Contents

Preface xi

PART I PRELIMINARIES

1 Introduction 3
   1.1 What are Clinical Trials?, 3
   1.2 History of Clinical Trials, 4
   1.3 Regulatory Process and Requirements, 10
   1.4 Investigational New Drug Application, 17
   1.5 New Drug Application, 24
   1.6 Clinical Development and Practice, 31
   1.7 AIMS and Structure of the Book, 42

2 Basic Statistical Concepts 45
   2.1 Introduction, 45
   2.2 Uncertainty and Probability, 46
   2.3 Bias and Variability, 49
   2.4 Confounding and Interaction, 57
   2.5 Descriptive and Inferential Statistics, 66
   2.6 Hypotheses Testing and $p$-Values, 68
   2.7 Clinical Significance and Clinical Equivalence, 75
   2.8 Reproducibility and Generalizability, 79

3 Basic Design Considerations 85
   3.1 Introduction, 85
   3.2 Goals of Clinical Trials, 86
   3.3 Target Population and Patient Selection, 90
   3.4 Selection of Controls, 97
   3.5 Statistical Considerations, 105
CONTENTS

3.6 Other Issues, 112
3.7 Discussion, 115

4 Randomization and Blinding 117
4.1 Introduction, 117
4.2 Randomization Models, 118
4.3 Randomization Methods, 124
4.4 Implementation of Randomization, 144
4.5 Generalization of Controlled Randomized Trials, 149
4.6 Blinding, 153
4.7 Discussion, 160

PART II DESIGNS AND THEIR CLASSIFICATIONS

5 Designs for Clinical Trials 165
5.1 Introduction, 165
5.2 Parallel Group Designs, 167
5.3 Clustered Randomized Designs, 172
5.4 Crossover Designs, 177
5.5 Titration Designs, 185
5.6 Enrichment Designs, 191
5.7 Group Sequential Designs, 195
5.8 Placebo-Challenging Designs, 197
5.9 Blinded Reader Designs, 203
5.10 Discussion, 207

6 Designs for Cancer Clinical Trials 211
6.1 Introduction, 211
6.2 General Considerations for Phase I Cancer Clinical Trials, 213
6.3 Single-Stage Up-and-Down Phase I Designs, 214
6.4 Two-Stage Up-and-Down Phase I Designs, 217
6.5 Continual Reassessment Method Phase I Designs, 219
6.6 Optimal and Flexible Multiple-Stage Designs, 222
6.7 Randomized Phase II Designs, 229
6.8 Discussion, 232

7 Classification of Clinical Trials 237
7.1 Introduction, 237
7.2 Multicenter Trials, 238
7.3 Superiority Trials, 245
7.4 Active Control and Equivalence/Noninferiority Trials, 248
CONTENTS

7.5 Dose–Response Trials, 261
7.6 Combination Trials, 266
7.7 Bridging Studies and Global Trials, 278
7.8 Vaccine Clinical Trials, 285
7.9 QT Studies, 291
7.10 Discussion, 299

PART III ANALYSIS OF CLINICAL DATA

8 Analysis of Continuous Data 305
8.1 Introduction, 305
8.2 Estimation, 306
8.3 Test Statistics, 310
8.4 Analysis of Variance, 316
8.5 Analysis of Covariance, 323
8.6 Nonparametric Methods, 325
8.7 Repeated Measures, 332
8.8 Discussion, 341

9 Analysis of Categorical Data 343
9.1 Introduction, 343
9.2 Statistical Inference for One Sample, 345
9.3 Inference of Independent Samples, 358
9.4 Ordered Categorical Data, 364
9.5 Combining Categorical Data, 368
9.6 Model-Based Methods, 374
9.7 Repeated Categorical Data, 382
9.8 Discussion, 387

10 Censored Data and Interim Analysis 389
10.1 Introduction, 389
10.2 Estimation of the Survival Function, 391
10.3 Comparison Between Survival Functions, 399
10.4 Cox’s Proportional Hazard Model, 405
10.5 Calendar Time and Information Time, 419
10.6 Group Sequential Methods, 424
10.7 Discussion, 438

