
Contents

Preface.....	xxiii
1. Overview of Clinical Trial Methodology	1
1.1 Clinical Trials	1
1.2 Clinical Trial Methodology	1
1.2.1 Randomization and Control.....	1
1.2.2 Kefauver–Harris Amendment and Its Impact on Clinical Trial Methodology	2
1.2.3 Categorization of Clinical Trial Methodology	3
1.3 Summary of Clinical Trial Methodology	4
References.....	7
2. Overview of the Drug Development Process and Regulation of Clinical Trials	9
2.1 Introduction.....	9
2.2 The Drug Development Process.....	10
2.2.1 Pre-Investigational New Drug Exemption Application....	10
2.2.2 Investigational New Drug Exemption Application	10
2.2.3 Phases of Clinical Trials	11
2.2.4 The New Drug Application.....	13
2.2.5 Post-FDA NDA Review Activities	14
2.3 History of Drug Regulation.....	15
2.3.1 The Pure Food and Drugs Act—1906	15
2.3.2 The Sherley Amendment—1912	15
2.3.3 The Food and Drug Administration—1930	15
2.3.4 The Food, Drug, and Cosmetic Act—1938.....	15
2.3.5 The Durham–Humphrey Amendment Act—1951.....	16
2.3.6 The Kefauver–Harris Drug Amendments—1962.....	16
2.3.7 The Fair Packaging and Labeling Act—1966.....	16
2.3.8 The DESI Review—1970	16
2.3.9 The FDA Package Insert Requirement—1970.....	17
2.3.10 FDA Review of OTC Products—1972.....	17
2.3.11 The National Research Act—1974	17
2.3.12 The Medical Device Amendments—1976	17
2.3.13 The Good Laboratory Practices—1978	18
2.3.14 Good Clinical Practice Guidelines—1978	18
2.3.15 Protection of Human Subjects and IRB Standards—1981.....	18
2.3.16 The Federal Anti-Tampering Regulations—1983	19
2.3.17 The Orphan Drug Act—1983	19

2.3.18	The Hatch–Waxman Act—1984.....	19
2.3.19	The IND/NDA Rewrite—1983–1987	20
2.3.20	Drugs for Life-Threatening Illnesses—1987	20
2.3.21	Inclusion of Older Patients in Clinical Trials—1989	20
2.3.22	Accelerated Approval—1992.....	21
2.3.23	The Prescription Drug User Fee Act—1992	21
2.3.24	MedWatch—1993	21
2.3.25	The Food and Drug Modernization Act—1997.....	21
2.3.26	PDUFA Renewed—1997, 2002, and 2007.....	22
2.3.27	The Gender Guideline—1993	22
2.3.28	The Demographic Rule—1998	22
2.3.29	Best Pharmaceuticals for Children Act—2002	22
2.3.30	Pediatric Research Equity Act—2003.....	22
2.3.31	Drug Safety Oversight Board—2005.....	23
2.3.32	Other Regulations and Guidances.....	23
2.4	Principles of Adequate and Controlled Investigations.....	23
2.5	Content and Format of the IND.....	26
2.6	Content and Format of the NDA.....	28
2.6.1	Overall Summary	29
2.6.2	Technical Sections	29
2.6.3	Integrated Summaries	32
2.6.3.1	Integrated Summary of Efficacy.....	32
2.6.3.2	Integrated Summary of Safety	33
2.6.3.3	Integrated Summary of Benefit to Risk.....	34
2.7	Organizational Structure of the FDA	35
2.7.1	Overview of FDA Responsibilities	35
2.7.2	Centers and Offices of the FDA.....	35
2.7.3	Center for Biologics Evaluation and Research	36
2.7.4	Center for Devices and Radiological Health.....	37
2.7.5	Center for Drug Evaluation and Research.....	37
2.8	The FDA Review Process	39
2.9	Labeling and the Package Insert	41
2.10	Pharmaceutical Company Organization and Role of the Biostatistician.....	43
2.10.1	Pharmaceutical Company Organization Overview	43
2.10.2	Role of the Biostatistician.....	44
2.11	Concluding Remarks	45
	References.....	49
3.	Ethical Considerations in the Design and Conduct of Clinical Trials	55
3.1	Introduction.....	55
3.2	History and Evolution of Ethical Considerations in Clinical Trials: Key Milestones	56
3.2.1	The Nuremberg Code.....	56

