
Preface

We statisticians, especially those of us who work with randomized clinical trials within a regulatory environment, typically operate within the constraints of careful prespecification of analyses. We worry lest ad hoc response to data that we see affect the integrity of our inference. When we are involved in interim monitoring of clinical trials, however, we must have the latitude to respond with intellectual agility to unexpected findings. Perhaps that very mixture of careful prespecification—to protect the scientific integrity of the study—and data-driven modifications—to protect the interest of the participants in the trial—explains why so many of us enjoy the challenge of interim monitoring of clinical trials. Of course we must, even in that context, carefully describe the analyses we plan to conduct and the nature of the inference to which various outcomes will lead us; on the other hand, if our analyses lead to a premature—in contrast to an early—stopping of the clinical trial, there is no putting the train back on the track. The past half century has seen an explosion of methods for statistical monitoring of ongoing clinical trials with the view toward stopping the trial if the interim data show unequivocal evidence of benefit, worrisome evidence of harm, or a strong indication that the completed trial will likely show equivocal results. The methods appear to come from a variety of different underlying statistical frameworks. In this book we stress that a common mathematical unifying formulation—Brownian motion—underlies most of the basic methods. We aim to show when and how the statistician can use that framework and when the statistician must modify it to produce valid inference. We hope that our presentation will help the reader understand the relationships among commonly used methods of group-sequential analysis, conditional power, and futility analysis. The level of the book is appropriate to graduate students in biostatistics and to statisticians involved in clinical trials. One of our goals is to provide biostatisticians with tools not only to perform the necessary calculations but to be able to explain the methodology to our clinical colleagues. When the process of statistical decision-making becomes too opaque, the clinicians with whom we work tune out and leave important parts of the discussion to the statisticians.

We believe the stark separation of clinical and biostatistical thinking cannot be healthy to intelligent, thoughtful decision-making, especially when it occurs in the middle of a trial. The book represents our distillation of years of collaboration with many colleagues, both from the clinical and biostatistical worlds. All three of us spent formative years at the National Heart, Lung, and Blood Institute where Claude Lenfant, Director, encouraged the growth of biostatistics. We learned much from the many lively discussions we had there with coworkers as we grappled collectively with issues related to ongoing monitoring of clinical trials. Especially useful was the opportunity we had to attend as many Data Safety Monitoring Board meetings as we desired; those experiences formed the basis for our view of data monitoring. We hope that the next generation of biostatisticians will find themselves in an organization that recognizes the value of training by apprenticeship. We particularly want to acknowledge the insights we gained from other members of the biostatistics group—Kent Bailey, Erica Brittain, Dave DeMets, Dean Follmann, Max Halperin, Marian Fisher, Nancy Geller, Ed Lakatos, Joel Verter, Margaret Wu, and David Zucker. Physician colleagues who, while they were at NHBLI and in later years, have been especially influential have been the two Bills (William Friedewald and William Harlan), as well as Larry Friedman, Curt Furberg (who pointed out to us the distinction between premature and early stopping of trials), Gene Passamani, and Salim Yusuf. One of us (it is not hard to guess which one) is especially indebted to insights gained from Robert Wittes, who for four decades has provided thoughtful balanced judgment to a variety of issues related to clinical trials (and many other topics). And then there have been so many others with whom we have had fruitful discussions about monitoring trials over the years. Of particular note are Jonas Ellenberg, Susan Ellenberg, Tom Fleming, Genell Knatterud, and Scott Emerson. Dave DeMets has kindly agreed to maintain a constant free version of his software so that readers of this book would have access to it. We thank Mary Foulkes, Tony Lachenbruch, Jon Turk, and Joe Shih for their helpful comments on earlier versions of the book. Their suggestions helped strengthen the presentations. It goes without saying that any errors or lapses of clarity remaining are our fault. Without further ado, we stop this preface early.

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3/2006

Statistical Monitoring of Clinical Trials
A Unified Approach

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2006, XIV, 268 p. 32 illus.,

ISBN: 978-0-387-44970-8