

# Research made Easy: Answering Important Questions with Valid Designs

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## ABSTRACT

Clinical research fundamentally involves finding answers to questions. Next to asking important questions, determining what type of study design to use is arguably the most pivotal step for a researcher. In this article, we provide an overview of various clinical study designs, including case reports and series, case-control studies, observational cohort studies, randomized controlled trials and systematic reviews. We aim to elucidate the utility, advantages and drawbacks of these study designs in order to assist researchers in selecting the most valid design for their research question.

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## INTRODUCTION

Clinical research fundamentally involves finding answers to questions. Next to asking important questions, determining what type of study design to use is arguably the most pivotal step for a researcher. Without the right methodology, any answers found are certain to be erroneous.

Organizational frameworks, such as the levels of evidence proposed by the Oxford Centre for Evidence-Based Medicine,<sup>1</sup> are able to assist researchers in the selection of a study design. However, a basic understanding of study designs is absolutely necessary to navigate these frameworks. As Sackett<sup>2</sup> has argued, it is the question being asked that ultimately determines the study design that should be used. Every clinical researcher must understand this basic premise.

In this article, we aim to elucidate the utility, advantages and drawbacks of various clinical study designs in order to assist researchers in selecting the most valid design for their research question.

## CASE REPORTS AND CASE SERIES

A case report is a detailed description of a clinical case. The structure of this study design typically mirrors a detailed clinical consultation note, beginning with a thorough summary of history, physical examination and laboratory findings, and concluding with a comprehensive discussion of these findings. The aim is to convey very detailed

observations pertaining to the clinical case. A case series is similar to a case report but involves a collection of several clinical cases in which outcomes may be pooled and reported in aggregate.

Case reports and series are considered low-level evidence.<sup>1,3</sup> This is because the lack of a comparator group makes any conclusions regarding relative efficacy or harm meaningless.<sup>4</sup> Nevertheless, there are situations in which case reports and series are critically important.

For instance, a possible association of bisphosphonates with atypical femoral shaft fractures was initially brought to the forefront by a number of case reports and case series.<sup>5-8</sup> Although no definitive conclusions could be made, the circumstances for further inquiry were established and subsequent studies were undertaken with higher level designs to better define this relationship.<sup>9,10</sup>

As this example demonstrates, more than answering any specific question, case reports and series can be thought of as question generators. Indeed, these study designs best serve as a means for hypothesis generation; they create the fodder for future, in-depth inquiry with higher level comparative studies.

## CASE-CONTROL STUDIES

A case-control study is a retrospective study design in which a group of subjects with an outcome of interest (i.e. 'cases') are compared with a group of subjects without the outcome of interest (i.e. 'controls') in order to identify any difference in risk factors. Conceptually, it can be thought of as 'research in reverse'.<sup>11</sup> In other words, the outcome of interest is identified first and subsequently exposures are compared to determine if and how these have influenced the chosen outcome.

Unlike case reports and series, the case-control design offers a true comparator (i.e. 'control') group. Therefore conclusions regarding relative effect can be proposed. However, of the study designs with a control group, case-control studies are the most prone to both bias and confounding. Bias is a systematic error that occurs due to both the nature of the available data sources and the retrospective study design (Table 1), and may lead to false conclusions. Confounding refers to the presence of one or more often unknown variables that are associated with both the exposure and the outcome. Confounding leads to spurious or coincidental conclusions.

**Table 1:** Examples of bias in case-control studies

Type of bias	Explanation
Case ascertainment	A systematic error in which exposures or risk factors are more likely to be identified in the cases than in the controls because investigators are disproportionately attentive to, or more likely to alter their interpretation of data.
Recall	A systematic error that occurs in retrospective studies that base some degree of data on the past recall of events. For various reasons, subjects with a disease often demonstrate a more vivid memory of possible exposures or risk factors than those without the disease.
Misclassification	Systematic error inherent in a measurement instrument results in subjects being wrongly classified as 'cases' when in fact they do not have the condition being studied or <i>vice versa</i> .
Selection	A systematic error that results when patients that have a certain quality are excluded from selection in one group more than another. For instance, patients that have several comorbidities are overlooked when selecting subjects for the 'cases' group but not the 'control' group.

The high susceptibility of case-control studies to bias and confounding makes the determination of a true cause-and-effect relationship difficult, if not impossible. As such, these studies cannot and should not be the conclusion of any line of comparative inquiry. Higher levels of evidence must subsequently be sought to corroborate any conclusions.

Still, case-control studies serve a useful function when looking at rare outcomes, such as femoral neck stress fractures in young military recruits,<sup>12</sup> because the researcher is able to achieve a large sample size by directly identifying cases. To be able to come to a similar number of subjects with a prospective design would require a financially or practically unattainable sample size due to the low incidence of the condition. Case-control studies are also useful because they are relatively cheap, fast and can evaluate many exposures for a given outcome. Therefore, a case-control study may be an excellent starting point when the question being asked requires an answer within a limited period of time or within a limited budget.