3.2.2	The Declaration of Helsinki.....	58
3.2.3	The Belmont Report.....	59
3.2.4	21 CFR Parts 50 and 56.....	60
3.2.5	45 CFR Part 46.....	60
3.2.6	International Conference on Harmonization on Good Clinical Practices.....	61
3.3	Independent Review Boards.....	61
3.3.1	Investigational Review Board.....	61
3.3.2	Data Safety Monitoring Board.....	62
3.4	Clinical Trial Ethics: Who Should Practice?.....	62
3.4.1	Protocol Development.....	62
3.4.1.1	The Physician.....	63
3.4.1.2	The Biostatistician.....	63
3.4.1.3	Regulatory Affairs Expert.....	64
3.4.2	Clinical Trial Operations.....	64
3.4.2.1	Investigator and Site Personnel.....	64
3.4.2.2	Field Monitoring.....	65
3.4.3	Clinical Data Management.....	65
3.4.4	Biostatistical Analysis.....	65
3.4.5	Clinical Trial Study Report.....	66
3.4.6	Dissemination of Results.....	67
3.5	Informed Consent, Sample Size and Power.....	67
3.6	Common Ethical Principles of Various Codes and Regulations.....	69
3.7	Concluding Remarks.....	70
	References.....	70

4. Sample Size Considerations in Clinical Trials Pre-Market

Approval	73
4.1 Introduction.....	73
4.2 Phases of Clinical Trials and Objectives.....	73
4.2.1 Phase I Trials.....	74
4.2.2 Phase II Trials.....	74
4.2.3 Phase III Trials.....	75
4.3 The Clinical Development Plan: Pre-Market Approval.....	75
4.4 Sample Size Requirements.....	76
4.4.1 Protocol Objectives as Specific Statistical Questions.....	76
4.4.2 Endpoints.....	78
4.4.3 Statistical Methods.....	79
4.4.4 Statistical Design Considerations.....	80
4.4.5 Numbers in Phase I Program.....	82
4.4.6 Numbers in Phase II Program.....	82
4.4.7 Numbers in Phase III Program.....	83
4.4.8 Other Sample Size Considerations.....	83

4.4.8.1	Relative Size of Trials and Detectable Differences.....	83
4.4.8.2	Three-Arm Efficacy Trial: Dose of New Drug, Placebo, and Dose of Marketed Drug.....	86
4.4.8.3	Interim Analyses.....	87
4.5	Examples.....	89
4.5.1	H ₂ -Receptor Antagonist Duodenal Ulcer SNDA Program.....	89
4.5.2	Two Identical Studies in the Prevention of NSAID-Induced Gastric Ulceration.....	91
4.6	Philosophical Issues.....	96
4.6.1	Axioms of Drug Development.....	96
4.6.2	Sample Size: Efficacy or Ethical Imperative?.....	97
4.6.3	Larger versus Smaller Trials.....	98
4.6.4	One-Sided versus Two-Sided Tests.....	99
4.6.5	Amalgamation of Phase IIB and Phase III Trials.....	99
4.7	Concluding Remarks.....	100
	References.....	100
5.	Sequential, Group Sequential, Stochastic Curtailment, and Adaptive Design Procedures in Clinical Trials.....	103
5.1	Introduction.....	103
5.2	Sequential Procedures.....	103
5.3	Group Sequential Procedures.....	104
5.3.1	Definitions.....	104
5.3.2	Computational Aspects of the Contributions from Each Planned Interim Analysis to Overall <i>P</i> -Value and Power.....	106
5.3.3	A Three-Stage, Two-Treatment Trial.....	110
5.3.4	Application.....	112
5.3.4.1	Conditional Partitioning of α or α Spending Method.....	112
5.3.4.2	Pocock's Method.....	113
5.3.4.3	The O'Brien/Fleming Method.....	113
5.3.4.4	Minimum Detectable Difference.....	114
5.3.4.5	Power.....	115
5.3.5	Summary.....	115
5.4	Stochastic Curtailment.....	116
5.4.1	Introduction.....	116
5.4.2	Methods.....	117
5.4.3	Application.....	120
5.5	Adaptively Designed Clinical Trials.....	121
5.5.1	Introduction.....	121

