

Chapter 4

Study Designs

The term study design is used to describe the combination of ways in which study groups are formed, and the timing of measurements of the variables. Choosing a study design appropriate for the research question is important. No amount of statistical adjustment can compensate for not having a firm idea about the research question and how it is to be developed.

The Three Axes of Epidemiologic Research Design

Once the research objective for a study has been adequately specified in terms of the target population, exposure (or interventions as the case may be), and outcomes, the next step is to consider the design of the study.

The design of a study can be considered from three aspects related to the recording of exposure and outcome, as follows:

- i). the direction e.g. looking forward (prospective) from exposure to outcome, or backwards (retrospective) from outcome to exposure, or mixed (cross-sectional) when exposure and outcome get measured together.
- ii). sample selection e.g. by exposure, by outcome, or by other criteria.
- iii). Historical, concurrent or mixed, depending on the calendar timing of measurement of exposure and outcome, and the actual time of conducting the study.

Direction

Direction refers to the order in which exposure and outcome are investigated. Forward → from exposure to outcome; backward ← from outcome to exposure; or simultaneously where exposure and outcome are determined at the same time.

Sample selection

This refers to the criteria used to choose study subjects; it can be based on exposure or outcome or other criteria.

Timing

Timing refers to the relation between the time of the study and the calendar time of exposure and outcome. Thus, historical means that both exposure and outcome occurred before the study; concurrent means that exposure and outcome are occurring at the same time as the study; or mixed timing.

The fundamentals of a study

All studies require the following:

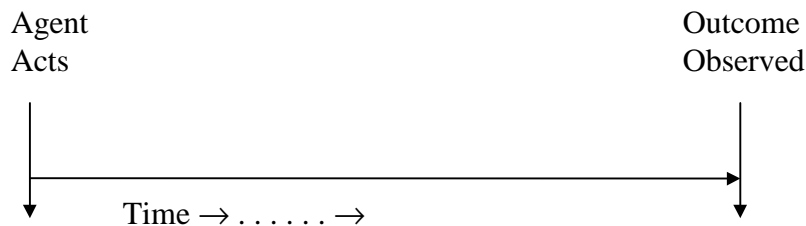
1. Firmly established study objectives or hypothesis.
2. Carefully defined methods of assembling study subjects, including case definitions and avoidance of bias in selection.
3. Making valid and reliable observations, which includes avoiding biased surveillance, variability among observers, and "blinding" of observers or subjects where necessary. (In the context of research 'blinding' means that the observer or subjects or both would be kept unaware of the research question (or hypothesis) or treatment so as to avoid bias).
4. Handling of incomplete observations, including how to handle those subjects who are lost to follow-up, are non-responders, or change status during the study e.g. from being "controls" to "cases".
5. Selecting appropriate comparison groups, including identifying beforehand important factors that may influence the study hypothesis, and controlling for them.

When planning a study it is always useful to consider how the following attributes may apply to the research question:

Is the aim of the study to describe or to compare?

- Will the study be observational or is an intervention planned?
- The orientation of the study in time.
- The orientation with regard to the process? For example, prospective or retrospective?
- If determining a cause is the aim, then what strength of causation is to be looked for. Will it be speculation or causation?

In most studies the researcher is attempting to demonstrate that a process begins with an agent acting and an outcome or event happens, as shown in the diagram below:



If the observation is made at a single point in time, the agent and the outcome as well as other factors are measured simultaneously. One can only hypothesize which came first. But by observing the process at two or more points in time one is better able to determine the sequence of events.

The standard approach is to move along in time with the process. This is called concurrent research. On the other hand the researcher may know that an exposure or intervention has occurred in the past, and is observing the results now. In this case the process has been going on non-concurrently.

Descriptive	Observational	Explanatory	Experimental
Document experience, observations, unusual events, programmes, treatments	Seek causes, predictors, risk factors. Researcher observes phenomenon without intervention.	Examine aetiology, efficacy or cause using strategy of comparison	Evaluate efficacy of therapeutic and other interventions.
Begin search for explanations.			
Examples:	Examples:		Examples:
- Case Reports or Series - Prevalence Studies - Surveys	- Case-control studies - Cohort studies		- Clinical trials - Educational interventions - Health care interventions.

