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An overview of study designs

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Abstract

The numbers of clinical trials have increased exponentially over the last decade, amplifying the pressure to select an appropriate study design to obtain reliable and valid evidence. The ability to find, critically appraise and use evidence to develop new interventions is fundamental to evidence-based medicine. Different study designs have their own advantages and disadvantages, and provide different evidentiary value. This article provides an overview of clinical trials, illustrating that, ultimately, the study design chosen needs to meet experimental and funding limitations, while minimising error.

Key words: Bias; Clinical trials; Cohort embedded RCT; Evidence; Study designs

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Introduction

A study in Switzerland concluded that one in four randomised controlled trials is discontinued, with 40% of completed trials remaining unpublished (Amstutz et al, 2017), highlighting the importance of appropriate selection of study design. The number of clinical trials being performed has exponentially increased over the last decade and is forecast to continue on this upward trend. Research teams need to plan and develop relevant study designs to address their experimental needs, while complying with funding restraints and minimising error. This article describes different study designs, including novel designs, focusing on their most important strengths and weaknesses.

Levels of evidence

Finding, critically appraising and using evidence to make clinical decisions is fundamental to evidence-based medicine. A traditional pyramid diagram (Figure 1) was designed to show the hierarchy of levels of evidence, where weaker study designs such as case reports are at the bottom, followed by case-control and cohort studies, randomised controlled trials, and systematic reviews of multiple randomised controlled trials at the top of the pyramid, along with society guidelines. These classifications are mostly based on the internal validity of the study design.

Another common evidence classification system is the Oxford Centre for Evidence-Based Medicine levels of evidence. This system comprises five main evidence levels, with some split into sub-levels.

- Level 1a, the highest evidence level, describes a systematic review with homogeneity of randomised controlled trials
- Level 1b is an individual randomised controlled trial with a narrow confidence interval
- Level 1c describes 'all or none' studies, whereby all patients died before the intervention became available, but now some patients survive with the intervention. Level 1c evidence can also be assigned when some patients died before the intervention became available, but none currently die on it
- Level 2a describes a systematic review with homogeneity of cohort studies
- Level 2b includes individual cohort studies, including low quality randomised controlled trials (such as those with <80% follow up)
- Level 2c describes research outcomes, such as audits and ecological studies
- Level 3a describes a systematic review with homogeneity of case-control studies
- Level 3b describes an individual case-control study
- Level 4 describes a case series and a poor quality case-control study
- Level 5, the lowest evidentiary level, describes 'expert opinion without explicit critical appraisal' (Centre for Evidence-Based Medicine, 2009).

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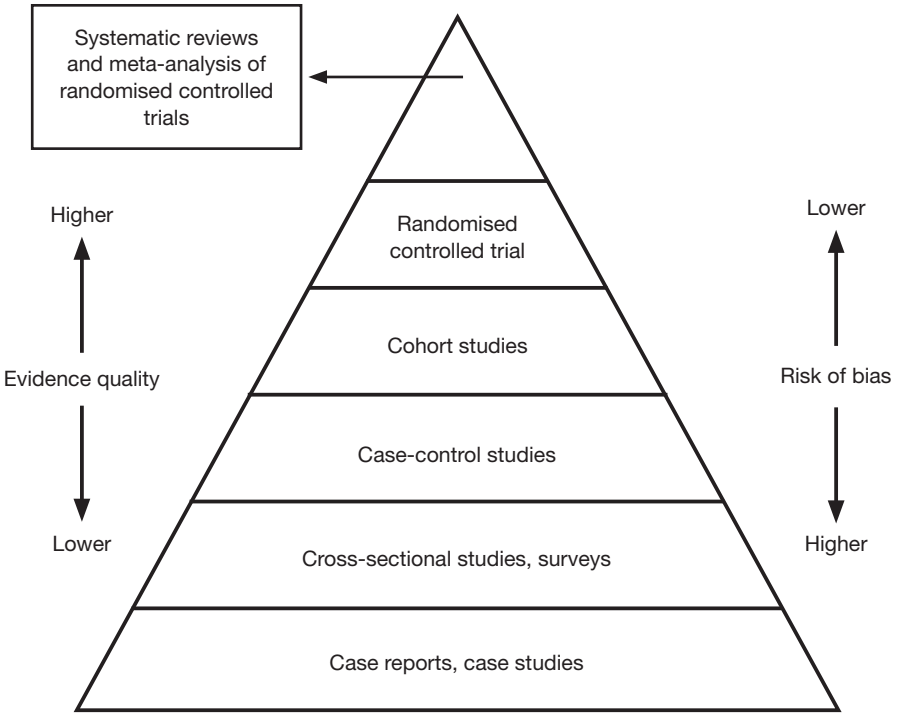

Figure 1. Hierarchy of evidence pyramid.

