RESEARCH DESIGN

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In contrast to laboratory or animal research, clinical studies use patients or volunteers in an attempt to address questions of direct clinical significance. The aim of this chapter is to present principles and guidelines on how to design clinical research.

Types of clinical research

Clinical research may be broadly classified as experimental studies or observational studies. These may be further subdivided into longitudinal or cross-sectional and prospective or retrospective (see Figure 1).

1. Experimental studies. In experimental studies the investigator makes an intervention, for example gives a drug, then studies the effects of the intervention.

(a). Features of experimental studies.

- A particularly common form of experimental trial is one involving a comparison between two or more groups of patients.
- They are always longitudinal – they study changes in the subjects in response to the intervention over a period of time.
They are always prospective – data are collected from the start of the study onwards.

(b). Terminology.

- Experimental studies are referred to as experimental trials, or clinical trials or just trials.
- Because they are typically randomised and controlled, they may also be referred to as randomised controlled trials.
- They may also be blinded although in some circumstances this may not be possible.

2. Observational studies. In observational studies the investigator observes, describes, analyses and interprets an existing or pre-existing situation but does nothing to influence events. They may be longitudinal or cross-sectional.

(a). Longitudinal observational studies.

Longitudinal studies may be divided into case-control studies and cohort studies.

- Case control studies are retrospective, moving backwards in time from effect to cause (from disease to exposure).
- Cohort studies are prospective, moving forwards in time from cause to effect (from exposure to disease).

(b). Cross-sectional observational studies.
• Cross-sectional studies are surveys which examine subjects at just one point of time.
• They are often based on a random sample of a particular population, for example, patients presenting with a specific disease or medical students or smokers, etc.

Experimental studies

1. Rationale. The purpose of an experimental trial is to evaluate the effectiveness of an intervention or therapy. The different interventions are applied to similar groups of individuals, who should reflect the population concerned. The differences in observed outcomes should therefore be a direct consequence of the relative efficacy of the interventions tested. Hence, the best evidence of cause and effect may be derived from this type of study.

2. Types of experimental studies. Experimental trials may study differences between subjects or within subjects.

   (a). Between subjects (independent data).
   • In parallel studies, each group of patients receives a different treatment or intervention concurrently.

   (b). Within subjects (paired data).
Within subject designs have the important advantage that the subject acts as his or her own control and therefore between-subject variability is removed.

In cross-over studies, each patient receives each treatment in sequence, with a ‘washout’ period between the two (or more) treatments. It is important that the order of the treatments is randomised.

A matched pairs design is a parallel study in which each subject in one arm is matched with a subject in the other arm for all known prognostic factors. Here the data are clearly linked and they should be treated as paired individuals in the same group.

In paired studies, measurements on each patient are taken more than once, usually in different circumstances, e.g. before and after treatment.

Principles of the design of experimental trials

This section discusses the established principles and methods upon which experimental trials are based.

1. Avoiding bias. The validity of the results of both experimental and observational studies depends on the extent to which
investigators have been able to avoid all possible sources of bias.

(a). Bias.

- Bias is a systematic distortion of a result due to a factor not allowed for in the design of the study. For example, bias would occur, if, when testing two different treatments, the two groups were given tablets that looked different; or if one group was given a tablet and the control group was not given a tablet. The two groups are handled differently and it is possible this might influence and thereby complicate the trial results.

- A fundamental flaw in design might confound a trial, invalidating the results. For example, if the investigator, when studying the incidence of upper respiratory tract infections (URTI) in doctors and ancillary staff in a hospital, failed to take into account their smoking histories. It is likely that there would be a significant difference in this regard between the two groups. Therefore, it becomes impossible to distinguish the effects of occupation from the effects of smoking on the incidence of URTI.

- The control group, randomisation and blinding are the classical techniques that have evolved to minimise bias in experimental trials.

2. Control group.

(a). Importance.
When testing the effectiveness of a new treatment or procedure in medicine, it is essential to have a concurrent comparison, a control group, to whom the experimental treatment is not given. Without a control group it is impossible to make an objective evaluation of the effect (if any) of a treatment.

There are many reasons why bias can occur in an uncontrolled or open study. Any increase in well-being or relief of symptoms experienced by the subjects cannot be safely ascribed to the treatment they have been given since the simple knowledge that they are receiving a treatment may alone have beneficial effects, even if the treatment is completely inactive (the placebo effect). The patients’ responses may also be greatly influenced by the investigators enthusiasm or (unconscious) reassurance, etc. Since the investigator knows exactly what treatment is being given, it is almost impossible for his assessments of its efficacy to be impartial.

(b). Types of control groups.