11 Sample Size Determination 441
11.1 Introduction, 441
11.2 Basic Concept, 442
CONTENTS

11.3 Two Samples, 447
11.4 Multiple Samples, 456
11.5 Censored Data, 459
11.6 Dose–Response Studies, 464
11.7 Crossover Designs, 471
11.8 Equivalence and Noninferiority Trials, 481
11.9 Multiple-Stage Design in Cancer Trials, 490
11.10 Multinational Trials, 490
11.11 Comparing Variabilities, 500
11.12 Discussion, 517

PART IV ISSUES IN EVALUATION

12 Issues in Efficacy Evaluation 521

12.1 Introduction, 521
12.2 Baseline Comparison, 523
12.3 Intention-to-Treat Principle and Efficacy Analysis, 528
12.4 Adjustment for Covariates, 536
12.5 Multicenter Trials, 541
12.6 Multiplicity, 548
12.7 Data Monitoring, 558
12.8 Use of Genetic Information for Evaluation of Efficacy, 564
12.9 Sample Size Reestimation, 570
12.10 Discussion, 572

13 Safety Assessment 573

13.1 Introduction, 573
13.2 Extent of Exposure, 574
13.3 Coding of Adverse Events, 582
13.4 Analysis of Adverse Events, 595
13.5 Analysis of Laboratory Data, 602
13.6 Analysis of QT/QTc Prolongation, 610
13.7 Discussion, 615

PART V RECENT DEVELOPMENT

14 Biomarkers and Targeted Clinical Trials 619

14.1 Introduction, 619
14.2 Concepts and Strategies, 620
CONTENTS

14.3 Biomarker Development and Validation, 623
14.4 Designs of Targeted Clinical Trials, 630
14.5 Analyses of Targeted Clinical Trials, 640
14.6 Discussion, 647

15 Trials for Evaluating Accuracy of Diagnostic Devices 649
15.1 Introduction, 649
15.2 Study Design, 651
15.3 Measures of Diagnostic Accuracy, 656
15.4 Reporting Results, 663
15.5 Sample Size Estimation, 672
15.6 Discussion, 675

16 Statistical Methods in Translational Medicine 677
16.1 Introduction, 677
16.2 Biomarker Development, 678
16.3 Bench-to-Bedside, 682
16.4 Animal Model Versus Human Model, 689
16.5 Translation in Study Endpoints, 691
16.6 Bridging Studies, 696
16.7 Discussion, 699
16.8 Appendix, 700

17 Adaptive Clinical Trial Designs 703
17.1 Introduction, 703
17.2 What Is Adaptive Design?, 704
17.3 Well-Understood and Less Well-Understood Designs, 709
17.4 Clinical/Statistical and Regulatory Perspectives, 713
17.5 Impact of Protocol Amendments, 716
17.6 Challenges in By-Design Adaptations, 721
17.7 Obstacles of Retrospective Adaptations, 727
17.8 Discussion, 729

18 Traditional Chinese Medicine 733
18.1 Introduction, 733
18.2 Fundamental Differences, 734
18.3 Basic Considerations of TCM Clinical Trials, 741
18.4 Other Issues in TCM Research and Development, 744
18.5 Consortium for Globalization of Traditional Chinese Medicine, 751
18.6 Discussion, 752
PART VI CONDUCT OF CLINICAL TRIALS

19 Preparation and Implementation of a Clinical Protocol 755
   19.1 Introduction, 755
   19.2 Structure and Components of a Protocol, 756
   19.3 Points to be Considered and Common Pitfalls During Development and Preparation of a Protocol, 762
   19.4 Common Departures for Implementation of a Protocol, 765
   19.5 Monitoring, Audit, and Inspection, 771
   19.6 Quality Assessment of a Clinical Trial, 775
   19.7 Discussion, 777

20 Data Management of a Clinical Trial 779
   20.1 Introduction, 779
   20.2 Regulatory Requirements, 781
   20.3 Development of Case Report Forms, 783
   20.4 Database Development, 787
   20.5 Data Entry, Query, and Correction, 788
   20.6 Data Validation and Quality, 791
   20.7 Database Lock, Archive, and Transfer, 792
   20.8 Critical Issues, 795

References 799

Appendix A 845

Index 851