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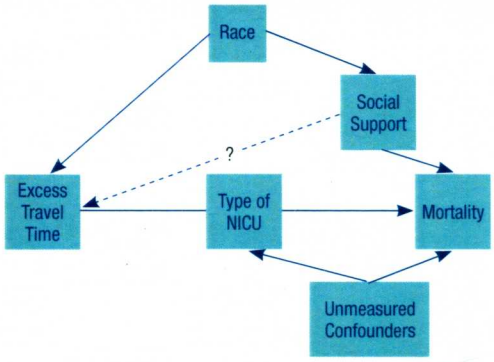

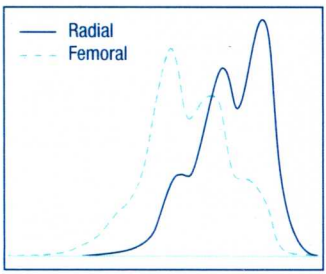

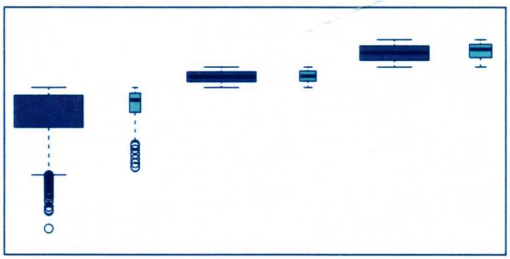

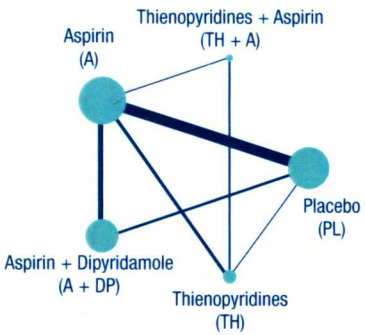

Edited by

Constantine Gatsonis

Sally C. Morton

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Edited by
Constantine Gatsonis
Brown University, Providence, Rhode Island, USA
Sally C. Morton
Virginia Tech, Blacksburg, Virginia, USA

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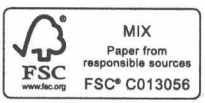

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Contributors

Heather D. Anderson
Department of Clinical Pharmacy
University of Colorado
Aurora, Colorado

Michael Baiocchi
Department of Medicine
Stanford University
Stanford, California

Jeffrey A. Bridge
The Research Institute at Nationwide Children's Hospital
Columbus, Ohio

Bradley P. Carlin
Division of Biostatistics
School of Public Health
University of Minnesota
Minneapolis, Minnesota

Anna Chaimani
Department of Hygiene and Epidemiology
University of Ioannina School of Medicine
Ioannina, Greece

Jing Cheng
Department of Preventive and Restorative Dental Science
UCSF School of Dentistry
San Francisco, California

Jagpreet Chhatwal
MGH Institute for Technology Assessment
Harvard Medical School
Boston, Massachusetts

Jason T. Connor
Berry Consultants, LLC
Orlando, Florida

Issa J. Dahabreh
Department of Health Services, Policy and Practice
Center for Evidence Synthesis in Health
Brown University School of Public Health
Providence, Rhode Island

Orestis Efthimiou
Department of Hygiene and Epidemiology
University of Ioannina School of Medicine
Ioannina, Greece

Haoda Fu
Clinical Research Department
Eli Lilly and Company
Indianapolis, Indiana

Constantine Gatsonis
Department of Biostatistics
Brown University School of Public Health
Providence, Rhode Island

Joel B. Greenhouse
Department of Statistics
Carnegie Mellon University
Pittsburgh, Pennsylvania

Sebastien J-P.A. Haneuse
Department of Biostatistics
Harvard Chan School of Public Health
Boston, Massachusetts

Miguel A. Hernán
Departments of Epidemiology and Biostatistics
Harvard T.H. Chan School of Public Health
Harvard University
Cambridge, Massachusetts

Hwanhee Hong
Department of Mental Health
Johns Hopkins University
Baltimore, Maryland

Kelly J. Kelleher
The Research Institute at Nationwide Children's Hospital
Columbus, Ohio

David M. Kent
Predictive Analytics and Comparative Effectiveness Center
Tufts Medical Center
Boston, Massachusetts

Ken Kleinman
Department of Biostatistics and Epidemiology
University of Massachusetts
Amherst, Massachusetts

Lauren M. Kunz
Office of Biostatistics Research
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Eric B. Laber
Department of Statistics
North Carolina State University
Raleigh, North Carolina

Joseph Lau
Department of Health Services, Policy and Practice
Center for Evidence Synthesis in Health
Brown University School of Public Health
Providence, Rhode Island

