

Contents

Part I Group Sequential Designs

1	Repeated Significance Tests	3
1.1	Introduction	3
1.2	Basics	7
1.3	Power and Average Sample Size	15
1.4	The Recursive Integration Formula	20
2	Procedures with Equally Sized Stages	25
2.1	Classical Designs	26
2.1.1	Definition	26
2.1.2	Power and Average Sample Size	30
2.1.3	Wang and Tsiasis Power Family	36
2.1.4	Other Designs	42
2.2	Symmetric Designs	43
2.3	One-Sided Designs	50
2.4	A Note on Two-Sided Designs	62
3	Procedures with Unequally Sized Stages	63
3.1	Effect of Using Boundaries for Equally Sized Stages	64
3.2	Sample Sizes Fixed in Advance	69
3.3	The α -Spending Function Approach	74
4	Confidence Intervals, p-Values, and Point Estimation	83
4.1	Confidence Intervals and p -Values	84
4.1.1	Sample Space Orderings	84
4.1.2	Monitoring a Trial	91
4.2	Point Estimation	95

5 Applications	101
5.1 Normal Response	102
5.2 Binary Response	110
5.2.1 Testing a Single Rate	110
5.2.2 Parallel Group Design	116
5.3 Survival Data	122
Part II Confirmatory Adaptive Designs with a Single Hypothesis	
6 Adaptive Group Sequential Tests	133
6.1 Basic Principle and Assumptions	134
6.2 Combination Tests	135
6.2.1 General Methodology	135
6.2.2 Fisher's Product Test	137
6.2.3 Weighted Fisher's Product Test	141
6.2.4 Inverse Normal Combination Test	143
6.2.5 Sample Size Adaptations in Group Sequential Designs	146
6.3 Conditional Error Function Approach	151
6.3.1 Proschan and Hunsberger's Method	151
6.3.2 Relationship Between Conditional Error Functions and Combination Tests	153
6.3.3 The CRP Principle	155
6.3.4 Type I Error Maximization Method	159
6.4 Two-Sided Adaptive Tests	164
6.5 The Multi-Stage Case	167
7 Decision Tools for Adaptive Designs	171
7.1 Conditional Power	171
7.1.1 The Conditional Power of Combination Tests	172
7.1.2 Conditional Power with Fisher's Product Test and Inverse Normal Method	173
7.2 Futility Stopping Based on Conditional Power	175
7.3 Sample Size Modification Based on Conditional Power	176
7.4 On the Parameter Value Used in the Conditional Power and Sample Size Calculation	178
7.4.1 Using a Minimal Clinically Relevant Effect Size	178
7.4.2 Using the Interim Estimate	179
7.4.3 Using the Bayesian Posterior Mean	180
7.4.4 Bayesian Predictive Power	181
7.4.5 Discussion	185
7.5 A Case Study	187
8 Estimation and p-Values for Two-Stage Adaptive Designs	189
8.1 Overall p -Values for Adaptive Two-Stage Designs	189
8.1.1 Stage-Wise Ordering and Related p -Values	190

8.1.2 Repeated p -Values for Two-Stage Combination Tests	193
8.1.3 Numerical Examples	198
8.2 Adaptive Confidence Intervals	200
8.2.1 Exact Confidence Bounds for Combination Tests	201
8.2.2 Repeated Confidence Bounds for Combination Tests	204
8.2.3 Two-Sided Confidence Intervals	205
8.2.4 Numerical Examples	206
8.3 Point Estimation in Adaptive Designs	209
8.3.1 Maximum Likelihood Estimate	209
8.3.2 Fixed Weighted ML-Estimate	211
8.3.3 Median Unbiased Point Estimation	212
8.3.4 Adaptively Weighted ML-Estimate	213
8.3.5 Comparison of Point Estimates	214
8.4 Extensions	218
9 Adaptive Designs with Survival Data	221
9.1 Combination of p -Values from Log-Rank Tests	221
9.1.1 Use of Independent Increments	222
9.1.2 Applying Left Truncation at the Second Stage	223
9.2 Restriction of the Information Used for the Adaptations	224
9.3 Sample Size Reassessment Rules	226
9.4 Estimation of the Hazard Ratio	227
Part III Adaptive Designs with Multiple Hypotheses	
10 Multiple Testing in Adaptive Designs	231
10.1 Sources of Multiplicity	232
10.2 The Closure Principle	233
10.3 Closed Testing in Adaptive Designs	235
11 Applications and Case Studies	241
11.1 Adaptive Treatment Selection in Multi-Arm Clinical Trials	241
11.1.1 Test Procedure	242
11.1.2 Intersection Tests	245
11.1.3 Overall p -Values and Confidence Intervals	247
11.1.4 Numerical Example	249
11.1.5 Adaptive Dunnett Test	252
11.1.6 Other Endpoints	258
11.1.7 Case Studies	259
11.2 Adaptive Enrichment Designs	261
11.2.1 Test Procedure	262
11.2.2 Intersection Tests	264
11.2.3 Effect Specification	266
11.2.4 Overall p -Values and Confidence Intervals	266

