

Getting Started in Clinical Pharmacy Research

Albert Wertheimer and Qian Ding*

Department of Pharmaceutical Sciences, Ferris State University, College of Pharmacy, USA

*Corresponding author: Qian Ding, Department of Pharmaceutical Sciences, Ferris State University, College of Pharmacy, 220 Ferris Drive, Big Rapids, Michigan 49307, USA, Tel: 2315912230; E-mail: qianding@ferris.edu

Received date: July 10, 2016; Accepted date: August 04, 2016; Published date: August 10, 2016

Copyright: © 2016 Wertheimer A, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

As a profound increase of health care expenditure and demand of chronic diseases management in the United States, the purpose of this review is to provide clinicians fundamental theory of how to conduct a scientific research in the health settings. Given different patients with a variety of disease status in the real world, randomized control trial (RCT) may not satisfy all the research questions. Therefore, evidence based outcomes research has been widely used for treatment guidance, reimbursement purposes and marketing strategy. An increasing use of evidence-based outcomes research raises awareness of the potential for choosing an appropriate research method in their clinical settings. This article summarizes the existing research methods and identifies the implications for practice in real world settings. After learning the pros and cons of each study design and the method of data collection in evidence based research, the clinicians are able to choose an appropriate method for their outcome measurement purposes. This article leads the clinicians step by step from propose a research question to conduct an observational study, and finally to disseminate the findings and publications. Therefore, effectively translate a normal question into a measurable research question may lead them to successfully conduct a scientific research. After learning the pros and cons of each study design and the method of data collection, the clinicians are able to choose an appropriate method for their outcome measurement purposes.

Keywords: Research methods; Evidence-based; Outcomes research; Clinical real-world settings

Introduction

Pharmacists can play a significant role through the provision of a variety of pharmaceutical services, highlighted as reviewers of medication charts, laboratory results and medication prescribing, as well as providers of pharmacotherapeutic education to both patients and other healthcare professionals [1]. As a clinical pharmacy practitioner, have you ever wondered you might do something further to help optimize the medication therapy improve the health-related quality of life, and reduce the health care costs?

In particular, the national health expenditure in the United States has rapidly increases in the 2000s, which has reached \$3.0 trillion in 2014, with an expense of \$9,523 per capita [2]. After a medication has been approved by the government, it is unknown how well it works on specific human patients in real-world settings. The randomized controlled trials (RCTs) usually have the limitations that only placebo was compared with the medication and a limited number of patients were enrolled in the study. However, RCTs may not be sufficient for health care providers in making a decision of what type of intervention should be chosen. In real-world settings, patients are generally experiencing different health status such as the duration of the disease, severity of the disease, co-morbidities, and medication history. Some medicines might work better than conventional therapies but cost more. In light of no health insurance or limited health insurance coverage, the patient may not successfully choose the prescribed treatments. In 2014, the percentage uninsured population was 11.5% (95% confidence interval= 11.06%-11.94%) in the United States [3]. Many observational studies can be utilized for treatment guidance, reimbursement purposes, and marketing strategy. The growing

number of resources and the improved accessibility help clinicians understand how to use this information when it is available are making this aspect of personalized or precision medicine a reality [4]. A systematic review has shown that there is little evidence for significant effect estimate differences between observational studies and RCTs [5].

Understanding the reasons to perform a study, your next question might be: How can I get started by looking at the practices and procedures at my clinic setting?.

Clinical Question in Evidence-Based Medicine

The first step is to clearly formulate your clinical research question, also called problem statement, in a reasonable and measurable form, which usually expresses a relation between two or more variables [6-9].

The PICO (Patient/population, intervention, comparison, and outcomes) model has been widely used as a means of identifying a research question in evidence-based medicine research. In this model, four major questions are used to help conduct a further literature search and finally establish your clinical question [10]. What group of patients/population am I interested?. What is the major intervention or exposure that I am going to test?. What comparisons (placebo or conventional therapies) am I considering to compare with the intervention?. What outcomes do I want to measure and/or to improve?.

Typically, it is highly recommended that a literature review of your questions should be conducted before you start collecting data. Literature review helps you better understand what has been studied in the published articles and identify the research gap in the future. A strategy of searching by modifying and grouping the keywords will provide you a variety of results to serve your interests. The most frequent searching websites include, but not limited to MEDLINE (via

PubMed), EMBASE (via EMBASE.com), psycINFO. The Cochrane database provides systematic reviews of the literature which comprehensively covers the current state of knowledge on related topics. Besides this database, you can also do hand search by looking at the references at the end of your reading article as a supplemental search strategy. In light of the finding in a literature review, you would modify your research questions by selecting a different group of patients, exposures, or outcomes in the PICO model. In addition, literature software, such as Endnote or Mendeley, is a powerful tool to manage the literature articles effectively.