Figure 4.1: Basic Study Designs.

Prospective/Retrospective research relates to the way subjects are selected. In prospective research groups of individuals are assembled who would have been exposed to a risk factor or intervention. The researcher then waits for the outcome to happen. In the case of retrospective research, a group of individuals has been assembled because they have already experienced the exposure or intervention in question. Thus, prospective/retrospective research differ from each other in their orientation in time as well as what observation is being made. In prospective studies the research commences in the present and moves forward in time collecting data about a population whose outcome lies in the future.

In retrospective research the study begins and ends in the present but involves a major backward glance to collect information about past events. A great deal of confusion has arisen in the past by these terms being applied loosely to describe study designs. It is more informative to use prospective and retrospective to refer to the temporal relationship between the initiation of the study and the occurrence of outcome. Thinking of prospective and retrospective as clock-watchers rather than forms of study designs can avoid much of the unnecessary confusion.

Descriptive Studies

Descriptive studies are undertaken to note the characteristics of a group of subjects. There is no testing of a causal hypothesis or any comparisons with other groups. But descriptive studies can help support a hypothesis by demonstrating a phenomenon that the hypothesis states.

Descriptive studies document facts of clinical or theoretical significance. Comparative research draws contrasts between two or more groups with the intent that the comparison will test a particular hypothesis. Both descriptive and comparative research have scientific value when used to address the appropriate question. In certain situations one type of research is more informative than the other. For example, if we are looking at the effectiveness of a new treatment there are pitfalls in concluding from descriptions alone. Most diseases have an unpredictable outcome. Some resolve spontaneously. It would be better to compare the outcome in a group of patients given the new treatment with that in a similar group given the conventional treatment or placebo. This would be a comparative study in its simplest form. As we would see later both descriptive and comparative studies have their uses. It is not unusual for researchers to conduct a descriptive study first, and follow it up with a comparative study later.

All studies involve some description. Even those which are undertaken primarily to compare two groups of subjects contain an element of description of multiple groups or of one group at multiple points in time. The special use of descriptive studies is in providing much of the information on which future more complex study designs would rely. Researchers generally follow a sequential development of knowledge about a topic under study by sequential use of different research designs. If very little is known about a subject a general sequence of research designs proceeding from descriptive to correlational to analytical design will be efficient in building up reliable information. The concept of progression within research designs is a general one, and there will be significant variation from one topic to another depending on the nature of the subject and what is known about it.

Descriptive studies have three goals:

- (i). What characteristics are present in members of the group.
- (ii). How are these characteristics distributed in the members of the group.
- (iii). How may these characteristics be expressed in a summary form that aids comprehension and allows for later comparisons.

The simplest form of descriptive studies are Case Reports and Case Series.

The latter describe a small group of patients thought to share one or more important attributes e.g. side-effects of drugs.

Cross-sectional studies form a bridge between simple descriptive studies like case reports and case series and those that can be used to test hypotheses. They can suggest the presence of relationships. Their major flaw lies in the lack of measurement over time. On the other hand they have the advantage of being economical (see figure 4.2a).

Cross-sectional studies are also called prevalence studies. They are used to document comparisons among various attributes of a group. *But at a single point in time.* They take a slice across a process flowing from a point of onset towards an outcome. In such a slice it is not possible to say that change in variable A occurred because of change in variable B (or vice versa), even though the subjects may have the two variables in different levels of magnitude. However, a cross sectional study can say that if it was true that factor A came before B then a cause-effect relationship might be present. Further designs can then prove or refute this point. For example, a study of first time mothers in a squatter settlement in Brazil revealed that one in ten mothers were less than 15 years old. (*J.Trop.Ped.1990;36:14-19*). The authors speculated that occurrence of pregnancy was responsible for leaving school and explained the low literacy rates among the young mothers. A second study in the same settlement was undertaken to compare the characteristics of teenage mothers with those of the older ones. (*J.Trop.Ped.1991;37:194-198*). This study revealed that a majority had already dropped out of school before they became pregnant.

Children's growth charts are often made up of cross-sectional observations. The popularity of cross-sectional studies besides economy is due to two factors viz .

