Fundamentals of Clinical Trials

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About the Authors

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Curt D. Furberg is Professor Emeritus of the Division of Public Health Sciences of the Wake Forest University School of Medicine. He received his M.D. and Ph.D. at the University of Umea, Sweden, and is a former chief, Clinical Trials Branch and Associate Director, Clinical Applications and Prevention Program, National Heart, Lung, and Blood Institute. Dr. Furberg established the Department of Public Health Sciences and served as its chair from 1986 to 1999. He has played major scientific and administrative roles in numerous multicenter clinical trials and has served in a consultative or advisory capacity on others. Dr. Furberg's research activities include the areas of clinical trials methodology and cardiovascular epidemiology. He is actively involved in the debate about the need for better documentation of meaningful clinical efficacy and long-term safety for drugs intended for chronic use.

David L. DeMets, Ph.D., is currently the Max Halperin Professor of Biostatistics and former Chair of the Department of Biostatistics and Medical Informatics at the University of Wisconsin—Madison He has co-authored numerous papers on statistical methods and four texts on clinical trials, two specifically on data monitoring. He has served on many NIH and industry-sponsored data monitoring committees for clinical trials in diverse disciplines. He served on the Board of Directors of the American Statistical Association, as well as having been President of the Society

for Clinical Trials and President of the Eastern North American Region (ENAR) of the Biometric Society. In addition he was Elected Fellow of the International Statistics Institute, the American Statistical Association, the Association for the Advancement of Science, the Society for Clinical Trials and the American Medical Informatics Association. In 2013, he was elected as a member of the Institute of Medicine.

David M. Reboussin is a Professor in the Department of Biostatistical Science at the Wake Forest University School of Medicine, where he has worked since 1992. He has a master's degree in Statistics from the University of Chicago and received his doctorate in Statistics from the University of Wisconsin at Madison. He is currently Principal Investigator for the Systolic Blood Pressure Intervention Trial Coordinating Center and has been a co-investigator in the coordinating centers for several NIH and industry funded clinical trials including Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action for Health in Diabetes (Look AHEAD), the Combined Oral and Nutritional Treatment of Late-Onset Diabetes Trial (CONTROL DM) and the Estrogen Replacement and Atherosclerosis (ERA) Trial. Dr. Reboussin has served on the data and safety monitoring boards for many National Institutes of Health trials within areas including cardiology, diabetes, nephrology, pulmonology, liver disease, psychiatry, pediatrics, weight loss and smoking cessation. His work in statistical methodology has included techniques and software for sequential monitoring of clinical trials.

Christopher B. Granger is Professor of Medicine at Duke University, where he is an active clinical cardiologist and a clinical trialist at the Duke Clinical Research Institute. He received his M.D. at University of Connecticut and his residency training at the University of Colorado. He has had Steering Committee, academic leadership, and operational responsibilities for many clinical trials in cardiology. He has been on numerous data monitoring committees. He serves on the National Heart, Lung, and Blood Institute Board of External Experts. He works with the Clinical Trials Transformation Initiative, a partnership between the U.S. Food and Drug Administration and Duke aiming to increase the quality and efficiency of clinical trials. He is a founding member of the Sensible Guidelines for the Conduct of Clinical Trials group, a collaboration between McMaster, Oxford, and Duke Universities.

Preface

The clinical trial is "the most definitive tool for evaluation of the applicability of clinical research." It represents "a key research activity with the potential to improve the quality of health care and control costs through careful comparison of alternative treatments" [1]. It has been called on many occasions, "the gold standard" against which all other clinical research is measured.

Although many clinical trials are of high quality, a careful reader of the medical literature will notice that a large number have deficiencies in design, conduct, analysis, presentation, and/or interpretation of results. Improvements have occurred over the past few decades, but too many trials are still conducted without adequate attention to the fundamental principles. Certainly, numerous studies could have been improved if the authors had had a better understanding of the fundamentals.