A problem statement cannot be solved unless it is reduced to one or more hypotheses that can be directly tested [6]. There are two types of hypotheses: the null hypothesis and alternative hypothesis. The null hypothesis states that one variable has no effect on another variable. The alternative hypothesis states that there is some kind of relation, in particular, two-sided effect “has some effect on” or one-sided effect with either positive or negative effect.

If the clinical question has been well established and the hypothesis has been adequately formulated, the next step is to test the relations between variables expressed by the hypothesis. A study design plays the role to translate the clinical question into a practical test.

Study Design

The study design is essentially considered as a structure of the research framework by which to direct data collection, data extraction, as well as data analyses.

An RCT design has been widely used in clinical trials for FDA drug approvals, by which the patients are randomly selected and assigned to control or experimental groups, such as placebo group and a group with an intervention treatment. In addition, a double-blind strategy, neither the participant nor the investigator knows the participants' group assignment, is preferred to be added in the RCT design [11].

The RCTs, with the “gold standard” of randomized selections and assignments, would more likely to build the causal association than other study designs, by minimizing the threats to both internal and external validities [12]. However, this most expensive study design requires high control of the characteristics of the patients, which on the other side may limit the external validity, the generalization ability of the findings to the populations in other clinical settings.

Besides RCTs, observational studies, including case report, case series, case-control study, cohort study and cross-sectional study, offer the opportunity to study the effects of various treatments in real-world settings [13]. Specifically, a case report describes a clinical experience observed in patients that are rare or unknown but useful for new hypotheses about drug effects [14]. Case series are simply the collections of the unusual clinical experience observed in multiple patients. A case-control study compares patients who have a disease with those who do not have the disease and identifies the differences of exposures in each group. A cohort study is a prospective study which identifies a sample of a defined population who are exposed and unexposed to an intervention or treatment and observes them for the outcomes by following them over time. A cross-sectional study is a study of a subset of a defined population at a given point in time, which is called index date. An index date is assigned to the date of which the outcome was noted for each patient and the exposure status is then determined in the period before the index date.

Bias is a systematic error of deviations due to extraneous factors that will reduce the validity of the study. Validity is the extent to which the results of a study are truly measured, which can be affected by internal threats such as history, maturation, temporal precedence, selection procedure, regression to the mean, mortality/attrition, and instrumentation itself. You may also expect to maximize the external validity, the ability to be generalized to a population of interest.

Data Collection

After you've defined the population, the process of drawing a sample from the defined population is called sampling. And your sample is the group of participants who were selected for your study. An IRB approved consent form is needed to be sent to the participants who will be recruited for the observation/ interview part in your study. You may not recruit all the people you sampled. There is a response rate to agree in participating in the study. The participants, who have signed the consent forms for the agreements in your study, also have the absolute right to withdraw from the study without jeopardizing the rest of their employment, or other situation. Due to a nonresponse rate and withdraw rate, the sample size is required to be large enough to produce enough power to represent the whole population or greater generalizability of the results to the population, where power is pre-determined to be larger than 0.8 in the study. An effect size is usually used to estimate sample size in the power analyses.

If your study involves data related to patients, you will need an institutional review board (IRB) approval at your institution before you start data collection or extraction. There is no perfect data collection method, as each data collection contains strengths and weaknesses, as well as potential threats for errors. Overall, data for conducting clinical research can be obtained from the following categories:

- Direct observation
- Clinical chart data
- Self-report
- Secondary data: medical and prescription claims database or public available database

Data can be collected either prospectively or retrospectively. The prospective data collection procedure is time-consuming. In addition, what samples and how many participants are selected for study are extremely important for prospective studies, such as direct observation and self-report research. In particular, the observer follows the participant, observes and writes notes on what medications administered to the patients. Later the notes are compared with the physician orders to identify the medication errors. The direct observation method is tested to be the effective method in medication safety study by collecting more medication errors than clinical chart review and self-report [15]. However, direct observation method is energy consuming and has a limitation of Hawthorne effect on participants' performance due to the observer. Patient charts include the information of clinical diagnoses and lab tests about the patients, which is used for collecting medication adverse drug events [16]. Self-report data collection is widely used in social and administrative pharmacy research, where the data are obtained through questionnaires (mail or electronic surveys) and personal interviews (telephone or face-to-face). The participants may over or under report the data given a different situation, for example, medication errors may be under-reported if the errors are not noticed by the healthcare providers.

