Preface

With advances in medical sciences, cancer research no longer focuses primarily on effective treatments, but rather a host of other issues such as tools for early diagnosis, cost of treatment and long-term care, and quality of life. Thus, in addition to traditional survival analyses for comparing treatment differences, modern clinical trials in cancer research are also designed to address these new emerging issues. This volume covers classic as well as cutting-edge topics on the analysis of clinical trial data in biomedical and psychosocial research and discusses each topic in an expository and user-friendly fashion. The intent of the book is to provide an overview of the primary statistical and data analytic issues associated with each of the selected topics, followed by a discussion of approaches for tackling such issues and available software packages for carrying out the analyses.

Some of the topics covered are quite standard, such as survival data analysis and longitudinal data. Although in-depth discussions of such classic topics can be found in various topic-specific texts, our coverage highlights their specific and important roles in clinical trials. Further, by presenting the topics in a self-contained fashion, the materials become more assessable by researchers in other disciplines, particularly clinicians and medical investigators who seek a "crash course" to understand the "nuts and bolts" of clinical trials.

With new medical discoveries, advances in technology and treatment delivery, rises in health-care cost, and emphasis on quality of life and patient-centered care, clinical trials have become increasingly complex in design to address all these concerns. For example, in most randomized controlled trials, patients are randomized to a particular treatment at baseline, regardless of whether the treatment is optimized for the patient. Although it is a necessary step to study the efficacy of a treatment, this traditional approach does not fully reflect how patients are treated in practice, when multiple treatments are generally used either sequentially or in combination to effectively treat a patient. In fact, dynamically adjusting treatment in accordance with the patient response to the previously assigned treatment is the only viable option for treating many mental disorders. Some of the chapters are devoted to addressing such cutting-edge issues to reflect advances in statistical methodology for clinical trials.

As a series to provide an overview of the core concepts of clinical trials and a guide to statistical methods for analyzing data from such studies, the chapters are organized in an order following the logical considerations of the issues arising from the design to the execution of clinical trials. Thus, we start with two chapters focusing on the classic topics of survival and longitudinal data analysis. Treatment evaluations in clinical trials generally center on two types of outcome. If the study involves patients with terminal illnesses such as advanced cancers, the duration from a certain time point such as the initiation or termination of the treatment is often of primary interest. Survival analysis models are uniquely suited to comparing survival times between different treatment groups.

In most clinical trials, treatment differences are evaluated by comparing changes in an outcome of interest over time such as tumor volume in cancer studies between different treatment groups. Longitudinal models are applied to facilitate comparisons of such temporal changes. These models extend classic methods for cross-sectional data to address the within-subject correlations in the repeated assessments of the individual and missing data due primarily to premature dropout by study subjects. Chapter 2 discusses these distinctive features of longitudinal data and associated models.

Valid inference not only replies on correct statistical models, but on quality and fidelity of outcomes of clinical trials as well. Although clinical trials typically use measures with established fidelity and reliability, it is important to have some level of understanding of the inner workings of the process to develop and validate such measures, especially for outcomes derived from measures of latent constructs such as quality of life. Chapter 3 provides an overview of such measurement error issues and methods to address them.

Upon settling down on the measures of treatment effect, the next step is to decide on the length of the study. In particular, we may want to know whether we can expedite the trial as soon as evidence of treatment efficacy emerges, especially for treatments with adverse reactions and side effects and studies with serious deterioration of health and fatality outcomes. Chapter 4 discusses dynamic decision rules to stop a trial as soon as there is indication of treatment difference.

As noted earlier, the standard protocol in clinical trials is to randomize patients at baseline, which, although a necessary step to study the efficacy of a single treatment, does not reflect real clinical practice. Also, with new discoveries on genetic linkage in disease predisposition and treatment response and recent emphasis on patient-centered outcome research, this standard treatment protocol does not meet the needs of the new patient-specific treatment and care model. Chapter 5 focuses on this new person-centered treatment approach by dynamically adjusting treatment in accordance with the patient response to the previously assigned treatment. The dynamic treatment regime, which continuously adjusts treatment type and dosage, is particularly effective for effectiveness research, because of the diverse range of patients' conditions and disease progression in such studies.