Since the publication of the first edition of this book in 1981, a large number of other texts on clinical trials have appeared, most of which are indicated here [2–21]. Several of them, however, discuss only specific issues involved in clinical trials. Additionally, many are no longer current. The purpose of this fifth edition is to update areas in which major progress has been made since the publication of the fourth edition. We have revised most chapters considerably. Because it was becoming unwieldy, we divided the chapter on monitoring response variables into two chapters, one on monitoring committees and the other on monitoring approaches. We also added a chapter on regulatory issues.

Importantly, two new authors are now involved. This brings fresh perspectives to a book originally published over three decades ago.

In this book, we hope to assist investigators in improving the quality of their clinical trials by discussing fundamental concepts with examples from our experience and the literature. The book is intended both for investigators with some clinical trial experience and for those who plan to conduct a trial for the first time. It is also intended to be used in the teaching of clinical trial methodology and to assist members of the scientific and medical community who wish to evaluate and interpret published reports of trials. Although not a technically oriented book, it may be used

as a reference for graduate courses in clinical trials. Those readers who wish to consult more technical books and articles are provided with the relevant literature.

Because of the considerable differences in background and objectives of the intended readership, we have not attempted to provide exercises at the end of each chapter. We have, however, found two exercises to be quite useful and that apply most of the fundamental principles of this text. First, ask students to critique a clinical trial article from the current literature. Second, have each student develop a protocol on a clinically relevant research question that is of interest to the student. These draft protocols can often be turned into protocols that are implemented. Although there is a chapter on regulatory issues, this book is not meant to replace going to the actual agencies for guidance on regulations and policies. Those differ among countries and frequently change. Rather, as the title indicates, we hope to provide the fundamentals of clinical trials ethics, design, conduct, analysis, and reporting.

The first chapter describes the rationale and phases of clinical trials. Chapter 2 covers selected ethical issues. Chapter 3 describes the questions that clinical trials seek to answer and Chap. 4 discusses the populations from which the study samples are derived. The strengths and weaknesses of various kinds of study designs, including noninferiority trials, are reviewed in Chap. 5. The process of randomization is covered in Chap. 6. In Chap. 7, we discuss the importance of and difficulties in maintaining blinding. How the sample size is estimated is covered in Chap. 8. Chapter 9 describes what constitutes the baseline measures. Chapter 10 reviews recruitment techniques and may be of special interest to investigators not having ready access to trial participants. Methods for collecting high-quality data and some common problems in data collection are included in Chap. 11. Chapters 12 and 13 focus on assessment of harm and health-related quality of life that are important clinical trial outcomes. Measures to enhance and monitor participant adherence are presented in Chap. 14. Chapter 15 reviews techniques of survival analysis. Chapter 16 presents the functions of data monitoring committees and Chap. 17 reviews methods of data monitoring. Which data should be analyzed? The authors develop this question in Chap. 18 by discussing reasons for not withdrawing participants from analysis. Topics such as subgroup analysis and meta-analysis are also addressed. Chapter 19 deals with phasing out clinical trials and Chap. 20 with reporting and interpretation of results. In Chap. 21, we present information about multicenter, including multinational, studies, which have features requiring special attention. Several points covered in Chap. 21 may also be of value to investigators conducting single center studies. Finally, selected regulatory issues, as they apply to clinical trials are reviewed in Chap. 22.

This book is a collaborative effort and is based on knowledge gained in over four decades of developing, conducting, overseeing, and analyzing data from a number of clinical trials. This experience is chiefly, but not exclusively, in trials of heart and lung diseases, AIDS, and cancer. As a consequence, many of the examples cited are based on work done in these fields. However, the principles are applicable to clinical trials in general. The reader will note that although the book contains examples that are relatively recent, others are quite old. The fundamentals of

clinical trials were developed in those older studies, and we cite them because, despite important advances, many of the basic features remain unchanged.

In the first edition, the authors had read or were familiar with much of the relevant literature on the design, conduct, and analysis of clinical trials. Today, that task would be nearly impossible as the literature over the past three and a half decades has expanded enormously. The references used in this text are not meant to be exhaustive but rather to include the literature that established the fundamentals and newer publications that support the basic concepts.

The views expressed in this book are those of the authors and do not necessarily represent the views of the institutions with which the authors have been or are affiliated.

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