Contents

Preface xi

1 Randomization and the Clinical Trial 1
   1.1 Introduction 1
   1.2 Causation and Association 2
   1.3 Randomized Clinical Trials 6
   1.4 Ethics of Randomization 9
   1.5 Problems 12
   1.6 References 13

2 Issues in the Design of Clinical Trials 15
   2.1 Introduction 15
   2.2 Study Outcomes 15
   2.3 Sources of Bias 18
      2.3.1 Selection and ascertainment bias 19
      2.3.2 Statistical analysis philosophy 20
      2.3.3 Losses to follow-up and noncompliance 21
      2.3.4 Covariates 21
   2.4 Experimental Design 23
   2.5 Recruitment and Follow-Up 25
   2.6 Determining the Number of Randomized Subjects 26
      2.6.1 Development of the main formula 27
      2.6.2 Example 29
      2.6.3 Survival trials 29
CONTENTS

2.6.4 Adjustment for noncompliance 32
2.6.5 Additional considerations 32
2.7 Problems 33
2.8 References 34

3 Randomization for Balancing Treatment Assignments 37
  3.1 Introduction 37
  3.2 Complete Randomization 38
  3.3 Forced Balance Procedures 40
    3.3.1 Random allocation rule 40
    3.3.2 Truncated binomial design 42
    3.3.3 Hadamard randomization 44
    3.3.4 Maximal procedure 46
  3.4 Forced Balance Randomization Within Blocks 46
    3.4.1 Permuted block design 46
    3.4.2 Random block design 47
  3.5 Efron’s Biased Coin Design 48
  3.6 Other Biased Coin Designs and Generalizations 51
  3.7 Wei’s Urn Design 52
  3.8 Other urn Models and Generalizations 54
  3.9 Comparison of Balancing Properties 55
  3.10 Restricted Randomization for Unbalanced Allocation 58
  3.11 $K > 2$ Treatments 61
  3.12 Problems 62
  3.13 References 64
  3.14 Appendix 66

4 The Effects of Unobserved Covariates 67
  4.1 Introduction 67
  4.2 A Bound on the Probability of a Covariate Imbalance 68
  4.3 Simulation Results 70
  4.4 Accidental Bias 71
  4.5 Maximum Eigenvalue of $\Sigma_T$ 73
  4.6 Accidental Bias for Biased Coin Designs 74
  4.7 Chronological Bias 75
  4.8 Problems 76
  4.9 References 76
  4.10 Appendix 77

5 Selection Bias 79
  5.1 Introduction 79
  5.2 The Blackwell–Hodges Model 81
  5.3 Predictability of a Randomization Sequence 83
5.4 Selection Bias for the Random Allocation Rule and Truncated Binomial Design 84
5.5 Selection Bias in a Permuted Block Design 87
  5.5.1 Permuted blocks using the random allocation rule 87
  5.5.2 Permuted blocks with truncated binomial randomization 87
  5.5.3 Random block design 87
  5.5.4 Conclusions 89
5.6 Selection Bias for Other Restricted Randomization Procedures 90
  5.6.1 Efron’s biased coin design 90
  5.6.2 Wei’s urn design 90
  5.6.3 Smith’s design 91
5.7 Simulation Results 91
5.8 Controlling and Testing for Selection Bias in Practice 93
5.9 Problems 94
5.10 References 94
5.11 Appendix 95

