

Contents

	<i>Preface</i>	<i>page</i> xix
	<i>Acknowledgments</i>	xxiii
	PART I INTRODUCTION	1
1.	Questions before Starting on the Details	3
	1.1 What Are the Broad Issues?	3
	1.2 Question 1: Why Do You Want to Do Research?	5
	1.3 Question 2: What Is Your Question?	7
	1.4 Question 3: Why Does Answering This Question Matter?	9
	1.5 Question 4: Why Are You the Person to Answer the Question?	10
	1.6 Question 5: How Will You Know Whether You Have Answered Your Question?	11
	1.7 Ethical Issues	12
	Key Points	13
	References	13
2.	Ethics	14
	2.1 How Ethical Guidelines Developed	14
	2.1.1 International Codes	15
	2.1.2 The United States	16
	2.2 Principles of Ethical Practice	18
	2.2.1 Social and Clinical Value	18
	2.2.2 Scientific Validity	19
	2.2.3 Fair Subject Selection	20
	2.2.4 Favorable Risk-Benefit Ratio	21
	2.2.5 Independent Review	21

viii	Contents	
	2.2.6 Informed Consent	22
	2.2.7 Respect for Potential and Enrolled Subjects	22
	2.3 The Institutional Review Board (IRB)	23
	2.4 The Data Safety and Monitoring Board (DSMB)	25
	2.5 Resources for Further Reading	26
	Key Points	26
3.	Informed Consent	28
	3.1 The Consent Process	28
	3.1.1 The Consent Document	29
	3.1.2 The Consent Interview	34
	3.2 The Authorization Form for Protecting Data	36
	3.3 Coercion and Undue Influence	37
	3.4 Special Populations	38
	3.4.1 Children	38
	3.4.2 Persons Unable to Understand and Agree to the Study	39
	3.4.3 Speakers of Other Languages	40
	3.4.4 Pregnant Women, Fetuses or Neonates	40
	3.4.5 Prisoners	41
	3.5 Use and Retention of Tissue Samples	41
	3.6 Situations When Consent Is Not Required or May Be Postponed	42
	3.7 Ethical Issues	42
	Key Points	43
	PART II STUDY DESIGNS	45
4.	Overview of Study Designs	47
	4.1 Interventional Designs	47
	4.2 Designs for Observational Studies	49
	4.3 Clinical Trials	52
	4.4 Different Questions May Represent Different Designs in the Same Study	53
	4.5 How You Frame the Question Affects the Types of Studies Possible	54
	4.6 Advantages of Interventional Studies	57
	4.7 Difficulties of Interventional Studies	58
	4.8 Ethical Issues	59
	Key Points	61

ix	Contents	
5.	Designs for Interventional Studies	62
5.1	Summary of Interventional Designs	62
5.2	The Question Being Studied	63
5.3	Studies in Which All Participants Receive the Intervention	64
5.3.1	Single Group of Participants	64
5.3.2	More Than One Group of Participants	66
5.4	Studies in Which Some Participants Receive the Intervention and Some Do Not: Parallel Group Studies	68
5.5	Studies in Which All Participants Are Studied with and without the Intervention	74
5.5.1	Comparison within a Single Participant with Intervention in Random Order (Crossover Study)	74
5.5.2	Comparison within a Single Participant with Intervention in Fixed Order (Pre-Post Study)	77
5.6	Ethical Issues	80
	Key Points	81
6.	Cohort Studies	82
6.1	Basic Designs	82
6.2	Advantages of Cohort Studies Compared to Interventional Studies	86
6.3	Disadvantages of Cohort Studies Compared to Interventional Studies	87
6.4	Prospective versus Retrospective Cohort Studies	90
6.5	Ethical Issues	92
	Key Points	93
7.	Case-Control Studies	95
7.1	Basic Design	95
7.2	Selecting Participants	97
7.3	Matching	98
7.4	Nested Case-Control Studies	99
7.5	Advantages and Disadvantages of Case-Control Studies	100
7.6	Ethical Issues	102
	Key Points	102
8.	Cross-Sectional Studies	104
8.1	Fundamental Features	104
8.2	Examples of Cross-Sectional Studies	105

x	Contents	
	8.3 Some Common Problems in Cross-Sectional Studies	108
	8.4 Ethical Issues	109
	Key Points	110
9.	Record Reviews	111
	9.1 Data Availability and Quality	111
	9.1.1 Data Availability	111
	9.1.2 Data Quality	113
	9.1.3 What Can Be Done about Data Problems?	114
	9.2 Examples of Record Reviews	115
	9.3 Ethical Issues	118
	Key Points	118
10.	Selecting a Design	119
	10.1 A Range of Designs	119
	10.2 Interventional or Observational Study?	120
	10.2.1 Is an Interventional Study Ethical?	120
	10.2.2 Is an Interventional Study Practical?	123
	10.3 Selecting an Interventional Study Design	124
	10.3.1 Randomized or Non-Randomized Study?	124
	10.3.2 Parallel Group or Crossover Study?	126
	10.4 Observational Studies	127
	10.4.1 Case-Control or Cohort Study?	127
	10.4.2 Cohort Study: Retrospective or Prospective?	129
	10.5 Example of Developing a Design	130
	10.6 Ethical Issues	132
	Key Points	133
	PART III CORE CONCEPTS APPLICABLE TO ALL STUDY DESIGNS	135
11.	Generalizability and Validity	137
	11.1 The Population	137
	11.2 Study Methods	140
	11.2.1 Treatment and Treatment Monitoring	140
	11.2.2 Assessment Methods	142
	11.3 Validity	143
	11.4 Ethical Issues	144
	Key Points	145