Study designs

There are three main categories of study designs in use: observational studies, intervention studies and systematic reviews. Observational studies, such as case reports, case-control and cohort studies are simply records of what happens to participants. These studies are towards the bottom of the hierarchy of evidence as they are affected by confounding bias, distorting the relationship.

Intervention (experimental) studies, such as randomised controlled trials, involve testing a new treatment or medicine, with results being evaluated prospectively through clinical trials. These are higher up the hierarchy of evidence than observational studies (Thiese, 2014).

A systematic review involves searching for all published research studies to address a specific research question, using pre-defined criteria and methods. PROSPERO (International prospective register of systematic reviews) is an international database of registered systematic reviews in healthcare, aiming to provide a registry of systematic reviews to prevent duplication (https://www.crd.york.ac.uk/PROSPERO/#aboutpage). Meta-analyses are statistical procedures for combining numerical data from multiple separate studies and are usually conducted on studies with high levels of evidence, such as randomised controlled trials and systematic reviews (Ahn and Kang, 2018).

Observational studies

Case reports

A case report is a descriptive case study written with a specific area of interest. Associations between observed outcomes and exposures are based on clinical histories and evaluations of a single subject, or group of subjects (case series). Case reports can provide clues to identify a new disease or adverse health effects from an exposure.

A major strength of case reports is that they are fast to complete and inexpensive to carry out. They can also play an important part in postulating new hypotheses for causal links, for example, between an exposure and an outcome that can be tested by further studies. However, a disadvantage is selection bias, for example, an ideal group of subjects unrepresentative of the population can be easily selected, generating skewed results with no control group present. Furthermore, case reports have a very limited potential to establish causal effects (Noordzij et al, 2009).

Table 1. The most common study designs

Study design	Description	Advantages	Disadvantages
Case report	Descriptive case study written with a specific area of interest	■ Quick ■ Inexpensive ■ Postulate new hypotheses	■ Selection bias: skewed results ■ Shows correlation but not causation ■ High chance of coincidental findings
Cross-sectional	Survey a defined population at a single point in time	■ Quick ■ Inexpensive	■ Difficult to know if exposure preceded outcome: uncertain correlation ■ Difficult to establish the exact incidence: no follow up
Case-control	Two groups of people selected: one group with disease, one without. Groups compared and risk factors regarding exposure are identified retrospectively	■ Quick ■ Inexpensive ■ Can study rare diseases and outbreaks ■ Can recruit control groups	■ Selection bias risk ■ Type 1 error, increased likelihood of a 'false positive' conclusion because participants need to recall past events
Cohort	Subjects classified according to a particular exposure and followed up prospectively to see who develops the disease. Risk of disease in those exposed to the risk factor is compared to that in the unexposed group (control)	■ Risk easily calculated to conclude correlation	■ Time consuming because of the need for follow up ■ Expensive ■ Risk of some subjects getting lost over long follow up: can lead to bias and type 2 error
Randomised controlled trial	Comparison of the group receiving the intervention with a control group	■ Randomisation reduces confounding ■ Flexible: can be double- or triple-blinded	■ Time consuming ■ Expensive ■ Sufficient recruitment can be difficult ■ Non-compliance
Cohort embedded randomised controlled trial	Large cohort of patients with regular measurements of outcomes across the cohort. Allows for multiple randomised intervention arms to be incorporated over time	■ Recruitment of a greater quantity and more representative sample of patients ■ Patients know what they are agreeing to on trial enrolment	■ Patient refusal can reduce statistical power ■ More research needed to fully evaluate the study design

Cross-sectional studies

Cross-sectional studies survey a defined population; exposure status or disease incidence are measured at a single point in time, with exposure and outcome being measured simultaneously to provide a snapshot of the disease. Repeated cross-sectional studies help identify trends in disease prevalence. Similarly to case reports, cross-sectional studies can be used as an initial exploration of a research hypothesis, before further exploration and validation studies.

Some advantages of cross-sectional studies are that they are also relatively quick to carry out and are relatively inexpensive, since data are usually collected via questionnaires and patient records. They can provide vital information about the burden of a disease within a particular community. However, since exposure and outcome are measured simultaneously, it can be difficult to establish whether the exposure preceded or followed the outcome, leading to an uncertain correlation. It may also be difficult to establish the exact incidence of a particular disease because of a lack of follow-up data (Omair, 2015).

Case-control studies

A case-control study involves selecting two groups of people – one group with a particular disease and one group without (control group). Both groups are compared and risk factors

regarding exposure are identified retrospectively using medical records. Case-control studies are particularly efficient at investigating outbreaks and rare outcomes.

An advantage of case-control studies is that, as with cross-sectional studies and case reports, they are relatively inexpensive and can be carried out quickly. A smaller sample size can also be used, allowing the study of rare diseases. Each case can have more than one comparative control (Lewallen and Courtright, 1998).

