

Preface

Research in response-adaptive randomization developed as a response to a classical ethical dilemma in clinical trials. While clinical trials may provide information on new treatments that can impact countless lives in the future, the act of randomization means that volunteers in the clinical trial will receive the benefit of the new treatment only by chance. In most clinical trials, an attempt is made to balance the treatment assignments equally, but the probability that a volunteer will receive the potentially better treatment is only $1/2$. Response-adaptive randomization uses accruing data to skew the allocation probabilities to favor the treatment performing better thus far in the trial, thereby mitigating the problem to some degree.

Response-adaptive allocation has a long history in the biostatistical literature, and the list of researchers who have worked (at least briefly) in the area reads like a Who's Who of modern statistics: Anscombe, Chernoff, Colton, Cornfield, Flournoy, Greenhouse, Halperin, Louis, Robbins, Siegmund, Wei, Woodrooffe, Zelen, and others. Largely because of the disastrous ECMO trial in the early 1980s, there was a general reluctance to use these procedures that has continued to this day. When the authors met in 1995, it was unclear whether these procedures were effective or could be adapted to modern clinical trials and whether certain fundamental questions could be answered. Our collaboration over the past 10 years has been an attempt to formalize the important questions regarding response-adaptive randomization in a rigorous mathematical framework and to systematically answer them. We generally had no idea that we were opening a can of worms that would require a demanding arsenal of mathematical tools. We set out to interest others in the problems, and this led to fruitful collaborations with many other investigators. This book is a result of

these collaborations. It represents what we now know about the subject, and it is our attempt to form a mathematically rigorous subdiscipline of experimental design involving randomization. Two individuals were particularly influential: Z. D. Bai of Singapore, whose collaborative work resulted in solutions to decades-old problems in urn models, largely forming the basis for Chapter 4; and L.-X. Zhang of China, whose collaborative work largely forms the basis of Chapter 5.

This book is aimed at Ph.D. students and researchers in response-adaptive randomization. It provides answers to some of the fundamental questions that have been asked over the years: How does response-adaptive randomization affect power? Can standard inferential tests be applied following response-adaptive randomization? What is the effect of delayed response? Which procedure is most appropriate, and how can "most appropriate" be quantified? How can heterogeneity of the patient population be incorporated? Can response-adaptive randomization be performed with more than two treatments or with continuous responses?

While the mathematics generated by these problems can sometimes be daunting, the response-adaptive randomization procedures themselves can be implemented in minutes by adding a loop to a standard randomization routine. Procedures can be simulated under various parameterizations to determine their appropriateness for use in clinical trials. Our hope is that any future objections to the use of response-adaptive randomization will not be based on logistical difficulties or the lack of theoretical justification of these procedures.

Most of the book is written at the level of graduate students in a statistics program. The technical portions of the book are mostly relegated to appendices and to brief descriptions in Chapters 4 and 5. That material requires advanced probability and stochastic processes as well as matrix theory. Prerequisite material can be found in Appendix A for those wishing to pursue the technical details. In addition, it is recommended that readers new to the area of response-adaptive randomization begin by reading Chapters 10–12 of Rosenberger and Lachin (*Randomization in Clinical Trials*, Wiley, New York, 2002).

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As we point out in Chapter 10, open problems abound in this area, and it is our sincere hope that more talented researchers will be attracted to the beauty of the complex stochastic structures encountered throughout this book. However, our greatest hope is that, by providing a firm theoretical underpinning to the concept of response-adaptive randomization in this book, clinical trialists will be motivated to apply these techniques in practice.

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