Secondary data, including medical & prescription claims database or public available database, means that the data was collected for other purposes from the proposed research and can be analyzed retrospectively. For example, the clinical chart data, including Electronic Medical Record (EMR) data, are collected for diagnosis purposes in clinics. The administrative claims data are usually collected for billing and reimbursement purposes. The government, such as Centres for Disease Control and Prevention (CDC), also collects and owns data for epidemiology purposes to promote disease control and public health. The researchers do not need to collect such data by themselves, but the data may not provide the expected variables and it also cost the researchers to purchase the data. Sometimes the government will provide a codebook and programming statements to help researchers retrieve and analyse the data due to the complexity of the large data [17]. Researchers may choose to use two databases to increase sample size and have to develop methods using combined demographic and pharmacy variables to minimize the overlapping patients in different databases [18]. In both clinical chart data and claims data, patients' information and the institutes' information should be de-identified with coding and the researcher should not contact any personnel at any situations under HIPAA (Health Insurance Portability and Accountability Act) protection.

Outcomes Measured

Demographic factors, such as age, gender, race, and marital status, usually are the basic measurements. Generally, outcomes measurement includes clinical outcomes, economic outcomes, and humanistic outcomes.

To measure the efficacy, effectiveness or safety of a treatment, clinical outcomes will be considered. For example, if a researcher is interested in an antihypertensive treatment, he or she might want to measure treatment adherence, comorbidity, and mortality, cardiovascular event, etc.

Economic outcomes, including health care utilization and cost expenditure (direct cost and indirect cost), are often used in post-marketing surveillance studies. The analyses usually include cost-minimization analysis, cost-effectiveness analysis, cost-utility analysis, or cost-benefit analysis [19]. Cost-minimization analysis compares the costs of the interventions when two therapies have an equal efficacy. The cost-effectiveness analysis includes the estimate of the incremental cost-effectiveness ratio (ICER) and the costs and effects are in different units. The cost-utility analysis is used when the outcomes are measured in Quality Adjusted Life Years (QALYs) or utilities. The cost-benefit analysis compares the costs and benefits in the same (monetary) units.

Humanistic outcomes, such as generic quality of life, health-related quality of life, and satisfaction with care, are gradually counted into the consideration for reimbursement, as the Constitution of WHO (1946) states that good health is a state of complete physical, social and mental well-being, and not merely the absence of disease or infirmity [20].

The generic quality of life (QOL) is a broad multidimensional concept that usually includes subjective evaluations (self-report measurement) of both positive and negative aspects of life [21]. Among the generic quality of life examples, the EuroQol or EQ-5D™ is a standardized instrument for use as a measure of health outcome, which has been validated and widely used in many countries. The EQ-5D-3L, which can identify 243 possible health states with 5 questions in 3 levels of responses, has been translated into 170 self-completed official language versions [22].

Comparing to generic quality of life, health-related quality of life (HRQoL) is more a disease-specific measurement that includes domains related to physical, mental, emotional, and social functioning [23]. The psychological factors such as anxiety, depression, and social function are more and more focused in the HRQoL studies.

Statistical Analysis

Statistical analysis, a study of organizing, analyzing, and interpreting data, contains two main types of analysis: descriptive statistics and inferential statistics [24]. Descriptive statistics measures the distribution (the central tendency and spread) using indexes such as the mean or standard deviation and inferential statistics draws conclusions from data that are subject to random variation (e.g., observational errors, sampling variation) [25]. The analysis can be as simple as an excel spreadsheet or using professional statistical analysis software SAS, SPSS, Stata, or many free, downloadable stats such as Quickcalcs on the website <http://www.graphpad.com/quickcalcs/>. Many online resources are accessible for you to learn and select an appropriate analysis for your study, such as the website owned by the Institute for Digital Research and Education (IDRE) at UCLA (University of California, Los Angeles): http://www.ats.ucla.edu/stat/mult_pkg/whatstat/.