xi	Contents	
12.	Study Population	147
	12.1 The Target Population and the Study Pool	147
	12.2 The Eligible Group	148
	12.3 The Study Group	157
	12.4 Ethical Issues	158
	Key Points	159
13.	Getting and Keeping Participants	161
	13.1 Recruiting the Right Number of Participants	161
	13.2 Recruitment and Retention Is Part of Planning	163
	13.3 Locating and Recruiting Participants	164
	13.4 Retention and Adherence	168
	13.5 Use of the Internet	171
	13.6 Ethical Issues	172
	Key Points	174
14.	Study Data: How Variables Are Used	175
	14.1 Types of Variables	175
	14.2 Role of Variables in an Interventional Study	176
	14.3 Role of Variables in Observational Studies	181
	14.4 Measuring Variables	183
	14.5 Recoding Data	184
	14.6 Storing Data	184
	14.7 Ethical Issues	185
	Key Points	186
15.	Study Data: Endpoints	187
	15.1 Defining the Outcome Variables	187
	15.2 Derived Outcomes	190
	15.3 Time-Related Outcomes	192
	15.4 Ethical Issues	194
	Key Points	195
16.	Study Data: Predictor and Confounding Variables	196
	16.1 Predictor Variables	196
	16.2 Confounding Variables	198
	16.3 Predictors versus Confounders	199
	16.4 Ethical Issues	200
	Key Points	201

xii	Contents	
17.	Bias	203
	17.1 Common Sources of Bias	203
	17.1.1 Prognostic Bias	204
	17.1.2 Selection Bias	206
	17.1.3 Participant Bias	208
	17.1.4 Recall Bias	208
	17.1.5 Bias Due to the Learning Effect	209
	17.1.6 Care Provider Bias	210
	17.1.7 Assessor (Rater) Bias	211
	17.1.8 Laboratory Bias	212
	17.1.9 Analysis Bias	212
	17.1.10 Interpretation Bias	213
	17.1.11 Publication Bias	213
	17.2 Non-Differential Bias	214
	17.3 Ethical Issues	214
	Key Points	215
18.	Avoiding Bias	217
	18.1 Selection of Study Population	217
	18.2 Randomization	219
	18.3 Blinding	221
	18.4 Assessment Methods and Training	223
	18.5 Data Monitoring during the Study	224
	18.6 Ethical Issues	225
	Key Points	226
	PART IV ADDITIONAL CONCEPTS FOR INTERVENTIONAL STUDIES	227
19.	Describing the Intervention	229
	19.1 Problems in Describing an Intervention	229
	19.2 Determining the Control Intervention	231
	19.3 Describing the Control Intervention	234
	19.4 Ethical Issues	235
	Key Points	235

xiii	Contents	
20.	Randomization: What and Why	237
	20.1 What Is Randomization?	237
	20.2 Why Randomize?	240
	20.3 Why Randomize Individuals?	242
	20.4 Ethical Issues	243
	Key Points	244
21.	Techniques for Randomization	245
	21.1 Requirements for a Valid Randomized Study	245
	21.2 Creating a Randomization Schedule	246
	21.3 Adding Special Features to the Randomization Schedule	249
	21.3.1 Stratification	250
	21.3.2 Blocking	252
	21.3.3 Benefits and Pitfalls of Stratification and Blocking	254
	21.4 Unbalanced Randomization	255
	21.5 Ethical Issues	256
	Key Points	257
22.	Blinding in Interventional Studies	258
	22.1 Why Blinding Is Used	258
	22.2 The Hierarchy of Blinding	259
	22.2.1 Double-Blind Studies	260
	22.2.2 Complete Blinding	261
	22.2.3 Single-Blind Studies	262
	22.2.4 Open-Label Studies	264
	22.2.5 Multiple Levels of Blinding	266
	22.3 Monitoring Safety and Breaking the Blind	266
	22.4 When the Blind Is Broken	267
	22.5 Ethical Issues	268
	Key Points	269
23.	Techniques to Blind Interventional Studies	270
	23.1 Masking the Intervention	270
	23.1.1 Masking a Pharmaceutical Intervention	270
	23.1.2 Maintaining the Mask When Dosage Levels Change	272
	23.1.3 Masking a Non-Pharmaceutical Intervention	273

