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### Book Review

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## BOOK REVIEW

***Clinical Trial Design: Bayesian and Frequentist Adaptive Methods***, by Guosheng Yin, Hoboken, NJ: John Wiley & Sons, 2012. ISBN: 978-0-470-58171-1, 364 pp., \$115.

The adaptive design methods in clinical trials have received much attention in the past decade due to their flexibility, and reflect the need of conducting clinical studies. In addition, there is great interest in the possibility that clinical trials can be designed with the adaptive features that may make the studies more efficient, more likely to demonstrate an effect of the drug if one exists, or more informative (Food and Drug Administration [FDA], 2010). The first published book on adaptive design methods, *Adaptive Design Methods in Clinical Trials*, was written by Chow and Chang in 2006. Updated methodologies were then available in *Handbook of Adaptive Designs in Pharmaceutical and Clinical Development* by Pong and Chow in 2010. This textbook by Dr. Yin is an excellent and welcome addition to the growing area of adaptive designs in modern clinical trials. This book is comprehensive and covers a wide range of statistical methods on both Bayesian and frequentist perspectives. It contains more details on Bayesian clinical trial designs than the two books just mentioned, and other great features. First, the author discusses a diverse set of clinical trial designs and statistical methods that are applied at the world's leading medical centers. In addition, the software used in this book can be downloaded for free from the designated website. Another good aspect of this book is the methods presented, which are classified into three critical phases, Phases I, II, and III of clinical trials in drug development. This is particular helpful for readers who work within biopharmaceutical research and development.

This book has 10 chapters with 309 pages, excluding references and subject index. After the first chapter for introduction, an exercise section with 3–10 questions is included at the end of each chapter. The exercise section is not only beneficial for the assessment of readers' knowledge on the specific topics in the chapter, but also provides additional perspectives for discussion. Furthermore, a short summary section of each chapter is also useful to preserve the reader's focus. Approximately half of the book focuses on the adaptive clinical trial designs and statistical methods of Phases I, II, and III, which are presented in Chapters 4, 5, and 6, respectively. It is not surprising that the majority of the Bayesian approaches are seen in early Phase I and II trials in Chapters 4 and 5 and the frequentist methods dominate in Phase III confirmatory trials in Chapter 6. The rest of the book contains the background of clinical trials with statistical concepts and with particular discussion on specific topics in clinical developments, such as adaptive randomization, late-onset toxicity, drug-combination trials, and target therapy design. It is a big plus that this book has many good examples and impressive figures.

Chapter 1 is an introduction to clinical trials with a brief history of adaptive designs. The process and emerging challenges of new drug development are deliberated in this chapter. Chapter 2 presents the key components that are essential to clinical trial, such as the study protocol, primary objective(s), patients' eligibility criteria and accrual, power and sample size, blinding, randomization, parallel versus crossover designs, data collection, adverse events, and study close-out. The terminologies and concepts on pharmacokinetics/pharmacodynamics and Phase I–IV are also provided.

The title of Chapter 3 is “Frequentist versus Bayesian Statistics.” Needless to say, it is the intention of the author to highlight the difference between these two approaches. This chapter starts with basic concepts in statistics, such as univariate and multivariate distributions, copula function, and convergence of sequences of random variables. Thereafter the basic estimations and inferences procedures for frequentist and Bayesian methods are presented in different sections. The last section of this chapter is on the Markov-chain Monte Carlo sampling algorithm, which is well accepted within the scientific community. Four sampling methods are briefly introduced in this section: the inverse sampling, rejection sampling, Gibbs sampling, and Metropolis–Hastings algorithm sampling procedures. This chapter is suitable for readers who have at least undergraduate-level statistical training.

The Phase I clinical trial is the first stage of drug testing in humans. The ultimate goal of the Phase I trial is to evaluate drug safety and find future dosing. Chapter 4 emphasizes Phase I clinical trials; a variety of innovative statistical methods for dose-finding are briefly introduced, such as the 3 + 3 design of finding the maximum tolerated dose (MTD), the A + B design that is the extension of 3 + 3, the accelerated titration design, biased coin dose-finding method, continual reassessment method (CRM) and the Bayesian model averaging CRM method, escalation with overdose control (EWOC) method, and Bayesian hybrid design of dose-finding.

Chapter 5 is for Phase II trial design. Compared to Phase I, the Phase II trial is larger. The typical objective of a Phase II trial is to measure the treatment response of efficacy. The frequentist hypothesis testing approach on Gehan's two-stage design and Simon's optimal and minimax two-stage design are introduced in this section. An example is then provided for each design. In addition, the advanced methodological development of the early-phase trial, including Bayesian predictive probability trial monitoring, seamless Phase I/II trial designs, and time-to-event toxicity and efficacy trade-offs of multiple outcomes with the corresponding stopping rules, are all presented in this chapter.

Chapter 6 is the longest chapter of this book and is dominated by frequentist approaches in the hypothesis testing framework. The first five sections concentrate on power and sample size calculation for Phase III fixed-sample clinical trials with continuous, binary, and survival endpoints, respectively. The remaining four sections mix with group sequential methods, adaptive reestimated in light of interim data, noncompliance issues, intent-to-treat analysis, and there is a little discussion on Phase IV clinical trials.

Adaptive randomization is illustrated in Chapter 7. The methods accessible in this chapter are abundant and updated. The popular methods in the area of adaptive clinical trials, such as optimal adaptive randomization and Bayesian adaptive randomization, are clearly described in the book. In addition, the cutting-edge approach of adaptive randomization with efficacy and toxicity trade-offs is

summarized in section 7.12. The last portion of this chapter is “Fixed or Adaptive Randomization?” The author concluded this chapter by presenting the recent research on comparing adaptive randomization (AR) and the conventional fixed randomization (FR).

Unlike the standard 3 + 3 design and the CRM, which requires the toxicity outcome to be detected shortly after the treatments, Chapter 8 introduces some statistical designs for the circumstance in which toxicity outcomes were not observed sooner enough in a dose-finding study. This chapter summarizes the author’s research published in 2011. The methods illustrated in the chapter are the fractional 3 + 3, fractional continual reassessment method (fCRM), time-to-event continual reassessment method (TITE-CRM), and EM continual reassessment method (EM-CRM). These approaches not only allow for delayed toxicity outcome responses, but also allow shortening the trial duration.

Chapter 9 covers the statistical methods for dose-finding in two-drug combination trials. The author provides in-depth discussions on a simple sequential dose-finding scheme based on both simple and partial orders of dose combinations. In addition, the copula regression is introduced to incorporate the single-agent toxicity information to model the joint toxicity probability, and a latent contingency table approach is presented. The last section of the chapter is on the Phase I/II seamless drug-combination trial. The method, with transition from Phase I to Phase II, adopts the copula model to select admissible doses and the moving-reference adaptive randomization to efficacy.

Chapter 10 has 14 pages, the second shortest chapter after Chapter 1. The chapter starts with terminologies on cytostatic/cytotoxic agents and prognostic/predictive biomarkers. Four targeted therapy designs are then illustrated in four succeeding sections. They are (1) the predictive biomarker validation on marker-by-treatment interaction and targeted therapy design with marker-based strategy, (2) randomized discontinuation design, (3) adaptive signature designs, and (4) adaptive threshold design.

In summary, this book is useful for anyone interested in design and analysis of clinical studies. The main strengths of this book are the well-balanced approach between statistical theories and statistical analysis methods of the design issues involved in clinical trials. I would suggest the use of this book in a master’s-level course in biostatistics.

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