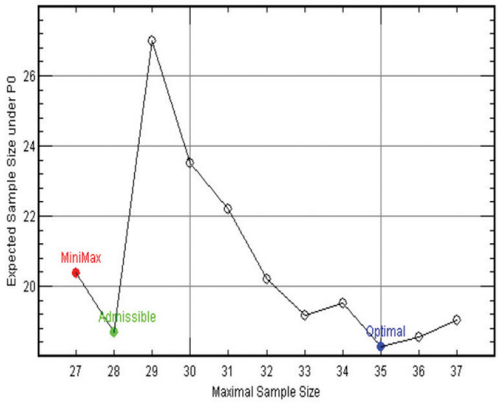
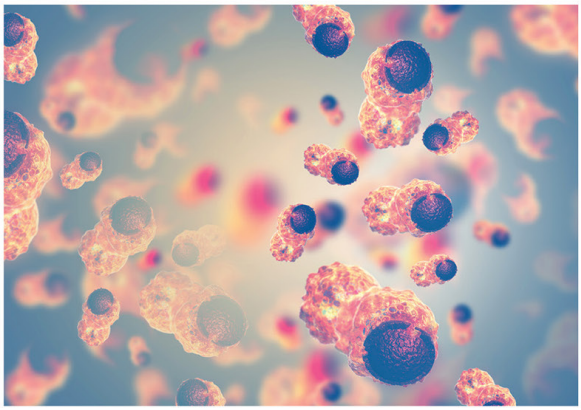
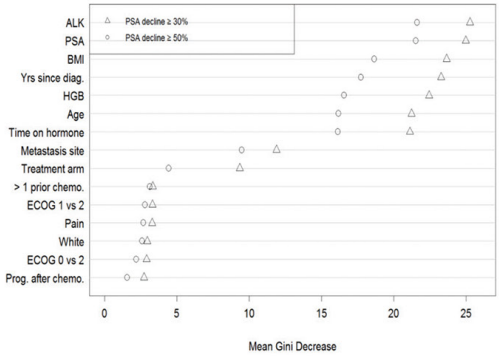
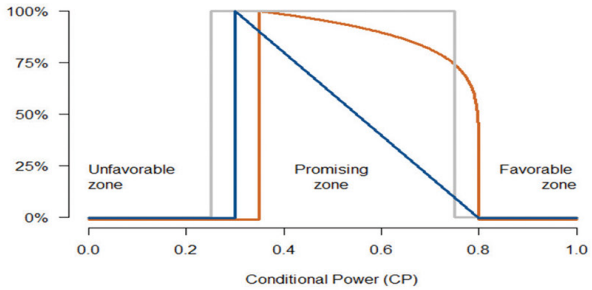
TEXTBOOK OF CLINICAL TRIALS IN ONCOLOGY

A STATISTICAL PERSPECTIVE









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Susan Halabi and Stefan Michiels

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Textbook of Clinical Trials in Oncology

A Statistical Perspective

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Edited by

Susan Halabi

Department of Biostatistics and Bioinformatics, Duke University, Durham, North Carolina

Stefan Michiels

Unit of Biostatistics and Epidemiology, Gustave Roussy, CESP Inserm, University Paris-Sud, University Paris-Saclay, Villejuif, France

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We dedicate this book to our mentors, collaborators, researchers and, most importantly, those patients who participate in clinical trials. The patients are not only scientific collaborators but, in many ways, are the ones who make the greatest contribution to the advancement of our collective quest to conquer cancer.

To Nicholas Robins and Saskia Ooms, for their unwavering support.

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Acknowledgment

This book is principally targeted to intermediate level statisticians who are in graduate programs in biostatistics. It evolved from the need for training the next generation of statisticians to become clinical trialists. In addition, we hope this book will serve as a guide for statisticians with minimal clinical trial experience, who are interested in pursuing a career in clinical trials.

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Editors

Susan Halabi, PhD, is a Professor of Biostatistics and Bioinformatics, Duke University. She has extensive experience in the design and analysis of clinical trials in oncology. Dr. Halabi is a fellow of the American Statistical Association, the Society of Clinical Trials, and the American Society of Clinical Oncology. She serves on the Oncologic Drugs Advisory Committee for the Food and Drug Administration.

