Contents

1	Introduction to Clinical Trials
	Fundamental Point
	What Is a Clinical Trial?
	Clinical Trial Phases
	Phase I Studies
	Phase II Studies
	Phase III/IV Trials
	Why Are Clinical Trials Needed?
	Problems in the Timing of a Trial
	Study Protocol
	Appendices
	References
2	Ethical Issues
	Fundamental Point
	Planning and Design
	Ethics Training
	Does the Question Require a Clinical Trial?
	Randomization
	Control Group
	Protection from Conflicts of Interest
	Informed Consent
	Conduct
	Trials in Low- and Middle-Income Countries
	Recruitment
	Safety and Efficacy Monitoring
	Early Termination for Other Than Scientific
	or Safety Reasons
	Privacy and Confidentiality
	Data Falsification

xiv Contents

	Reporting	42 42 43 43
3	What Is the Question? Fundamental Point. Selection of the Questions. Primary Question. Secondary Questions Regarding Benefit. Questions Regarding Harm Ancillary Questions. Kinds of Trials. Trials with Extensive Data Collection	49 50 50 50 51 52 53 54
	vs. Large, Simple Superiority vs. Noninferiority Trials Comparative Effectiveness Trials Intervention Response Variables Kinds of Response Variables Specifying the Question	54 55 55 56 57 57 60
	Biomarkers and Surrogate Response Variables	62 65 66 67
4	Study Population	73 73 74
	Population . Potential for Benefit . High Likelihood of Showing Benefit . Avoiding Adverse Effects . Competing Risk . Avoiding Poor Adherers . Pharmacogenetics . Generalization . Recruitment . References .	75 76 78 80 81 81 82 83 85 86
5	Basic Study Design	89 90 90 92

Contents

	Nonrandomized Concurrent Control Studies Historical Controls and Databases Strengths of Historical Control Studies Limitations of Historical Control Studies Role of Historical Controls Cross-Over Designs Withdrawal Studies Factorial Design Group Allocation Designs Hybrid Designs Large, Simple and Pragmatic Clinical Trials Studies of Equivalency and Noninferiority Adaptive Designs References	94 95 95 96 100 102 103 104 107 107 109 114 115
6	The Randomization Process	123
U	Fundamental Point	123
	Fixed Allocation Randomization	123
	Simple Randomization	125
	Blocked Randomization	126
	Stratified Randomization	128
	Adaptive Randomization Procedures	131
	Baseline Adaptive Randomization	
	Procedures	132
	Minimization	133
	Response Adaptive Randomization	135
	Mechanics of Randomization	137
	Recommendations	139
	Appendix: Adaptive Randomization Algorithm	139
	References	141
7	Blinding	147
•	Fundamental Point	148
	Who Is Blinded?	148
	Types of Blinding	148
	Unblinded	148
	Single-Blind	150
	Double-Blind	151
	Triple-Blind	153
	Protecting the Double-Blind Design	154
	Matching of Drugs	155
	Coding of Drugs	157
	Official Unblinding	158
	Inadvertent Unblinding	159
	Assessment and Reporting of Blinding	160
	Debriefing of Participants	161
	References	162

xvi Contents

8	Sample Size	165
	Fundamental Point	166
	Statistical Concepts	167
	Dichotomous Response Variables	171
	Two Independent Samples	171
	Paired Dichotomous Response	177
	Adjusting Sample Size to Compensate for Nonadherence	178
	Sample Size Calculations for Continuous Response Variables	179
	Two Independent Samples	180
	Paired Data	181
	Sample Size for Repeated Measures	183
	Sample Size for Repeated Measures	184
	Sample Size Calculations for "Time to Failure"	104
	Sample Size for Testing "Equivalency" or Noninferiority	100
	of Interventions	188
	Sample Size for Cluster Randomization	189
	Multiple Response Variables	192
	Estimating Sample Size Parameters	193
	References	195
		201
9	Baseline Assessment	201
	Fundamental Point	201
	Uses of Baseline Data	201
	Description of Trial Participants	201
	Baseline Comparability	202
	Controlling for Imbalances in the Analysis	204
	Subgrouping	205
	What Constitutes a True Baseline Measurement?	207
	Screening for Participants	207
	Regression Toward the Mean	208
	Interim Events	210
	Uncertainty About Qualifying Diagnosis	210
	Contamination of the Intervention	211
	Changes of Baseline Measurement	212
	References	212
	References	213
10	Recruitment of Study Participants	215
	Fundamental Point	215
	Considerations Before Participant Enrollment	216
	Selection of Study Sample	216
	Common Recruitment Problems	217
	Planning	219
	Recruitment Sources	
		221
	Conduct	223
	Monitoring	225
	Approaches to Lagging Recruitment	229
	References	230