Sandra Lee
Department of Biostatistics and Computational Biology
Dana-Farber Cancer Institute and Harvard Medical School
and
Department of Biostatistics
Harvard T.H. Chan School of Public Health
Boston, Massachusetts

Anne M. Libby
Department of Emergency Medicine
University of Colorado
Aurora, Colorado

Dimitris Mavridis
Department of Hygiene and Epidemiology
University of Ioannina School of Medicine
and
Department of Primary Education
University of Ioannina
Ioannina, Greece

Sally C. Morton
College of Science and Department of Statistics
Virginia Tech
Blacksburg, Virginia

Sharon-Lise T. Normand
Department of Health Care Policy
(Biostatistics)
Harvard T.H. Chan School of
Public Health
Boston, Massachusetts

Robert T. O'Neill
Office of Translational Sciences
Center for Drug Evaluation and
Research
Silver Spring, Maryland

Karen L. Price
Eli Lilly and Company
Indianapolis, Indiana

Min Qian
Department of Biostatistics
Columbia University
New York, New York

Mark S. Roberts
Department of Health Policy and
Management
University of Pittsburgh
Pittsburgh, Pennsylvania

James M. Robins
Departments of Epidemiology and
Biostatistics
Harvard T.H. Chan School of
Public Health
Harvard University
Cambridge, Massachusetts

Sherri Rose
Department of Health Care Policy
(Biostatistics)
Harvard T.H. Chan School of
Public Health
Boston, Massachusetts

Georgia Salanti
Faculty of Medicine
Institute of Social and Preventive
Medicine
University of Bern
Bern, Switzerland

Christopher H. Schmid
Department of Biostatistics
Center for Evidence Synthesis in
Health
Brown University School of
Public Health
Providence, Rhode Island

Susan M. Shortreed
Biostatistics Unit
Group Health Research Institute
Seattle, Washington

Dylan S. Small
Department of Statistics
The Wharton School of the
University of Pennsylvania
Philadelphia, Pennsylvania

Kenneth J. Smith
Department of Medicine
School of Medicine
University of Pittsburgh
Pittsburgh, Pennsylvania

Donna Spiegelman
Departments of Epidemiology,
Biostatistics, and Nutrition
Harvard T.H. Chan School of
Public Health
Boston, Massachusetts

Elizabeth A. Stuart
Department of Mental Health
Johns Hopkins University
Baltimore, Maryland

Thomas A. Trikalinos
Department of Health Services, Policy and Practice
Center for Evidence Synthesis in Health
Brown University School of Public Health
Providence, Rhode Island

Robert Valuck
Department of Clinical Pharmacy
University of Colorado
Aurora, Colorado

Marvin Zelen
Department of Biostatistics
Harvard T.H. Chan School of Public Health
Boston, Massachusetts

Introduction

What Is Comparative Effectiveness Research?

Comparative effectiveness research (CER) has emerged as a major component of health care and policy research over the past two decades. Several definitions of CER have been proposed. The most widely used is the definition provided by the Institute of Medicine (IOM; now the National Academy of Medicine) committee convened to define national priorities for CER in 2009. According to this definition, "Comparative effectiveness research (CER) is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care" [1]. According to the IOM report, CER is conducted in order to develop evidence that will aid patients, clinicians, purchasers, and health policy makers in making informed decisions. The overarching goal is to improve health care *at both the individual and population levels.*

Insofar as the focus of CER is *on effectiveness*, the contrast with *efficacy* needs to be made. Efficacy refers to the performance of a medical intervention under "ideal" circumstances, whereas *effectiveness* refers to the performance of the intervention in "real-world" clinical settings. With efficacy and effectiveness defining the two ends of a continuum, actual studies typically occupy one of the intermediate points. However, effectiveness trials are expected to formulate their aims and design based on the realities of routine clinical practice and to assess outcomes that are directly relevant to clinical decisions. Such trials are often termed "pragmatic clinical trials" in the CER lexicon [2].

In order to maintain the focus on effectiveness, CER studies involve populations that are broadly representative of clinical practice. CER also calls for comparative studies, including two or more alternative interventions with the potential to be the best practice and assessing both harms and benefits. CER studies often involve multiple arms and rarely include placebo arms. Importantly, CER aspires to focus on the *individual* rather than the *average* patient. As a result, the goal of CER is to develop as granular information as possible, in order to assist medical decision making for individuals. Comparative results on subgroups are very important in the CER context.

