Fundamentals of Clinical Trials

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Fourth Edition

Springer

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ISBN 978-1-4419-1585-6 e-ISBN 978-1-4419-1586-3
DOI 10.1007/978-1-4419-1586-3
Springer New York Dordrecht Heidelberg London

Library of Congress Control Number: xxxxxxxxxx

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

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 its fundamental principles. Certainly, numerous studies could have been upgraded if the authors had had a better understanding of the fundamentals.

Since the publication of the first edition of this book, 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 Additionally, many are no longer current.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 fourth edition is to update areas in which major progress has been made since the publication of the third edition. We have revised most chapters considerably and added one on ethical issues.

In this book, we hope to assist investigators in improving the quality of 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, require students to develop a protocol on a medically relevant research question that is of interest to

the student. These draft protocols often can be turned into protocols that are implemented. This book is also not meant to serve as guide to regulatory requirements. Those differ among countries and frequently change. Rather, as the title indicates, we hope to provide the fundamentals of clinical trials design, conduct, analysis, and reporting.

The first chapter describes the rationale and phases of clinical trials. Chapter 2 is an addition and it 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 blindness. 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 the important areas of assessment of adverse events and quality of life. Measures to enhance and monitor participant adherence are presented in Chap. 14. Chapter 15 reviews techniques of survival analysis. Chapter 16 covers data and safety monitoring. Which data should be analyzed? The authors develop this question in Chap. 17 by discussing reasons for not withdrawing participants from analysis. Topics such as subgroup analysis and meta-analysis are also addressed. Chapter 18 deals with phasing out clinical trials, and Chap. 19 with reporting and interpretation of results. Finally, in Chap. 20 we present information about multicenter, including multinational, studies, which have features requiring special attention. Several points covered in the final chapter may also be of value to investigators conducting single center studies.

This book is a collaborative effort and is based on knowledge gained over almost 4 decades in 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 3 decades has expanded enormously. The references used in this text are not meant to be exhaustive but rather to include the older literature that established the fundamentals and newer publications that support those fundamentals.

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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Acknowledgments

Most of the ideas and concepts discussed in this book represent what we first learned during our years at the National Heart, Lung, and Blood Institute. We are indebted to many colleagues, particularly Dr. William T. Friedewald and the late Dr. Max Halperin, with whom we had numerous hours of discussion for the earlier editions concerning theoretical and operational aspects of the design, conduct, and analysis of clinical trials.

Many have contributed to this edition of the book. We appreciate the efforts of Dr. Michelle Naughton and Dr. Sally Shumaker in revising the chapter on health-related quality of life. Also appreciated are the constructive comments of Drs. Rick Chappell, Mark Espeland, Bengt Furberg, Nancy King, Jeffrey Probstfield, and Dave Reboussin. Finally, we want to particularly acknowledge the outstanding secretarial support of Sarah Hutchens and Sue Parman. Nobody deserves more credit than our wives, Gene Friedman, Birgitta Furberg, and Kathy DeMets. Over the years their support of our professional activities, including the numerous hours put into the four editions of this book, has been unfailing.

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