

Principles of Research Design and Drug Literature Evaluation

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and John P. Bentley

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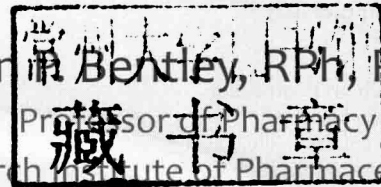
Principles of Research Design and Drug Literature Evaluation

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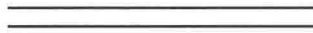
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*To my dear wife, Anu,
and to my lovely kids, Shravya and Saureesh*

Aparasu



*To my wife and partner, Sandy,
and to my teacher, mentor, and friend, Lon Larson*

Bentley

PREFACE

With the increasing emphasis on evidence-based practices, there is a greater need for pharmacists to understand clinical research, evaluate scientific findings, and translate evidence to support patient-care decisions. This requires a comprehensive understanding of the principles and practice of drug literature evaluation with a strong grounding in research design and statistical methods. Most available texts emphasize statistical approaches and/or scientific literature evaluation techniques. Although there may be comprehensive books in other health professions, it is challenging to find a pharmacy textbook that covers all critical research design and evaluation elements to translate evidence into practice. We decided to edit this book to provide a balanced approach to the principles of clinical research and statistics for evaluating pharmacy literature to implement evidence-based pharmacotherapy.

Most pharmacy schools offer a course in the pharmacy professional program that covers fundamentals of research design, biostatistics, and evaluation of pharmacy literature, as required by the Accreditation Council for Pharmacy Education (ACPE). Consequently, this book is divided into three sections to provide comprehensive course content to meet and exceed these curriculum standards set by the ACPE. Section 1 of the book covers principles of scientific research with an emphasis on clinical research designs ranging from randomized controlled trials to case reports. Section 2 of the book provides the foundation necessary to understand statistics and to critically evaluate results from statistical analyses reported in the medical literature with a focus on common statistical methods. Section 3 of the book covers principles of evidence-based medicine, drug literature sources and evaluation techniques, and application of evidence to patient care. There are seven chapters in each section of the book.

Chapter 1 defines basic, applied, clinical, and translational research, and describes the steps in scientific research and evidence-based medicine. Chapter 2 explains the guiding ethical principles in clinical research and discusses the regulatory framework governing clinical research. Chapter 3 provides the basics of designing clinical research, with an emphasis on common clinical research designs and methodologies. Chapter 4 discusses the design considerations associated with randomized controlled trials, including common clinical designs and analytical framework. Chapters 5 and 6 provide observational approaches for conducting clinical research. Chapter 5 describes case-control and cohort designs and includes a discussion of common biases and analytical approaches to minimize such biases. Chapter 6 provides an overview of cross-sectional studies, pre- and post-observational studies, ecological studies, and time series evaluations. Chapter 7 presents the key steps in designing a case report and case series studies along with tools to critically evaluate these designs.

Chapter 8 discusses the summarizing, organizing, and presenting functions of statistics, commonly referred to as descriptive statistics, and also introduces the different kinds of data that are collected in clinical research. Chapter 9 provides the general foundation for applying basic tools of statistical inference, focusing on the related mechanisms of estimation and hypothesis testing. Given that many studies in the drug literature involve the comparison of two or more groups, Chapter 10 discusses commonly used statistical procedures that are used to answer research questions involving group comparisons; in addition, it describes statistical methods for assessing the correlation between two variables. Chapters 11 and 12 provide an overview of regression analysis methods that can be used to account and/or adjust for variables that cannot be handled at the design stage of an experiment. Chapter 11 describes simple linear and multiple regression approaches to address a number of research problems, such as confounding and effect modification. Chapter 12 introduces logistic regression and Cox regression methods to analyze binary and time-to-event outcomes, respectively. Chapter 13 introduces the statistical principles' underlying sample size calculation. Chapter 14 presents the elements of the systematic review process and describes meta-analysis as a method to quantitatively synthesize evidence from studies identified in a systematic review.

Chapter 15 identifies the steps involved in evidence-based medicine along with the discussion of its strengths and limitations. Chapter 16 discusses the sources and use of primary, secondary, and tertiary literature to identify clinical evidence for evidence-based medicine. Chapters 17, 18, and 19 discuss approaches to assess published primary literature for patient care. Chapter 17 provides a stepwise approach to assess published literature with an emphasis on evaluating the study objectives, methods and design, statistics, results, and discussion. Chapter 18 describes the key considerations for evaluating methodological rigor in randomized controlled trials using an example. Chapter 19 describes and applies formal criteria to evaluate observational studies using an example. Chapter 20 discusses general principles of applying evidence to patient care with an emphasis on evidence from clinical trials and practice guidelines. Finally, Chapter 21 describes the general format of a journal club and examines the characteristics of an effective journal club.

