A Critical Evaluation of Clinical Research Study Designs

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INTRODUCTION

Prior to starting any clinical research, an investigator must determine the appropriate study design to answer the question at hand. Selecting the correct study type also depends on ethical considerations, disease of interest, and the resources available. A well-designed study will clearly identify an exposure and an outcome in an objective, quantifiable manner to answer a defined hypothesis. After thorough data analysis and discussion of the results, the study will ideally prompt further research on the subject. Understanding the various indications for different study designs is important not only for devising one's own study but also for critically reviewing the literature. This article outlines frequently encountered study designs in clinical research and their respective strengths and drawbacks (Table 1).

OVERVIEW

In clinical research, studies can be classified as either interventional (experimental) or noninterventional (observational) studies. The National Institutes of Health defines an interventional study as one in which "participants receive specific interventions according to the research plan created by the investigators. These interventions may be medical products, such as drugs or devices; procedures; or changes to participants' behavior" (http://www.clinicaltrials.gov). Subcategories include randomized controlled trials (RCTs) and clinical trials. This article addresses RCTs.

In observational studies, there is no intervention; that is, subjects are observed and evaluated for exposures encountered as part of the natural course of their lives. This article will address the following types of studies: case–control, cohort, cross-sectional, and case reports/series.

RANDOMIZED CONTROLLED TRIALS

RCTs are considered the "gold standard" for evaluating a given therapy and its causal impact on an outcome. In an RCT, study subjects are randomly assigned to one of two groups: the treatment arm, which receives the therapy, or the control arm, which receives a placebo or no treatment. Both study arms are subsequently followed in an identical manner and analyzed for differences in outcomes.

WHAT CLINICAL RESEARCH DESIGNS DO

- Clinical research studies are often divided into two main categories: interventional and observational (noninterventional). An example of an interventional study is a randomized controlled trial (RCT). Observational studies include case–controls, cohorts, cross-sectional, and case reports/series.
- RCTs help evaluate effectiveness of a therapy and the causal impact on an outcome. Observational studies answer questions of epidemiology of disease and possible associations between exposure and an outcome.

LIMITATIONS

- Selection of an appropriate study design is limited by the research question, the disease of interest, availability of time and resources, and ethical considerations.

Unlike other studies, the intrinsic design of an RCT allows investigators to assess causality of a variable of interest, rather than simply a correlation. These studies generally have stringent selection criteria to ensure that subjects are comparable in most respects, thereby reducing confounding and isolating the effect of the intervention. Randomization ensures that any confounding factors are equally divided between groups. Furthermore, blinding reduces the likelihood that behaviors of subjects or investigators could influence the results of the study. In a single-blinded study, subjects are unaware of their treatment status, whereas in a double-blinded study both the investigators and the subjects are unaware of which intervention the subjects receive (Röhrig *et al.*, 2009).

Advantages

RCT is considered the most reliable study design and a high-impact method when practicing evidence-based medicine because of its ability to minimize confounding factors through randomization. By reducing biases, causality of an intervention on a defined outcome can be most effectively determined (Fletcher *et al.*, 1996).

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Disadvantages

The main disadvantage of RCTs compared to other prospective studies is that they are typically more expensive and tedious to perform. In addition, the applicability of the study results to real-world situations may be limited by the study population characteristics, procedures implemented, or outcomes measured (Fletcher *et al*., 1996).

COHORT STUDIES

Unlike RCTs, there is no intervention in a cohort study. Cohort studies are useful when determining a correlation between cause and effect. First, investigators select a group of people who share a common characteristic or exposure, such as a medication or procedure, but do not have the disease or outcome of interest. A control group is often selected from the general population that has not previously encountered the exposure. In a prospective study, both groups are followed over time to determine whether they develop the outcome of interest. In a retrospective cohort study, cohorts are identified by the same process, but are instead followed via historical data. Analysis of risk factors aids in studying causal associations between exposures and disease, but does not identify true causality (Mann, 2003).

Several important epidemiological measures can be obtained from cohort studies. Investigators can determine the relative risk, or the likelihood that an exposed individual will develop a given disease when compared to a nonexposed individual. In addition, the incidence, or development of new cases of an outcome, can be determined based on their prospective nature (Röhrig *et al*., 2009).

Recently, Chren *et al*. (2013) conducted a prospective cohort study consisting of 1,253 patients with a history of nonmelanoma skin cancers (NMSCs) to determine the recurrence of skin cancer. The cohort of patients was grouped according to treatment of the primary NMSC by destruction, excision, or Mohs surgery (Figure 1).This study design allowed investigators to conclude there was no difference in recurrence rates for these treatments (Chren *et al*., 2013).

Advantages

A main advantage of a cohort study is that multiple variables may be assessed concurrently and disease risk factors may be identified. The population evaluated in a cohort study is not as restrictive as that in an RCT. As a result, the findings of a cohort study may be more generalizable. Finally, cohort studies can prospectively study the relationship between certain outcomes and exposures that could not otherwise be ethically administered to subjects (Mann, 2003).