Cross - Sectional Study

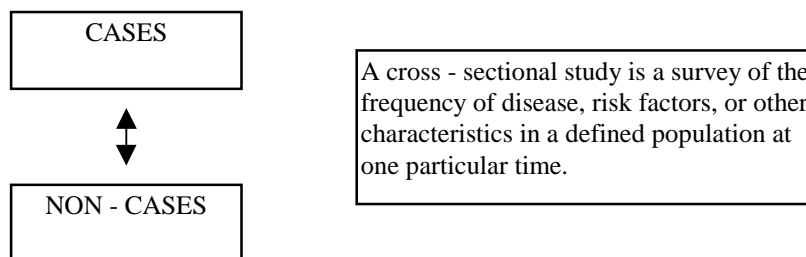


Figure 4.2a: Cross-Sectional Study.

i). One avoids the difficulty of tracking the subjects over long periods of time.

ii). A great deal of data exists in hospital files, which can be analyzed in a cross-sectional manner. (e.g. diabetics attending a clinic. Patients with different stages of the disease may be found some with renal, some with ocular and others with vascular complications). But a word of caution is needed. When archival data has been used it is necessary to prove their validity and accuracy, especially when data has come from sources set up initially not for research purposes. Most hospitals and clinical departments have computerized systems for storing clinical information about the patients. All such systems are primarily set up as health information systems. They are useful for audit and for analyzing patient load, types of diagnoses made, laboratory and other investigations, and response to treatment. But they cannot be expected to answer a research question which was not even remotely considered when the systems were first set up.

Major weaknesses, which limit cross-sectional studies to the preliminary and early stages of exploring hypotheses, are:

- If subjects are of different ages or in different stages of advancement of a disease false conclusions may be derived. The apparently homogeneous group may have been exposed to different risks or subjected to different treatments.
- It is not possible to demonstrate a temporal sequence in terms of causality. The researcher must not only prove that the study results fit the hypothesis regarding causality but also that they do not fit any competing hypotheses. And the correlations between the cause and effect variables also apply to other variables that seem logically related.

In short, researchers performing cross-sectional studies must be careful to show that they have not simply sifted the data until they found a relationship, which fitted their need.

Ecologic studies

When data are gathered which describe what happens in a group rather than the individual, for example, exposure to radiation or fluoridation of water supply, the studies are called ecological. Ecologic variables of this nature are used in a variety of study designs and not just in cross-sectional studies. More frequently they are found in time series analyses e.g. time since establishment of intensive care units and perinatal mortality trends.

Ecologic studies take populations rather than individuals as the unit of measurement. At their simplest they explore differences in disease rates by geographical regions, or by differences in time in the same region to identify disease patterns that suggest a hypothesis about the cause of disease. (A good example is cigarette smoking and lung cancer rates). The weakness of ecological approach is that exposure and prevalence are measured at the population level. So there is assumption that all members of a given population share the same exposure and same risk of disease. This is a major assumption since there may well be large within-group differences. Confounding variables like social status, habit and life-style are not taken into account. Hence caution must be exercised in drawing conclusions for

the individual based on the results of an ecological study. The term “ecological fallacy” is applied to such conclusions, since the true relation between exposure and disease is distorted by the inability to control for other confounding variables.

Comparative studies

Case-control studies are the next level up from cross-sectional studies in attempts to show causal relationships (see figure 4.2b). In a case-control study the observer starts with a group who have already experienced an outcome and one or more groups who have not. The investigator determines the proportion in each group who have experienced an exposure of interest. The hypothesis of causation is supported if the proportion of subjects exposed is greater in the "cases" than in the "controls".

A variant of the case-control study uses pairs i.e. one "case" with one or more "controls". The controls are matched to the case on one or more attributes. In such a design the outcome is determined by the proportion of pairs for which the exposure status of the case and control are different.