This book is designed for professional pharmacy (PharmD) students. Instructors teaching principles of research and drug literature evaluation can design the professional course primarily based on this book or can supplement this book with research articles. The contents of the book can be delivered in one or two semesters. Chapters were written by expert authors specializing in pharmacy practice and research. Each chapter includes the following elements:

- *Learning Objectives* present the chapter's desired outcomes to the reader.
- *Key Terminology* helps the reader quickly identify critical new terms.
- *Review Questions* allow readers to apply what has been learned in the chapter and assess their understanding of the content.
- *Online Resources* direct students to web sites relevant to the content.

The chapters are designed to provide the knowledge base and application techniques for research design and drug literature evaluation. In addition to figures and tables, numerous pharmacy examples and case studies are provided to aid student learning. Additional readings from pharmacy journals and a drug literature evaluation project can improve the critical thinking skills of pharmacy students. The online sources and chapter references can be used to supplement the content. This book can also be an excellent resource for students in residency and fellowship training programs. In addition, this

book can be beneficial to pharmacy practitioners and professionals, especially those involved in training students, residents, and fellows.

We would greatly appreciate feedback from students and faculty for future editions. All knowledge is considered as work in progress, including the contents of this book.

Rajender R. Aparasu, MPharm, PhD, FAPhA
John P. Bentley, RPh, PhD, FAPhA

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FOREWORD

When Drs. Aparasu and Bentley asked me to write the foreword for this book, I hesitated. It took me a long while to finally agree. I hesitated because a book's foreword is supposed to be written by someone famous who tells the readers why the authors are qualified to write the book and why the book is important. I hesitated because I could only fulfill two of the three conditions by writing the foreword to this book: the editors are eminently qualified and it is an important contribution to the library of students and practitioners. Both of the editors are seasoned, knowledgeable, and experienced with decades of direct involvement in evidence-based research. More importantly, they have convinced a veritable "who's who" of clinical trial, health services, and comparative effectiveness researchers and drug information experts to share their expertise, insights, and pearls of wisdom.

Second, why is this book important? Dr. Bentley and I served together on the editorial staff of the *Journal of the American Pharmacists Association (JAPhA)* for years. During our time together, we had innumerable discussions about the importance of study design and statistical methods to the appropriate interpretation and clinical application of research findings. Through these often lengthy discussions—discussions that we had more than once because they are difficult issues to resolve when interpreting a study's findings and conclusions—we came to understand the power of the statement "every study has limitations based on its design and statistical methods." It became abundantly clear to us that while these limitations are generally *listed* in a specific section designed for that purpose in most articles, the implications of those limitations are not. What does this statement mean? Let me provide an example to illustrate.

While a research article might list "confounding by severity" as a potential study limitation in an observational study, what are the implications of that bias for someone trying to use the information contained in the article in their practice? What cautions should the practitioner exercise in interpreting and adopting the researcher's conclusions into their personal practice? Should an author present the implications of various decisions a practitioner could make based on the limitations? Should the practitioner suddenly stop prescribing beta-agonist medications because a study found a greater risk of asthma-related deaths with increasing beta-agonist use? Should the practitioner deny additional use of the medication after a certain point? What are the implications of stopping or reducing the use of rescue inhalers among severely ill asthmatics? Disease severity is a potential confounder in observational studies. Severely ill patients need their rescue inhalers more frequently because their asthma is uncontrolled and, even then, they cannot all be rescued unless the underlying reason for life threatening asthma is directly addressed. This book was designed to provide and encourage practitioner's development and use of critical drug information evaluation skills through a deeper understanding of

the foundational principles of study design and statistical methods. Because guidance on how a study's limited findings should *not* be used is rare, practitioners must understand and evaluate for themselves the veracity and implications of the inherently limited primary literature findings they use as sources of drug information to make evidence-based decisions together with their patients.

The editors organized the book into three supporting sections to meet their pedagogical goals and address practitioners' needs in translating research into practice. Section 1 is titled "Principles of Clinical Research." After a discussion of the scientific method and ethical considerations associated with research, Section 1 examines the strengths, weaknesses, and implications of major experimental and nonexperimental (e.g., observational) study designs. Section 2, "Statistical Principles and Data Analysis," introduces the reader to the principles of statistical methods, data analysis, and the interpretation of statistical results, including power analysis and systematic reviews. Finally, Section 3, "Principles of Drug Literature Evaluation," introduces the reader to the principles of drug literature evaluation. From the perspective of a former editor-in-chief of a pharmacy professional journal, Section 3 provides the most important applications for translating research into practice. Section 3 provides the reader with the skills needed to evaluate studies ranging from randomized controlled trials to observational studies. It facilitates the application of the information contained in these studies. Furthermore, it assists readers in their attempts to apply information from these studies, with their limitations, to support pharmacy practice and patient-care decisions—applications that are commonly lacking with simple lists of the study's limitations. Although Section 3 is the heart of the book, it cannot survive without the study design and statistical methods foundations.