From a statistical point of view, variables can be classified into four different categories (nominal, ordinal, interval and ratio variables). Nominal variable comes from the name and there is no measurement of how far apart it is between the values. For example, the color of roses (red, pink, and yellow) is a nominal variable. There is no way to measure the order and distance between these colors. An ordinal variable implies the order or rank of the values. For example, the disease severity (mild, moderate, and severe) is an ordinal variable which tells you the order of the disease severity, but nothing else. An interval variable scales the meaningful differences between values but the value of zero is arbitrary. The most common examples of interval variables are the Fahrenheit and Celsius temperatures. Ratio variables have all the features of interval variables plus a real absolute zero. For example, it is meaningful to say a weight of 100 lbs. is twice as heavy as a weight of 50 lbs. But there is no meaning to say the temperature of 20 Fahrenheit is twice as hot as the temperature of 10 Fahrenheit.

Based on the characteristics, variables can also be divided into continuous and categorical variables. A categorical variable, including nominal variable and ordinal variable, contains names or labels that can divide individuals into particular categories. A dichotomous or binary variable is also a categorical variable that has only 2 levels, for example, "Did you have any biologic treatment on your rheumatoid arthritis in the past one year?" (Yes/no). A categorical variable can also assign values to group the ratio or interval variables, such as age group 1-5 (1=0-20 years, 2=21-40 years old, 3=41-60 years old, 4=61-80 years old, 5=81 or older). A continuous variable is capable of taking any value between a range of the minimum and maximum values. An example of the continuous variable in clinical research includes medical expenditure, the length of hospital stay, EuroQol utility score (0-1) etc.

In addition, statistical analysis includes two types of analyses: parametric analysis (assumption of a normal distribution) and non-parametric analysis (no assumption of a normal distribution). The analyses such as two samples T-Test or ANOVA to test the mean difference are parametric analyses. If the normal distribution

assumption is violated, nonparametric analyses like the Mann-Whitney test, Kruskal-Wallis test, or Chi-square test will be selected.

In a clinical study, you will often see correlation and regression analyses. Correlation is used to test the relationship (not the causal relationship) of variables and regression is used to establish a model (or equation) with a group of independent variables for predicting and explaining the dependent variable.

Discussion and Limitations

In the discussion section, you need to explain the reason why such results are obtained in your study. This section is not simply just a repeat of the findings, however, to interpret and describe the significance of your findings in light of what was already known about the research problem being investigated, and to explain any new understanding or fresh insights about the problem after you've taken the findings into consideration [26]. In this section, the literature will be compared with this research for further explanations. By comparing previous findings from other researchers, it addresses the importance role of your study in contributing new findings to the clinical research. Limitation in the discussion section is also a self-reflection part, by self-diagnosing any deficiencies in the study designs that may impact the generalizability of your research. when pharmaceutical human biomedical research as a multi-dimensional endeavour requires a collaboration among many parties including industry sponsors, stakeholders, and third-party delegates (e.g., clinical research organization or academic research organization), industry sponsors need to develop control systems to address bioethical responsibilities such as independent ethic review, equitable selection of countries/communities and participants, and public transparency [27-29]. Industry sponsors have the responsibility to manage the relationships with investigators and study sites in a manner that will enhance transparency and mitigate conflicts of interest and circumstances that could introduce bias into the clinical trial process [27,30]. Therefore, the opportunity of the future studies can be directed to the focus on the unanswered questions from your study.

Present Your Findings

As you have received the results and interpreted the results from your study, the last step is to disseminate your findings. You may choose to publish your findings in a peer-reviewed journal with a target audience who are interested in your field of endeavor since you want your article to be read and generalized to other clinical settings. In that way, your findings will be connected with peer findings in science. There are several other choices, such as presenting your data in annual meetings of American Pharmacists Association (APhA) and American Society of HealthSystem Pharmacists (ASHP). You can also choose to present your findings at professional conferences with a high impact on the treatment of disease of interest. For example, if you are studying rheumatoid diseases, you might want to choose the congresses like American College of Rheumatology (ACR), or The European League against Rheumatism (EULAR).

With an access to a clinic setting, it is now the right time for you to start a research project. Isn't that an exciting moment that your work might improve the outcomes of disease treatment, the quality of health care, and contribute to the science theory eventually?.