Contents xvii

11	Data Collection and Quality Control	233
	Fundamental Point	234
	Problems in Data Collection	235
	Major Types	235
	Minimizing Poor Quality Data	238
	Design of Protocol and Manual	238
	Development of Forms and Data Entry Tools	239
	Training and Certification	239
	Pretesting	241
	Techniques to Reduce Variability Including Central	
	Adjudication of Events	241
	Data Entry	243
	Electronic Source Data	243
	Quality Monitoring	244
	Monitoring of Data	246
	Monitoring of Procedures	246
	Monitoring of Drug Handling	247
	Audits	248
	References	250
12	Assessment and Reporting of Harm	255
	Fundamental Point	256
	Assessment of Harm	256
	Strengths	256
	Limitations	257
	Identification of Harm in Clinical Trials	259
	Classification of Adverse Events	260
	Ascertainment	262
	Prespecified Adverse Events	263
	Characteristics of Adverse Events	264
	Length of Follow-up	264
	Analyzing Adverse Events	266
	Standard Reporting	266
	Prespecified Analysis	267
	Post Hoc Analysis	267
	Meta-analysis	268
	Reporting of Harm	269
	Scientific Journal Publication	271
	Regulatory Considerations	272
	Recommendations for Assessing and Reporting Harm	273
	References	274
13	Assessment of Health Related Quality of Life	279
	Fundamental Point	279
	Types of HRQL Measures	280

xviii Contents

	Primary Measures	280
	Additional Measures	281
	Uses of HRQL Measures	282
	Methodological Issues	284
	Design Issues	284
	Study Population	285
	Type of Intervention	285
	Frequency of Assessment (Acute Versus Chronic)	286
	Protocol Considerations	287
	Modifying and Mediating Factors	288
	Selection of HRQL Instruments	288
	Types of Measures	289
	Scoring of HRQL Measures	290
	Determining the Significance of HRQL Measures	290
	Utility Measures/Preference Scaling and Comparative	
	Effectiveness Research	291
	References	292
14	Participant Adherence	297
	Fundamental Point	298
	Definitions	298
	Medication Adherence	299
	Considerations Before Participant Enrollment	300
	Design Factors	300
	Participant Factors	302
	Maintaining Good Participant Adherence	306
	Adherence Monitoring	311
	Dealing with Low Adherence	314
	Special Populations	315
	References	315
15	Survival Analysis	319
13	Fundamental Point	319
	Estimation of the Survival Curve	320
	Cutler-Ederer Estimate	320
		324
	Kaplan-Meier Estimate	
	Comparison of Two Survival Curves	
	Point-by-Point Comparison	329
	Comparison of Median	220
	Survival Times	329
	Total Curve Comparison	330
	Generalizations	335
	Covariate Adjusted Analysis	337
	References	340

Contents

16	Monitoring Committee Structure and Function Fundamental Point . Monitoring Committee . Repeated Testing for Significance . Decision for Early Termination . Decision to Extend a Trial . Accelerated Approval Paradigm . References .	343 346 346 350 352 363 367 368
17	Statistical Methods Used in Interim Monitoring	373 373 374 375
	Alpha Spending Functions Applications of Group Sequential Boundaries Asymmetric Boundaries Curtailed Sampling and Conditional Power Procedures Other Approaches Trend Adaptive Designs and Sample Size Adjustments References	378 381 384 386 391 392 395
18	Issues in Data Analysis Fundamental Point Which Participants Should Be Analyzed? Ineligibility Nonadherence Missing or Poor Quality Data Competing Events Composite Outcomes Covariate Adjustment Surrogates as a Covariate Baseline Variables as Covariates Subgroup Analyses Not Counting Some Events Comparison of Multiple Variables Use of Cutpoints Noninferiority Trial Analysis Analysis Following Trend Adaptive Designs Meta-analysis of Multiple Studies Rationale and Issues Statistical Methods Analysis for Harmful Effects References	403 404 404 406 410 414 421 422 424 425 428 431 438 439 440 442 444 445 445 445 445 445

xx Contents

19	Closeout	463
	Fundamental Point	463
	Termination Procedures	463
	Planning	463
	Scheduling of Closeout Visits	464
	Final Response Ascertainment	465
	Transfer of Post-trial Care	468
	Data and Other Study Material	469
	Cleanup and Verification	469
	Storage	470
	Dissemination of Results	471
	Post Study Follow-up	473
	References	475
20	Reporting and Interpreting of Results	479
	Fundamental Point	480
	Guidelines for Reporting	480
	Authorship	482
	Duplicate Publication	483
	Disclosure of Conflict of Interest	483
	Presentation of Data	483
	Interpretation	484
	Publication Bias	485
	Did the Trial Work as Planned?	487
	Baseline Comparability	487
	Blinding	487
	Adherence and Concomitant Treatment	488
	What Are the Limitations?	488
	What Kinds of Analyses?	489
	How Do the Findings Compare with Those	
	from Other Studies?	491
	What Are the Clinical Implications of the Findings?	492
	Data Sharing	493
	References	494
21	Multicenter Trials	501
~-	Fundamental Point	502
	Reasons for Multicenter Trials	502
	Conduct of Multicenter Trials.	504
	Globalization of Trials	511
	Large. Simple Trials.	514
	References	515
22	Regulatory Issues	519
	Fundamental Point	520
	Background	521

Contents xxi

Overview	521
History	521
Regulatory Requirements	523
Trial Phases	523
Pretrial Requirements	525
Conduct	526
Interventions: Drugs	528
Interventions: Devices	529
Interventions: Biologics	532
Post-trial Requirements	533
Documents for FDA submission	534
Advisory Committee Meeting	535
Post-approval Issues and Postmarketing	
Investigations	535
Key Links	537
International Conference on Harmonisation	537
U.S. Food and Drug Administration	537
European Medicines Agency	538
Health Canada	538
Pharmaceuticals and Medical Devices Agency, Japan	538
Bioethics Resources	538
References	538
Index	543