## OBSERVATIONAL COHORT STUDIES

Observational cohort studies involve identifying two or more groups (or cohorts) that differ only by a specific exposure. The patients that comprise the groups are not selected by the researcher; it is the exposure that defines the groups. These self-defined groups are followed prospectively for preestablished outcomes. Observational cohort studies can be classified as retrospective or prospective, depending on whether the outcome of interest has or has not already manifested in the study subjects, respectively.

There are several questions for which observational cohort studies are indicated. When a question involves determining the natural history of a condition, it only makes sense to follow a cohort of patients forward through time. In this situation, a control group helps to distinguish how the natural history differs from a population of normal subjects.

Questions of comparison where an experimental study would be unethical can also be studied with observational designs. For example, harmful exposures must be studied with observational designs because study subjects cannot ethically be assigned to experience a harmful exposure, such as smoking. A more subtle situation where it would be unethical to conduct an experimental trial is where clinical equipoise does not exist. As an example, if there is no debate or difference in opinion about operative management being superior to nonoperative management for calcaneus fractures, an experimental design comparing the two would be unethical. This is because one group of patients would be subjected to what is generally considered to be an inferior form of treatment. If, however, an observational study is able to demonstrate similarity or superiority of nonoperative treatment, then it helps overcome dogma and create the equipoise necessary to ethically initiate a randomized controlled trial.

Observational studies also have the potential to achieve large sample sizes that could not possibly be achieved in an experimental design. Having very large sample sizes enables the identification of significant differences for rare outcomes.

Although a well-conducted prospective observational study is better able to eliminate systematic sources of error or bias, the issue of confounding remains and leads to the potential for spurious conclusions. Only a well-conducted RCT is best able to minimize the effect of confounders and systematic bias.

## RANDOMIZED CONTROLLED TRIALS

A RCT is an experimental study design in which patients are allocated to one group or another through a completely random process. Each randomly selected group receives a different intervention (or placebo), is prospectively followed and outcomes are compared. The RCT has been placed at the pinnacle of the hierarchy of primary study

**Table 2:** Five important elements of an RCT

Component	Explanation
Prospective design	Ensures an RCT provides evidence of a temporal relationship between the intervention and the outcome, one of the key components of establishing a cause-and-effect relationship. Also eliminates bias present in retrospective study designs (see Table 1).
A priori outcomes	Primary and secondary outcomes are typically established at the beginning of the study or <i>a priori</i> , thereby preventing data-mining for coincidental relationships.
Randomization	Equally distributes potentially confounding variables among the different study groups. One is able to attribute the final effect to the intervention or exposure being tested with greater certainty.
Allocation concealment	Refers to a concept in which investigators are not aware which group a subject will be assigned to, such as through the use of sealed envelopes or a central call-in center. Therefore, the results cannot be unintentionally (or intentionally) influenced by, e.g. placing younger and healthier patients in one group over another.
Blinding	Refers to the concept that study investigators, health care practitioners and other parties are not made aware of which group is receiving which intervention until the analysis is complete. This prevents biased behavior or biased collection and interpretation of outcome data.

designs.<sup>1,3</sup> There are several components of an RCT that contribute to its strengths, including a prospective design, *a priori* establishment of outcomes, randomization, allocation concealment and blinding (Table 2). A more thorough discussion of the elements of an RCT is beyond the scope of this article, and we refer readers to the CONSORT statement and two well-conducted surgical RCTs.<sup>13-15</sup>

The RCT is truly the strongest study design for determining superiority of one intervention over another. Not only is there a control group, but through the use of the aforementioned methods, confounding variables are minimized and any associations that are found are more likely than not to be true associations. Given these advantages, if an RCT is feasible it is certainly the best option for comparing interventions.

## SYSTEMATIC REVIEWS AND META-ANALYSES

A systematic review is a study design that aims to systematically collect primary articles, extract data using standardized forms and synthesize these findings. If the data is synthesized through quantitative methods, it is referred to as a meta-analysis. Systematic review methodology is not only rigorous and thorough but also reproducible. For these reasons, the systematic review is a more evidence-based choice to synthesis and summarization than the traditional narrative review.

The specific question that a systematic review aims to answer is analogous to that of its component studies. In other words, a systematic review of studies on early vs delayed surgery for hip fractures will answer that very same question.<sup>16</sup> However, the broader question that each systematic review aims to answer is, given all the available evidence on a certain topic, what conclusions can be made?

A systematic review's strength is in its ability to pool or summarize multiple studies on a topic. However, the strength of any conclusions is limited by the quality of the component studies. For example, a systematic review of case series would be far inferior to a systematic review of high-quality, large-scale RCTs with homogeneous outcomes. In fact, the latter case represents the pinnacle of the evidence-based hierarchy,<sup>1,3</sup> and the clinician may be assured that the conclusions are very likely to be valid.

## CONCLUSION

In this article, we have attempted to summarize major features of the various available clinical study designs. Furthermore, we have tried to provide the benefits and limitations of each. As we hope is clear from this brief review, it is the question being asked alongside other secondary considerations, such as time and financial context, which ultimately determine the most valid study design for any research question.

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