study will be the focus of subsequent chapters.

## Observational studies

Case-control, cohort, and cross-sectional studies are *observational* designs, meaning the treatment(s) taken or other exposures studied were *not given* by the study investigators. Although the controlled experimental study design is best, observational designs are generally used when it is not possible, feasible (e.g., for rare conditions or those that require a long time to develop), or ethical to use an experimental design. In these situations, they can provide very helpful information.

## Key Points

### Example – coffee consumption and pancreatic cancer

Investigators are interested in studying whether coffee intake is associated with an increased risk of pancreatic cancer development. They suspect that coffee might be a risk factor for pancreatic cancer.

### Would it be appropriate for the investigators to use an experimental design to test their hypothesis?

No. It is unethical for investigators to administer a therapy (coffee) to study subjects for the primary purpose of determining if they are more likely to develop an adverse

outcome (pancreatic cancer, usually fatal), without any possible offsetting advantages. Since cancer generally takes a long time to develop, an experimental study would also not be practical. An observational study design enrolling subjects already drinking coffee or diagnosed with pancreatic cancer would be appropriate here.

Table 5.1 provides a summary of each of the observational designs. The *case-control* design is used to determine the possible factors (e.g., exposures, drugs) influencing or causing an event or outcome. It is always *retrospective* (looking backward). Why? This design begins with patients who already have the event or outcome (cases) and another group of similar patients who lack the event or outcome (controls). The investigators need to look back in time in order to compare drug use or the extent of exposure in both groups *prior to* when they developed the outcome. If the cases are found to have significantly greater drug use or extent of exposure than the controls, a possible association exists between the drug/exposure and outcome development.

## Key Points

### Prospective versus retrospective cohort studies

A cohort study can be *prospective (concurrent)* or *retrospective (nonconcurrent, historical)* in nature. The basic design of each is the same: (1) first identify groups (cohorts) with and without the drug use/exposures of interest – no one has the outcome at the start; (2) follow the groups forward over time and measure differences in outcome development.

The nonconcurrent or retrospective design differs from the prospective cohort study in that *all* information (drug use/exposures and outcomes) is obtained from already existing medical records or databases. The start of a nonconcurrent cohort study occurs at a designated point in the past. The investigators initially select the cohorts for inclusion in either the study or control groups *with no knowledge* of whether or not the outcome later develops. Once all subjects are included the investigators examine the existing data, going forward in time from the starting point, to determine whether or not the subjects in each group developed the outcome of interest.

### Which cohort design, prospective or retrospective, is strongest?

The prospective concurrent design is best because it is less subject to bias and inaccuracies. The nonconcurrent or retrospective design is dependent upon existing records or databases that might be incomplete or incorrect.

The *cohort* design follows a study “cohort” (a group of individuals/subjects who share a common characteristic) over time to determine if a drug or other exposure will lead to the development of an outcome of interest. Unlike the case-control design, the subjects in a cohort study do not have the outcome at the start of the study. Instead, investigators identify subjects who are taking the drug or have the exposure of interest (study subjects), as well as similar subjects who are not taking the drug or who lack the exposure (control/comparison subjects). The investigators then follow the subjects

**Table 5.1** Observational study features, advantages, and disadvantages

Study type	Key features	Advantages (A) and disadvantages (D)
Case-control	<p><b>At start</b></p> <p>Select:</p> <p>Cases: patients who already have condition or outcome being studied</p> <p>Controls: patients who do not have the condition or outcome being studied but are otherwise similar to cases</p> <p><b>Compare in the groups:</b></p> <p>Extent of exposure to drugs or other factors thought to affect development of the condition or outcome: done <i>retrospectively</i> (looking back in past) through use of surveys, interviews, medical records, or medical databases</p> <p><b>Analyze and determine:</b></p> <p>Were cases more likely than controls to have been exposed to drugs or other possible causes of the condition/outcome?</p>	<p>A: Good for studying possible causes of adverse events or negative outcomes, especially rare/infrequent outcomes or those that take a long time to develop; faster, less expensive than prospective study designs</p> <p>D: Possible selection bias (are cases truly comparable to controls?); recall bias (patients' memories of an exposure might be inaccurate); interviewer/observer bias (interviewer might slant data collection if aware of who is a case or control); records or databases could be inaccurate or incomplete</p>
Cohort (follow-up)	<p><b>At start</b></p> <p>Select:</p> <p>Study subjects: subjects already taking certain drug(s) or who have an exposure(s) that might affect the outcome of interest</p> <p>Control/comparison subjects: subjects who are not taking the drug(s) or who do not have the exposure, but who are otherwise similar to study subjects</p> <p><b>Compare in the groups:</b></p> <p>Extent to which subjects in each group develop the condition/outcome: done by following subjects forward over time (<i>prospectively</i>, if starting point in present time and data about outcome development obtained in future; <i>retrospectively</i>, if complete medical records exist over an extended time that allow the starting point (exposure or no exposure) to be in the past, with data about outcome development obtained by looking through subsequent medical records)</p> <p><b>Analyze and determine:</b></p> <p>Were the study subjects more likely than the comparison subjects to develop the condition or outcome?</p>	<p>A: Good for studying possible causes of adverse events or outcomes especially if they occur relatively commonly, or how/if certain exposures or characteristics might affect later outcome development</p> <p>D: Possible selection bias (are study subjects truly comparable to control/comparison subjects?); with prospective design: can take long time to complete, subject drop-out (loss to follow-up) could occur, potential expense; retrospective design shares disadvantages of case-control design</p>