References

- Richardson TE, O'Reilly CL, Chen TF (2014) A comprehensive review of the impact of clinical pharmacy services on patient outcomes in mental health. *Int J Clin Pharm* 36: 222-232.
- Centers for Disease Control and Prevention (2016) Health Expenditures. National Center for Health Statistics.
- Centers for Disease Control and Prevention (2016) Health Insurance Coverage. National Center for Health Statistics.
- Drozda K, Müller DJ, Bishop JR (2014) Pharmacogenomic testing for neuropsychiatric drugs: Current status of drug labeling, guidelines for using genetic information, and test options. *Pharmacotherapy* 34: 166-184.
- Anglemyer A, Horvath HT, Bero L (2014) Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. *Cochrane database Syst Rev*.
- Kerlinger FN (1986) Foundations of behavioural research. (3rdedn), Holt, Rinehart and Winston, London.
- American Society of Hospital Pharmacists (1978) ASHP guidelines for scientific research in institutional pharmacy. *Am J Hosp Pharm* 35: 323-326.
- Nelson A (1981) Research in Pharmacy Practice: Principles and Methods. American Society of Hospitals Pharmacists.
- Dewey J (1999) How We Think. DC Heath and Co-publishers, Massachusetts.
- University of Illinois at Chicago University Library (2016) Evidence Based Medicine: PICO.
- West A, Spring B (2007) Randomized Controlled Trials.
- Strom BL, Kimmel SE, Hennessy S (2013) Textbook of Pharmacoepidemiology. (2ndedn), John Wiley and Sons, New Jersey.
- MacKinnon GE (2013) Understanding Health Outcomes and Pharmacoepidemiology. (3rdedn), Jones and Bartlett Learning, Burlington.
- Garg R, Laxhan SE, Dhanasekaran AK (2016) How to review a case report. *J Med Case Rep* 10: 88.
- Flynn EA, Barker KN, Pepper GA, Bates DW, Mikeal RL (2002) Comparison of methods for detecting medication errors in 36 hospitals and skilled-nursing facilities. *Am J Health Pharm* 59: 436-446.
- Bates DW, Cullen DJ, Laird N, Petersen LA, Small SD, et al. (1995) Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. *JAMA* 274: 29-34.
- Agency for Healthcare Research and Quality (2012) Hospital Inpatient Stays File. Medical Expenditure Panel Survey.
- Carbonari DM, Saine ME, Newcomb CW, Blak B, Roy JA, et al. (2015) Use of demographic and pharmacy data to identify patients included within both the Clinical Practice Research Datalink (CPRD) and The Health Improvement Network (THIN). *Pharmacoepidemiol Drug Saf* 24: 999-1003.
- MacKinnon GE (2013) Understanding Health Outcomes and Pharmacoepidemiology. (3rdedn), Jones and Bartlett Learning, Burlington.
- World Health Organization (2016) Health statistics. Health topics.
- The WHOQOL Group (1998) The World Health Organization quality of life assessment (WHOQOL): Development and general psychometric properties. *Soc Sci Med* 46: 1569-1585.
- EuroQol Group (1990) EuroQol-a new facility for the measurement of health related quality of life. *Health Policy* 16: 199-208.
- Healthy People 2020 (2016) Health-Related Quality of Life and Well-Being. Foundation Health Measures.
- Dodge Y (2006) The Oxford dictionary of statistical terms. Oxford University Press.
- Laerd Statistics (2013) Descriptive and Inferential Statistics.

-
26. Annesley TM (2010) The discussion section: Your closing argument. *Clinical Chemistry* 56: 1671-1674.
 27. Van Campen LE, Therasse DG, Klopfenstein M, Levine RJ (2015) Development, implementation and critique of a bioethics framework for pharmaceutical sponsors of human biomedical research. *Curr Med Res Opin* 31: 2071-2080.
 28. Myerson AS, Krumme M, Nasr M, Thomas H, Braatz RD (2015) Control systems engineering in continuous pharmaceutical manufacturing may 20-21, 2014 continuous manufacturing symposium. *J Pharm Sci* 104: 832-839.
 29. Grevsen JV, Kirkegaard H, Kruse E, Kruse PR (2014) Early achievements of the Danish pharmaceutical industry-7. *Theriaca* 42: 31-62.
 30. Van Assche G, Peyrin-Biroulet L, Fan T, Lynam M, Ferreras SR, et al. (2014) Disease Control and Unmet Needs among Moderate to Severe Ulcerative Colitis Patients Treated with Conventional Therapies in Europe: The UC CARES (Ulcerative Colitis Condition, Attitude, Resources and Educational Study) study. *J Cohn's Colitis* 8: S165.