Case - Control Study

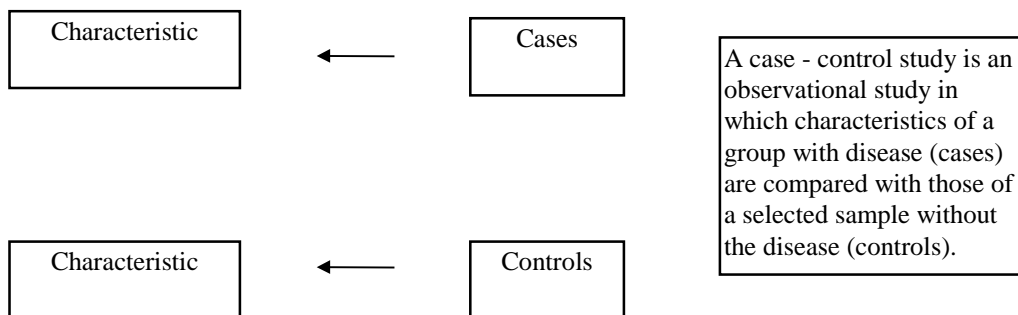


Figure 4.2b: Case-Control Study.

Cohort Studies

Prospective studies could be either concurrent (i.e. moving with the researcher on the axis of time) or non-concurrent (constructed from exposure events in the past and the outcome measured in the present). Prospective studies may also be classified either as observational cohort studies or experimental clinical trials.

Cohort Study

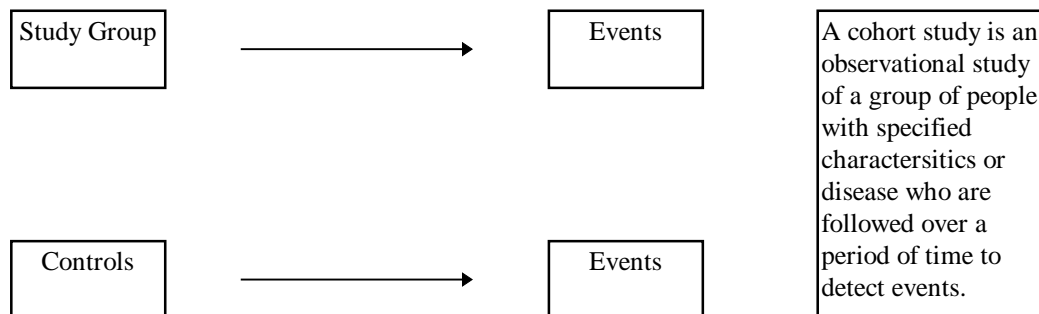


Figure 4.2c: Cohort Study.

Cohort studies can be carried out in four general ways:

- (i). Single heterogeneous group followed from baseline to outcome.

The cohorts are homogeneous in one or more characteristics (e.g. birth date, residence, or socioeconomic status), but heterogeneous for other characteristics that are related to the outcome of interest (e.g. occupation or exposure to a risk factor). At the time of analysis, the researcher attempts to find a relationship among the heterogeneous characteristics and the outcome. This type of study is comparative since it compares outcome among subjects, and observational in that it does not actively allocate groups to exposure. An example of a cohort study is a group of infants followed since birth to age one year, some exclusively breastfed and others bottle fed. The number of episodes of diarrhoea and their severity are compared between the two groups.

- (ii). Two homogeneous groups followed from baseline to outcome.

The researcher assembles a cohort of subjects who all have a condition or characteristic of interest. e.g. failure to thrive in infancy. A control cohort is then assembled with normal growth in infancy, but who are otherwise similar to the other cohort in all possible ways. The two cohorts are followed to a specified outcome e.g. school entry. At this time comparison is made e.g. by developmental tests.

- iii). Purely descriptive cohort study.

Only one group is followed and attributes of interest are documented as they change over time. e.g. a longitudinal study of blood pressure or linear growth. If the study is purely descriptive no attempt

would be made to identify patient characteristics responsible for the pattern of change over time, or to draw contrasts between subgroups who have different patterns of change.

iv). Epidemiologic cohorts.

The three types of cohort studies described all follow individual cases, and assess their status at one or more points in time. In epidemiologic cohorts aggregate characteristics of groups are measured at one or more points in time. For example, measuring fertility rates of women born in 1950, as compared to those born in 1970. No individual is singled out for study.

Cohort and Case-control studies are the two basic types of observational analytic studies. In theory it is possible to test a hypothesis using either design. However, each design offers certain unique advantages and disadvantages. The decision to use a particular design is based on features of exposure and disease, current state of knowledge, and the logistics of time and resource.