Disadvantages

Similar to RCTs, cohort studies are costly and time-consuming, as well as vulnerable to subject attrition or loss to follow-up during the course of the study. They are not ideal for studying rare diseases because very few patients will develop the disease. Finally, because of the absence of randomization, cohort studies are more prone to bias and confounding than are RCTs (Mann, 2003).

CASE–CONTROL STUDIES

In a case–control study, those affected by a disease (cases) are compared to disease-free controls from within the population. This type of study is frequently retrospective and aims to identify an association between a disease and potential risk factors. Figure 2 compares the designs of case–control and cohort studies. These studies may be performed through interviews or patient chart review. This allows investigators to determine prior exposure to a potential risk factor and the weight of its impact on disease development. An approximation of the relative risk, known as an odds ratio, can be calculated (Mann, 2003).

Robinson *et al*. (2013) identified patients with NMSC (cases) matched by age and gender to a population of control subjects within the same geographic region. Subjects were assessed for use of photosensitizing medications and odds ratios were calculated. This allowed the authors to postulate that the risk of developing certain skin cancers was enhanced by use of these medications (Robinson *et al*., 2013).

Table 1. Comparing study designs in clinical research

Study design	Description	Advantages	Disadvantages
RCT	Interventional Subjects randomized to treatment or control	Gold standard for evaluating therapy effects Can determine causality Minimizes bias/confounding	Cost and time Potential for low generalizability
Cohort	Observational Subjects followed over time for disease development	Can help identify risk factors of disease More generalizable than RCT	Cost and time Difficult to show causality Potential for bias/confounding
Case–control	Observational Disease cases retrospectively compared with controls for exposure status	Fewer cost and time concerns Ideal for rare diseases No patient follow-up needed	Difficult to show causality Potential for bias/confounding
Cross-sectional	Observational Assess prevalence of disease and exposure status at one time point	Fewer cost and time concerns Evaluates associations between exposure and disease	Cannot determine causality Potential for bias/confounding
Case report/case series	Observational Describes a rare finding in a patient or group of patients	Rapidly bring attention to new findings Preliminary research	Definitive conclusions cannot be made Potential for bias/confounding

RCT, randomized controlled trial.

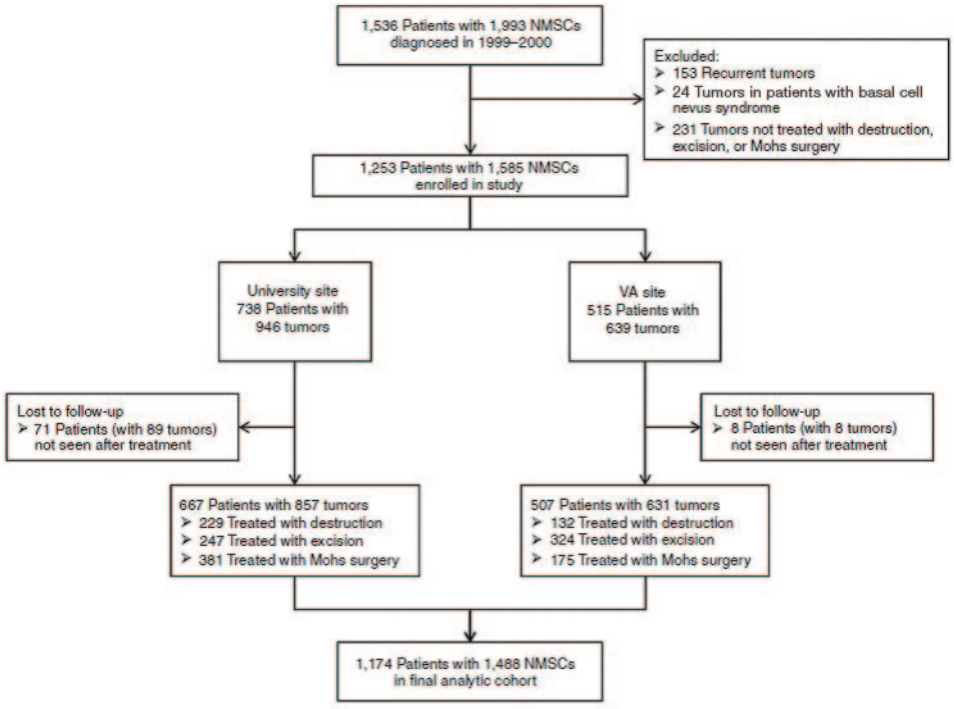

Figure 1. Prospective cohort design. A cohort of patients with a history of nonmelanoma skin cancer (NMSC) was grouped based on treatment for primary skin cancer with destruction, excision, or Mohs surgery. Patients were followed for tumor recurrence. Reprinted with permission from Chren *et al.* (2013).

Advantages

Case–control studies do not rely on patient follow-up and therefore require less time and cost than the aforementioned studies. It is the ideal design for researching rare diseases because disease status is known from the beginning of the study. Although it is difficult to show causality, associations may be observed that can be studied further using a more rigorous method (Fletcher *et al.*, 1996).