Stefan Michiels, PhD, is the Head of the Oncostat team of the Center for Research in Epidemiology and Population Health (INSERM U1018, University of Paris-Saclay, University Paris-Sud) at Gustave Roussy. His areas of expertise are clinical trials, meta-analyses, and prediction models in oncology. Dr. Michiels is the currently chair of the biostatisticians at Unicancer, a French collaborative cancer clinical trials group.

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Contributors

William T. Barry, PhD
Rho Federal Systems Division
Chapel Hill, North Carolina

Robert A. Beckman, MD
Professor
Department of Oncology
and
Department of Biostatistics, Bioinformatics, and Biomathematics
Lombardi Comprehensive Cancer Center and Innovation Center for Biomedical Informatics
Georgetown University Medical Center
Georgetown, Washington, District of Columbia

Aurélie Bertrand, PhD
Institute of Statistics, Biostatistics and Actuarial Sciences
Louvain Institute of Data Analysis and Modeling in Economics and Statistics
Université catholique de Louvain
Louvain-la-Neuve, Belgium

Jan Beyersmann, PhD
Professor
Institute of Statistics
Ulm University
Ulm, Germany

Cong Chen, PhD
Executive Director
Early Oncology Statistics BARDS
Merck & Co., Inc
Kenilworth, New Jersey

Cody Chiuzan, PhD
Assistant Professor
Department of Biostatistics
Mailman School of Public Health
Columbia University
New York, New York

Catherine M. Crespi, PhD
Professor
Department of Biostatistics
University of California
Los Angeles, California

James J. Dignam, PhD
Professor
Department of Public Health Sciences
The University of Chicago
Chicago, Illinois

Keyue Ding, PhD
Canadian Cancer Trials Group
Department of Public Health Sciences
Queen's University
Kingston, Ontario, Canada

Alex Dmitrienko, PhD
Mediana, Inc.
Overland Park, Kansas

Paul Gallo, PhD
Novartis Pharmaceuticals
East Hanover, New Jersey

Ekkehard Glimm, PhD
Novartis Pharma AG
Basel, Switzerland

Susan Halabi, PhD
Professor
Department of Biostatistics and Bioinformatics
School of Medicine
Duke University
Durham, North Carolina

Jay Herson, PhD
Senior Associate
Department of Biostatistics
Johns Hopkins Bloomberg School of Public Health
Johns Hopkins University
Baltimore, Maryland

Chen Hu, PhD
Assistant Professor
Division of Biostatistics and Bioinformatics
Sidney Kimmel Comprehensive Cancer Center
Johns Hopkins University School of Medicine
Baltimore, Maryland

Masataka Igeta, PhD
Department of Biostatistics
Hyogo College of Medicine
Hyogo, Japan

Sin-Ho Jung, PhD
Professor
Department of Biostatistics and Bioinformatics
School of Medicine
Duke University
Durham, North Carolina

Kelley M. Kidwell, PhD
Associate Professor
Department of Biostatistics
University of Michigan School of Public Health
Ann Arbor, Michigan

Andrea Knezevic, MS
Research Biostatistician
Department of Epidemiology & Biostatistics
Memorial Sloan Kettering Cancer Center
New York, New York

Aya Kuchiba, PhD
Biostatistics Division
CRAS
National Cancer Center
Tokyo, Japan

Nicholas R. Latimer, PhD
Reader
School of Health and Related Research
University of Sheffield
Sheffield, United Kingdom

Aurelien Latouche, PhD
Professor
Conservatoire National des Arts et Métiers
Institut Curie
Paris, France

Catherine Legrand, PhD
Professor
Institute of Statistics, Biostatistics and Actuarial Sciences
Louvain Institute of Data Analysis and Modeling in Economics and Statistics
Université catholique de Louvain
Louvain-la-Neuve, Belgium

Gang Li, PhD
Professor
Department of Biostatistics and Biomathematics
University of California
Los Angeles, California

Chen-Yen Lin, PhD
Senior Research Scientist
Eli Lilly and Company
Indianapolis, Indiana

Ilya Lipkovich, PhD
Eli Lilly and Company
Indianapolis, Indiana

Shigeyuki Matsui, PhD
Professor
Department of Biostatistics
Nagoya University Graduate School of Medicine
Nagoya, Japan