Table 5.1 (continued)

Study type	Key features	Advantages (A) and disadvantages (D)
Cross-sectional (prevalence, survey)	<p><b>At start:</b> Subjects identified who represent a population of interest; they might/might not have the exposure(s) or the outcome(s) of interest</p> <p><b>Compare in group:</b> Presence and absence of both exposures and the condition or outcome of interest: determined at same time, resulting in “snapshot” or “cross-section” of the exposures and outcomes present at one given time (done through use of surveys, questionnaires, or examination of databases or patient records)</p> <p><b>Analyze and determine:</b> What are the factors or exposures associated with certain conditions or outcomes, and what is their prevalence?</p>	<p>A: Can identify possible risk factors for or potential causes of a disease or condition, the prevalence of a disease or condition at a specific point in time, or if beliefs or practices affect health or behavioral outcomes; relatively quick, inexpensive</p> <p>D: Cannot determine whether the “cause” (characteristics or exposures) actually preceded or resulted in the “effect” (outcomes); group identified for study inclusion might not adequately represent desired population of interest; subject self-reporting in surveys or questionnaires might not be accurate or nonresponse might be a problem</p>

in both groups (through scheduled visits, by examining medical records) over a certain period of time to compare the extent to which they develop the outcome. If significantly more subjects in the study group develop the outcome compared to the control subjects, it is concluded that the drug or exposure might contribute to outcome development.

In a *cross-sectional* design, the study sample is selected from a targeted population of interest and information about both the extent of drug use/other exposures as well as the presence of the outcome is obtained from the sample at the same time. Thus, the cross-sectional study provides a “cross-section” snapshot of the prevalence or existence of specific conditions, characteristics, and outcomes at *one point in time*. The investigators obtain all the exposure and outcome information from the study sample through the use of questionnaires or surveys. The data from subjects within the sample are compared and analyzed based on the presence or absence of these factors. Since a cross-sectional study collects data about past exposures or drug use from subjects’ recollections or records, it is subject to similar limitations as the case-control study. The cross-sectional study also lacks a separate control/comparison group.

Please refer to Abate (2012) for further details about the types of studies and their advantages and disadvantages.

## Worked example

### Example 5.1

Investigators wish to study if aspirin might lead to Reye's syndrome development in small children who take aspirin for a viral illness. Children with a viral illness who later developed Reye's syndrome were identified, along with other children with a viral illness who did not develop Reye's syndrome. The use of aspirin during the viral illness, including dose and duration of therapy, was analyzed and compared in both groups through interviews with parents.

#### What study design was used?

Case-control. The children with Reye's syndrome (condition/outcome present) were the cases, and the children without Reye's syndrome were the controls.

#### What was compared/analyzed?

Use of aspirin in both groups. Since the exposure (in this case, aspirin use) must *precede* development of the condition/outcome (Reye's syndrome), information about the exposure is obtained by looking in the past (retrospective). Greater aspirin use in the cases might indicate a link between aspirin use and development of Reye's syndrome. However, even if aspirin use was much greater in the cases, this study design cannot *prove* that aspirin causes Reye's syndrome.

## Worked example

### Example 5.2

Previous studies in adults have indicated a possible link between low vitamin D levels and depression symptoms. Since children can also develop depression, investigators studied whether low vitamin D levels might be associated with depression in children. Several hundred children were identified and their vitamin D concentrations were measured. The children were then divided into groups based upon their vitamin D level: low, normal, or high. The children were followed over the next 3–4 years and were periodically tested to determine if they developed symptoms of depression.

