
Contents

1	Introduction	1
2	A General Framework	9
2.1	Hypothesis Testing: The Null Distribution of Test Statistics Over Time	10
2.1.1	Continuous Outcomes	10
2.1.2	Dichotomous Outcomes	14
2.1.3	Survival Outcomes	15
2.1.4	Summary of Sums	17
2.2	An Estimation Perspective	18
2.2.1	Information	18
2.2.2	Summary of Treatment Effect Estimators	21
2.3	Connection Between Estimators, Sums, Z-Scores, and Brownian Motion	21
2.4	Maximum Likelihood Estimation	24
2.5	Other Settings Leading to E-Processes and Brownian Motion	28
2.5.1	Minimum Variance Unbiased Estimators	28
2.5.2	Complete Sufficient Statistics	29
2.6	The Normal Linear and Mixed Models	30
2.6.1	The Linear Model	30
2.6.2	The Mixed Model	31
2.7	When Is Brownian Motion Not Appropriate?	36
2.8	Summary	38
2.9	Appendix	39
2.9.1	Asymptotic Validity of Using Estimated Standard Errors	39
2.9.2	Proof of Result 2.1	40
2.9.3	Proof that for the Logrank Test, $D_i = O_i - E_i$ Are Uncorrelated Under H_0	41
2.9.4	A Rigorous Justification of Brownian Motion with Drift: Local Alternatives	41

2.9.5	Basu's Theorem	42
3	Power: Conditional, Unconditional, and Predictive	43
3.1	Unconditional Power	43
3.2	Conditional Power for Futility	45
3.3	Varied Uses of Conditional Power	53
3.4	Properties of Conditional Power	57
3.5	A Bayesian Alternative: Predictive Power	60
3.6	Summary	63
3.7	Appendix	64
3.7.1	Proof of Result 3.1	64
3.7.2	Formula for $\text{corr}\{B(t), \theta\}$ and $\text{var}\{\theta \mid B(t) = b\}$	65
3.7.3	Simplification of Formula (3.8)	66
4	Historical Monitoring Boundaries	67
4.1	How Bad Can the Naive Approach Be?	67
4.2	The Pocock Procedure	69
4.3	The Haybittle Procedure and Variants	69
4.4	The O'Brien-Fleming Procedure	71
4.5	A Comparison of the Pocock and O'Brien-Fleming Boundaries	72
4.6	Effect of Monitoring on Power	75
4.7	Appendix: Computation of Boundaries Using Numerical Integration	77
5	Spending Functions	81
5.1	Upper Boundaries	81
5.1.1	Using a Different Time Scale for Spending	87
5.1.2	Data-Driven Looks	89
5.2	Upper and Lower Boundaries	90
5.3	Summary	92
5.4	Appendix	92
5.4.1	Proof of Result 5.1	92
5.4.2	Proof of Result 5.2	93
5.4.3	An S-Plus or R Program to Compute Boundaries	93
6	Practical Survival Monitoring	99
6.1	Introduction	99
6.2	Survival Trials with Staggered Entry	99
6.3	Stochastic Process Formulation and Linear Trends	101
6.4	A Real Example	102
6.5	Nonlinear Trends of the Statistics: Analogy with Monitoring a t-Test	103
6.6	Considerations for Early Termination	104
6.7	The Information Fraction with Survival Data	105

7	Inference Following a Group-Sequential Trial	113
7.1	Likelihood, Sufficiency, and (Lack of) Completeness	113
7.2	One-Tailed p -Values	116
7.2.1	Definitions of a p -Value	116
7.2.2	Stagewise Ordering	122
7.2.3	Two-Tailed p -Values	124
7.3	Properties of p -Values	125
7.4	Confidence Intervals	126
7.5	Estimation	131
7.6	Summary	135
7.7	Appendix: Proof that $B(\tau)/\tau$ Overestimates θ in the One-Tailed Setting	135
8	Options When Brownian Motion Does Not Hold	137
8.1	Small Sample Sizes	137
8.2	Permutation Tests	143
8.2.1	Continuous Outcomes	143
8.2.2	Binary Outcomes	145
8.3	The Bonferroni Method	149
8.4	Summary	150
8.5	Appendix	151
8.5.1	Simulating the Distribution of t-Statistics Over Information Time	151
8.5.2	The Noncentral Hypergeometric Distribution	152
9	Monitoring for Safety	155
9.1	Example: Inference from a Sample Size of One	155
9.2	Example: Inference from Multiple Endpoints	156
9.3	General Considerations	157
9.4	What Safety Data Look Like	160
9.5	Looking for a Single Adverse Event	163
9.5.1	Monitoring for the Flip-Side of the Efficacy Endpoint	164
9.5.2	Monitoring for Unexpected Serious Adverse Events that Would Stop a Study	167
9.5.3	Monitoring for Adverse Events that the DSMB Should Report	169
9.6	Looking for Multiple Adverse Events	172
9.7	Summary	173
10	Bayesian Monitoring	175
10.1	Introduction	175
10.2	The Bayesian Paradigm Applied to B-Values	176
10.3	The Need for a Skeptical Prior	177
10.4	A Comparison of Bayesian and Frequentist Boundaries	180
10.5	Example	182

10.6 Summary	184
11 Adaptive Sample Size Methods	185
11.1 Introduction	185
11.2 Methods Using Nuisance Parameter Estimates: The Continuous Outcome Case	186
11.2.1 Stein's Method	187
11.2.2 The Naive t-Test	191
11.2.3 A Restricted t-Test	192
11.2.4 Variance Shmariance?	193
11.2.5 Incorporating Monitoring	195
11.2.6 Blinded Sample Size Reassessment	197
11.3 Methods Using Nuisance Parameter Estimates: The Binary Outcome Case	199
11.3.1 Blinded Sample Size Reassessment	201
11.4 Adaptive Methods Based on the Treatment Effect	203
11.4.1 Methods	203
11.4.2 Pros and Cons	209
11.5 Summary	210
12 Topics Not Covered	213
12.1 Introduction	213
12.2 Continuous Sequential Boundaries	214
12.3 Other Types of Group-Sequential Boundaries	215
12.4 Reverse Stochastic Curtailing	216
12.5 Monitoring Studies with More Than Two Arms	217
12.6 Monitoring for Equivalence and Noninferiority	218
12.7 Repeated Confidence Intervals	218
13 Appendix I: The Logrank and Related Tests	221
13.1 Hazard Functions	222
13.2 Linear Rank Statistics	225
13.2.1 Complete Survival Times: Which Group Is Better? ...	226
13.2.2 Ratings, Score Functions, and Payments	227
13.3 Payment Functions and Score Functions	231
13.4 Censored Survival Data	233
13.5 The U-Statistic Approach to the Wilcoxon Statistic	234
13.6 The Logrank and Weighted Mantel-Haenszel Statistics	235
13.7 Monitoring Survival Trials	237
14 Appendix II: Group-Sequential Software	239
14.1 Introduction	239
14.2 Before the Trial Begins: Power and Sample Size	239
14.3 During the Trial: Computation of Boundaries	241
14.3.1 A Note on Upper and Lower Boundaries	242

14.4 After the Trial: p -Value, Parameter Estimate, and Confidence Interval	242
14.5 Other Features of the Program	244
References	247
Index	255

Statistical Monitoring of Clinical Trials
A Unified Approach

Proschan, M.A.; Lan, K.K.G.; Wittes, J.T.

2006, XIV, 268 p. 32 illus.,

ISBN: 978-0-387-44970-8