As the cost for research in developing and delivering new treatment becomes increasingly high, health care has become quite expensive, especially in the USA. In recent years, more and more clinical trials have included a cost–effectiveness

component to also examine the cost for the new intervention. The cost–effectiveness analysis allows one to see if the added benefit is worth the increased cost and how to maximize such benefit-to-cost margins for a population of interest. Chapter 6 is devoted to addressing these issues.

In most clinical trials, we are interested in establishing the superiority of the new intervention over existing or conventional treatment. But, in some cases, we may be interested in equivalence between a new and conventional treatment, such as in replacing costly name brand medications with less expensive generic alternatives, and a simplified instrument for diagnosis of disease. More importantly, such equivalence tests are employed in early drug development to assess the potential of drug induced, prolonged duration of ventricular depolarization and subsequent repolarization, or QT interval, as the duration is derived from the interval of ECG tracing from the beginning of Q wave to the end of T wave. For some drugs, significant prolongation of the absolute QT interval has been associated with the precipitation of a potentially fatal cardiac arrhythmia and can degenerate into ventricular fibrillation, leading to sudden cardiac death. To ensure drug safety, thorough QT (TQT) trials are recommended by FDA drug regulatory requirements to assess the treatment response of a new drug and ensure that it does not induce prolonged QT intervals. Thus, the primary object of the TQT is to demonstrate equivalence, rather than superiority as in most clinical trials.

In Chap. 7, we first discuss the fundamental issues arising from the paradigm shift from superiority to equivalence and methods for addressing them under this alternative inference paradigm for equivalence. We then turn our attention to the design and analysis of TQT trials by applying the models for equivalence in Chap. 8.

Randomized controlled clinical trials rely on randomization, the hallmark of modern clinical research, to deliver valid conclusions regarding treatment differences. In some studies, it may not be possible to conduct such a trial. For example, it is clearly unethical to contemplate a randomized controlled trial to study the effect of smoking on lung cancer by randomizing subjects to a smoking group. In some other studies, decision to treat may also depend on the health condition of a subject, in which case treatment assignment is no longer random and treatment differences cannot be evaluated as in randomized trials. Chapter 9 discusses issues in assessing treatment difference in such nonrandomized trials and methods for addressing them to enable valid inference.

We conclude this series with a chapter discussing the opportunities and challenges that lie ahead in developing on person-centered treatment regimens. The advances in cancer biology and the genetics of cancer have rapidly provided us with a better fundamental understanding of cancer. These new developments require a new generation of clinical trials that modernize the processes and methods used to examine the safety and efficacy of novel, gene-based therapies without sacrificing high standards. Chapter 10 revisits some of the basic components of clinical trial design within the context of timely areas of vaccine trials, cancer stem cell trials, and trials of epigenetic targeted therapies.

This book is intended for biostatisticians with special interest in cancer research or medical researchers with some background in biostatistics such as a working

knowledge of clinical trial designs and regression analysis. Since the authors for all the chapters are experienced in modern clinical trial data analysis and are at the forefront of their respective areas, this book should enable them to quickly apply these methods to their own studies, especially considering the fact that most chapters contain illustrative real study data and associated software.

We would like to express our appreciation to all who have contributed to this book. We are also thankful to editors Fiona Sarne and Rachel Warren for their patience and continuing support, despite multiple delays on the project on our part.

http://www.springer.com/978-1-4614-4321-6

Modern Clinical Trial Analysis
Tang, W.; Tu, X. (Eds.)
2013, X, 254 p., Hardcover
ISBN: 978-1-4614-4321-6