Stefan Michiels, PhD
INSERM CESP—Oncostat Team
Biostatistics and Epidemiology Department
Paris Saclay University/UVSQ
Paris, France

Koji Oba, PhD
Associate Professor
Interfaculty Initiative in Information Studies
and
Department of Biostatistics
School of Public Health
Graduate School of Medicine
The University of Tokyo
Tokyo, Japan

Chris O'Callaghan, PhD
Canadian Cancer Trials Group
Department of Public Health Sciences
Queen's University
Kingston, Ontario, Canada

Nathaniel O'Connell, PhD
Department of Biostatistical Sciences
Wake Forest School of Medicine
Wake Forest University
Winston-Salem, North Carolina

Megan Othus, PhD
Associate Member
Fred Hutchinson Cancer Research Center
Seattle, Washington

Katherine S. Panageas, DrPH
Associate Attending Biostatistician
Department of Epidemiology & Biostatistics
Memorial Sloan Kettering Cancer Center
New York, New York

Xavier Paoletti, PhD
INSERM CESP—Oncostat Team
Biostatistics and Epidemiology Department
Paris Saclay University/UVSQ
Paris, France

Lira Pi, PhD
Duke University
Durham, North Carolina

Martin Posch, PhD
Center for Medical Statistics, Informatics, and Intelligent Systems
Medical University of Vienna
Vienna, Austria

Stephanie Pugh, PhD
Director of Statistics
American College of Radiology
Philadelphia, Pennsylvania

Bohdana Ratitch, PhD
Eli Lilly and Company
Montreal, Quebec, Canada

Federico Rotolo, PhD
Biostatistician
Innate Pharma
Marseille, France

Claudia Schmoor, PhD
Clinical Trials Unit
Faculty of Medicine and Medical Center
University of Freiburg
Freiburg, Germany

Juned Siddique, DrPH
Associate Professor
Division of Biostatistics
Department of Preventive Medicine
Northwestern University Feinberg School of Medicine
Chicago, Illinois

Richard Simon, DSc
R Simon Consulting
Potomac, Maryland

Kelly Speth, MS, PhD
Department of Biostatistics
University of Michigan School of Public Health
Ann Arbor, Michigan

Nils Ternès, PhD
Biostatistician
Sanofi-Aventis
Chilly-Mazarin, France

Kiichiro Toyoizumi, PhD
Biometrics
Shionogi Inc
Florham Park, New Jersey

Stephen Walters, PhD
Professor
Medical Statistics and Clinical Trials
School of Health and Related Research
University of Sheffield
Sheffield, United Kingdom

James Wason, PhD
Professor
Institute of Health and Society
Newcastle University
Newcastle, United Kingdom

and

Medical Research Council Biostatistics Unit
University of Cambridge
Cambridge, United Kingdom

Ian R. White, PhD
Professor
Statistical Methods for Medicine
Medical Research Council Clinical Trials Unit at University College London
London, United Kingdom

Yuan Wu, PhD
Assistant Professor
Department of Biostatistics and Bioinformatics
School of Medicine
Duke University
Durham, North California

Dong Xi, PhD
Novartis Pharmaceuticals
East Hanover, New Jersey

Qing Yang, PhD
Assistant Research Professor
School of Nursing
Duke University
Durham, North California

Sarah Zohar, PhD
INSERM, UMRS 1138, Team 22, CRC
University Paris 5
University Paris 6
Paris, France

1

Introduction to Clinical Trials

Susan Halabi and Stefan Michiels

CONTENTS

The first documented clinical trial dates back to May 20, 1747, to a study conducted on board the British naval vessel HMS *Salisbury* [1]. During the voyage, 12 sailors suffered from scurvy, prompting the vessel's surgeon, James Lind, to experiment by assigning groups of two patients to six different treatments [1]. One of those treatments included the consumption of oranges and lemons, which was found to be effective [1]. Despite this and other early achievements, it was not until 1926 that the modern concept of randomization was pioneered by Sir Ronald A. Fisher in his agricultural research [2,3]. Building on these methodological accomplishments, subsequent researchers introduced randomization in human experiments in 1936 [4]. The first trial to be conducted by the Medical Research Council was on the effectiveness of streptomycin in patients with tuberculosis, in 1948 [4].

