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Review article

Comparative effectiveness research methodology using secondary data: A starting user's guide

Maxine Sun, Ph.D., M.P.H.[a,b,*], Stuart R. Lipsitz, Sc.D.[a]

[a] *Division of Urological Surgery and Center for Surgery and Public Health, Brigham and Women's Hospital, Harvard Medical School, Boston, MA*
[b] *The Lank Center for Genitourinary Oncology, Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*

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Abstract

Background: The use of secondary data, such as claims or administrative data, in comparative effectiveness research has grown tremendously in recent years.

Purpose: We believe that the current review can help investigators relying on secondary data to (1) gain insight into both the methodologies and statistical methods, (2) better understand the necessity of a rigorous planning before initiating a comparative effectiveness investigation, and (3) optimize the quality of their investigations.

Main Findings: Specifically, we review concepts of adjusted analyses and confounders, methods of propensity score analyses, and instrumental variable analyses, risk prediction models (logistic and time-to-event), decision-curve analysis, as well as the interpretation of the P value and hypothesis testing.

Conclusions: Overall, we hope that the current review article can help research investigators relying on secondary data to perform comparative effectiveness research better understand the necessity of a rigorous planning before study start, and gain better insight in the choice of statistical methods so as to optimize the quality of the research study.

Keywords: Comparative effectiveness research; Review; Secondary data; Urology; Oncology

1. Introduction

According to the Agency of Healthcare Research and Quality, comparative effectiveness research is designed to inform health-care decisions by providing evidence on the effectiveness, benefits, and harms of different treatment options. The evidence is generated from research studies that compare drugs, medical devices, tests, surgeries, or ways to deliver health care. [1] Owing to high costs and logistical barriers associated with the use of primary data and primary data collection, the reliance on secondary data, such as claims or administrative data, in comparative effectiveness research has grown tremendously in recent years. Examples of secondary data sources include large datasets collected by governments, research institutions, and other organizations. These may consist of administrative datasets funded by governmental organizations [2,3], as well as private companies such as Premier, Optum or MarketScan [4–6]. Examples of data sources include insurance claims [7], data abstracted from electronic medical records [8], from previously conducted clinical trials [9–11], and surveys [12].

Although there are many advantages associated with conducting comparative effectiveness research using secondary data [13], there are noteworthy aspects that need to be taken into consideration when performing research studies on such datasets. Research that relies on secondary data are often deemed to be inferior to randomized trials, as they have in some cases, been shown to overestimate treatment effects. Nonetheless, comparative effectiveness research using secondary data, if well-designed and conducted appropriately, can be valuable and effective. Although we fully acknowledge that the risk of biases associated with such data, we believe that rigorous study design and methodologies, austerity in handling the data, and careful use of statistical techniques can result in high-quality research that can be fundamental for physicians

*Corresponding author. Tel.: +1-617-505-4091.
E-mail address: Maxine_Sun@dfci.harvard.edu (M. Sun).

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and patients. In fact, observational studies have the ability to complement clinical trials and provide additional information on comparative effectiveness of treatment options and safety in populations not well included in clinical trials.

In the current review, we sought first and foremost to convey the importance of a preplanned detailed protocol, which includes the definition of endpoints, hypotheses, and all analytical procedures before study start. Second, we sought to provide readers with a basic understanding of the primary and most prevalent statistical methods and methodologies used in comparative effectiveness research that rely on secondary data.

2. Statistical analysis plan

Contrary to observational research, clinical trials are under strict regulations and are usually required to submit a detailed protocol with precise planning and statistical analysis. Although the protocol of any observational research does not need to be as rigorously comprehensive as that of a clinical trial, the lack of any plan determined a priori to study start will result in unnecessary data dredging and inefficient analytical procedures. Consequently, it has been previously suggested that in order to improve the quality of observational research, the use of a formal, prospectively designed statistical analysis plan (SAP) should be implemented [14]. Thomas and Peterson state that the advantages of having a SAP before each study include the promotion of good planning (1), an adept use of statistical resources (2), a facilitation of transparency (3), the prevention of multiple hypotheses testing and data dredging (4), as well as the avoidance of misunderstandings or misleading communications between the clinician research scientist and the statistician (5).

The items within a SAP that should be included are the aims (primary and secondary) and its associated hypotheses, the data source and its inclusion and exclusion criteria (e.g., a flowchart), the primary variable and its covariates (including variable transformations), handling of missing data [15,16], statistical methods, risk of biases, subanalyses and sensitivity analyses, as well as a power analysis [17].

The main purpose of a SAP is that someone else reading it can reproduce the study's methodology and arrive at the same conclusions. Additionally, the SAP also serves to enhance the communications between the clinician scientist and the statistician, as it helps to translate the clinical question into descriptive objectives and testable hypotheses. It is important that the SAP is drafted and finalized before the analyses begin. During the analytical process, various situations may arise leading to a modification of the existing SAP. This is certainly permissible, as long as the changes are indicated and justified.

Some have debated whether SAPs of observational research studies should be submitted and published, or even possibly registered and approved before data access [18]. Although this is not currently common practice, some research scientists may consider doing this within their own institutions.

3. Adjusted analyses and confounding

Randomized-controlled trials are designed to ensure that treatment and control groups are balanced with regard to both known and unknown factors that could be associated with the measured outcome. Therefore, they represent the most suitable approach in addressing questions about the harms and benefits of interventions [19]. Yet, randomized-controlled trials are not always realistically feasible or ethical. As such, researchers often turn to observational studies. In this context, many have adopted and expanded on complex statistical methods in comparative effectiveness research and purported that such studies optimize the generalizability or "real-world clinical scenario" that randomized-controlled trials lack [20–22]. However, it is important for researchers performing such studies, and for readers interpreting these studies to acknowledge that improper observational designs can produce deceitful results if the real-life treatment decisions are actually commanded by, for example, patient characteristics associated with the examined outcome of interest, what researchers refer to as the "confounding" effect [23,24]. Specifically, "confounding by indication" occurs when the indication for selecting a candidate for a specific treatment also affects the outcome. For example, healthier and younger patients are more likely to undergo radical prostatectomy; therefore, radical prostatectomy will *appear* to result in better overall survival compared to external beam radiation therapy, when in fact the results are driven (partially) by confounding.

A confounder can be identified if it meets three specific criteria: (1) A confounder must be an independent risk factor, either causal or surrogate, of the outcome (e.g., smoking and lung cancer), (2) a confounder must be associated with the exposure (e.g., drinking coffee is often related to smoking), and (3) a confounder cannot be an intermediate variable between the exposure and the outcome (e.g., smoking is not caused by drinking coffee) [25].

Since confounding can misconstrue the real association between the exposure of interest and the outcome, failure to adjust for confounding during the statistical analysis can result in incorrect estimates of the relationship between the exposure and the outcome [26]. More importantly, it must be understood that even when investigators adjust for all known prognostic factors, there will still remain biases where some distributions will not be adequately controlled or where some prognostic factors are simply not available to be adjusted for. This effect is called "residual confounding" [27,28].

Given a database and a research project to compare 2 treatment modalities, one is faced with multiple prognostic factors to account for. Research investigators are then required to perform a multivariable regression analysis, where a single equation can predict the outcome interest,