Observation vs. experimental

An intervention can occur in two ways:

- A naturally occurring situation where intervention has been differentially applied to the members of a population. For example, two neighbouring towns with one receiving its water supply from a source of surface water, and the other from deep tube wells. Studies in such situation are called observational. They simply document processes without the researcher's intervention.
- Purposefully manipulating events. Interventions are deliberately applied, and other circumstances altered in a way as to clarify the impact of intervention (see figure 4.2d).

In between the two are the quasi-experimental studies. These studies may be described as nature's experiments. For example, one community in which a particular intervention has been applied, and is being compared with another community where the intervention programme has not yet reached. A good example is that of a nationwide programme of immunization.

Experimental Studies

Clinical trials are the common forms of experimental studies undertaken in clinical practice. They have five key elements:

1. They are concurrent, prospective comparisons of two or more groups.
2. One or more of the groups is deliberately exposed to an intervention, usually a treatment, while at least one group (the controls) is not exposed or receives a standard treatment or placebo.

3. The groups are recruited from one single, homogeneous pool of subjects. Assignment of individuals to study or control group is determined by random allocation, and without any form of consideration as to who gets assigned to which group.

4. All study participants (clinicians and all care providers, subjects, outcome evaluators) are unaware of which subject belongs to which group. The "blinding" may be extended to any knowledge about the study hypothesis or outcome measures.

5. Control subjects receive an intervention, which is indistinguishable in appearance, taste and other ways from the standard intervention. This includes attention to psychological factors like the placebo effect or Hawthorne effect, so that subjects do not change behavior because they know they are being treated or know they are being observed. Experimental and control subjects experience same amount of intervention and observation.

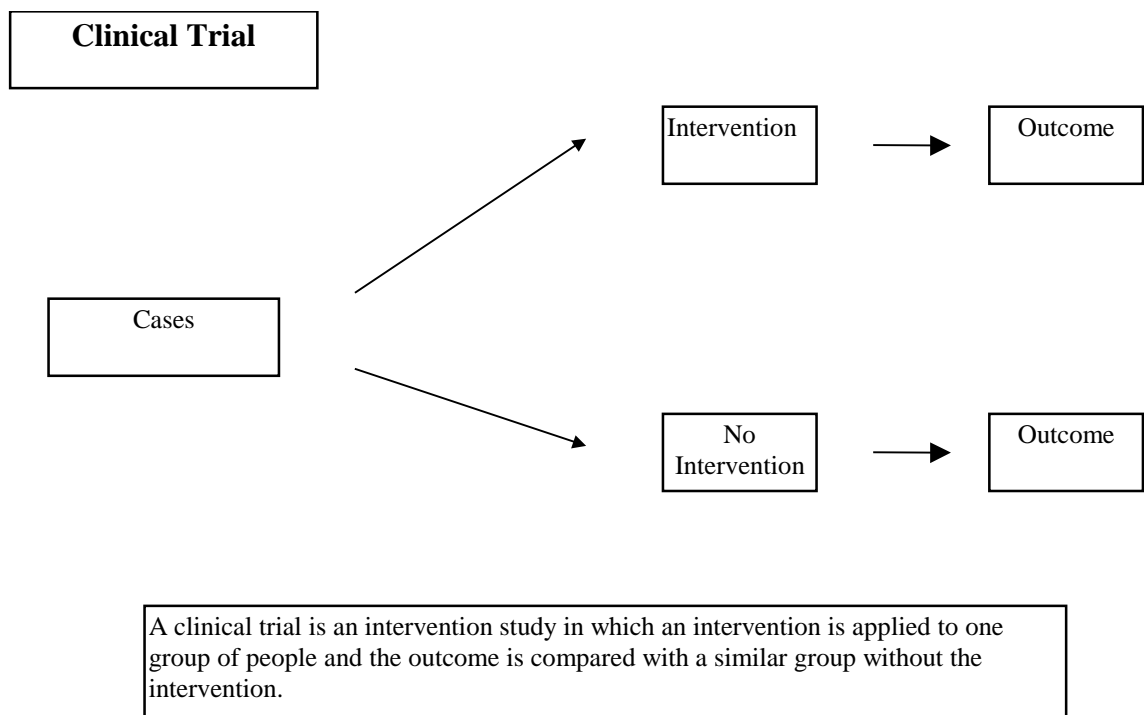


Figure 4.2d: Clinical trial.