Disadvantages

Case–control studies are limited by the potential for confounding. There is the additional risk of recall bias, in which case subjects may have a skewed recollection of exposure to a potential risk factor as compared with controls (Mann, 2003).

CROSS-SECTIONAL STUDIES

Whereas RCTs and cohort studies study subjects longitudinally, cross-sectional studies are a "snapshot" and assess disease and exposure status of a population at one particular time point. A survey is one prototypical example. As a descriptive study, the cross-sectional design evaluates the association between certain factors and an outcome of interest. The most important epidemiological contribution is the prevalence of disease, or the number of cases in a population (Mann, 2003).

Advantages

Cross-sectional studies are cost-efficient and can be completed in a relatively short amount of time on a large scale. The initial associations observed in this type of study are ideal for prompting further research using study designs that yield a stronger level of evidence, such as case–control or cohort studies (Noordzij *et al.*, 2009).

Disadvantages

Causality cannot be determined with this study design. It is also prone to the forms of bias associated with other observational studies, such as recall and selection bias.

CASE SERIES/REPORT

A case report details a rare finding, such as a peculiar drug reaction or a new disease entity. Case series chronicle multiple patients with the same finding. Typically, these studies are retrospective and serve to garner attention for unique findings.

Advantages

Case reports can be an excellent way to rapidly and inexpensively disseminate information about a new finding to the medical community. They can help generate awareness of new disease entities and spark hypotheses about pathophysiology (Noordzij *et al.*, 2009).

Disadvantages

Given that there may be a limited number of cases and absence of a control group, no definitive conclusions can be drawn from case reports. They serve as a preliminary study.

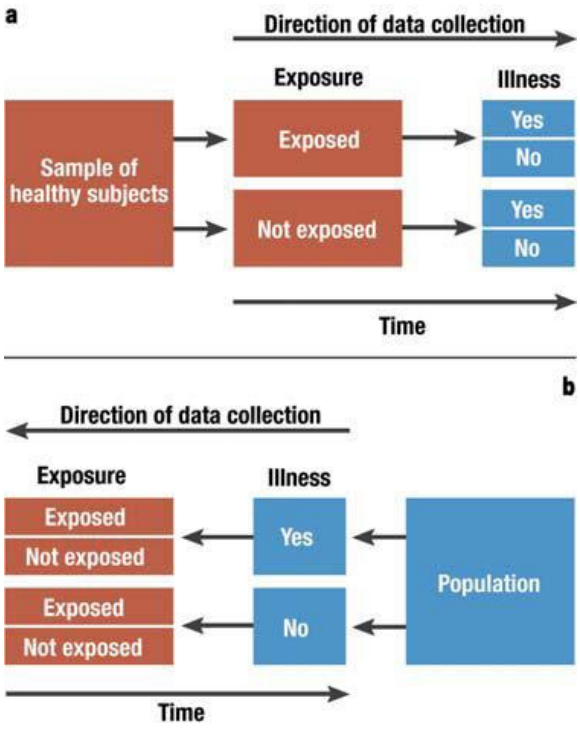

Figure 2. Comparison of cohort and case–control study designs. (**a**) In a prospective cohort study, healthy subjects are followed over time and assessed for exposure status and disease development. (**b**) In a retrospective case–control study, historical data are reviewed to compare exposure status in diseased (case) and nondiseased (control) individuals. Reprinted with permission from Röhrig *et al.* (2009).

SUMMARY

Interventional and observational studies have important roles in dermatology. The results from any study must be put in the context of the appropriate research design selection. RCTs are most useful in determining causality and effectiveness of treatment. Observational studies provide information about epidemiology and possible links between exposure and disease. Understanding the fundamentals underlying the various study designs is critical to both investigators and clinicians alike.

CONFLICT OF INTEREST

The authors state no conflict of interest.

CME ACCREDITATION

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http://www.classmarker.com/online-test/start/?quiz=nta52b8684581d68

SUPPLEMENTARY MATERIAL

A PowerPoint slide presentation appropriate for journal club or other teaching exercises is available at http://dx.doi.org/10.1038/jid.2013.545.

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QUESTIONS

This article has been approved for 1 hour of Category 1 CME credit. To take the quiz, with or without CME credit, follow the link under the "CME ACCREDITATION" heading.

1. **Which of the following study designs allows for the calculation of the relative risk?**
   - A. Case–control.
   - B. Case series.
   - C. RCT.
   - D. Cohort study.
   - E. Cross-sectional.
2. **Which of the following study designs allows for the calculation of an odds ratio?**
   - A. Case–control.
   - B. Case series.
   - C. RCT.
   - D. Cohort study.
   - E. Cross-sectional.
3. **Which of the following research questions is NOT an appropriate candidate for evaluation by a randomized controlled trial?**
   - A. Does contact with arsenic lead to increased development of squamous cell carcinoma?
   - B. Can multivitamin supplementation decrease mortality in elderly patients?
   - C. Could classroom lectures increase sun-protective behaviors in elementary-school children?
   - D. What is the incidence of infection by cytomegalovirus in AIDS patients?
   - E. Both a and d.