6 Randomization as a Basis for Inference 97
  6.1 Introduction 97
  6.2 The Population Model 97
  6.3 The Randomization Model 100
  6.4 Randomization Tests 103
  6.5 Linear Rank Tests 105
  6.6 Variance of the Linear Rank Test 108
  6.7 Optimal Rank Scores 110
  6.8 Exact and Large-Sample Randomization Tests 111
    6.8.1 Computation of exact tests 112
    6.8.2 Large sample randomization tests 113
  6.9 Monte Carlo Re-Randomization Tests 115
    6.9.1 Unconditional tests 115
    6.9.2 Example 116
    6.9.3 Conditional tests 117
  6.10 Preservation of Error Rates 118
  6.11 Regression Modeling 120
  6.12 Analyses with Missing Data 121
  6.13 Sample Size Considerations for Random Sample Fractions 122
  6.14 Group Sequential Monitoring 123
    6.14.1 Establishing a stopping boundary 124
    6.14.2 Information fraction 125
  6.15 Problems 126
  6.16 References 127
  6.17 Appendix A 129
  6.18 Appendix B 131
7 Stratification 133
7.1 Introduction 133
7.2 Stratified Randomization 134
7.3 Is Stratification Necessary? 135
7.4 Treatment Imbalances in Stratified Trials 136
7.5 Stratified Analysis Using Randomization Tests 138
7.6 Efficiency of Stratified Randomization in a Stratified Analysis 140
7.7 Conclusions 144
7.8 Problems 144
7.9 References 145

8 Restricted Randomization in Practice 147
8.1 Introduction 147
8.2 Stratification 148
8.3 Characteristics of Randomization Procedures 149
8.3.1 Consideration of selection bias 149
8.3.2 Implications for analysis 151
8.4 Selecting a Randomization Procedure 151
8.4.1 Choosing parameter values 152
8.4.2 Comparing procedures 153
8.4.3 Conclusions 156
8.5 Generation of Sequences 156
8.6 Implementation 157
8.6.1 Packaging and labeling 158
8.6.2 The actual randomization 159
8.7 Special Situations 160
8.8 Some Examples 163
8.8.1 The optic neuritis treatment trial 163
8.8.2 Vesnarinone in congestive heart failure 163
8.8.3 The diabetes control and complications trial 163
8.8.4 Captopril in diabetic nephropathy 164
8.8.5 The diabetes prevention program 164
8.8.6 Scleral buckling versus primary vitrectomy in retinal detachment (The SPR Study) 164
8.9 Problems 165
8.10 References 166

9 Covariate-Adaptive Randomization 169
9.1 Early Work 169
9.1.1 Zelen’s rule 170
9.1.2 The Pocock–Simon procedure 170
9.1.3 Example: Adjuvant chemotherapy for locally invasive bladder cancer 171
9.1.4 Wei’s marginal urn design 171
9.1.5 Is marginal balance sufficient? 171
9.1.6 Is randomization necessary? 172
9.2 More Recent Covariate-Adaptive Randomization Procedures 173
  9.2.1 Balancing within strata 173
  9.2.2 Balancing with respect to continuous covariates 174
9.3 Optimal Design Based on a Linear Model 175
9.4 The Trade-Off Among Balance, Efficiency, and Ethics 177
9.5 Inference for Covariate-Adaptive Randomization 179
  9.5.1 Model-based inference 179
  9.5.2 Randomization-based inference 180
9.6 Conclusions 181
9.7 Problems 182
9.8 References 185

10 Response-Adaptive Randomization 189
10.1 Introduction 189
10.2 Historical Notes 190
  10.2.1 Roots in bandit problems 190
  10.2.2 Roots in sequential stopping problems 191
  10.2.3 Roots in randomization 192
10.3 Optimal Allocation 193
10.4 Response-Adaptive Randomization to Target $R^*$ 196
  10.4.1 Sequential maximum likelihood procedure 196
  10.4.2 Doubly adaptive biased coin design 198
  10.4.3 Example 200
  10.4.4 Efficient randomized-adaptive design 201
10.5 Urn Models 201
  10.5.1 The generalized Friedman’s urn model 201
  10.5.2 The randomized play-the-winner rule 202
  10.5.3 Designs to target any allocation 205
  10.5.4 Ternary urn models 206
  10.5.5 Klein urn 207
10.6 Treatment Effect Mappings 207
10.7 Covariate-Adjusted Response-Adaptive Randomization 208
10.8 Problems 209
10.9 References 211
10.10 Appendix 214

11 Inference for Response-Adaptive Randomization 217
11.1 Introduction 217
11.2 Population-Based Inference 217
  11.2.1 The likelihood 217
  11.2.2 Sufficiency 220
  11.2.3 Bias of the maximum likelihood estimators 220
  11.2.4 Confidence interval procedures 222