What differentiates cohort studies from clinical trials is that in the case of the former the intervention has not been applied by the researcher. Intervention studies are in effect a form of prospective cohort. Participants are identified on the basis of their exposure to intervention and followed up to determine the outcome. The distinguishing feature is the researcher determines that exposure. Two major tasks facing the researcher in conducting clinical trials are:

i). to make sure that no biases were operating at the time the subjects were being exposed to the agent. Randomization helps to control for all recognized factors that may influence the outcome as well as the more subtle and unrecognized ones.

ii). exposure did indeed take place. In the case of treatment with a drug it means full compliance.

Clinical trials are suited best for trying out new treatments for known diseases. This is so because the subjects have in common some easily defined characteristics that would be expected to change rapidly and visibly in response to treatment. It is easy for the researcher to find a uniform pool of subjects, and to conduct the study over a manageable period of time.

Clinical trials are less suited to studies of preventive measures, because the duration of time for observation is prolonged and it is not possible to prevent the subjects from being exposed to other treatments or exposures. Nevertheless, they are a powerful research strategy. When well designed and conducted they provide the most direct evidence for judging whether an exposure ameliorates and cures a disease.

Quasi-experimental studies.

In the social and behavioral sciences it is often not possible to follow the ground rules of classic experimental studies. For example, two or more clinics may need to be compared or two or more geographical communities are to be compared such that one is receiving an intervention and the other is not. Or there may be only one group in which an intervention is being made, in which case a time series design may be feasible.

Which study design to use?

The foregoing account of descriptive and analytic studies may have given the reader an impression of clear-cut distinction between the two types of studies. In reality, this is not so. There is invariably an overlap. Most descriptive studies tend to analyze and compare. Similarly, most analytical studies provide descriptions of the attributes of the subjects. In general, descriptive studies are useful for describing patterns of disease occurrence, and for allowing the formulation of hypotheses. The chief contribution of analytical studies is in testing hypotheses. A given research question may be addressed

using different approaches. Each has its specific advantages and disadvantages. (See Tables 4.1 and 4.2) The choice of study design is largely influenced by specific features of exposure and disease, logistics of time and resources, results from previous studies and gaps in the knowledge to be filled. For most situations both strategies need to be employed.

Table 4.1. Advantages and Disadvantages of common study designs.

Study design	Advantages	Disadvantages
Case reports	Cheap and easy for generating hypotheses	Cannot be used for testing hypotheses.
Case series	Provide descriptive data on disease characteristics	No control group. Cannot be used for hypotheses testing.
Cross-sectional	Can assess prevalence easy; can generate hypotheses.	Cannot evaluate timing of exposure
Ecological	Rapid answers. Can generate hypotheses	Difficult to control for confounding.
Case-control	Can study multiple exposures and uncommon diseases Requires few subjects logistics are easy, less expensive.	Selection of controls difficult; possibly biased exposure data; incidence cannot be measured.
Cohort	Can study multiple outcomes and uncommon exposures, selection bias and biased exposure data less likely, incidence can be assessed	Possibly biased outcome data, expensive, long duration when done prospectively, not suited to rare diseases, can study few exposures, loss of subjects by drop-out
Randomized Clinical Trial.	Most convincing design, controls for known and unknown confounders	Expensive, logistics difficult, ethical problems.

Table 4.2. Choice between observational and experimental studies in medical research

Observational studies	Experimental studies
ADVANTAGES	
<p>1. Practicality, greater variety and larger scale of tests of hypothesis, as compared with experiments</p>	<p>1. Safety relatively few individuals exposed to unpredicted risks in untried interventions</p>
<p>2. Few ethical objections since interventions are not imposed by pre-planned designs</p>	<p>2. Vigour capable of critical tests of limits of applicability.</p>
<p>3. Relatively large number of participants can be recruited</p>	<p>3. Precision theorized causal factor can be defined and limited exposure of test factor under control of researcher.</p>
<p>4. Duration is relatively short when observations are from existing records</p>	<p>4 Efficiency relatively few observa- tions needed to refute some hypotheses.</p>
<p>5. relatively inexpensive in time and personnel</p>	<p>5. Assumptions random allotment of treatments is assured by the design.</p>
DISADVANTAGES	
<p>1. Documentation exposure to causal factor less certain</p>	<p>1. Impracticality inborn attributes cannot be manipulated</p>
<p>2. Specificity isolating causal factor is difficult</p>	<p>2. Predicted risk of intervention is great. long term observation is difficult</p>

