An Overview of Study Designs

Abstract

Numbers of clinical trials have increased exponentially over the last decade, amplifying the pressure for appropriate study design selection 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, whilst providing different evidentiary value. Ultimately, the study design chosen needs to meet experimental and funding limitations, whilst minimising error.

Introduction

A study in Switzerland concluded that one in four randomised controlled trials (RCTs) are discontinued, with 40% of completed trials remaining unpublished (Amstutz et al., 2017), highlighting the importance of study design selection**.** Clinical trial numbers have exponentially increased over the last decade and are forecast to continue on this upward trend. Research teams need to plan and develop relevant study designs to address their experimental needs, whilst complying with funding restraints and minimising error. This review aims to describe different study designs, including novel designs, focusing on their most important strengths and weaknesses.

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, RTCs, and systematic reviews of multi-

RCTs at the top of the pyramid, along with society guidelines. These classifications are mostly based on 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 of five main evidence levels, with some levels split into sub-levels. Level 1a, the highest evidence level, describes a systematic review with homogeneity of RCTs. Level 1b is an individual RCT with a narrow confidence interval and 1c describes "all or none" studies, whereby all patients died before the intervention became available, but now some patients survive with the intervention. An "all or none' study can also be met 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, with level 2b describing individual cohort studies, including low quality RCTs (such as those with <80% follow-up). Level 2c of the classification system describes research outcomes, such as audits and ecological studies. Level 3 is comprised of two sub-levels, with level 3a describing a systematic review with homogeneity of case-control studies and 3b an individual case-control study. Level 4 describes a case series and a poor quality case-control study and level 5, the lowest evidentiary level, describes "expert opinion without explicit critical appraisal"(CEBM, n.d.).

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 RCTs involve testing new treatment or medicine, with results being evaluated prospectively through clinical trials, and 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 ("PROSPERO," n.d.). 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 RCTs and systematic reviews (Ahn and Kang, 2018).

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 effect 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).

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, prior to 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 is 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 due to 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 get 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 RCT or other intervention studies.

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

Randomised Controlled Trials

RCTs 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.

RCTs eliminate confounding due to randomisation between groups, however they can be time consuming and expensive. Patient recruitment is also difficult; target sample size was achieved

in just 56% of RCTs 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). Frequent follow-up visits also increase susceptibility to participant non-compliance.

Despite their limitations, RCTs are the best source of evidence to aid clinical management.

Systematic Reviews

Systematic reviews draw on multiple RCTs to come to conclusions, also considering the quality of the studies included. These top the hierarchy of evidence pyramid as they mitigate bias of individual studies to give a more complete picture. Systematic reviews give more precise results due to a large overall sample size. The Cochrane Collaboration provides a database of systematic reviews and critically evaluated RCTs. Though 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. Mean systematic review length from project start date to publication was found to be 67.3 weeks (Borah et al., 2017).

Cohort Embedded RCTs

The cohort embedded RCT 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 RCTs over time. For each RCT in this study, a random selection of patients from the cohort are invited to consider the new intervention (Relton et al., 2010).

Using an observational cohort over a sufficient time period aids the discovery of significant long-term patient outcomes and a greater 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 RCT- 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).

Conclusion

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

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 RCT is the gold standard study design to compare new interventions to current practice.
- Novel study designs such as the cohort embedded RCT are being developed to make trials more feasible, ethical and representative of the population.

Key Words

Study Designs; Clinical trials; Evidence; Cohort embedded RCT; Bias.

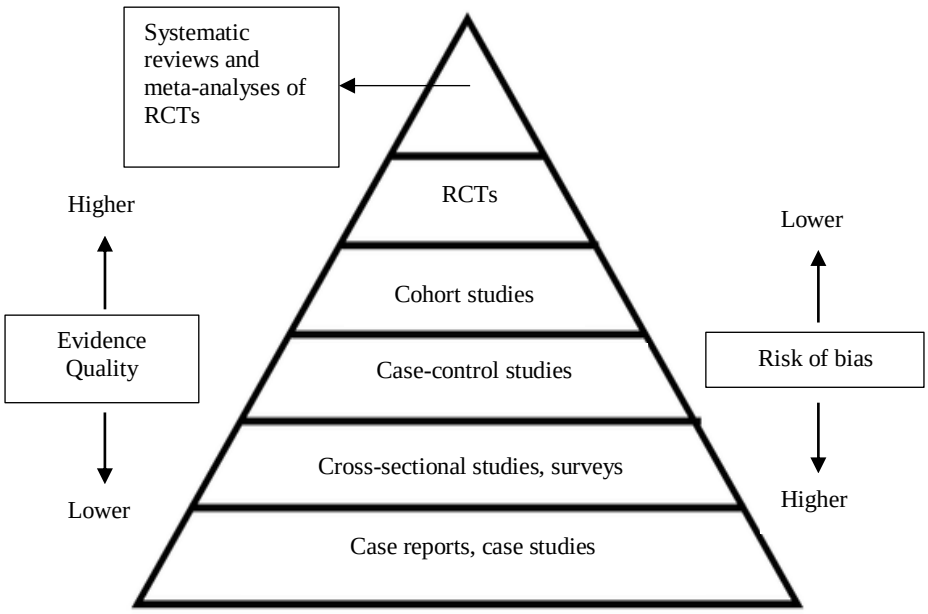

Figure 1

Table 1

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 due to recalling past events
Cohort	Subjects classified according to a particular exposure and followed up prospectively to see who get 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- due to follow up • Expensive • Risk of some subjects getting lost over long follow up- can lead to bias and type 2 error
RCT	Comparison of the group receiving the intervention with a control group.	• Randomisation reduces confounding • Flexible - Can be double/ triple blinded	• Time consuming • Expensive • Sufficient recruitment can be difficult • Non-compliance
Cohort Embedded RCT	Large cohort of patients with regular measurements of outcomes across the cohort. Allows for multiple RCTs over time- intervention arms.	• 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

Figure Legends

Figure 1. Hierarchy of evidence pyramid.

Table 1. Summary table of the most common study designs.

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