



How to conduct well-designed clinical research

Da Jung Kim, Song Yi Kil, Jongwon Son, Ho Sup Lee

Department of Internal Medicine, Kosin University College of Medicine, Busan, Korea

Clinicians and healthcare decision-makers conduct their clinical practice based on the results of clinical trials. However, some health problems remain unresolved; in such cases, further research is required. To ensure reliable research results, it is important to understand the study design and conduct well-designed clinical trials. Many study designs can be chosen within the two broad categories of observational and interventional. Clinical studies have a variety of designs, including case series, case-control, cross-sectional, and prospective and retrospective cohort studies. Well-designed clinical studies can clarify important differences between treatment options and provide data on long-term drug efficacy and safety. Interpreting the results of clinical trials can be difficult because weaknesses in research design, data collection methods, analytic methods, and reporting can compromise their value and usefulness. However, although randomized controlled trials are limited owing to ethical and practical issues, they are optimal for investigating the effects of therapy and establishing causality. Here we present an overview of different clinical research designs and review their advantages and limitations.

Keywords: Clinical study; Clinical trial; Research; Research design

Introduction

In the era of evidence-based medicine, clinicians and healthcare decision-makers treat patients based on the results of clinical trials [1]. However, information presented in clinical trials is only useful if the trial is well planned. Thus, well-designed study plans and appropriate definitions of eligible participants are required to minimize confusion and other biases [2]. An accurate understanding of the research design is critical to the professional interpretation and determination of the validity and generalizability of the results [2]. Trial participants are randomized to experimental or control regimens [3].

In a real clinical setting, researchers frequently encounter situations lacking exact solutions to patients' health prob-

lems. Although many studies have investigated various diseases, some health problems remain unsolved. As a result, physicians and researchers have started reviewing related clinical trials to find applicable solutions. If useful results have not yet been published, a major conference may be a source of valuable information. However, if a definite solution is unavailable, further clinical research is desirable. Similar study designs can be found at clinicaltrials.gov. If a newly conceived clinical study has not yet been published, the potential new study may have sufficient value. Thus, one can create a simple synopsis of the proposed clinical research, contact pharmaceutical companies for new drugs, and obtain research funding. The proposed clinical research is reviewed by the global review committee. The proposed clinical study will proceed upon receiving ap-

Received: July 15, 2022; **Revised:** September 6, 2022; **Accepted:** September 7, 2022

Corresponding Author: Ho Sup Lee, MD, PhD

Department of Internal Medicine, Kosin University College of Medicine, 262 Gamcheon-ro, Seo-gu, Busan 49267, Korea

Tel: +82-51-990-6107 Fax: +82-51-990-5820 E-mail: hs52silver@gmail.com

© 2022 Kosin University College of Medicine

© This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

proval. However, various difficulties can be encountered in the process of obtaining valuable research results.

This study aimed to help researchers who have started clinical studies present their research results more effectively. It provides an overview of different research designs and comments on the strengths and limitations of each. The characteristics of the study designs used in the clinical trials are summarized in [Table 1](#).

Retrospective study

It is difficult for novice researchers to start prospective studies such as randomized controlled trials (RCTs) [4]. Therefore, retrospective studies are more suitable for these researchers as they are easily conducted. This involves col-

lecting information from previously treated patients and deriving results through statistical analyses of the content. Retrospective studies can be divided into case reports or case series, cross-sectional, case-control, and cohort studies according to the data collection method [5].

1. Case reports and case series

Case reports and case series have a profound impact on the literature in medicine and continue to advance our medical knowledge [6]. The authors reported a possible association between specific exposure and the observed results on the clinical records of one or more subjects. These studies may be the first to reveal a new disease or adverse treatment effects. The results of cost-effective studies help generate hypotheses that may later be explored using more

Table 1. Characteristics of study designs used in clinical research

Study design	Characteristics	Advantage	Limitation
Retrospective study designs			
Case series	Detailed description of cases	Fast and inexpensive Hypothesis-generating	Very limited potential to establish causal effects Selection bias
Cross-sectional study	Exposure and outcome measured at the same time point	Useful for describing disease prevalence	Very limited potential to establish causal effects
	Subjects with and without outcomes are compared	Fast and inexpensive Hypothesis-generating	Selection bias Survival bias
Case-control study	Cases (those with the outcome of interest) are compared with controls (those without the outcome of interest) with respect to exposure	Efficient Suitable for studying rare outcomes and multiple exposures Relatively inexpensive Hypothesis-generating	Some potential to establish causal effects Can only study one outcome Choice of the control group can be difficult Selection bias Recall bias
Retrospective cohort study	A cohort of subjects free of the outcome is followed and compared based on the exposure	Suitable for studying multiple exposures, rare exposures, and multiple outcomes Hypothesis-generating High generalizability	Some potential to establish causal effects Selection bias
Prospective study designs			
Prospective cohort study		The most accurate and objective method of collecting information from numerous patients	Can take a long time Can be expensive
Randomized controlled trial	Randomization: allocation of subjects to experimental or control group by chance	Gold standard in establishing causal effects in studies on therapy Suitable for studying more than one intervention	Very expensive Can take a long time Not suitable for studying rare events Can be unethical Often low generalizability due to strict selection criteria

Each study design may suffer from a specific type of bias. These are explained in the manuscript.

advanced research designs; however, causality is seldom established [5]. However, owing to the potential existence of weak inferences and the bias associated with such case reports, researchers are not passionate about developing frameworks for assessing, evaluating, synthesizing, and applying the evidence derived from the results of case reports or case series [6].