	23.1.4 Masking Laboratory Staff	274
	23.1.5 Masking Data Management Staff	275
23.2	Providing the Intervention in Blinded Studies	275
	23.2.1 Treatment Allocation by the Manufacturer	276
	23.2.2 The Institutional Pharmacy	276
	23.2.3 Allocation by a Member of the Study Team	277
	23.2.4 Keeping the Randomization Confidential	278
23.3	Common Problems Maintaining Masking	279
	23.3.1 Side Effects	279
	23.3.2 Efficacy	280
	23.3.3 Leaks and Guesses	281
23.4	Ethical Issues	281
	Key Points	282
24.	Adherence and Compliance	284
	24.1 Efficacy versus Effectiveness	284
	24.2 Adherence: How Is It Assessed?	286
	24.3 Overall Measures to Improve Adherence	289
	24.4 Measures to Improve Retention in the Study	292
	24.5 Ethical Issues	293
	Key Points	294
	PART V ADDITIONAL CONCEPTS FOR OBSERVATIONAL STUDIES	295
25.	Defining Populations for Cohort Studies	297
	25.1 Data Availability	297
	25.1.1 Data Sources	299
	25.1.2 Stratified Sampling	299
	25.2 Quality of Information	300
	25.3 Study Time Line	302
	25.4 Multiple Cohort Studies	304
	25.5 Ethical Issues	305
	Key Points	306
26.	Participants in Case-Control Studies	307
	26.1 Identifying Cases and Controls	307
	26.1.1 General Considerations	307
	26.1.2 Identifying Cases	308

xv	Contents	
	26.1.3 Identifying Controls	311
	26.2 Inclusion and Exclusion Criteria for Controls	313
	26.3 Special Situations	316
	26.3.1 Multiple Control Groups	316
	26.3.2 Case-Control Studies within Cohort Studies	317
	26.3.3 Historical Controls	317
	26.4 Should the Sizes of the Groups Be the Same?	318
	26.5 Ethical Issues	319
	Key Points	319
27.	Matching in Observational Studies	321
	27.1 Why Match?	321
	27.2 Who Are You Matching?	322
	27.3 When Is Matching Done?	323
	27.4 Individual Matching	325
	27.4.1 Defining Matching Criteria	325
	27.4.2 Choosing between Eligible Controls	327
	27.5 Frequency Matching	328
	27.6 Practical Issues	329
	27.6.1 Overmatching	329
	27.6.2 Excessive Matching Criteria	330
	27.6.3 Special Problems	330
	27.6.4 Data Analysis	332
	27.7 Ethical Issues	332
	Key Points	333
28.	Blinding in Observational Studies	334
	28.1 What Can Be Blinded?	334
	28.2 Blinding of Written Records	335
	28.3 Blinding When Assessors Have Contact with Participants	335
	28.4 What to Do When Blinding Is Not Possible	337
	28.5 Ethical Issues	338
	Key Points	339
	PART VI PRACTICAL ISSUES	341
29.	Acquiring High Quality Data	343
	29.1 Creating a Study ID	343
	29.2 Methods for Data Collection	344

xvi	Contents	
	29.2.1 Questionnaires	345
	29.2.2 Open-Ended Data Collection by an Interviewer	348
	29.2.3 Other Types of Procedures Done by Study Staff	351
	29.2.4 Tests Done by Non-Study Staff	353
	29.3 The Manual of Procedures (MOP)	354
	29.4 Ensuring Validity in a Multi-Site Study	354
	29.5 Ethical Issues	355
	Key Points	356
30.	Data Management	358
	30.1 Basic Approaches to Data Storage	358
	30.2 Documenting the Data	362
	30.2.1 Data Organization and Coding	362
	30.2.2 The Code Book	363
	30.3 Selecting a Data Storage Program	364
	30.4 Methods of Data Capture	365
	30.5 Verifying Data	367
	30.6 Preserving Confidentiality	371
	30.7 A Note on Programs	373
	30.8 Ethical Issue	373
	Key Points	374
	APPENDIXES STATISTICAL CONCEPTS	375
Appendix A.	Hypothesis Testing	377
	A.1 The Criminal Trial as an Analogy for Hypothesis Testing	377
	A.2 Hypothesis Testing	378
	A.3 Determining Statistical Significance	383
	A.4 Clinical Importance	386
	A.5 Ethical Issues	387
	Key Points	388
Appendix B.	Determining the Sample Size for a Study	390
	B.1 Why Sample Size Matters	390
	B.2 Calculating a “Just Right Number”	391

xvii **Contents**

B.3	The Problem with the “Just Right Number”	393
B.4	Legitimate Ways to Reduce the “Just Right Number”	394
B.5	The Magical Thinking Way to Reduce the “Just Right Number”	397
B.6	An Alternative Way of Thinking about Sample Size	398
B.7	Ratio of Sample Sizes between Different Groups	399
B.8	Calculating the “Just Right Number”	400
B.9	Ethical Issues	400
	Key Points	401
	<i>Index</i>	403