- A no treatment group study is likely to be confounded because of the placebo effect in the treatment group, even if the treatment is inactive.
- Placebo: the control group receive an inert, dummy treatment which is a indistinguishable from the treatment under study.
- A low dose group: for the situation when a placebo group can not be used because of ethical issues.
• A group treated with a standard current therapy.
• ‘Gold Standard’ treatment group receiving the best current therapy.
• Historical controls, where the treatment group is compared with results obtained in previous ‘similar’ patients, are unreliable. The controls may well be significantly different than the current treatment group. The general management of patients with the condition in question may be different, the prognosis may be different, the natural history of the disease may be different, the state of nutrition be different, the current patients may be more knowledgeable or may have been diagnosed earlier, and so on.

3. Randomisation.
(a). Random allocation to groups.
• Randomisation is used to ensure that the allocation of patients to the groups is independent of the characteristics of the patient. Thus all patients have the same chance of being assigned to either intervention.
• If patients were allocated to groups by the investigator, it is impossible to exclude the possibility that, albeit unconsciously, the allocation is affected by patient factors that may influence the trial outcome, e.g. low risk patients may be allocated to the treatment group. Randomisation thus removes any chance of allocation bias.
• It is highly desirable that the treatment and control groups are similar with regard to factors that might affect outcome. Randomisation, however, does not guarantee that this will be the case, although it does guarantee that differences will only occur by chance. For instance, there may be more females in one group than in the other, or the average age or the average weight of patients in the groups may be significantly different.

• Stratified randomisation should therefore be used for factors that are believed to significantly influence the outcome.

(b). Random sample of population.

• If the results of a trial are to be generalisable, it is also important to ensure that the patients entering the trial are a random sample from the population of interest. Studies based on hospital admissions, for example, may not be generalisable to all patients with a particular disease since the types of patients admitted to different hospitals is very variable, depending on factors like the particular hospital’s catchment population, reputation, facilities, and so on.

• There is a better chance of detecting a treatment effect if there is little variability between the subjects. Restriction may be used achieve this uniformity – e.g. by using only patients of a similar age, or a similar weight or similar severity of disease, etc. However, the danger is that the more uniform the sample, the less
generalisable are the results. Trials should investigate a sufficiently large sample of the population that the treatment will be used in.

(c). Methods.
• The three commonly used methods of randomisation into groups are simple, restricted (or block) and stratified. They can be applied to parallel groups, cross-over or matched pairs design trials.
• The methods of randomisation are discussed further in the chapter ‘Randomisation’.

(a). Importance.
• Bias may occur when either the investigator or the subject knows which treatment is being given. The investigator’s observations and judgements may become less objective and the patient’s responses may become more positive or more negative depending on whether or not he is in the active treatment arm of the study.
• Therefore, clinical trials should use the maximum degree of blindness that is possible, so that patients or both patients and investigators are unaware of what treatment has been given.

(b). Methods of blindness.
• Double-blind means that neither the patient nor the investigator is aware of the treatment. This is the most desirable method to
prevent assessment and response biases. However, in several fields, such as surgery, it may be impossible to run a double-blind study.

- In a single-blind trial, only the patient is unaware of the treatment.
- In a triple-blind trial, patient, investigator and also the data monitoring body are unaware of the treatment group.
- The double dummy technique is used for drug trials comparing two active treatments, e.g. each patient receives one of the active tablets and a dummy tablet that looks like the alternative active tablet.
- In open trials, the investigators and patients know what treatment each patient is getting.

(c). Randomisation in a double-blind trial.

- The most practical method of doing this is to use a series of consecutively numbered sealed opaque envelopes, each containing a treatment specification.
- For stratified randomisation, it is necessary to use two or more sets of envelopes.

5. Unblinding.

(a). Situations when blindness must be broken.

- If the patient experiences symptoms or signs that may indicate an adverse reaction to the active treatment or if there is a significant
deterioration in his medical condition, the blindness of the study must be broken.

(b). Managing unblinding.

- “Breaking the code” should always be allowed for in the planning stage of the trial. The criteria for unblinding should be listed before the trial starts.
- The investigators should always be able to have emergency access to the randomisation schedule.
- Treatment should be stopped and the patient withdrawn from the study.
- The code should be broken.
- The patient should receive the appropriate medical treatment.
- A formal safety monitoring committee should review the incident and make recommendations, if necessary.

Observational studies

- The purpose of an observational study is to look for an association between a cause and an effect, between an exposure to a risk factor and the development of a particular disease.
• Observational studies are particularly relevant in epidemiology which is the branch of medicine that deals with the incidence, cause and prevention of disease.

• When looking for a link, for example, between smoking and lung cancer, the investigator cannot use the classical tools of experimental research – he cannot randomise patients into a control group or a treatment group in order to confirm or refute a hypothesis, for obvious reasons. He must use other methods. He can observe a situation and analyse and interpret it, but he cannot intervene. Because subjects cannot be controlled or randomised, many observational studies are fraught with problems of bias.

**Case-control study**

1. **Definition.**

• The retrospective case-control study starts with the identification of a group of individuals with the disease or condition of interest (cases) and a group of individuals without the disease (controls).