2. Cross-sectional studies

Most cross-sectional studies using descriptive methods based on data from a population or representative group aim to estimate a prevalence [7]. Most cross-sectional studies account for the prevalence of disease in a population or treatment in specific patient groups [5]. However, since exposures and outcomes are identified simultaneously, authors and readers should not infer causality unless it can be safely assumed that the exposure is stable over time and unaffected by the outcome [7].

3. Case-control studies

Case-control studies can achieve significant scientific findings with little cost, time, and effort relative to other study designs. This fast road to research results attracts many young researchers [8]. This study type selects participants based on outcome variables and compares participants with conditions (cases) to participants without conditions (controls). Previous studies compared cases and controls based on exposure [5]. However, case-control studies tend to be more sensitive to bias than other comparative studies [8].

4. Retrospective cohort studies

Cohort studies are observational studies in which a cohort of individuals sharing some characteristics is followed over time and the outcomes are measured at certain time points. Cohort studies can be categorized as prospective or retrospective [9]. A cohort study allows researchers to investigate multiple outcomes and exposure variables [5]. A major advantage of a cohort study is its ability to examine multiple results that can be related to single or multiple exposures in a single study [9]. In longitudinal cohort studies, measuring changes in exposure levels and outcomes over time can provide insight into the dynamic relationship between exposure and outcomes [9]. In addition, registry cohort studies collect data retrospectively and prospec-

tively. Several retrospective cohort studies have used data collected previously for other purposes. As a result, investigators have little control over the data collection process. Thus, the measurement of variables may be inaccurate or inconsistent, resulting in information bias. However, this research method is useful for analyzing the results of unusual or occupational exposure [9].

Retrospective cohort studies use big data from healthcare companies. The potential of big data in the healthcare field depends on the ability to detect specific patterns and convert high volumes of data into practical knowledge for decision-makers and precision medicine [10]. In healthcare systems, big data and data collection are valuable. The establishment of a big data platform will enable easy operation, remote consultation, and low cost; strengthen global cooperation to improve clinical practice, education, and scientific research; and support the global application of precision medicine and emerging health management models [11]. However, the major drawbacks of relying on large datasets to guide healthcare decision making have been well documented. The sensitive nature of stored and analyzed big healthcare data poses a unique challenge [12].

Prospective study

Since retrospective studies use previously collected data, it is necessary to recognize the possibility of selection bias and acknowledge the limitations of accepting data based on statistical results. RCTs are considered the gold standard for evaluating treatments and other interventions. A definite advantage of RCTs over observational studies is that they provide evidence of causality and are unlikely to have selection bias and prognostic selection [13,14].

1. Prospective cohort studies

A prospective registry cohort study is the most accurate and objective method to collect information from numerous patients. However, it requires a long follow-up period of waiting for events to occur; thus, it features a high risk of loss to follow-up.

2. Phases of clinical trials

Clinical trials can be divided into stages at which a new drug is tested [4].

1) Phase I trial

A phase I trial, which is usually conducted in healthy volunteers [15], aims to test the safety of a new drug in humans and determine its ideal administration method. A phase I trial is usually not randomized or controlled and does not include a control group. It mainly consists of a series of cases in which participants are administered the drug progressively while being monitored carefully by the research team [1].

2) Phase II trial

Once a drug's safety has been evaluated in a phase I trial, a phase II trial attempts to determine the efficacy of various doses and frequencies of its administration in a small, non-randomized group [16]. If the drug is ineffective or excessively virulent in a small group of patients, no further testing is performed. If the drug is effective and its side effects are tolerable, the researcher can proceed to a phase III trial [1,16].

3) Phase III trial

A phase III trial, which is usually considered a full-scale RCT, is a comparative definitive study that compares the effectiveness of a new drug with that of a standard drug [16,17]. Phase I trials enroll a large number of patients, often in the thousands, to determine whether the new treatment is more effective and less toxic than the standard treatment [17,18]. Because it requires reliable results from earlier clinical trials, a phase I trial is the ultimate test of a new treatment [5]. Although RCTs have powerful study designs, they are costly because of the large number of enrolled patients and interventions. Moreover, it is unethical to expose patients to an intervention considered inferior to the standard treatment [4].

4) Phase IV trial

A phase IV trial, usually called post-marketing surveillance, is a large-scale study that attempts to monitor the adverse effects of a new treatment after marketing approval. However, the sample size is often insufficient to identify rare adverse reactions [19]. Also, since this is a non-interventional study lacking close monitoring, reports of adverse reactions may be omitted.