Sometimes, the difference between a foreword and a book review gets blurred—even to the writer. However, one primer on writing a book foreword that I consulted stated "...in the conclusion, remind the readers why you are writing the foreword and why it matters." As health professionals, we are tasked with protecting the lives of our patients; it is our *sine qua non*. Unfortunately, as multiple examples in this book and the literature point out, published research is not without its shortcomings and failings. Therefore, as health professionals we must be able to evaluate the strengths, weaknesses, and implications of the evidence, both new and not-so-new, for ourselves. There is no such thing as the perfect study. As health professionals, we cannot simply rely on the lists and conclusions of others; we must be prepared to make decisions based on the scientific evidence for ourselves. Thanks to the editors, authors, and content of this book, you can now be more prepared than ever for translating research into practice.

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Many individuals have contributed to the fruition of this book. The concepts and vision for this book have evolved over 18 years of teaching professional courses in research design, biostatistics, and drug literature evaluation. Feedback from pharmacy students and regular discussions with colleagues, especially Dr. Rebecca Baer at South Dakota State University (Aparasu) and Dr. Kim Adcock at the University of Mississippi (Bentley), were instrumental in developing the master plan for this book. Sincere thanks to all of the authors for patiently working with us in developing the chapter content and for contributing their expertise to this project. The feedback from the reviewers was very helpful in improving the content and formatting of the book. The insight and support of Dr. Albert Wertheimer was instrumental in undertaking this book.

We greatly appreciate Dr. Jeffrey Sherer for helping us recruit the authors for the third section of the book and overseeing the development of initial chapter outlines. Our gratitude also goes to several of our graduate students, who offered input from a student's perspective on several chapters. We also would like to thank our respective university and college/school faculty colleagues and administration teams for providing us the time and encouragement to complete this project. Finally, we are grateful to the publishing team, both past and present, at Jones & Bartlett Learning, especially Katey Birtcher, Teresa Reilly, and Sean Fabery, for their help and support. The editorial assistance of the production staff at Jones & Bartlett Learning, especially Tina Chen, is also very much appreciated.

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Rajender R. Aparasu, MPharm, PhD, FAPhA, is a Professor and Chair of the Department of Pharmaceutical Health Outcomes and Policy at the University of Houston College of Pharmacy. He has more than 18 years of experience in teaching and research in the area of pharmaceutical practice and policy. He has taught various professional and graduate courses in colleges of pharmacy. Dr. Aparasu is a recognized educational leader and researcher in pharmaceutical practice and policy. He was instrumental in the growth of graduate programs at the University of Houston to train the next generation of pharmacy leaders. He led the creation of one of the largest MS/Residency programs in the country in collaboration with six Texas Medical Center institutions in Houston. He has served on patient safety and medication therapy management task forces.

Dr. Aparasu has received several federal and non-federal grants to address a broad array of quality of pharmaceutical care issues, especially among the elderly. He is a peer-reviewer for numerous pharmacy and medical journals and has more than 100 presentations in national/international meetings and more than 70 peer-reviewed publications. He serves on the editorial boards of several pharmacy and healthcare journals, and has been recognized as an Exceptional Peer Reviewer by several journals. Dr. Aparasu is a grant reviewer for the American Heart Association (AHA) and the Patient-Centered Outcomes Research Institute (PCORI). He is an Associate Editor of *BMC Geriatrics* and has edited a book for graduate students titled *Research Methods for Pharmaceutical Practice and Policy*. He was recognized by his peers as a 2012 Fellow of the American Pharmacists Association for his exemplary professional achievements in practice and outstanding service to the profession.

John P. Bentley, RPh, PhD, FAPhA, is a Professor of Pharmacy Administration and a Research Professor in the Research Institute of Pharmaceutical Sciences at The University of Mississippi School of Pharmacy. In the professional pharmacy curriculum, Dr. Bentley teaches elements of research design, biostatistics, epidemiology, and drug literature evaluation. At the graduate level, he teaches several applied statistics courses, including general linear models, multivariate statistics, and elective courses focusing on the application of modern longitudinal data analysis methods and principles of statistical mediation and moderation. He has conducted research projects in a variety of areas, including quality of life; medication adherence; medication use, misuse, and outcomes; pharmaceutical marketing and patient behavior; patients' evaluation of health-care providers; pharmacy practice management; tobacco use, control, and cessation among college students; and ethics and professionalism. His statistics research interests include statistical mediation analysis and longitudinal data analysis.

Dr. Bentley has worked as a member of a number of interdisciplinary research teams and has consulted with numerous researchers concerning statistical analysis. In 2009, he was named a Fellow of the American Pharmacists Association and has been recognized as a Thelma Cerniglia Distinguished Teaching Scholar at The University of Mississippi School of Pharmacy. He has served as a peer reviewer for a number of journals and as an Associate Editor for the *Journal of the American Pharmacists Association*. Dr. Bentley received his BS in pharmacy and MBA from Drake University, his MS and PhD in pharmacy administration from The University of Mississippi, and his MS and PhD in biostatistics from The University of Alabama at Birmingham (UAB).

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