11.2.5	Other Endpoints	267
11.2.6	A Clinical Trial Example	268
11.3	Other Types of Adaptations	271
11.3.1	A Case Study with Adaptive Multiple Endpoint Selection	272
11.4	Regulatory and Logistical Issues	274
Appendix: Software for Adaptive Designs		277
References		281
Index		297
1.1	Introduction	1
1.1.1	Background	1
1.1.2	Objectives	1
1.1.3	Structure	1
1.2	Adaptive Designs	2
1.2.1	Definition	2
1.2.2	Classification	2
1.2.3	Advantages	2
1.2.4	Challenges	2
1.2.5	Regulatory Considerations	2
1.2.6	Logistical Considerations	2
1.2.7	Statistical Considerations	2
1.2.8	Future Directions	2
1.3	Designs for Multiple Endpoints	3
1.3.1	Overview	3
1.3.2	Correlation	3
1.3.3	Adjustment	3
1.3.4	Simulation	3
1.3.5	Case Studies	3
1.3.6	Conclusion	3
1.4	Designs for Adaptive Trials	4
1.4.1	Overview	4
1.4.2	Designs for Adaptive Trials	4
1.4.3	Designs for Adaptive Trials	4
1.4.4	Designs for Adaptive Trials	4
1.4.5	Designs for Adaptive Trials	4
1.4.6	Designs for Adaptive Trials	4
1.4.7	Designs for Adaptive Trials	4
1.4.8	Designs for Adaptive Trials	4
1.4.9	Designs for Adaptive Trials	4
1.4.10	Designs for Adaptive Trials	4
1.4.11	Designs for Adaptive Trials	4
1.4.12	Designs for Adaptive Trials	4
1.4.13	Designs for Adaptive Trials	4
1.4.14	Designs for Adaptive Trials	4
1.4.15	Designs for Adaptive Trials	4
1.4.16	Designs for Adaptive Trials	4
1.4.17	Designs for Adaptive Trials	4
1.4.18	Designs for Adaptive Trials	4
1.4.19	Designs for Adaptive Trials	4
1.4.20	Designs for Adaptive Trials	4
1.4.21	Designs for Adaptive Trials	4
1.4.22	Designs for Adaptive Trials	4
1.4.23	Designs for Adaptive Trials	4
1.4.24	Designs for Adaptive Trials	4
1.4.25	Designs for Adaptive Trials	4
1.4.26	Designs for Adaptive Trials	4
1.4.27	Designs for Adaptive Trials	4
1.4.28	Designs for Adaptive Trials	4
1.4.29	Designs for Adaptive Trials	4
1.4.30	Designs for Adaptive Trials	4
1.4.31	Designs for Adaptive Trials	4
1.4.32	Designs for Adaptive Trials	4
1.4.33	Designs for Adaptive Trials	4
1.4.34	Designs for Adaptive Trials	4
1.4.35	Designs for Adaptive Trials	4
1.4.36	Designs for Adaptive Trials	4
1.4.37	Designs for Adaptive Trials	4
1.4.38	Designs for Adaptive Trials	4
1.4.39	Designs for Adaptive Trials	4
1.4.40	Designs for Adaptive Trials	4
1.4.41	Designs for Adaptive Trials	4
1.4.42	Designs for Adaptive Trials	4
1.4.43	Designs for Adaptive Trials	4
1.4.44	Designs for Adaptive Trials	4
1.4.45	Designs for Adaptive Trials	4
1.4.46	Designs for Adaptive Trials	4
1.4.47	Designs for Adaptive Trials	4
1.4.48	Designs for Adaptive Trials	4
1.4.49	Designs for Adaptive Trials	4
1.4.50	Designs for Adaptive Trials	4
1.4.51	Designs for Adaptive Trials	4
1.4.52	Designs for Adaptive Trials	4
1.4.53	Designs for Adaptive Trials	4
1.4.54	Designs for Adaptive Trials	4
1.4.55	Designs for Adaptive Trials	4
1.4.56	Designs for Adaptive Trials	4
1.4.57	Designs for Adaptive Trials	4
1.4.58	Designs for Adaptive Trials	4
1.4.59	Designs for Adaptive Trials	4
1.4.60	Designs for Adaptive Trials	4
1.4.61	Designs for Adaptive Trials	4
1.4.62	Designs for Adaptive Trials	4
1.4.63	Designs for Adaptive Trials	4
1.4.64	Designs for Adaptive Trials	4
1.4.65	Designs for Adaptive Trials	4
1.4.66	Designs for Adaptive Trials	4
1.4.67	Designs for Adaptive Trials	4
1.4.68	Designs for Adaptive Trials	4
1.4.69	Designs for Adaptive Trials	4
1.4.70	Designs for Adaptive Trials	4
1.4.71	Designs for Adaptive Trials	4
1.4.72	Designs for Adaptive Trials	4
1.4.73	Designs for Adaptive Trials	4
1.4.74	Designs for Adaptive Trials	4
1.4.75	Designs for Adaptive Trials	4
1.4.76	Designs for Adaptive Trials	4
1.4.77	Designs for Adaptive Trials	4
1.4.78	Designs for Adaptive Trials	4
1.4.79	Designs for Adaptive Trials	4
1.4.80	Designs for Adaptive Trials	4
1.4.81	Designs for Adaptive Trials	4
1.4.82	Designs for Adaptive Trials	4
1.4.83	Designs for Adaptive Trials	4
1.4.84	Designs for Adaptive Trials	4
1.4.85	Designs for Adaptive Trials	4
1.4.86	Designs for Adaptive Trials	4
1.4.87	Designs for Adaptive Trials	4
1.4.88	Designs for Adaptive Trials	4
1.4.89	Designs for Adaptive Trials	4
1.4.90	Designs for Adaptive Trials	4
1.4.91	Designs for Adaptive Trials	4
1.4.92	Designs for Adaptive Trials	4
1.4.93	Designs for Adaptive Trials	4
1.4.94	Designs for Adaptive Trials	4
1.4.95	Designs for Adaptive Trials	4
1.4.96	Designs for Adaptive Trials	4
1.4.97	Designs for Adaptive Trials	4
1.4.98	Designs for Adaptive Trials	4
1.4.99	Designs for Adaptive Trials	4
1.4.100	Designs for Adaptive Trials	4