5.5.2	Group Sequential Design.....	122
5.5.3	Sample-Size Reestimation Design	122
5.5.4	Drop-Loser Design.....	123
5.5.5	Adaptive-Randomization Design	124
5.5.6	Biomarker-Adaptive Design.....	124
5.5.7	Multiple Adaptive Designs.....	124
5.6	Concluding Remarks	125
	References.....	126
6.	Biostatistical Aspects of the Protocol.....	129
6.1	The Background or Rationale.....	129
6.2	Objective	129
6.3	Plan of Study.....	130
6.3.1	Study Population	130
6.3.2	Study Design.....	131
6.3.2.1	Type of Study.....	131
6.3.2.2	Treatment Group Specification and Assignment.....	131
6.3.2.3	Packaging to Achieve Blinding	131
6.3.2.4	Concomitant Medication	132
6.3.2.5	Procedures	132
6.3.3	Problem Management	132
6.4	Statistical Analysis Section.....	132
6.4.1	Study Objectives as Statistical Hypotheses.....	133
6.4.1.1	Primary, Secondary, Safety, or Other Objectives.....	133
6.4.1.2	Translating Protocol Objectives into Statistical Hypotheses	133
6.4.2	Endpoints	134
6.4.3	Statistical Methods.....	135
6.4.4	Statistical Monitoring Procedures.....	135
6.4.5	Statistical Design Considerations	136
6.4.6	Subset Analyses.....	137
6.5	Administration.....	138
6.5.1	Review and Consent Requirements	138
6.5.2	Record Keeping	139
6.5.3	Monitoring	139
6.6	Protocol References Section	140
6.7	Concluding Remarks	140
	References.....	140
7.	The Statistical Analysis Plan.....	143
7.1	Introduction.....	143
7.2	Protocol Objective.....	143

7.3	Efficacy Data Collected and Protocol Schema	143
7.4	Primary and Secondary Efficacy Endpoints.....	144
7.4.1	Primary Efficacy Endpoint	144
7.4.2	Secondary Efficacy Endpoints.....	145
7.5	Objectives, Translated as Statistical Hypotheses	145
7.5.1	Primary Efficacy Objective as a Statistical Hypothesis	145
7.5.2	Secondary Efficacy Objectives as Statistical Hypotheses.....	145
7.5.2.1	Percent of Patients with Acute Kidney Injury by Study Day 56	146
7.5.2.2	Cumulative Percent of Patients Surviving by Study Day 56.....	146
7.5.2.3	SOFA Score at Study Day 28	146
7.5.2.4	SOFA Score at Study Day 56	147
7.6	Protocol Design Features.....	147
7.6.1	Experimental Design	147
7.6.2	Treatment or Intervention Groups	147
7.6.3	Randomization	148
7.6.4	Blinding	148
7.6.5	Number of Patients.....	148
7.6.6	Number of Protocol Centers.....	148
7.7	Statistical Analyses.....	148
7.7.1	Trial Populations for Statistical Analyses.....	149
7.7.2	Demographics, Baseline Characteristics, Eligibility, and Disposition	149
7.7.3	Efficacy Analyses	150
7.7.3.1	Primary Efficacy Analyses	150
7.7.3.2	Secondary Efficacy Analyses	150
7.7.3.3	Analyses of Generalizability across Subpopulations	151
7.7.4	Interim Analyses	151
7.8	Concluding Remarks	151
	References.....	152
8.	Pooling of Data from Multicenter Clinical Trials.....	153
8.1	Introduction.....	153
8.2	Multicenter Clinical Trial Experimental Setting	154
8.3	Pre-Study Planning	155
8.4	Multicenter Clinical Trial Conduct	155
8.5	Biostatistical Analysis	156
8.5.1	Design-Based Analysis Strategy	156
8.5.1.1	Weighted Means and Variances.....	156
8.5.1.2	Inference on Treatment Effect.....	158