• The two groups are then compared with respect to their previous exposure to the risk factor or factors. A greater degree of exposure in the cases than in the controls suggests that the factor might be causally related to the disease.
2. **Advantages and disadvantages.**

- These studies can be carried out more speedily and cheaply than cohort studies, and they are particularly useful for rare diseases.
- However, difficulties and biases can occur at several points in the procedure, particularly when selecting controls.

3. **Methods.**

(a). *Selection of cases.*

- It is important to try to admit patients into the study at the same fixed point in the natural history of the disease, otherwise considerable bias will ensue.
- Often, only newly-diagnosed patients are admitted, though even this is a variable feast, some patients being diagnosed earlier than others (lead time bias).

(b). *Selection of controls.*

- As in experimental studies, controls should be as similar to cases as possible, though without having the disease in question.
- The control may be another patient in the same hospital with another diagnosis. However, the risk factor may be linked to other diseases as well as the one under investigation e.g. smoking may be associated with cardiac disease, stroke, gastrointestinal disease,
respiratory disease as well as lung cancer. This may lead to an underestimation of the link.

- Alternatively, healthy subjects in the community may be selected but there may be difficulties in identifying a group with comparable characteristics to the cases.
- It may be helpful to match each case individually with a control rather than take a large random sample from the control population.
- It may also be possible to have more than one control per case if necessary. The two most frequently used variables used for matching are age and gender.

4. Other potential biases.

(a). Recall bias.

- Cases may be more likely to find stronger associations with the risk factors having had the time and the inclination to think of possible reasons for their problems.

(b). Unreliable memories.

- In a retrospective study, much of the evidence depends on the possibly unreliable memories of the subjects.

(c). Unreliable records.

- In many studies evidence may have to be elicited from notoriously unreliable hospital records.

(d). Interview bias.
It is acknowledged that different interviewers may obtain different information from the same patient.

**Cohort study**

1. **Definition.**

   - The prospective cohort study starts with the identity and examination of a group of subjects (the cohort) who are then followed up over a period of time looking for the development of a disease or another specified end-point.

2. **Advantages and disadvantages.**

   (a). **Advantages.**

   - Cohort studies can be used to investigate the aetiology of a disease, e.g. diet and cardiovascular disease, or the prognosis of a disease e.g. diet following myocardial infarction.
   - Because the study is prospective, data should be more accurate and reliable than in case-control studies. Thus, cohort studies should have major advantages over case-control studies.

   (b). **Disadvantages.**

   - However, a cohort study usually requires that a large number of patients are followed up for a long period of time so that a sufficient number of subjects will develop the outcome of interest. They are
therefore relatively inefficient and expensive, particularly when studying rare outcomes.


- Subjects are classified at the beginning of the study into two (or more) groups, one exposed (e.g. cigarette smoker) and the other not exposed (non-smoker).
- At the end of the study the subgroups can be compared with respect to exposure to risk factors and disease outcome.
- In the simplest type of study the results can be summarised and compared in a 2 x 2 table (disease plus or minus versus exposure plus or minus, [see chapter on Chi Squared Test]).


- Subjects may be lost to follow-up during a long cohort study. This may lead to bias if the reason for loss of contact is related to the risk factors or the outcomes. A large loss to follow-up may significantly affect the validity of the results.
- Exposed subjects may reduce, while other subjects might increase, their exposure to the risk factors e.g. by giving up or starting smoking.
- A change of occupation may reduce or increase exposure to, for example, asbestos.
• If the investigators are aware of the subject’s group they may investigate exposed subjects more closely, so that ‘surveillance bias’ occurs.

Cross-sectional study

1. Methods.
• In a cross-sectional study all the subjects are contacted or surveyed just once and at about the same time, usually by means of a questionnaire.
• The subjects may be a random sample of a defined population such as general practitioners or patients presenting with arthritis.

2. Advantages and disadvantages.
• They may be designed to examine associations between risk factors and diseases. But since they do not examine temporal relationships, they may not be able to distinguish cause from effect. Therefore, they do not usually provide an insight into disease aetiology.
• They are a much better source of descriptive information, particularly about the prevalence rate of a disease or condition.

- Volunteer bias.

Non-response in cross-sectional surveys can be a major problem. There are likely to be important differences between the people who respond to surveys and the people who do not respond, which may have a major impact on the results of the study. For example, responders may be healthier or older or more altruistic-minded or females. Hence the subjects responding to a survey may not be representative of the subjects invited to take part in it. Hence it may not be possible to extrapolate the results to the population under review.

Further reading


Related topics of interest

Conducing clinical trials, p. xxx; Randomisation, p. xxx; Medical research, p. xxx, Research process, p. xxx
Figure 1. Types of clinical research.

- **Experimental**
  - Longitudinal
    - Prospective
      - Randomised controlled trial
  - Cross-sectional

- **Observational**
  - Longitudinal
    - Prospective
    - Retrospective
    - Survey
    - Cohort studies
    - Case control studies