

# Preface

The idea of writing a book on sequential experimentation in clinical trials arose 25 years ago when Lai was at Columbia University, collaborating with Dan Anbar of Abbott Laboratories on a university-industry cooperative research project, “Sequential Statistical Methods in Biopharmaceutical Research,” funded by the National Science Foundation. Anbar and Lai, together with Gordon K.K. Lan and Anastasio Tsiatis (at that time, at the NIH and Harvard, respectively), formed a focused research group that held a week-long meeting every 2 months and organized an annual workshop, with invited speakers from academia, industry, and the FDA and NIH, and dedicated to the development and discussion of sequential methods in the design and analysis of clinical trials. Although substantial progress was made by the group to advance this new area that attracted considerable attention from the pharmaceutical industry after the early termination of the Beta-Blocker Heart Attack Trial in 1981, the book project could not materialize when Lai moved to the West Coast in 1987, joining Stanford University, while the other collaborators remained on the East Coast but were busy with their own moves to new positions. On the other hand, the group members continued their separate research efforts in this area. These efforts and those by other researchers led to major advances and eventual widespread use of group sequential designs and interim analysis methods by the pharmaceutical industry and their acceptance by the FDA.

At the turn of the new century, the monograph by [Jennison and Turnbull \(2000\)](#) appeared, giving a comprehensive overview of group sequential methods developed up to that time. Besides continual developments in interim analysis and group sequential methods, the past decade has also witnessed new developments and growing interest in adaptive designs of clinical trials. The books by [Proschan et al. \(2006\)](#), [Chow and Chang \(2006\)](#), [Chang \(2007\)](#), and [Berry et al. \(2011\)](#) describe some of these developments and their applications. However, as pointed out in Chap. 8, there is substantial disagreement in the literature concerning the appropriateness of these adaptive designs, which either use inefficient test statistics that are not supported by mainstream statistical principles to adjust for the adaptation in maintaining the Type I error of the test or use Bayesian posterior probabilities that do not guarantee the prescribed Type I error. Chapter 8 describes our recent work that provides a new

class of adaptive designs which are both flexible and efficient, thereby resolving the dilemma between efficiency and flexibility in the adaptive design literature. Prior to this work, we have also developed a comprehensive methodology of flexible and efficient group sequential designs, to which Chap. 4 is devoted. In fact, the new adaptive designs in Chap. 8 are modifications of the corresponding group sequential designs in Chap. 4, and a unified approach is provided for the methodology and implementation of group sequential and adaptive designs.

Besides giving an up-to-date account of these flexible designs, we also present in Chap. 7 a comprehensive overview, including the most recent developments of inference after the termination of these clinical trials. Chapter 6 describes the Beta-Blocker Heart Attack Trial as an example for the design and analysis of clinical trials with failure-time endpoints and interim analyses. The material in Chaps. 4, 6, 7, and 8 can be used for short courses on group sequential and adaptive designs. We have given short courses based on this material in the First Joint Biostatistics Symposium in Beijing, July 2010, the Applied Statistics Symposium of the International Chinese Statistical Association in New York, June 2011, and the Workshop on the Design and Analysis of Clinical Trials at National University of Singapore, October 2011. We were greatly encouraged by the enthusiastic response and stimulating comments of the participants.

This book has also benefited from the Third International Workshop in Sequential Methodologies at Stanford University, June 2011. The workshop was very well attended and was truly international in nature. There it was pointed out that despite a resurgence of interest in sequential analysis, the subject was not in the graduate curriculum of most statistics departments. One reason that was mentioned was the lack of textbooks that could present the material in an appealing way to today's graduate students. In fact, only a handful of such books had been written and they were published more than 20 years ago. Although there are more recent books which we have mentioned in the second paragraph of this preface, they all deal with the specialized topics of group sequential and adaptive designs rather than general methods and principles in sequential analysis. Another reason that came up during workshop discussions was that sequential methods and adaptive designs seemed to involve special techniques and ideas that are detached from mainstream topics taught in the modern graduate statistics curriculum, e.g., likelihood inference, regression analysis, resampling, semiparametric theory, to name a few. Spurred by these comments, we have made particular efforts to change this perception in the selection and presentation of the materials. To make it suitable for an introductory course on sequential analysis, the book covers the much broader subject of sequential experimentation that includes group sequential and adaptive designs of Phase II and III clinical trials, which have attracted much attention in the past three decades. In particular, the broad scope of design and analysis problems in sequential experimentation clearly requires a wide range of statistical methods and models from nonlinear regression analysis, experimental design, dynamic programming, survival analysis, resampling, and likelihood and Bayesian inference. The background material in these building blocks is summarized in Chaps. 2 and 3 and certain sections in Chaps. 6 and 7. Besides group sequential tests and adaptive

designs, we also introduce sequential change-point detection methods in Chap. 5 in connection with pharmacovigilance and public health surveillance. Together with dynamic programming and approximate dynamic programming in Chap. 3, the book therefore covers all basic topics for a graduate course in sequential analysis.

Different parts of the book can be used for short courses on clinical trials, translational medical research, and sequential experimentation. Lai has used an early draft of the book to teach a course on innovative clinical trial designs and statistical methods for second-year Ph.D. students in the Department of Statistics at Stanford University. The course has led to supplements and exercises for various chapters and also to the web site for the book, <http://meichiun.web.stanford.edu/clinicaltrials/>, to which different parts of the book refer for links to software.

We thank the teaching assistant Alex Deng and the students in the aforementioned course for their stimulating interest and helpful comments on a first draft of the book that was used as lecture notes. In particular, we want to mention Olivia Liao who subsequently wrote her Ph.D. thesis on the subject and contributed to some recent publications that we have referenced. We also thank our collaborators Philip Lavori, Zheng Su, Ray Zhu, Joe Heyse, Jie Chen, Sam Wong, and Hock Peng Chan for working with us on related projects and for their valuable suggestions. We are particularly grateful to Balasubramanian Narasimhan who has been helping us develop open-source software for the innovative designs and analyses that will be posted at the book's web site and to Cindy Kirby who has put together the separate chapters in an efficient and timely fashion. We also acknowledge grant support for the research projects related to this book by the National Science Foundation (DMS-0907241 and 0403105 for Bartroff and 1106535 and 0805879 for Lai), the National Institutes of Health (GMS-068968 for Bartroff and 1 P30 CA124435 for Lai), the U.S. Department of Veterans Affairs Cooperative Studies Program (for Shih), and the Stanford Center for Clinical and Translational Education and Research (for Lai and Shih).

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