8.5.2	Model-Based Analysis Strategies.....	160
8.5.2.1	Fixed Center and Treatment Effects: No Interaction or No Significant Interaction...	160
8.5.2.2	Center and Treatment as Fixed Effects: Significant Interaction	160
8.5.2.3	Random Center and Fixed Treatment Effects ...	161
8.6	Concluding Remarks	161
8.6.1	Design-Based Inference	162
8.6.2	Model-Based Inference	162
	References.....	163
9.	Validity of Statistical Inference	165
9.1	Introduction.....	165
9.2	Planning the Investigation	166
9.2.1	Research Question and Endpoints	166
9.2.2	Hypothesis Testing Framework.....	167
9.2.3	The Number of Subjects.....	167
9.2.4	Procedures for Conducting the Investigation.....	168
9.2.5	Data Collection, Computerization, and Quality Assurance.....	168
9.2.6	Statistical Methods.....	169
9.3	Conducting the Investigation	170
9.4	Statistical Analyses, Interpretation, and Inference	170
9.5	Reporting Results of Investigations	172
9.6	Concluding Remarks	172
	References.....	173
10.	Bioequivalence Clinical Trials	175
10.1	Introduction.....	175
10.2	Absorption, Distribution, Metabolism, and Excretion (ADME).....	175
10.3	Bioavailability	176
10.3.1	Basis for Estimating Bioavailability.....	176
10.3.2	Relative Bioavailability.....	177
10.3.3	Absolute Bioavailability	177
10.4	Factors that Affect Bioavailability.....	178
10.4.1	Formulation or Dosage Form.....	178
10.4.2	Routes of Administration.....	178
10.4.3	State of the Biological System	178
10.5	Blood Level Clinical Trials	179
10.6	Bioequivalence	179
10.6.1	Bioavailability Parameters or Endpoints Needed for Bioequivalence.....	180
10.6.2	Decision Criterion for Concluding Bioequivalence.....	181

10.7	Design of Bioequivalence Trials	182
10.7.1	The Objective of Bioequivalence.....	182
10.7.2	Experimental Design Considerations.....	183
10.7.2.1	The Type of Experimental Design.....	183
10.7.2.2	Drug Elimination Period	184
10.7.2.3	Times of Collection of Blood Samples.....	184
10.7.2.4	Specific Experimental Designs.....	184
10.7.3	Endpoints	193
10.7.4	Sample Size Determination	193
10.7.5	Randomization and Blinding	196
10.7.6	The Statistical Analysis Section.....	197
10.7.6.1	Computation of Endpoints for Each Subject.....	197
10.7.6.2	Statistical Analysis of Concentrations and Bioavailability Endpoints	198
10.8	Analysis of Bioequivalence Trials	199
10.9	Analysis of Ratios.....	200
10.10	Pharmacokinetic Models	201
10.11	Support of Bioequivalence Trials in the Pharmaceutical Industry	202
10.12	Examples.....	203
10.12.1	Parallel Bioequivalence Clinical Trial of Six Formulations with Sample Size Reestimation	203
10.12.1.1	Background	203
10.12.1.2	Six-by-Six Latin Square Design versus Six-Group Parallel Design.....	203
10.12.1.3	Sample Size Reestimation	204
10.12.2	Crossover Bioequivalence Trial.....	204
10.12.2.1	Background and Endpoint Computations	204
10.12.2.2	Test for Differential Carryover Effect.....	206
10.12.2.3	Inferential Analysis of Bioequivalence: Confidence Interval Approaches	209
10.12.2.4	Inferential Analysis of Bioequivalence: Bayesian Approaches.....	213
10.12.2.5	Inferential Analysis of Bioequivalence: Two One-Sided Tests.....	214
10.13	Concluding Remarks	215
	Appendix 10.A Bioequivalence Dataset.....	216
	Appendix 10.B R Code with Detailed Annotations	222
	References.....	226
11.	Dose and Frequency Determination from Phase II Clinical Trials in Stress Test–Induced Angina	229
11.1	Introduction.....	229
11.2	Overview of Response Surface Methodology	230