3. Remoteness causal factor and outcome tend to be separated in time.	3. Large number of subjects need to detect small differences
4. Time order direction of relationship between cause and effect less certain	4. Reductionism. focus on one independent variable excludes others from attention.
5. Systematic selection availability of patients for treatments allotment of treatments	5. Representativeness difficult to recruit a truly random sample from 'universe'
6. Efficiency of statistical tests lower than in experimental designs.	6. Expense relatively great in staff and logistics
	7. Public acceptance undue suspicion of outcomes

The same research question may be answered by several different ways depending upon the available resources. For example, let us consider the following:

DOES SMOKING CAUSE CORONARY ARTERY DISEASE ?

The question may be answered by any of the seven basic designs (A to G) shown in Table 4.3 below in accordance with directionality and sample selection:

Table 4.3 Research design defined by directionality and sample selection

	Directionality		
	Cohort	Case-control	Cross-sectional
Sample Selection by			
Exposure	A	-	E
Outcome	-	C	F
Other	B	D	G

A: Cohort study with sample selection by exposure, e.g. smokers and non-smokers.

B: Cohort study with "other" sample selection e.g. instead of sampling exposed (i.e. smokers) and unexposed (i.e. non-smokers) we may select all subjects in a target population, determine their smoking habits and then follow them up for a given period of time.

C: Case-control study with sample selection by outcome. Presence of coronary artery disease is defined on the basis of symptoms, abnormality of E.C.G. at rest or after exercise, and so on. Those diagnosed as suffering from coronary artery disease are compared with healthy controls with regard to their smoking habits.

D: Case control with "other" sample selection. This is similar to C but instead of choosing those with coronary artery disease and comparing them with those without, all the subjects in the target population are recruited into the study. This design turns out to be less robust than C, since very few subjects would be expected to have coronary disease recognizable by non-invasive methods at a given point in time.

E: Cross-sectional study with sample selection by exposure. People who smoke and who do not smoke are compared for the presence or absence of coronary disease. This design is as inefficient as D.

F: Cross-sectional study with sample selection by outcome. The records of people attending a hospital for chest pain with and without coronary disease are compared for exposure to smoking. This design is more efficient than E but there may be problems with determining causality.

G: Cross-sectional study with "other" sample selection. All the subjects in a target population are classified according to smoking habits and coronary artery disease status. The design is inefficient like D and E, and shares the same problems with regard to causality as E and F.

Now that we have seen the strengths and weaknesses inherent in different study designs what strategy should one follow? In general, research proceeds from case reports and case series, which suggest an association to case-control studies for exploring the association further. Cohorts may be studied to further establish the association. Finally, clinical trials may be used for therapeutic or preventive measures. The ultimate aim of research is to explore the relationship between two or more variables with a view to exploring why events happen. In general the more one can control the circumstances of the study (i.e. influence of other factors; the way in which study intervention is applied, the measurement of the outcome, and so on) the stronger is the ground for demonstrating a cause-effect relationship. These remarks are best exemplified by the way research has proceeded with regard to HIV infection. The first published reports were in the form of case series. As the epidemic unfolded there were cross-sectional studies and other descriptive analyses of the prevalence in different groups. Next, case-control and cohort studies were designed to identify risk factors and outcome. In the meantime a great deal of knowledge was being assembled from virological studies and animal experiments whilst simultaneously therapeutic measures were evaluated by means of clinical trials. Hopefully in the near future there would be trials to test and evaluate vaccines.

This has been an introductory chapter wherein the broad characteristics of different varieties of study designs are described. Some of their strengths and weaknesses have been mentioned. In the chapters that follow each design is explored more fully.