Recalling past events may lead to confounding, bias and type 1 error (false positive result). These disadvantages make case-control studies perhaps more useful at generating hypotheses at initial research stages.

Cohort studies

Cohort studies aim to determine the factors associated with a particular outcome. Subjects are classified according to exposure of a chosen risk factor and followed up prospectively to see who develops the disease. Risk of disease in the exposed group is compared to that in the unexposed group (control). The presence of a control group distinguishes cohort studies from a case series, allowing for a better comparison between the two groups. Cohort studies provide the best information about causes of the disease that can be further analysed in a randomised controlled trial or other intervention study.

The main advantage of cohort studies is that a direct measurement of risk can be easily calculated to conclude correlation. Some disadvantages are the requirement for a large sample size, increasing the study timeline and cost. There is also a significant chance of losing subjects during follow up, potentially leading to bias and type 1 error (Bhalerao and Parab, 2010).

Intervention studies

Randomised controlled trials

Randomised controlled trials compare the group receiving the intervention with a control group. Recruited participants are randomly allocated into either group, with the control group receiving placebo or standard care. To eliminate selection bias, the gold standard is for participants, investigators and data analysts to be blinded to study arm allocation. All participants are followed up and risks of disease in both groups are compared.

Randomised controlled trials eliminate confounding as a result of the randomisation between groups, but they can be time consuming and expensive. Patient recruitment is also difficult; target sample size was achieved in just 56% of randomised controlled trials published from 2004 to April 2016 (Walters et al, 2017). Possible reasons for low recruitment are poor recruitment strategy, breakdown of communication between healthcare centres and fewer eligible patients being identified than anticipated. Patients may also have strong treatment preferences, and be unwilling to accept randomisation (Paramasivan et al, 2011). The need for frequent follow-up visits also increases susceptibility to participant non-compliance.

Cohort embedded randomised controlled trials

The cohort embedded randomised controlled trial is a novel study design involving a large cohort of people of interest with regular measurements of outcomes across the cohort. The study design also allows for multiple randomised controlled trials over time. For each randomised controlled trial in this study, a random selection of patients from the cohort is invited to consider the new intervention (Relton et al, 2010).

Using an observational cohort over a sufficient time period helps the discovery of significant long-term patient outcomes and increases efficiency, especially for expensive and high-risk interventions. Patients also know what they are agreeing to on enrolment into the trial, and have the right to refuse post-randomisation. Although allowing for greater patient autonomy, refusal can be a significant disadvantage of the cohort embedded randomised controlled trial, potentially leading to results being unrepresentative of the population. Refusal can also reduce statistical power and influence the estimation of the treatment effect. Use of an intention to treat analysis can help mitigate this effect (Pate et al, 2016).

Despite their limitations, randomised controlled trials are the best source of evidence to aid clinical management.

Systematic reviews

Systematic reviews draw on multiple randomised controlled trials to come to conclusions, also considering the quality of the studies included. These top the hierarchy of the evidence pyramid as they mitigate bias of individual studies to give a more complete picture. Systematic reviews give more precise results because of the large overall sample size. The Cochrane Collaboration provides a database of systematic reviews and critically evaluated randomised controlled trials. Although considered very high-quality evidence, systematic reviews are highly time consuming and expensive; a research team often needs to be assembled, committed to the entire duration of the project. The mean length of time to perform a systematic review from project start date to publication was found to be 67.3 weeks (Borah et al, 2017).

Conclusions

Designing a research study is a challenging process. There are many factors to be considered, most importantly funding, timescale and subject recruitment. Each study design has its own benefits and drawbacks. Case reports may be more suited to identifying new diseases, whereas randomised controlled trials require much more time and are best suited to comparing differences between control and intervention groups. Novel study designs such as the cohort embedded randomised controlled trial have been developed and appear to be a useful approach to pragmatic research questions, although more research is needed to fully evaluate the design. Ultimately, the study design chosen needs to deliver the intended outcomes of the study, while minimising error, within the confines of funding available.

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Conflicts of interest

The authors declare no conflicts of interest.

Key points

- Each study design has its own evidential value based on internal validity.
- Studies with little evidential value can generate important hypotheses that can be tested by further studies.
- The double blinded randomised controlled trial is the gold standard study design to compare new interventions to current practice.
- Novel study designs, such as the cohort embedded randomised controlled trial, are being developed to make trials more feasible, ethical and representative of the population.

Curriculum checklist

This article addresses the following requirements from the general internal medicine training curriculum

- Communicates effectively and is able to share decision making, while maintaining appropriate situational awareness, professional behaviour and professional judgement
- Is focussed on patient safety and delivers effective quality improvement in patient care
- Carrying out research and managing data appropriately

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