#### What study design was used?

Cohort. The children were initially divided into groups based upon the extent to which they had the exposure/factor of interest (vitamin D level); the study subjects had low vitamin D levels and children in the comparison groups had normal or high levels. There was no therapy intervention. The investigators did not administer vitamin D to the children but rather measured existing concentrations, so the design was not experimental.

#### What was compared/analyzed?

Development of depressive symptoms (condition/outcome) in all children. Children were followed prospectively over time to determine the extent to which depression occurred. Greater depressive symptoms in children with low vitamin D levels compared to those with normal to high levels could indicate a link between vitamin D deficiency and depression. However, even if depression developed to a much larger degree in children with low vitamin D concentrations, this study design cannot *prove* that a vitamin D deficiency causes depression.

A summary of key points and how to apply the information from this chapter to practice follow.

## Key Points

- In general, the order of the study designs from strongest (best) to weakest (most limitations/disadvantages) is: (1) controlled experimental; (2) prospective cohort; (3) case-control/cross-sectional/retrospective cohort.
- Due to their possible disadvantages, observational studies (case-control, cohort, cross-sectional) *cannot prove* that a drug or exposure caused a certain outcome; only well-designed controlled experimental studies can do this.
- Observational studies can still provide very useful information when it is not possible, feasible, or ethical to conduct an experimental study (for example, to study whether a drug or other exposure might cause an adverse outcome or to study the factors that might predispose to development of a rare or infrequently occurring condition).

### How to apply to practice

- If a news report claims that a drug or other exposure causes a certain adverse outcome based upon findings from an observational study, this might not be accurate. Further investigation is generally needed for confirmation.
- For the weakest study designs (case-control, cross-sectional, retrospective cohort), confirmation of their results by further study is even more important.

## Self-assessment questions

### Question 1

A study was conducted to determine whether daily users of nonsteroidal anti-inflammatory drugs (NSAIDs) were at lower risk of developing benign prostatic hyperplasia (BPH) than nondaily NSAID users. The medical records from a large health center were used to identify men who were either daily (536 men) or nondaily (659 men) NSAID users. The men then received twice-yearly examinations for the next 5 years for signs and symptoms of BPH. After adjusting for age differences between groups, greater daily NSAID use was associated with less BPH development compared to nondaily NSAID use. The authors concluded that regular NSAID use might prevent or delay the development of BPH.

Which type of design was used in this study? Can this study be used to prove that daily NSAIDs can decrease the risk of BPH development?

### Question 2

Investigators wish to conduct a study with the following objective: to determine whether statins used to reduce cholesterol might increase the likelihood of developing type 2 diabetes. Briefly describe how this study could be conducted using: (1) a prospective cohort design and (2) a case-control design.

### Question 3

A study was performed to determine the effects of garlic powder tablets on blood glucose levels and plasma lipids in patients with type 2 diabetes. Fifty-six type 2 diabetes patients were randomized to receive either two garlic tablets BID or a placebo control for 4 weeks.

Fasting blood glucose was measured daily, and plasma cholesterol and triglycerides were measured at baseline and after 2 and 4 weeks. At the end of 4 weeks, blood glucose and cholesterol levels were found to be significantly reduced in patients receiving the garlic tablets compared to placebo. It was concluded that garlic tablets might be a useful supplement to reduce cardiovascular risk in diabetic patients. Was this an experimental or observational study? Explain.

#### Question 4

Acetaminophen is often responsible for poisonings and is a leading cause of acute liver failure in the USA. The investigators wanted to study the extent to which adults are knowledgeable about acetaminophen and its potential toxicity and whether this knowledge increased their likelihood of recognizing available acetaminophen-containing medications. Subjects at least 19 years of age who were being seen for a variety of reasons in a large outpatient clinic in Boston were given a survey to assess their knowledge about acetaminophen dosing and toxicity, and whether they could identify commonly used non-prescription combination drug products that contained acetaminophen. Results showed that many patients had difficulty recognizing acetaminophen-containing products by name and were lacking knowledge of acetaminophen dosing and toxicity. No association was found between having greater knowledge of acetaminophen dosing and toxicity and the ability to recognize products that contained acetaminophen.

What type of design was used in this study? Is this considered a strong study design?

#### Question 5

Which of the following studies is *least* likely to be affected by selection bias: a case-control, cohort, or a controlled experimental study?

## Summary

It is important to know the overall design used in a study since each design has inherent strengths and limitations. This chapter reviewed the structure of the observational and experimental study designs along with their advantages and limitations in practice.