11.3	Full Quadratic Response Surface Model.....	231
11.4	Phase II Clinical Trial Program in Stress Test–Induced Angina.....	232
11.4.1	Treatment Groups in the Original Protocols	233
11.4.2	Efficacy Measures.....	233
11.4.3	Stress Testing and Dosing Considerations.....	234
11.4.4	Design	234
11.4.5	Model	235
11.4.6	Statistical Analyses	236
11.4.6.1	Data and Descriptive Analyses	236
11.4.6.2	Response Surface Methods Analyses	236
11.5	Concluding Remarks	246
	References.....	247
12.	Confirmation of Clinically Optimal Dosing in the Treatment of Duodenal Ulcers: A Phase III Dose Comparison Trial.....	249
12.1	Introduction.....	249
12.2	Background	250
12.3	Objective	251
12.4	Designing and Planning the Investigation	252
12.4.1	Blinded Treatment Groups.....	252
12.4.2	Sample Size Determination	253
12.4.3	Entry Requirements and Assessment Schedule	253
12.4.4	Primary and Secondary Endpoints	254
12.5	Conducting the Investigation	254
12.6	Statistical Analyses.....	255
12.6.1	Statistical Analysis Methods.....	255
12.6.1.1	Methods	255
12.6.1.2	Interim Analysis.....	256
12.6.2	Interim Analysis Results	257
12.6.2.1	Numbers of Patients and Baseline Characteristics.....	257
12.6.2.2	Distribution of Patients according to Ulcer Size.....	258
12.6.2.3	Influence of Smoking Status and Ulcer Size on Ulcer Healing.....	258
12.6.2.4	Cumulative Ulcer Healing	260
12.6.2.5	Generalizability Assessment	261
12.6.2.6	Complete UGI Pain Relief and Ulcer Healing.....	261
12.6.3	Final Analysis Results	263
12.7	Other Considerations	264
12.7.1	Bioequivalence Trial of Two 400 mg Tablets and One 800 mg Tablet.....	264
12.7.2	Cimetidine-by-Drug Interaction Trials	264
12.7.3	Study in the Elderly.....	264

12.8	Innovative Aspects of the Clinical Trial Program	265
12.8.1	Interim Analyses to Drop Placebo Arms.....	265
12.8.2	Third-Party Blinding during Interim Analyses	265
12.8.3	Trial Objectives as Only Three of Six Pair-Wise Comparisons.....	266
12.8.4	Giving Up Information on Center Differences.....	266
12.8.5	Assessment of Type of Monitoring by Treatment Group	266
12.8.6	Association between Ulcer Healing and Smoking Status and Ulcer Size	266
12.8.7	Utilization of Bivariate Graphical Methods	266
12.8.8	Establishing Effectiveness Based on a Subset Analysis.....	266
12.8.9	Maximum Use of Patients Screened with UGI Pain.....	267
12.9	Concluding Remarks	267
	References.....	267
13.	Pivotal Proof-of-Efficacy Clinical Trials in the Prevention of NANSOID-Induced Gastric Ulceration	271
13.1	Introduction.....	271
13.2	Rationale	271
13.3	The Protocols.....	272
13.3.1	Objectives	272
13.3.2	Inclusion Criteria.....	272
13.3.3	Efficacy Endpoints	273
13.3.4	Sample Size Determination	273
13.3.5	Statistical Methods.....	274
13.4	Monitoring and Data Management	274
13.5	FDA Meeting.....	276
13.6	Concluding Remarks	278
	References.....	280
14.	Clinical Trials in the Treatment of Alzheimer's Disease Based upon Enrichment Designs.....	283
14.1	Introduction.....	283
14.2	Enrichment Design Clinical Trials	285
14.3	Objective	286
14.4	Primary Efficacy Endpoints	286
14.5	Sample Size Determination.....	287
14.6	Statistical Methods	287
14.6.1	Linear Model Analyses of Primary Efficacy Measures.....	287
14.6.1.1	Titration Phase	288
14.6.1.2	Double-Blind Phase	291
14.6.1.3	Meta-Analyses of Results across Trials	292