Clinical trials have come a long way since then, and have become a keystone when evaluating the effectiveness of therapies [4,5]. Moreover, they are an engine of drug development and approval, which contributes to improved treatment and patient care. As such, they serve as the main conduit that regulatory agencies utilize to approve therapies in humans. We expect that clinical trials will play an ever increasing, and global, role in twenty-first-century medicine.

According to ClinicalTrials.gov, "a clinical trial is a research study to answer specific questions about vaccines or new therapies or new ways of using known treatments" [6]. We follow the clinical oncology paradigm in classifying clinical trials broadly into four phases: phase I (or early development), which examines an experimental treatment in a small group of patients in which the dose and safety are evaluated; phase II trials (or middle development), which refer to experimental therapies and their efficacy in tumor shrinkage in a larger group of patients; phase III trials (or late), which investigate and compare the experimental therapy to a placebo or control; and lastly, phase IV trials, which are conducted after an experimental treatment has been licensed and marketed [4,7,8].

Phase III clinical trials are crucial in determining the efficacy of innovative therapies and are considered the gold standard in assessing the efficacy of a new experimental arm or device. The basic principles of design in phase III trials are to minimize bias and increase precision in the estimation of the treatment effect [4,7]. Although the central objective of a phase III trial is to change medical practice, it is not always attained. Furthermore, results from a single phase III trial may not be sufficient for the intervention to be considered

definitive or to change medical practice. Green and Byar confirmed that phase III trials establish the strongest evidence for approving an intervention, but other supporting trials are needed [9].

In recent years, clinical trials have become increasingly sophisticated as they incorporate genomic studies and embed quality of life objectives [4,7]. Historically, trials with cytotoxic agents were conducted sequentially, starting with a phase I trial and advancing to phase II and phase III trials. With the advancement in genetic and molecular technologies, this paradigm has increasingly been challenged, resulting in more efficient designs [10–13]. We have seen an upsurge of innovative trial designs ranging from seamless phase II/III trials to adaptive studies [14–16]. Basket and umbrella trials have also evolved so that trials are conducted efficiently across genetic variants or cancer histologies [17–20]. While well-conducted phase III studies have and will continue to form the foundation for drug approval, well-designed phase II trials may also play a role in regulatory approval.

1.1 Scope and Motivation

There is an evolving need for educational resources for statisticians and investigators. Reflecting this, the goal of this book is to provide readers with a sound foundation for the design, conduct, and analysis of clinical trials. Furthermore, this book is intended as a guide for statisticians and investigators with minimal clinical trial experience who interested in pursuing a career in clinical trials.

The following chapters provide both the theoretical justification and practical solutions to the problems encountered in the design, conduct, and analysis of a clinical trial. We also seek to encourage and advance the development of novel statistical designs or analytical methods. Additionally, this book may be of interest for public-health students and public-health workers involved with clinical trials, reflecting its focus on practical issues encountered in clinical trials exemplified by real-life examples.

The development, design, and conduct of a trial require a multidisciplinary approach. Altman describes the general sequence of steps in a research project as follows: planning, design, execution (data collection), data processing, data analysis, presentation, interpretation, and publication [21]. Statistical thinking is vital at each of these steps, and statisticians play a fundamental role in ensuring the objectivity of clinical trials and that the trials produce valid and interpretable results.

This book focuses on human studies in oncology, ranging from early, middle, and late phase trials to advanced topics relevant in the era of precision medicine and immunotherapy. Developing an understanding of these issues is imperative for statisticians to contribute effectively in a dynamic, twenty-first-century environment. This work is divided into four sections. In the first section, the chapters focus on the early to middle development designs that new investigators need to consider as they prepare for phase I through II/III trials. Throughout these chapters, the authors share their experiences in trial design and provide examples and software to illustrate their points. The URL of the companion website is **https://www.crcpress.com//9781138083776**. This section begins with Panageas highlighting the salient issues in choosing an endpoint for a clinical trial. Responding to the rich literature on the drawbacks of the $3 + 3$ designs, Chiuzan and O'Connell promote innovative designs in phase I settings, while providing R functions and a tutorial for the design of phase I trials. Following this, Jung discusses phase II designs, focusing

on two-stage designs and advocating for reporting p-values in phase II settings. Othus outlines the challenges in the design and conduct of trials with immunotherapies, while Barry reviews adaptive designs, which have played a vital role in recent years.