Patient-Centered Research and PCORI

Among several entities that promote and fund studies of comparative effectiveness, a central role was given to the Patient-Centered Outcomes Research Institute (PCORI). This institute, a public–private partnership, was established and funded by the Patient Protection and Affordable Care Act (PPACA) to conduct CER and generate information needed for health care and policy decision making under PPACA. PCORI developed its own formulation of CER with an emphasis on patient-centeredness. In this formulation, an overarching goal of CER is to provide information that will address the following main questions faced by patients: (a) Given my personal characteristics, conditions, and preferences, what should I expect will happen to me? (b) What are my options, and what are the potential benefits and harms of those options? (c) What can I do to improve the outcomes that are most important to me? (d) How can clinicians and the healthcare delivery systems they work in help me make the best decisions about my health and health care? [3]. An important caveat here is that the class of patient-centered outcomes is not the same as the class of patient-reported outcomes. In addition, PCORI asks that studies include a wide array of stakeholders besides patients, including family members, informal and formal caregivers, purchasers, payers, and policy makers, but the patient remains the key stakeholder.

Evolution of CER

As Greenfield and Sox noted in summarizing the IOM CER Committee Report, "Research that informs clinical decisions is everywhere, yet a national research initiative to improve decision making by patients and their physicians is a novel concept" [4]. Healthcare reform, and particularly the establishment of PCORI and consequently targeted funding, accentuated CER. Notably, funding related to CER is not restricted to PCORI. Other agencies have adopted the CER paradigm in funding announcements and also recommend the involvement of stakeholders in studies [5].

CER has evolved in the 6 years since healthcare reform. Researchers and the patient advocacy community are designing and conducting CER studies, as well as developing the methodology to conduct such studies. The PCORI legislation required that methodological standards for conducting CER be established by the PCORI Methodology Committee. Forty-seven standards were constructed [6], with a current revision ongoing. These standards have increased the attention on methods, and the quality of CER studies. Methodological work is especially focused on trial design, for example, adaptive

designs, as well as causal inference in the observational setting. As discussed in the next section, this book addresses these methodological issues and more.

The scientific literature has responded with several special issues devoted to CER, including *Health Affairs* in October 2010 and the *Journal of the American Medical Association* (*JAMA*) in April 2012. A journal devoted to CER, the *Journal of Comparative Effectiveness Research*, was established in 2012. The renewed focus on causal inference has increased methodological work and resulted in new journals as well, including *Observational Studies*, established in 2015.

In terms of data availability, particularly for the conduct of large pragmatic trials, PCORI has funded the construction of a national clinical data research network PCORnet to facilitate the analysis of electronic health records (EHRs) and claims [7]. Funding for training and education is now available, particularly via the Agency for Healthcare Research and Quality (AHRQ), which receives a portion of PCORI funding for such activities. AHRQ has funded a K12 Scholars Program on patient-centered outcomes research, for example. The interested reader may also wish to take advantage of the methodology standards curriculum [8] and the continuing medical education material [9] available at PCORI. Dissemination and implementation of CER results are still in their infancy, though the spotlight has now turned to these essential next steps.

Scope and Organization of This Book

CER encompasses a very broad range of types of studies. In particular, studies of comparative effectiveness can be experimental, notably randomized-controlled trials, or observational. The latter can be prospective studies, for example, involving registries and EHR databases, or postmarketing safety studies. They can also be retrospective, for example, involving the analysis of data from healthcare claims. Research synthesis occupies a significant place in CER, including the conduct of systematic reviews and meta-analyses. The use of modeling is increasingly important in CER given CER's focus on decision making, including decision analysis and microsimulation modeling. Although the legal framework of PCORI does not cover cost-effectiveness analysis, the area is an important dimension of CER in the eyes of many in the research and health policy communities.

The choice of material and organization of this book is intended to cover the main areas of methodology for CER, to emphasize those aspects that are particularly important for the field, and to highlight their relevance to CER studies. Although the coverage of topics is not encyclopedic, we believe this book captures the majority of important areas.

The book is organized into four major sections. The first three cover the fundamentals of CER methods, including (I) Causal Inference Methods, (II) Clinical Trials, and (III) Research Synthesis. The fourth section is devoted to more specialized topics that round out the book. Each section contains several chapters written by teams of authors with deep expertise and extensive track record in their respective areas. The chapters are cross-referenced and provide an account of both theoretical and computational issues, always anchored in CER domain research. The chapter authors provide additional references for further study.

The book is primarily addressed to CER methodologists, quantitative trained researchers interested in CER, and graduate students in all branches of statistics, epidemiology, and health services and outcomes research. The intention is for the material to be accessible to anyone with a masters-level course in regression and some familiarity with clinical research.

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Constantine Gatsonis and Sally C. Morton

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