14.6.2	Population Pharmacodynamic/Pharmacokinetic, Nonlinear Mixed Effects Model Analyses.....	293
14.6.2.1	Objectives.....	294
14.6.2.2	Requirements of the Model.....	294
14.6.2.3	Model Parameters.....	295
14.6.2.4	Model Formulation.....	295
14.6.2.5	Computational Methods.....	297
14.7	Results.....	298
14.7.1	Titration Phase Data	298
14.7.1.1	Detailed Titration Phase Results: Protocol 01 ...	298
14.7.1.2	Titration Phase Results Summary: Protocols 01, 04, and 06	302
14.7.2	Double-Blind Parallel Phase Results Summary: Protocols 01, 04, and 06.....	302
14.7.3	Data from All Phases, PD/PK Results Summary: Protocols 01, 04, and 06.....	304
14.8	Concluding Remarks	306
	References.....	308
15.	A Clinical Trial to Establish Reduction of CHD Risk	311
15.1	Introduction.....	311
15.2	Objective	312
15.3	Designing and Planning the Investigation	312
15.3.1	Blinded Treatment Groups.....	313
15.3.2	Sample Size Determination	313
15.3.3	Entry Requirements	313
15.3.4	Primary Efficacy and Safety Endpoints.....	313
15.4	Conducting the Investigation	314
15.5	Data Management	315
15.6	Statistical Analyses.....	315
15.6.1	Methods for Double-Blind Phase.....	315
15.6.2	Methods for Double-Blind and Open-Label Phases	316
15.6.2.1	Classification Groups	316
15.6.2.2	Data on Major Events	316
15.6.2.3	Inferential Statistical Methods	324
15.7	Results.....	326
15.7.1	Double-Blind Phase	326
15.7.2	Double-Blind and Open-Label Phases.....	327
15.7.2.1	Cardiac Endpoints	327
15.7.2.2	All-Cause Mortality.....	328
15.7.2.3	Cardiac Deaths.....	328
15.7.2.4	Noncardiac Deaths	329
15.7.2.5	Noncardiac, Noncancer Deaths.....	329
15.7.2.6	Cancer Deaths	329
15.7.2.7	Cancer Diagnosis	329

15.8	Summary.....	330
15.9	Concluding Remarks	333
	References.....	334
16.	Pivotal Proof-of-Efficacy Clinical Trials in the Treatment of Panic Disorder	337
16.1	Introduction.....	337
16.2	Design of Pivotal Proof-of-Efficacy Trials.....	338
16.2.1	Forced Titration Dose–Response Trial: Experimental Design	340
16.2.2	Titration according to Response Trial: Experimental Design	340
16.2.3	Efficacy Endpoints	340
16.2.4	Trial Objectives.....	341
16.2.4.1	Forced Titration Dose–Response Trial Objective	341
16.2.4.2	Titration according to Response Trial Objective	341
16.2.5	Sample Size Determination	342
16.3	Traditional Statistical Analysis Methods	342
16.4	Overview of Efficacy Results of the Two Trials	343
16.5	Alternative Design and Analysis Strategies	343
16.6	Concluding Remarks	345
	References.....	345
17.	Combination Clinical Trials	347
17.1	Introduction.....	347
17.2	Two-by-Two Factorial Design.....	348
17.3	Effectiveness of the Combination.....	348
17.4	Contribution of Components to the Effectiveness of the Combination	350
17.5	Factorial Designs in Other Clinical Development Areas.....	350
17.6	Example 1: Actifed [®] in the Treatment of SAR Following DESI Review	351
17.6.1	Design and Randomized Treatment Groups.....	352
17.6.2	Objective.....	352
17.6.3	Efficacy Endpoints	352
17.6.4	Sample Size Requirements.....	352
17.6.5	Statistical Analysis Methods.....	352
17.7	Example 2: Crossover Trial of Actifed in the Treatment of SAR.....	355
17.8	Example 3: Parallel Trial of Actifed in the Treatment of the Common Cold.....	356
17.9	Concluding Remarks	358
	References.....	358

18. Monitoring Clinical Trials for Adverse Events	361
18.1 Introduction.....	361
18.2 Designing for Safety: Antibiotic Rash Example.....	361
18.3 Designing for Safety: Hypokalemia Example	362
18.4 Designing for Safety: Hypertensive Rebound Example	362
18.5 Premarket Approval Trials: Designed for Efficacy	363
18.6 Premarket Approval Trials: Quality of Adverse Event Information	364
18.7 Monitoring for Safety.....	366
18.8 Statistical Methodology: Individual Trial.....	367
18.8.1 Direct Comparison Methodology.....	368
18.8.2 Indirect Comparison Methodology.....	369
18.8.3 Connection between Direct and Indirect Comparison Methods.....	370
18.9 Example	371
18.9.1 Adverse Event Data from a Clinical Trial.....	371
18.9.2 The Classical Direct Comparison Confidence Interval Method.....	372
18.9.3 The Indirect Comparison Confidence Interval Method.....	373
18.9.4 Computing Significance or Confidence Levels for the Indirect Method.....	374
18.10 Statistical Methodology: Across Trials.....	376
18.11 Concluding Remarks	376
Appendix 18.A R Program to Analyze the Data in Table 18.2	378
References.....	381
Index	383