Section II explores late phase III trials. While Oba et al. describe the design of phase III trials, the gold-standard design in clinical trials, Ding and O'Callaghan focus on the principles of non-inferiority trial design. Wason examines multi-stage and multi-arm trials which have been successful in approving several drugs, and Glimm and colleagues consider multiple comparison and co-primary endpoints. Once the study is underway, the focus shifts to the conduct of the trial. Crespi provides an in-depth discussion on cluster randomization, which she illustrates with several examples. Monitoring of studies is taken up by Herson and Hu, who discuss the role of interim analysis and data monitoring during the conduct of the trial.

The third section deals with cutting-edge topics in personalized medicine. Matsui and colleagues detail the design of biomarker-driven trials, while Simon describes the statistical issues that arise in genomic studies. Beckmann et al. examine the challenges of designing a trial for rare diseases, and Lipkovich and colleagues review subgroup analysis and methods for biomarker analysis. The development and validation of prognostic models and genomic signatures has been embedded into many trials. While Halabi and colleagues share their expertise in developing and validating prognostic models in cancer studies, Rotolo et al. provide a detailed discussion on how signatures are developed and validated. This section ends with a thorough exposition by Kidwell and colleagues of the dynamic treatment regimen.

The final section is dedicated to advanced topics related to the analysis phase of clinical trials. Surrogate endpoints are examined by Paoletti and colleagues, reflecting the interest in decreasing the time for a new drug to be approved. Latouche and colleagues outline methods for competing risks analysis and when they should be implemented. We have seen an increased proportion of cancer patients surviving, and Legrand demonstrates the importance of the cure-rate models. Wu and Halabi discuss interval censoring, which is underutilized in clinical trials. Patients often are offered other therapies after they progress or relapse, and Latimer and White give an in-depth review of methods adjusting for treatment switches. Assessing and reporting the adverse events encountered during a trial are critical tasks, tackled by Beyersmann and Schmoor, who offer methods for the analysis of adverse events. Walters describes the design of a quality of life study, which increasingly are integrated into clinical trials, while Pugh and colleagues discuss how to deal with missing data in trials.

In summary, statistical input and thinking is critical at each stage of the process of a trial. The challenging issues that statisticians face from the design stage to the analysis stage are described in these chapters. Moreover, the contributors present theoretical and analytical solutions and highlight the practical approaches. We hope that this book will help advance the design of trials as they continue to evolve with the changes in therapeutic landscape in cancer and improve the delivery of treatment and care for oncology patients.

1.2 Resources

There are many resources dedicated to clinical trials (Table 1.1), and this list is not comprehensive. One great resource for statisticians and clinical trialists is the Society of

TABLE 1.1

Web-Based Resources

https://www.aacr.org/
https://www.asco.org/
http://www.cancer.gov/
https://www.canada.ca/en/services/health/drug-health-products.html
www.clinicaltrials.gov
www.cochrane.org
www.consort-statement.org
https://www.ctu.mrc.ac.uk/
http://www.ema.europa.eu/ema/
http://eng.sfda.gov.cn/WS03/CL0755/
http://www.esmo.org/
https://www.fda.gov/
https://latampharmara.com/mexico/cofepris-the-mexican-health-authority/
https://www.pmda.go.jp/english/
http://journals.sagepub.com/home/ctj
http://www.sctweb.org/public/home.cfm
https://seer.cancer.gov/
https://stattools.crab.org/
http://www.tga.gov.au/

Clinical Trials (www.sctweb.org), which is an organization dedicated to the study, design, and analysis of clinical trials, with a peer-reviewed journal (*Controlled Trials*).

1.3 Conclusion

Clinical trials are becoming increasingly sophisticated, are costly and time-consuming, and require expertise in their planning, execution, and reporting. It is our responsibility as statisticians and investigators to ensure that trials are rigorously planned, well conducted, and properly analyzed. This will enable them to continue to answer important clinical questions while improving the care of patients and their quality of life.

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