Tips for conducting well-designed clinical research

We offer young researchers the following tips for designing clinical trials: when you have an idea about a study, check clinicaltrials.gov to see if similar studies are already underway. Examine how other researchers have planned and conducted their studies. If a newly conceived clinical study has not yet been published, the potential new study has sufficient value.

- Researchers initially perform a retrospective study. From case reports or case series to cohort studies, an appropriate study design is chosen based on the available data and research ideas.
- Meaningful results are often obtained from multicenter prospective studies. Start by participating in multicenter studies, then lead a multicenter study.
- Combining clinical research and cell line-based experimental research compensates for the limitations of this research. When confirming the results of clinical research using clinical data alone, the results are best supplemented with cell line research. A factor that influences good clinical research is the researcher's ability to improve upon basic experimental research or collaborate with a basic researcher for a study [20].

Conclusion

For successful clinical research, it is important that one starts with a retrospective study, advances to a prospective study, participates in and then leads multicenter studies, and finally cooperates with experimental research teams.

Article information

Conflicts of interest

Ho Sup Lee is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

Funding

None.

Author contributions

Conceptualization: HSL. Data curation: DJK, SYK, JS, HSL. Investigation: HSL. Supervision: DJK, HSL. Writing - original draft: HSL. Writing - review & editing: DJK, SYK, JS, HSL. Approval of final manuscript: all authors.

ORCID

Da Jung Kim, <https://orcid.org/0000-0003-2375-8140>

Song Yi Kil, <https://orcid.org/0000-0003-1272-1334>

Jongwon Son, <https://orcid.org/0000-0001-7341-5256>

Ho Sup Lee, <https://orcid.org/0000-0001-5974-6884>

References

1. Jager KJ, Stel VS, Wanner C, Zoccali C, Dekker FW. The valuable contribution of observational studies to nephrology. *Kidney Int* 2007;72:671–5.
2. Schultz A, Saville BR, Marsh JA, Snelling TL. An introduction to clinical trial design. *Paediatr Respir Rev* 2019;32:30–5.
3. Berry DA. Emerging innovations in clinical trial design. *Clin Pharmacol Ther* 2016;99:82–91.
4. Kaptchuk TJ. The double-blind, randomized, placebo-controlled trial: gold standard or golden calf? *J Clin Epidemiol* 2001;54:541–9.
5. Noordzij M, Dekker FW, Zoccali C, Jager KJ. Study designs in clinical research. *Nephron Clin Pract* 2009;113:c218–21.
6. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. *BMJ Evid Based Med* 2018;23:60–3.
7. Kesmodel US. Cross-sectional studies: what are they good for? *Acta Obstet Gynecol Scand* 2018;97:388–93.
8. Schulz KF, Grimes DA. Case-control studies: research in reverse. *Lancet* 2002;359:431–4.
9. Wang X, Kattan MW. Cohort studies: design, analysis, and reporting. *Chest* 2020;158(1S):S72–8.
10. Pastorino R, De Vito C, Migliara G, Glocker K, Binenbaum I, Ricciardi W, et al. Benefits and challenges of Big Data in health-care: an overview of the European initiatives. *Eur J Public Health* 2019;29(Suppl 3):23–7.
11. Yang J, Li Y, Liu Q, Li L, Feng A, Wang T, et al. Brief introduction of medical database and data mining technology in big data era. *J Evid Based Med* 2020;13:57–69.
12. Austin C, Kusumoto F. The application of big data in medicine: current implications and future directions. *J Interv Card Electrophysiol* 2016;47:51–9.
13. Bamberger M, Moore N, Lechat P; Participants of Round Table N° 3 of Giens XXVI. How to improve the clinical development paradigm and its division into phases I, II and III. *Therapie* 2011;66:331–4.
14. Tripepi G, Jager KJ, Dekker FW, Wanner C, Zoccali C. Bias in clinical research. *Kidney Int* 2008;73:148–53.
15. Manton KJ, Gauld CS, White KM, Griffin PM, Elliott SL. Qualitative study investigating the underlying motivations of healthy participants in phase I clinical trials. *BMJ Open* 2019;9:e024224.
16. Thall PF. A review of phase 2-3 clinical trial designs. *Lifetime Data Anal* 2008;14:37–53.
17. Bhude A, Shah PS, Acharya G. A simplified guide to randomized controlled trials. *Acta Obstet Gynecol Scand* 2018;97:380–7.
18. Green JA. Clinical trials in cancer. *Br J Cancer* 2011;104:1521–2.
19. Cesana BM, Biganzoli EM. Phase IV studies: some insights, clarifications, and issues. *Curr Clin Pharmacol* 2018;13:14–20.
20. Shen J, Swift B, Mamelok R, Pine S, Sinclair J, Attar M. Design and conduct considerations for first-in-human trials. *Clin Transl Sci* 2019;12:6–19.